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# Predictive Value of Serial C-Reactive Protein in Diagnosing Neonatal Sepsis in A Tertiary Care Centre


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## ABSTRACT

***Aim***: *To evaluate the accuracy of serum C reactive protein levels for the diagnosis of neonatal infection.*

***Methods***: *A cross sectional study in neonates admitted with suspected septicemia, with birth weight > 1500 gm was included. Neonates with positive CRP measurements but with negative culture were considered septic and treated accordingly. The laboratory and radiological evaluation done for the diagnosis and confirmation of infection*

***Results***: *Out of 100 neonates, 58 (58%) were male, and 42(42%) were females. Late onset sepsis is more common than early onset sepsis. Out of 100 neonates, 20 neonates were proven sepsis, 51 were probable sepsis and 29 were clinical sepsis. The serial CRP measurement showed higher sensitivity and negative predictive value compared to early CRP (CRP 1) alone, in both early as well as late proven and probable sepsis.*

***Conclusion***: *Serial measurement of CRP should be used for the diagnostic evaluation of the neonates with suspected sepsis as it is a very good screening test for the early detection of sepsis.*


**KEYWORDS : neonate, sepsis, CRP, predictive value**

## INTRODUCTION

Neonatal sepsis is defined as invasive bacterial infection occurring in first 4 weeks of life. The incidence of neonatal sepsis varies in different countries. It varies from 2.7/1000 live birth in developed countries to 10-15/1000 live birth in developing countries. The Contribution of neonatal sepsis to high morbidity and mortality rate makes it an important subject for research so as to find out the possible solution. Prompt diagnosis of neonatal sepsis is of paramount importance. The diagnosis of neonatal sepsis is difficult to make solely on historical or clinical ground. Laboratory evaluation is essential in the diagnosis and confirmation of infection. There is no rapid and reliable test for confirmation of diagnosis yet. The treatment for sepsis is generally stated when clinical findings are supported by indirect early marker of infection. Positive culture of blood. CSF or urine is the gold standard for confirming sepsis, however in considerable proportion of neonates at risk of infection, Culture result may be influenced by previous antibiotic exposure! Also the bacteremic phase o the illness may be missed by poor timing or blood samples ie the sole use of culture to diagnose neonatal infection has limitations as it may take 24 to 72 hours to obtain culture reports.

## AIM

To evaluate the accuracy of serum C reactive protein levels for the diagnosis of neonatal infection.

## MATERIALS AND METHODS

A cross sectional study was done in Department of Pediatrics, Neonatal Unit, Tirunelveli Medical College Hospital. This study was approved by the Ethical Committee of our institute. Neonates with suspected sepsis whose parents gave consent were enrolled for the study. Neonates admitted in the neonatal unit of Tirunelveli Medical College Hospital, with suspected septicemia, with birth weight > 1500 gm were included. Neonates with meconium stained amniotic fluid, sere birth asphyxia and birth injuries, Neonates < 1500 gm, Neonates who were treated with antibiotic in other hospitals, Neonates who have undergone surgery were excluded. Neonates with positive CRP measurements but with negative culture were considered septic and treated accordingly. The neonates were evaluated by thorough history from mother and detail clinical examinations. The findings were recorded in the predesigned Proforma. The laboratory and radiological evaluation done for the diagnosis and confirmation of infection were following:

a. Serial Measurement of serum C-reactive protein.

b. WBC count, I : T ratio, Toxic granules.

c. Blood culture and sensitivity.

D. CSF analysis and culture.

e. Chest X-ray.

## RESULTS

100 neonates were included in the study, 58 (58%) were male and 42 (42%) were female. According to the age of onset of sepsis, neonates were classified to have early onset sepsis (onset at less than 3 days of life) or late onset sepsis (onset after 3 days of life). There were 41 cases of early onset sepsis and 59 cases of late onset sepsis. There were 20 cases of proven sepsis, 51 cases of probable sepsis and 29 cases of clinical sepsis. 23% of male and 18% of female neonates were on early onset sepsis, 35% of male and 24% of female were late onset sepsis. Out of 100 neonates, 20 neonates were proven sepsis, 51 were probable sepsis and 29 were clinical sepsis. Number of probable sepsis is high in both early and late onset sepsis. (Table 1)

**Table 1 Age and Type of Sepsis**

| | Early Onset (<3 days) | Late Onset (>3 days) | Total |
|---|---|---|---|
| Proven Sepsis | 8 (40.0%) | 12 (60.0%) | 20 |
| Probable Sepsis | 19 (37.3%) | 32 (62.7%) | 51 |
| Clinical Sepsis | 14 (48.3%) | 15 (51.7%) | 29 |
| Total | 41 (41.0%) | 59 (59.0%) | 100 |

Lethargy, Refusal to feed and fever is the most common clinical signs and symptoms. Lethargy and fever are more common in proven sepsis. It is also observed that the occurrence of signs like seizures, altered sensorium and poor neonatal reflexes were not found in the clinical sepsis group. WBC count was < 5000 in 21 cases, >20000 in 34 cases, I:T ratio >0.2 in 38 cases, toxic granules were found in 31 cases. Chest X ray showed significant abnormality in 17 cases. Cerebrospinal fluid analysis was abnormal in 4 cases: out of which CSF culture was

positive in 1 case. Similarly blood culture was positive in 19 cases. Among them, 8 of the culture positive cases were of early onset sepsis and 11 were of late onset sepsis. Klebsiella - pneumonia (35%) E. coli (25%) are the most common organism, sepsis caused by gram negative organisms are more common in early and late onset sepsis.

**Table 2 Distribution of Sepsis type and CRP**

| | CRP 1 | | CRP 2 | | CRP 3 | |
|---|---|---|---|---|---|---|
| | Positive | Negative | Positive | Negative | Positive | Negative |
| Early Onset | 10 (24.4%) | 31 (75.6%) | 19 (46.3%) | 22 (53.7%) | 24 (58.5%) | 17 (41.5%) |
| Late Onset | 19 (32.2%) | 40 (67.8%) | 36 (61.0%) | 23 (39.0%) | 42 (71.2%) | 17 (28.8%) |

CRP measurement was positive in 66 (66%) cases; with CRP 1 being positive in 27 cases, CRP 2 positive in 55 cases (55%) and CRP 3 positive in remaining 11 cases which had normal CRP 2 measurement. Among the 20 cases with positive culture, CRP 1 was positive in 5 cases; CRP 2 in 16 cases with no statistical significance, but on serial CRP measurement, positive CRP 3 level was seen in 18 cases showing significant correlation. Positive CRP 1 in 5 (7.5%) cases of proven sepsis and 22 (33.3%) cases of probable sepsis with no significant correlation. Positive CRP 2 in 16 (24.2%) cases of proven sepsis and 31 (46.9%) cases of probable sepsis with significant correlation. While CRP 2 and 3 measurement was positive in 18 (27.2%) cases of proven sepsis and 39 (59%) cases of probable sepsis with highly significant correlation. (Table 2)

The serial CRP measurement showed higher sensitivity and negative predictive value compared to early CRP (CRP 1) alone, in both early as well as late proven and probable sepsis.

**Table 3 Serial CRP Estimation in the Diagnosis of Neonatal Sepsis:**

| | Early onset | | | Late onset | | |
|---|---|---|---|---|---|---|
| Proven sepsis | CRP 1 | CRP 2 | CRP 3 | CRP 1 | CRP 2 | CRP 3 |
| Sensitivity | 13% | 75% | 88% | 33% | 83% | 92% |
| Specificity | 73% | 61% | 49% | 68% | 45% | 34% |
| PPV | 10% | 32% | 29% | 21% | 28% | 26% |
| NPV | 77% | 91% | 94% | 80% | 91% | 94% |
| Probable sepsis | | | | | | |
| Sensitivity | 42% | 58% | 79% | 44% | 63% | 75% |
| Specificity | 91% | 64% | 69% | 81% | 41% | 33% |
| PPV | 80% | 58% | 63% | 74% | 56% | 57% |
| NPV | 65% | 64% | 76% | 53% | 48% | 55% |

There was increase in sensitivity and NPV with decrease in specificity and PPV in CRP 1 CRP 2 and CRP 3 measurement, both in early and late onset proven and probable sepsis. (Table 3)

**Table 4 Tests against Blood Culture as Gold Standard Test**

| LAB TEST | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|
| WBC Abnormality | 40% | 41% | 15% | 73% |
| Toxic granules | 80% | 73% | 35% | 87% |
| IT Ratio > 0.2 | 80% | 75% | 42% | 89% |
| CRP 1 | 25% | 70% | 17% | 79% |
| CRP 2 | 80% | 51% | 29% | 91% |
| CRP 3 | 90% | 40% | 27% | 94% |

Among the individual lab tests CRP 3 has highest sensitivity 90%, and NPV 94%, whereas I:T ratio > 0.2 has highest specificity 75%, PPV 42%. (Table 4)

## DISCUSSION

The ratio of male; female was 1.38:1. Karen M. Puopolo have reported approximately two fold higher incidence of sepsis in male than female suggesting the possibility of a sex linked factor in host susceptibility. Jaswal et al, reported refusal to feed in 66%, lethargy 42%, icterus 30% which were consistent to our findings. Again Karen M. Puopolo reported fever in about 50% of infected neonates. The statistical analysis showed significant correlation of lethargy with CRP 1,2,3. Similarly significant correlation was observed between refusal of feed and positive CRP measurements.

Kaiser et al. reported, positive culture were 10.2% for blood and 5.4% for CSF. Our finding is consistent with this study but in several similar studies, the culture positive reports were high. Parikh and Singh reported 47% and Pourcyrous reported 27% of culture positive cases. Gram negative organisms predominated in this study, were consistent with the study carried out by Karthikeyan. et. al, with Klebsiella being the most common pathogen 61.5% followed by E. coli being 33.5%. Anwer et al reported that gram negative organism is causing majority of infection in Pakistan.

In the culture negative group CRP was positive in 48 (72.7%) cases. The negative culture group with CRP positive in 88% cases was found in study carried out by Pourcyrous et al. The findings of our study are consistent with this study. On the other hand the correlation between positive culture findings with CRP 3showed positive in 18 (27%) and negative in 2 (3%) cases. In negative culture group, CRP was positive in 48 (72.7%) cases. Elevated CRP levels were not observed in 2 (3%) cases in which culture yielded pathogenic organisms. This false negative result may be due to submission of small aliquots of blood for culture, intermittent or lower density bacteremia. The findings of our study showed significant correlation of serial measurement with positive culture.

Positive CRP 2 in 16 (24.2%) cases of proven sepsis and 31 (46.9%) cases of probable sepsis with significant correlation. While CRP 2 and 3 measurement was positive in 18 (27.2%) cases of proven sepsis and 39 (59%) cases of probable sepsis with highly significant correlation. which is consistent with the study of Benitiz et al indicating that serial CRP monitoring had clinical utility in diagnosis of neonatal sepsis.

It was found that the sensitivity of CRP 2 was substantially higher, but maximum sensitivities were achieved by combination of CRP 2 and 3. The sensitivity of CRP 2 ranged between 58% - 64%, specificity 41% - 64% and negative predicative value 94%. The statistical analysis showed CRP 2 and 3 had significantly high correlation compared to the single measurement of CRP 2 only with both the proven and probable sepsis of the early as well as the late onset sepsis. These findings were consistent with the findings of several other authors; Hengst, found the sensitivity between 78.9% - 98%, specificity between 84% - 97% and negative predictive value of 99% in detecting sepsis. Baptista et al also reported the sensitivity of 91% specificity of 93%. Similarly, Nuntnarumit et al reported sensitivity of even 100%, specificity 94% positive predictive value 91.6% and negative predictive value 100% and concluded that predictive value of CRP could be enhanced by serial rather than a single measurement.

The false negative results (positive cultures with normal CRP measurement) were most common when sample were obtained early in the evaluation. So the timing of CRP measurement is critical for achievement of optimal sensitivity and it was possible that positive measurement did develop but was not measured within 48 hours of diagnosis. It may also be associated with urinary tract infection and infection associated with Granulocytopenia.

## CONCLUSION

Serial measurement of CRP should be used for the diagnostic evaluation of the neonates with suspected sepsis as it is a very good screening test for the early detection of sepsis. Serial negative measurement of CRP could almost exclude the presence of infection in the neonate and can guide in deciding the duration of antibiotics. Since Role of CRP in guiding antibiotic therapy is outside the scope of our study, a prospective study should be carried out to detect the role of CRP measurement in deciding the duration of antibiotic therapy in neonatal sepsis.

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