

Role of C-Reactive Protein in the Diagnosis of Sepsis in Early Infancy

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ABSTRACT

Objectives: To assess the role of serial C-reactive protein in the diagnosis of sepsis during the early period of infancy (<90 days). **Materials and Methods:** This cross sectional study was conducted in the Pediatrics Department of Shaikh Zayed Hospital (SZH), Lahore. The duration of study was 6 months from 1st July to 31st December 2010. Total 150 cases fulfilling the inclusion criteria were enrolled randomly in the study. Babies were divided in two groups: Group I - Healthy babies. Group II- Babies with sign and symptoms of sepsis. The first C-reactive protein and blood cultures were sent in all cases at the time of admission. Antibiotics were started in the suspected cases of sepsis. After 48 hours of admission, second sample of C-reactive protein was again sent in all cases. **Results:** The study was carried out in babies <90 days admitted in the neonatal and pediatric unit. All the cases were divided into two categories. There were 68 (45.33%) culture proven cases of sepsis and 82 (54.67%) cases were culture negative. Escherichia coli was the most common organism isolated followed by Staphylococcus aureus. Males (63%) were predominant as compared to females (37%). 80% were term babies while 20% were preterm. 75% babies were born by lower segment caesarian section, 15% were delivered at home while 10% were born at the private clinics. Early onset sepsis was seen in 39.33% of cases while late onset sepsis was seen in 60.67% cases. Mechanical ventilation was done in 10 babies (6.6%). 97.4% babies survived and 2.6% babies expired. The sensitivity, specificity, PPV, NPV of C-reactive protein was 91.18%, 53.66%, 62% and 88% respectively at the time of admission. The CRP level was statistically different between the two groups ($p < 0.001$), at the time of admission and at 48 hours after admission. **Conclusion:** Babies during the early infancy period are susceptible of developing sepsis that may lead to potential consequences if not treated in proper time. Also babies may be over-treated and may have prolonged stay in the hospital if not properly investigated, which may itself be a burden to the family members and have a financial instability also. So keeping in mind all these factors, we performed a serial CRP test at admission and after 48 hours for treatment monitoring and observing the response. Sensitivity of C-reactive protein and negative predictive value was high in this study at the time of admission. So, serial monitoring of C-reactive protein is recommended for the monitoring treatment response.

Key Words: Early infancy Sepsis, C - reactive protein, Blood Culture.

INTRODUCTION

Septicemia remains a significant cause of morbidity and mortality in the newborn, more in the developing countries.¹ Annually, five million neonates die in Asia and Africa, out of which 1.6 million (20%) are due to neonatal sepsis.² The incidence of neonatal sepsis in the developed

countries is 1-10/1000 live births, whereas it is roughly three times more in developing countries like Pakistan.³ In developing countries incidence varies from 10-20/1000 live births.¹ Limited data is available about the incidence in Pakistan, it varies from 1.13/1000 to 3.8/1000 live births.² Infections like tetanus, pneumonia, septicemia, meningitis and diarrhea account for 30-50% of these deaths in

developing countries. In our country lack of education, poor antenatal care, poor sanitation, unhygienic conditions at home, multiparity, lack of trained staffs to conduct aseptic deliveries are important predisposing factors that result in sepsis.

Infants with bacterial sepsis usually have nonspecific symptoms and signs and symptoms including temperature instability, hypotension, poor perfusion with pallor, tachycardia or bradycardia, apnea, respiratory distress, grunting, cyanosis, irritability, lethargy, seizures, refusal to feed, abdominal distension, petechiae, purpura and bleeding.⁶

Sepsis is a common complication in the neonatal intensive care unit (NICU). It is common in premature infants, in whom the clinical presentation can be subtle and nonspecific. Its mortality rate is 5-20%.⁷ Moreover, a delay in the diagnosis and commencement of treatment results in high morbidity and mortality.⁸

Positive blood culture is considered gold standard for diagnosing of sepsis, which has an unacceptably low yield (30-40%).⁹ Furthermore, final results for negative blood cultures are not finalized until after 5 days. Using a more rapid assay for ruling out sepsis in the infant who is symptomatic would provide valuable information sooner for medical decision making.

A test with a rapid turnover with 100% sensitivity rather than high specificity, which allows accurate diagnosis and appropriate antimicrobial treatment, is desirable⁸. Therefore simple and rapid tests for detection of early infancy sepsis are required. Some evidence exists which supports the use of C-reactive protein measures sole or in conjunction with other tests to identify neonate at risk of septicemia.¹⁰

Early onset sepsis is a medical emergency and babies present with nonspecific clinical features. Therefore it is of prime importance that high index of suspicion should be kept in mind in babies admitted with nonspecific symptoms and signs.

MATERIAL AND METHODS

This study was conducted in the department of pediatrics, Shaikh Zayed Hospital, Lahore.150

babies between 0-90 days with suspicion of sepsis were admitted and written informed consent was taken from the parents. Babies receiving antibiotics for more than 48 hours prior to admission and weighing less than 1500 grams were excluded from this study. Relevant information including age, gender, weight, mode and place of delivery, presenting complaints and signs suggestive of sepsis were collected. Complete blood count, CRP at the time of admission and after 48 hours, blood culture, urine culture, and chest x-ray was done in all patients. Data was analyzed by using SPSS V-16.

Diagnostic criteria

- Temperature > 38.3°C (101°F) or < 36.0°C (96.8°F)
- Tachycardia > 90/min.
- Tachypnea > 20 / min.
- Hyperglycemia > 6.66 mmol/l in the absence of Diabetes mellitus
- WBC count > 12 x10⁹/L or < 4x10⁹/L

RESULTS

Total 150 babies with suspected sepsis were studied. 68 (45.33%) had blood culture proven sepsis while in 82(54.67%) cases, blood culture was negative. (Fig.1)

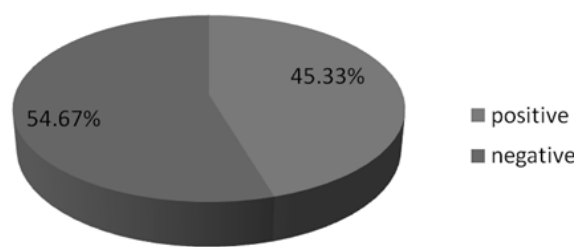


Fig.1: Distribution of positive and negative blood cultures (n=150).

The mean age at presentation was 15.2±12.9 days and mean age at admission was 18.2±10.5 days. There was a delay of approximately 3 days between the onset of the symptoms and admission of the baby in pediatric unit. The mean weight at the time of admission was 2.8±0.75 Kg.

According to the sex distribution, the male babies were 95 (63.3%) while the female babies were 55 (36.7%) (Fig.2)

Early onset sepsis was seen in 59 babies

(39.33%) while late onset sepsis was seen in 91 babies (60.67%). Twenty (13.33%) babies had congenital anomalies.

Out of total 150 babies, 30(20%) were preterm while 120(80%) were term babies.

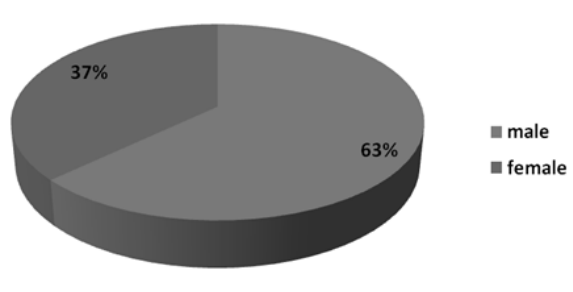


Fig. 2: Distribution of babies according to sex (n=150)

112 (74.7%) babies were delivered at hospitals, 23 (15.3%) babies were delivered at home while 15 (10%) at private clinics. 96 (64%) were born by LSCS, 40(26.7%) were delivered by SVD and while 14 (9.3%) were delivered by forceps and vacuum.

Different clinical features were also studied. Lethargy was the common presenting complaints in 65% (98 babies) followed by reluctance to feed (44%), fever (29%), tachypnea (25%), feeding difficulty (18%), vomiting (17%), hypothermia (14%), difficulty in breathing (12%), irritability (11%), abdominal distension (10%), loose motions (9%), (Fig.3).

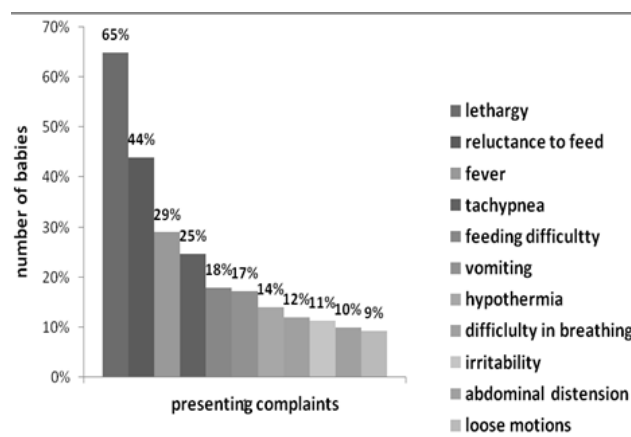


Fig 3: Major presenting complaints in babies (n=150)

History of P/V leaking was present in 7.33%

(for 6-12 hours), in 16% (for 12-18 hours), while in 19.33% (for >18 hours). In about 57.33% (86), there was no such history. History of maternal fever was present in about 47 cases (31.33%). Out of these, in 25 (53.2%) cases, fever was present at time of delivery while in 12 (25.5%), it was present during the last trimester and in 10 (21.3%) during the postpartum period.

Amongst the organisms isolated, Escherichia coli (45.16%) was the most frequently isolated organism followed by staphylococcus aureus (16.12%), Klebsiella (12.9%), pseudomonas (12.9%), Acinobacter (6.45%) and MRSA (6.45%) (Fig. 4)

The C-reactive protein level was measured. It was positive in 100 (66.67%) cases at the time of admission and negative in 50 (33.33%). After 48 hours of treatment, it was negative in 135 (90%) cases and remained positive in 15 (10%) cases. (Fig.5).

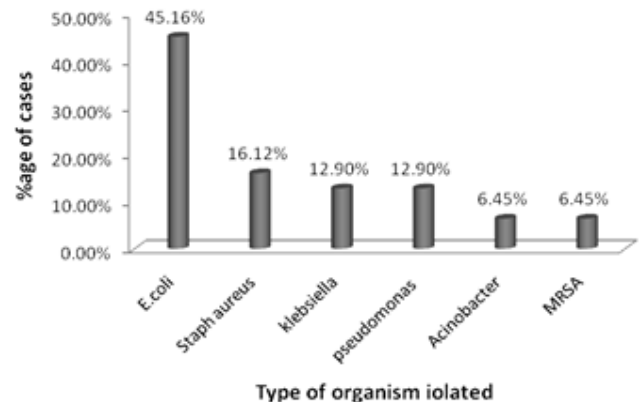


Fig 4: Bacterial isolates from blood culture (n=68)

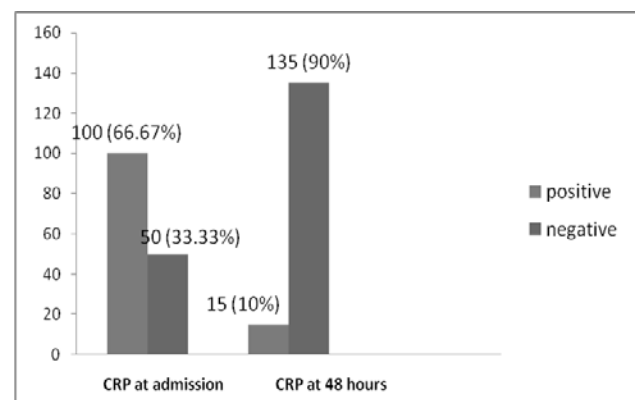


Fig 5: Comparison of CRP at admission and at 48 h (n=150)

Level of CRP was compared among the two groups and there was a significant difference between the groups with p-value of < 0.001 which was highly significant.

A comparison was also made between CRP and blood culture. (Table 1) and sensitivity, specificity, PPV and NPV of CRP at admission were calculated. The sensitivity, specificity, PPV, NPV of C-reactive protein was 91.18%, 53.66%, 62% and 88% respectively at the time of admission (Table 2).

Table 1: Blood culture and CRP comparison (n=150)

Blood culture → CRP ↓	Positive	Negative	Total
Positive	62	38	100
Negative	6	44	50
Total	68	82	150

Table 2: Sensitivity, specificity, positive & negative predictive values of CRP at admission.

	Estimated value	95% confidence interval
Prevalence	20.66%	0.146 - 0.52
Sensitivity	91.18%	0.6923 - 0.957
Specificity	53.66%	0.379 - 0.5638
PPV	62%	0.520 - 0.678
NPV	88%	0.32 - 0.48
False negative	8%	0.02 - 0.170
False positive	46.34%	0.60 - 0.79

In this study, 20 (13.33%) babies presented had congenital anomalies. Out of them, 13 (65%) had positive CRP at the time of admission. Gastrochisis, tracheoesophageal fistula, congenital diaphragmatic hernia, imperforate anus with rectovaginal fistula, galactosemia, barter syndrome, congenital nephrosis, and pyloric stenosis were found in the babies.

Out of 150 babies included in the study 3% expired while 97% were discharged after appropriate diagnosis and treatment.

DISCUSSION

Deterioration in the condition of an infant can occur in many conditions. It is always difficult to establish a definitive cause of deterioration. Of

various causes, bacterial infection is usually at the top. Neonatal are early onset sepsis with its high mortality rate still remains a diagnostic and treatment challenge for neonatal health care providers. Developing countries have both the highest incidence and mortality rate.¹¹ The gold standard of identifying bacterial infections; the blood culture has got a low yield. Therefore the pediatricians suggest certain surrogate tests to identify the early infancy sepsis.

This study was performed with an idea to assess the role of C-reactive protein in the diagnosis of early infancy sepsis and to see the sensitivity, specificity and predictive accuracy of CRP in early infancy sepsis. The comparison in the CRP level between the two groups was done at the time of admission and at 48 hours after admission and starting treatment of antibiotics. Difference between them was determined.

Earliest clinical features of neonatal sepsis are often subtle and nonspecific. Therefore a high index of suspicion is needed for early diagnosis especially if risk factors are also present. Clinical features and further course in neonatal sepsis depends on various factors like birth weight, place of delivery, age of newborn, availability, accessibility, affordability and timely referral of baby to an appropriate center.

Therefore variation in different parameters may be observed in various studies. Rapid and correct diagnosis and treatment of neonatal bacterial infection is an important priority.

Isolation of microorganism(s) in one or more blood cultures is the gold standard of diagnosis for neonatal sepsis, although it has some limitations. It may take 2 to 3 days to obtain culture results.³ Intrapartum antibiotic exposure of mothers may interfere with blood culture sensitivity. The most important criteria of a reliable diagnostic test are its high sensitivity combined with a high negative predictive value.

No single test is 100% reliable, but compared to other tests, serum CRP measurement is most useful to diagnose sepsis suggested to be most useful. CRP is a highly sensitive acute phase protein, with levels rising as much as 1000-fold during acute inflammatory processes. Inflammation caused by infection or damage stimulates the

circulating inflammatory cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF)- α . These cytokines stimulate hepatocytes to increase the synthesis and release of positive acute phase proteins, including CRP. IL-6 is the major cytokine which stimulates CRP production. CRP levels begin to rise within 4 to 6 hrs after the onset of signs of infection or tissue injury and peak 24 to 48 hours thereafter. They rapidly disappear as the infection or inflammatory process re-solves.¹³

Keeping these facts in mind, 150 cases were enrolled randomly which met the inclusion criteria set in this study. Blood culture and C-reactive protein was sent in every case at the time of admission. Test for C-reactive protein was repeated after 48 hours of admission and treatment in suspected cases of sepsis on clinical grounds and with certain risk factors was started.

As far as sex distribution was concerned, there were 63% males while 37% were females. Male neonates have been reported to be more affected with sepsis as compared to females in some studies.^{14,15} This is in concordance with our study as well (Fig. 3). LBW is a strong risk factor contributing to sepsis.

Late onset sepsis was documented significantly more as compared to early onset sepsis as in late onset sepsis age limit was up to 3 months. About 20% were preterm. This also confirms the fact that prematurity leads to infections in spite of age up to 3 months. The incidence of preterm births (<37 weeks gestation) is increasing in many countries around the world and has become a global health concern.^{16,17} The mean age at admission was 18.2 ± 10.5 days in which there was 2-days delay. This was accordance to one of the studies done¹⁷. There were 15% babies who were delivered at home. Home delivery is a risk factor for development of sepsis because of untrained staff and unclean environment including unsterilized techniques.¹⁸ Major presenting complaints like reluctance to feed; lethargy, temperature instability and respiratory distress are similar to other studies.¹⁴ Blood culture was positive in 45.33% cases, which follows the similar range of positivity throughout the world.¹⁸

The sensitivity, specificity, PPV, NPV of C-

reactive protein was 91.18%, 53.66%, 62% and 88% respectively. CRP showed high sensitivity, positive and negative predictive values but lower specificity.

In a study conducted at Johannesburg hospital, 100 infants with negative serial CRP values (≤ 10 mg/l) were evaluated for suspected sepsis in the first 24 h of life. Repeated CRP measurements were performed between 24 and 48 h after birth and it was found that 99% of neonates did not need further antibiotic therapy with negative predictive value of 99%.¹⁴ The results of the present study can be explained by the fact that we included normal babies also. Other studies having a control group have shown comparable range of sensitivity, specificity, PPV and NPV^{19,20,21}.

The result of this study has also shown the spectrum of organisms that are similar to other studies. Especially there is preponderance of organisms in early onset sepsis. This may be attributed to complicated deliveries, lack of aseptic techniques, untrained traditional birth attendants; increased handling and acquisition of infection from the environment.²²

In our study, 20 babies had congenital anomalies. Out of them, 13 had positive CRP at the time of admission. This was in accordance to one of the studies done.²³

Our study had the following limitations that need consideration:

- 1) The laboratory method used to measure CRP levels was semi-quantitative. This method of testing CRP levels was less expensive than quantitative method and is therefore, suitable for developing countries although it is not as sensitive as quantitative methods.
- 2) The CRP level of 6 mg/l was the cut off point for discontinuing antibiotic treatment. This level was lower than the traditional levels of 10 mg/l which was the criterion for selection of patients in most studies, but in our study it proved to be more sensitive.

CONCLUSION

High index of suspicion for diagnosis of neonatal sepsis is required especially in the presence of risk factors and baby presenting with non-specific clinical features. C-reactive protein determination is

an economical, rapid, safe and applicable technique through minimum expertise. CRP showed high sensitivity and negative predictive value and higher specificity but lower positive predictive value. Also it showed high specificity after 48 hours. So CRP is a good test to rule out sepsis.

Serial CRP levels are useful in the diagnostic evaluation of neonates with suspected infection and a good practical guide for discontinuing antibiotic therapy in neonates with suspected sepsis. The sensitivity of a normal CRP at the initial evaluation is not sufficient to justify with-holding antibiotic therapy. So serial CRP measurements should be done. These neonates can be discharged from the hospital earlier, with significantly reduced cost, complications of treatment and family anxiety.

Whenever there is strong clinical suspicion of sepsis benefit of doubt should be given to a baby, i.e. antibiotic therapy should be started. Therefore in order to treat rapidly all infants with early infancy sepsis and to avoid therapy in non-infected ones, one should use clinical and laboratory indicators of sepsis in order to achieve maximum results.

IMPLICATIONS

Early decision regarding presence or absence of infection saves time of physician, saves parent's money, shortens the length of hospital stay, and decreases the number of babies requiring antibiotic therapy and emergence of resistant strains.

So the greatest potential of CRP is to exclude the infection especially when there is uncertainty about clinical condition of an early infant e.g., when baby is delivered after prolonged rupture of membranes, has got jaundice, apnea or lethargy, and also when report of blood culture takes more than 72 hours.

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