

# C-Reactive Proteins as diagnostic and prognostic indicator in neonatal sepsis

Swati M. Bapat\*

Assistant Professor, Department of Paediatrics, GS Medical College and KEM Hospital Parel, Mumbai, Maharashtra-400012, India

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## \*Correspondence Info:

Dr. Swati M. Bapat  
Assistant Professor,  
Department of Paediatrics,  
GS medical college and KEM hospital Parel, Mumbai,  
Maharashtra-400012, India

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## Abstract

**Background:** Many biomarkers have been proposed and assessed clinically to optimize the survival rates in septic patients, but none alone is specific enough to definitively determine diagnosis. The present study was undertaken to assess the role of C-reactive proteins (CRP) as a promising marker in diagnosis of neonatal sepsis and also determine the utility of CRP as a prognostic indicator in neonatal sepsis.

**Methods:** The study was conducted in 200 neonates admitted in NICU who fulfilled criteria of neonatal sepsis as per guidelines of National Neonatology Forum over a period of 2 years. Detection of CRP in human serum was done by the rapid slide latex agglutination qualitative method with cut off value of CRP being 6mg/dl.

**Result:** CRP was positive in 71.60% and negative in 28.4% of babies on day 1 of admission. All the cases were followed subsequently with starting of empirical antibiotics therapy and CRP repeated on day 5 and day 10 / or on discharge. It showed that CRP positivity decreased over these periods to 10%. Negative predictive value of Serial CRP increases from 41% on day 1 to 96% on day 10 / or on discharge, which signifies that serial CRP value rules out sepsis with high accuracy and helpful in deciding duration of antibiotics in neonatal sepsis. Sensitivity of Serial CRP increases from 35% on day 1 to 59% on day 10 / or on discharge which was significant. Mean duration of antibiotics on the basis of serial CRP values in neonates was reduced from 13 days in non-study group to 8 days, which was significant.

**Conclusion:** The serial CRP measurement is a good indicator for discontinuing antibiotic therapy in neonates with suspected sepsis and a useful diagnostic and prognostic marker in neonatal sepsis.

**Keywords:** Sepsis, Biomarkers, C-reactive proteins, Prognostic indicator, National Neonatology Forum, Latex Agglutination.

## 1. Introduction

Neonatal sepsis can be devastating, leading to high morbidity and mortality in newborns, and is recognized as a global health challenge [1,2]. It has been defined as the presence of bacteria in sterile body fluids (blood, urine, cerebrospinal, peritoneal, and pleural fluid) [3,4] and classified as early onset sepsis (EOS) and late onset sepsis (LOS) on the basis of time of onset after neonatal birth [5]. EOS is defined when the onset of sepsis is within 72 h of postnatal life and the source of infection is vertical transmission of bacteria from mother to newborn. LOS has been defined as onset of sepsis after 72 h of postnatal life and the source of infection is horizontal transfer of bacteria

from health care personal [6]. The importance of defining neonatal sepsis as EOS and LOS is to guide for antibiotic pattern and prognostication [7]. Neonatal sepsis is a great mimicker giving rise to signs and symptoms compatible with almost every other neonatal problem thus making clinical diagnosis of sepsis very difficult [8].

Blood culture remains the gold standard for diagnosis of neonatal sepsis. As microbial culture reports are usually available after 48-72 hours, early identification of infected cases is a real diagnostic problem [9]. Many plasma proteins called Acute Phase Reactants become elevated acutely in response to illness, infection, and trauma

and tissue necrosis. These proteins include  $\alpha$ -1 acid glycoprotein,  $\alpha$ -1 antitrypsin, ceruloplasmin, haptoglobin, fibrinogen and CRP. The most useful of this is CRP based on its rapid rise in response to acute disease and rapid clearance once that stimulus is been aborted [10]. It was first discovered by Tillet and Francis (1930) in the serum of patients with pneumonia but was isolated in 1941 [11]. CRP is a serum acute phase reactant and a valuable inflammatory biomarker in various clinical conditions. However, it is readily quantitated by immunological methods. CRP is able to differentiate between viral and bacterial infections.

Numerous studies have reported the high sensitivity and specificity of CRP for the diagnosis of sepsis [12, 13] In ICU patients, elevated concentrations of serum CRP upon admission are correlated with an increased risk of organ failure and death [14]. Although many authors proposed that, persistent positive CRP test indicates bad prognosis. But the possible role of CRP in diagnosis of neonatal sepsis and its utility as a prognostic indicator is not confirmed so far. Hence in present study an attempt was made to evaluate role of CRP in diagnosis of neonatal sepsis and determine the utility of CRP as a prognostic indicator in neonatal sepsis.

## 2. Materials and Methods

After obtaining Institutional Ethical Committee approval and written informed consent from parents, this observational study was conducted on 200 neonates admitted in neonatal intensive care unit with signs and symptoms suggestive of neonatal sepsis over a study period of 2 years. Babies suspected of other systemic illness were excluded from the study. A detailed history regarding clinical features suggestive of sepsis and other relevant complaints was obtained from the mother / guardian. Weight and sex of the baby were recorded. A detailed clinical examination was done at the time of admission.

### CRP Estimation-

1) Sample collection: 1-2 cc of venous blood was drawn with sterile needle and kept in the test tube till complete clotting and separated serum was visible for testing. The laboratory requires 0.10-0.15 ml of serum; therefore 0.3-0.5ml (depending on hematocrit) of whole blood will be required, in a lithium heparin (green top) tube (plain bulb).

2) C- Reactive Protein Assay: CRP was done serially on day1, day 5 and day10 of admission / discharge whichever is earlier. This test was done by using diagnostic kit for in-vitro detection of CRP in human serum by the rapid slide latex agglutination qualitative method supplied commercially by Span Diagnostics Ltd. In current study CRP estimation done by microbiologist using same method with cut off value of CRP being 6mg/dl.

## 2.1 Statistical Analysis

Contingency table analysis and chi square ( $\chi^2$ ), Pearson Chi-Square, Onaway ANOVA test and McNemar-Bowker Test were applied wherever statistical analysis was necessary. All the statistical calculations were done through SPSS for Windows, Version 20.0.

## 3. Observations and Results

The present study enrolled total 200 neonates, amongst them 121 (60.5%) neonates were male and 79 (39.5%) neonates were female. The majority of babies were preterm i.e. 113 (56.5%) while remaining 87 (43.5%) cases were full term babies, (p value <0.05). Table 1 shows the percentage of risk factors present in suspected septic cases. Low Birth weight was the most common risk factor as observed in 145 (72.5%) cases followed by prematurity as seen in 120 (60%) cases. The third common risk factor was PROM as seen in 24 (12%) cases.

**Table 1: Percentage of Risk factors in Suspected Septic Cases**

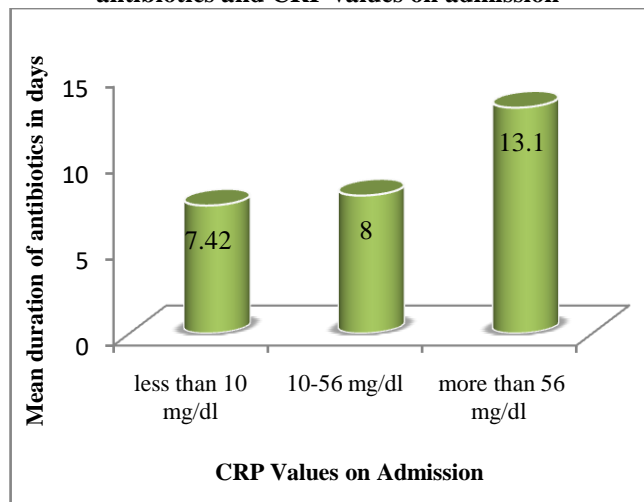
Predisposing factors	No. of cases	Percentage
Low Birth weight	145	72.5
Prematurity	120	60
Prolonged ruptures of membrane >18 hrs	24	12
Home delivery	12	6
Congenital anomalies	14	7
Birth Asphyxia	9	4.5
Meconium stained liquor	6	3
H/O intrapartum maternal infection	5	2.5
Instrumental delivery	2	1

Out of total cases, 71.60% had positive CRP and 28.4% had negative CRP on day 1 of admission. All the cases were followed subsequently with starting of empirical antibiotics therapy (IV cefotaxim and amikacin in 81% cases; IV ampicillin and gentamycin in 19% cases) and CRP repeated on day 5 and day 10 / or on discharge whichever is earlier, showed that CRP positivity decreased over this periods to 10% with mean duration of antibiotics was 8 days.

Negative predictive value of Serial CRP increases from 41% on day 1 to 96% on day 10 / or on discharge, which signifies that serial CRP value rules out sepsis with high accuracy and helpful in deciding duration of antibiotics in neonatal sepsis. Sensitivity of Serial CRP increases from 35% on day 1 to 59% on day10 / or on discharge which was significant, (Table 2). Mean duration of antibiotics on the basis of serial CRP values in neonates was reduced from 13 days in non-study group to 8 days, which was significant, (Figure 1).

**Table 2: Sensitivity, specificity, positive and negative predictive values of CRP**

CRP Values	Sensitivity	specificity	Positive predictive values	Negative predictive values
Day 1	35.20 %	87.54%	82.10%	40.98%
Day 2	47.84%	94.56%	93.20%	42.18%
Day 10/ Or on Discharge	59.33%	65.10%	15.30%	95.89%

**Figure 1: Correlation between mean duration of antibiotics and CRP values on admission**

The incidence of blood culture positive cases in neonatal sepsis was 31% (culture positivity rate). Of this 200 neonates, 15 (7.5%) died and 185 (92.5%) discharged after successful treatment. There was significant correlation between CRP values and outcome ( $p$  value  $<0.05$ ) of neonates with signs and symptoms of neonatal sepsis, (Table 3) as well as between CRP values and blood culture at any time of hospital stay for diagnosing sepsis shown by Pearson chi-square test with  $p$  value consistently less than 0.05 in this study.

**Table 3: Correlation between CRP on admission and outcome of patients**

CRP Day 1	Outcome		Total
	Die	Discharge	
<10 mg/dl	3 (5.08%)	59 (95.16%)	62 (100%)
10-56 mg/dl	6 (6.38%)	88 (93.61%)	94 (100%)
>56 mg/dl	6 (13.63%)	38 (86.36%)	44 (100%)
Total	15 (7.5)	185 (92.5%)	200 (100%)
P value- 0.074 (Significant)			

#### 4. Discussion

The early diagnosis and timely management of sepsis are known to be crucial in the reduction of sepsis-induced mortality. For that there is intense need for the search of a rapid, sensitive, and specific gold standard for diagnosis, predicting its severity and outcome of sepsis. The idea of a "Biomarker" for sepsis was enthusiastic for these issues with a resulting hundreds or even thousands of publications that studied numerous molecules that were supposed to be related to sepsis [15]. CRP is one of the

most widely available, most studied, and most used laboratory tests for neonatal bacterial infection and despite the continuing emergence of new infection markers it still plays a central role in the diagnosis of early onset sepsis of the neonate.

Serial measurements of serum CRP levels are useful in monitoring the course of neonatal septicemia. It provides an early indication of response of treatment. It can help in decision of initiating or discontinuing antibiotic therapy. The persistence or insignificant decline of serum CRP with treatment signifies about inadequate treatment or development of complications. In present study CRP was done serially on day 1, day 5 and day 10/ or on discharge. Sensitivity of single CRP for diagnosing neonatal sepsis was low but this can be increased by serial CRP measurement as evident in present study that was on day 1 sensitivity was 35.20%, on day 5 increased to 47.84% and on day 10 / or on discharge sensitivity reaching up to 59.33%. Sharma *et al* [9] reported that out of various test for rapid diagnosis of neonatal sepsis, CRP was one with maximum sensitivity 80%. Chandna *et al* [16] found that CRP is the most useful single test with high degree of sensitivity (83%). Similar study done by Chacha *et al* [17] showed that higher rates of CRP positive were observed among neonates with confirmed neonatal sepsis than those with negative blood culture. Thus the results of present study found that CRP is a useful marker for diagnosis of neonatal sepsis.

A negative CRP value is more important than a positive CRP value in that it excludes infection with a high certainty. In present study negative predictive values of serial CRP was as high as 95.89%, this observation was comparable with previous studies [18-20]. Also, our results concur best with a similar study conducted by Jaswal *et al* [21] who revealed 100% negative predictive value with no relapse following discontinuation of treatment after normalization of CRP levels. Eh *et al* [22] reported NPV of 99%, Gonzales [23] *et al* reported sensitivity of 91%, specificity of 93%, PPV of 87% and NPV of 95%, still other workers like Hindocha *et al* [24] and Adhikari *et al* [25] have reported sensitivities above 80%, specificities between 40 to 70%, PPV of 57% and Negative Predictive Value (NPV) between 73-95%.

Serial CRP measurement is a good practical guide for discontinuing antibiotic therapy in neonates with suspected sepsis. These neonates can be discharged from the hospital earlier, with significantly reduced cost, complications of treatment and family anxiety. In present study on the basis of serial CRP measurement mean duration of antibiotics was reduced from 13 days in non-study group to 8 days (approximately 42 % reduction in duration of empirical antibiotics treatment) with  $p$  value  $<0.004$ . This result was correlated with the study conducted by Khashabi *et al* [26] and Pryor *et al* [27].

## 5. Conclusion

The results of present study signify the possible role of CRP in diagnosis of neonatal sepsis. The sensitivity and negative predictive values of CRP was high in our study. Thus CRP can be used as screening test for early diagnosis as well as deciding duration of antibiotics in neonatal sepsis. Hence, in conclusion the serial CRP measurement is a good indicator for discontinuing antibiotic therapy in neonates with suspected sepsis and a useful diagnostic and prognostic marker in neonatal sepsis.

The current study suggested that the rational use of CRP levels not only can reduce the mortality and morbidity in neonatal sepsis but also it can prevent irrational use of antibiotics which may go a long way in preventing antibiotics resistance.

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