

SCREENING FOR NEONATAL SEPSIS BY DETERMINATION OF C-REACTIVE PROTEIN AT A PAEDIATRIC A WARD LRH HOSPITAL IN PESHAWAR, PAKISTAN

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ABSTRACT

Introduction: Infections are the leading cause of death among neonates and sepsis is one of the causative factor of neonatal morbidity and mortality. In developing countries such as Pakistan, mortality from neonatal sepsis is higher than that in developed countries. Without specific and sensitive biomarkers of infection and reliable interpretation of available biomarkers, embarking on antibiotic therapy is still largely dependent on clinical judgment. In neonates the blood concentration of C-reactive protein (CRP) escalates within 4 to 6 hours of an infectious episode, becomes abnormal by 24 hours and peaks at around 48 hours. Hence, CRP levels can be exploited as a biomarker for neonatal sepsis.

Objective: To determine the accuracy of CRP for diagnosing neonatal sepsis at a paediatric hospital in Peshawar, Pakistan.

Materials and Methods: The study setting was Paediatrics A ward at Lady Reading Hospital, Peshawar, Pakistan over six months (10th October 2014-20th April 2015). A total of 169 suspected neonates having sepsis were tested for CRP levels; blood culture was also done to confirm the findings on CRP levels.

Results: Study neonates had a mean age of 12.3 ± 7.3 days and most (52.7%) were aged up to 10 days. The gender ratio of neonates was 54.4% male to 45.6% female. There were positive CRP results for 81 (47.9%) neonates and negative CRP results for 88 (52.1%) neonates. Based on blood cultures, sepsis was detected in 60 (35.5%) neonates and was negative in 109 (64.5%) neonates. CRP determination had specificity of 75.2% and sensitivity of 90%, and had positive and negative predictive values of 66.7% and 93.2%, respectively.

Conclusion: CRP blood concentration is an accurate tool for high sensitivity detection of neonatal sepsis with acceptable specificity.

Keywords: Neonatal sepsis, Blood culture, White blood count, Platelet count, C-reactive protein, Neutrophil count.

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INTRODUCTION

Infections are the leading cause of death among neonates and sepsis is one of the causative factor of neonatal morbidity and mortality.¹ Neonatal sepsis is a global problem, with approximately 30 million neonates developing infections each year and 1-2 million of these neonates die.² In developing countries such as Pakistan, mortality from neonatal sepsis is 10.4%, which is higher than that in developed

countries, with an incidence of 0.69 deaths/1000 live births.³ Statistical data on neonatal sepsis from Pakistan is largely unavailable, but in India the National Neonatal Perinatal Database claims that the incidence of neonatal sepsis is 30 out of 1000 live births and in developing countries it accounts for 30-50% of all neonatal deaths. This sepsis-related mortality can be lowered by adopting an aggressive

approach towards the disease.⁴

Neonatal sepsis is a systematic inflammatory response to an infectious process with non-specific signs and symptoms or focal signs of infections. It carries potentially fatal complications affecting major organ systems including adrenal hemorrhage, cerebral edema or thrombosis, bone marrow dysfunction and disseminated intravascular coagulation.⁵ Without appropriate treatment, the fatality rate from neonatal sepsis is high. Thus with non-specific initial presentation a high index of suspicion should always be kept for early diagnosis and a favorable outcome.⁶

Neonatal sepsis is divided into two categories. Early neonatal sepsis develops within 48 hours of birth and is related to the acquisition of microorganisms from the mother; predominant culprits are *E. coli*, Group B Streptococci, coagulase-negative Staphylococci and *H. influenzae*. Late neonatal sepsis occurs at 48 hours and beyond and is acquired through the caregiving environment; predominant culprits are coagulase-negative Staphylococci and *Staphylococcus aureus*.^{7,8} The risk factors for neonatal infection in the first 72 hours following birth are well known and include high gravidity, maternal chorioamnionitis, prolonged rupture of membranes (PROM), advanced maternal age, maternal group B streptococcal infection or colonization, and a limited rate of breastfeeding.⁹ Without specific and sensitive biomarkers of infection and reliable interpretation of available biomarkers, embarking on antibiotic therapy is still largely dependent on clinical judgment. A wealth of facilities and management guidelines have been established for neonatal care to facilitate an empiric use of antibiotics.^{10,11}

For diagnosing neonatal sepsis, blood culture remains the gold standard.⁴ Blood culture reports show that organisms such as *Klebsiella*, *E. coli*, *Staphylococcus aureus*, Group B Streptococci and *S. pneumoniae* are principal pathogens involved. Gram-negative bacterial infections are more common than Gram-positive infections.¹² Because it takes 48-72 hours for the results of blood culture to be available, methods have been devised that make use of different hematological parameters to diagnose sepsis earlier and instigate proper antibiotic therapy.¹³

Hematological parameters could be used for the early detection of neonatal sepsis. These include immature neutrophils, total leukocyte and neutrophil counts, I:M and I:T ratios, platelet count and degenerative changes in neutrophils.¹⁴ Other diagnostic markers are also being evaluated, including C-reactive protein (CRP),^{7,10,11} proclacitonin¹¹, acute phase reactants, bacterial genomes and inflammatory

cytokines¹⁵ and CD 64 neutrophil cell surface marker.¹⁶

CRP crosses the placenta very poorly, so a rise of CRP in neonates always signifies endogenous synthesis. De novo hepatic synthesis of CRP begins very rapidly following a single stimulus and its serum concentration increases to above 5 mg/l by 4-6 hours, becomes abnormal by 24 hours and maximises after around 48 hours.¹⁷ The sensitivity of CRP detection improves if an initial determination is made at 6 to 12 hours following birth and excludes a value at birth. Two normal CRP determinations, one at 8-24 hours following birth and another 24 hours later, have a 99% negative predictive accuracy and there is a negative likelihood ratio of 0.15 for proven neonatal sepsis.

It is not recommended that blood CRP concentration is the only indicator of neonatal sepsis. It is better being part of a sepsis diagnosis regime or as a sequential study during infection for determining the duration of therapy, measuring the response to antibiotics or identifying a relapse of infection. Early diagnosis of sepsis in neonates can be difficult because signs and symptoms are usually non-specific.¹⁸ In one study, the specificity and sensitivity of CRP for diagnosing neonatal sepsis were 74% and 75%, respectively.¹⁹ In another study, the total proportion of blood culture proven neonatal sepsis was through CRP determination showing specificity and sensitivity values of 85.71% and 92.30%, respectively.¹⁸

The current study was designed to determine the accuracy of CRP for diagnosing neonatal sepsis at a paediatric hospital in Peshawar, keeping blood cultures as the gold standard. Neonatal sepsis is not uncommon in the Pakistan population, so early diagnosis along with early commencement of antibiotic treatment is of utmost importance for reducing morbidity and mortality.

METHODOLOGY

The study was conducted for a period of six months from 10th October 2014 to 20th April 2015 after ethical approval from the concerned. The study design was cross sectional validation study and the study setting was Paediatric A ward of Lady Reading Hospital Peshawar. The duration of the study was six months. The sample size was 169 using 75% sensitivity, 74% specificity, 30% proportion of neonatal sepsis and 10% margin of error. Inclusion criteria were neonates suspected of having sepsis (as per operational definitions) of both male and female gender. Exclusion criteria included patients with a history of surgical intervention, and those with history of

trauma and renal insufficiency (serum urea of > 50 mg/dl and creatinine of >1.1 mg/dl). The study was performed following written consent from the hospital ethical and research committee. Objectives and benefits coming from the study were explained to the parents of the neonate, they were assured about the risks involved and it was explained that the study was performed purely for academic research and for data publication. Following agreement, written informed consent was obtained from the parents of the neonate.

Operational definitions

Neonatal sepsis on blood culture: Considered positive if any type of microorganism was detected on blood culture using a variety of culture media in the hospital laboratory.

Neonatal sepsis on CRP: Positive blood CRP level (above 5 mg/dl) in the hospital laboratory at the time of presentation of the neonate suspected of having neonatal sepsis.

Clinical suspicion of neonatal sepsis: Neonates with a fever of more than 100 oF on clinical examination and having a total leukocyte count of >21,000 measured in the laboratory at the time of presentation, an absolute neutrophil count of <1500 or >8000, a platelet count of <150,000/mm³ of HPF measured in the laboratory at the time of presentation of the neonate.

Diagnosis accuracy: measured in terms of sensitivity, specificity, and positive and negative predicative values.

Sensitivity: the ability of CRP to identify those neonates that have sepsis, out of the total neonates with sepsis as confirmed by blood culture, determined as true positives/(true positive + false negatives) x 100.

Specificity: the ability of CRP to correctly identify neonates that do not have sepsis out of the total neonates not having sepsis as confirmed by blood culture, determined as true negative/(true negative + false positives) x 100.

Positive predictive value (PPV): the proportion of neonates who fulfill the criteria of CRP and have evidence of sepsis on blood culture, determined as true positive/true positive + false positive x 100.

Negative predictive value (NPV): the proportion of neonates who do not have sepsis and have no evidence of sepsis on blood culture, determined as true negative/true negative + false negative x 100.

True positive: neonates with sepsis (confirmed on blood culture) who are classified as having sepsis by CRP.

False positive: neonates who are misclassified as

having sepsis (confirmed on blood culture) by CRP. *False negative:* neonates who are misclassified as having no sepsis CRP (confirmed by blood culture).

Data collection

Detailed clinical examination of all neonates was completed and a brief history was obtained from their parents. From all neonates, 5 ml of blood was obtained under strict aseptic conditions and this was immediately transferred to the hospital laboratory for detecting neonatal sepsis on the basis of a serum CRP level above 5 mg/dl. The same blood specimen was also sent for complete blood culture in the same hospital laboratory to confirm neonatal sepsis. All laboratory investigations were done under supervision of a single expert microbiologist having a minimum experience of five years. All the above mentioned information was recorded on a pre-designed proforma. In order to avoid bias in the study results exclusion criteria were strictly followed.

Data analysis

Collected data were analysed using SPSS version 10. Category variables were gender, age, CRP findings and blood culture report. Values of frequency and percentage were calculated and mean ± standard deviation (SD) values were calculated for continuous variables such as age. Sensitivity, specificity, PPV and NPV were determined by taking blood culture as the gold standard from the following 2x2 table:

		Blood Culture (NS)	
		+	-
CRP (NS)	+	A	B
	-	C	D

Sensitivity of CRP = (A / A+C) x 100

Specificity of CRP = (D / B+D) x 100

PPV for CRP = (A / A+B) x 100

NPV for CRP = (D / C+D) x 100

Accuracy of CRP = (D+A) / overall patients

A = True positive, B = False positive, C = False negative, D = True negative

RESULTS

The study used 169 neonates with clinical features suspected of sepsis. Neonates were divided into different age groups: up to 10 days (89 neonates, 52.7%), 11 to 15 days (24 neonates, 14.2%), 16 to 20 days (3 neonates, 1.8%), 21 days and above (53 neonates, 31.4%). Neonates had an age range of 3 to 24 days and their mean age was 12.3 ± 7.3 days. Out of the 169 neonates included in the study, 54.4% were

male and 45.6% were female. There were positive CRP results for 81 (47.9%) neonates and negative CRP results for 88 (52.1%) neonates. Based on blood cultures, sepsis was detected in 60 (35.5%) neonates and negative in 109 (64.5%) neonates. On applying the formulae given further above, sensitivity for CRP was 90% and specificity was 75.2%. The PPV was 66.7% and the NPV was 93.2% (Table 1). The sensitivity and specificity of CRP with respect to gender were calculated. In male neonates, sensitivity was 90.6% and specificity was 81.7% (Table 2), whilst

in female neonates, sensitivity was 89.3% and specificity was 67.3% (Table 3). The sensitivity and specificity of CRP with respect to different age groups were also calculated. In neonates aged up to 10 days, sensitivity was 85.7% and specificity was 77% (Table 4). In the age group of 11 to 15 days, sensitivity and specificity were 100% and 81.2%, respectively (Table 5). In the age group of 16 to 20 days, sensitivity and specificity were both 100% (Table 6). In the age group of 21 days and above, sensitivity was 91.3% and specificity was 66.7% (Table 7).

Table-1: Neonatal sepsis detection based on CRP and blood cultures

Neonatal sepsis on CRP	Neonatal sepsis on blood culture		Total
	Positive	Negative	
Positive	54 (TP)	27 (FP)	81
Negative	6 (FN)	82 (TN)	88
Total	60	109	169

Sensitivity: $TP / (TP + FN) = 90\%$ PPV: $TP / (TP + FP) = 66.7\%$
 Specificity: $TN / (TN + FP) = 75.2\%$ NPV: $TN / (TN + FN) = 93.2\%$

Table-2: Sensitivity and specificity of CRP in male neonates (n = 92)

			Neonatal sepsis on CRP		Total
			Positive	Negative	
Neonatal sepsis on blood culture	Positive	Within neonatal sepsis on blood culture	29 (90.6%)	3 (9.4%)	32 (100%)
		Within neonatal sepsis on CRP	72.5%	5.8%	34.8%
	Negative	Within neonatal sepsis on blood culture	11 (18.3%)	49 (81.7%)	60 (100%)
		Within neonatal sepsis on CRP	27.5%	94.2%	65.2%
Total			100%	100%	100%

Sensitivity = 90.6% NPV = 94.2%
 Specificity = 81.7% P value = 0.000
 PPV = 72.5%

Table-3: Sensitivity and specificity of CRP in female neonates (n = 77)

			Neonatal sepsis on CRP		Total
			Positive	Negative	
Neonatal sepsis on blood culture	Positive	Within neonatal sepsis on blood culture	25 (89.3%)	3 (10.7%)	28 (100%)
		Within neonatal sepsis on CRP	61.0%	8.3%	36.4%
	Negative	Within neonatal sepsis on blood culture	16 (32.7%)	33 (67.3%)	49 (100%)
		Within neonatal sepsis on CRP	39.0%	91.7%	63.6%
Total			100%	100%	100%

Sensitivity = 89.3% NPV = 91.7%
 Specificity = 67.3% P value = 0.000
 PPV = 61.37%

Table-4: Sensitivity and specificity of CRP in neonates of age group up to 10 days (n = 89)

			Neonatal sepsis on CRP		Total
			Positive	Negative	
Neonatal sepsis on blood culture	Positive	Within neonatal sepsis on blood culture	24 (85.7%)	4 (14.3%)	28 (100%)
		Within neonatal sepsis on CRP	63.2%	7.8%	31.5%
	Negative	Within neonatal sepsis on blood culture	14 (23.0%)	47 (77.0%)	61 (100%)
		Within neonatal sepsis on CRP	36.8%	92.2%	68.5%
Total			100%	100%	100%

Sensitivity = 85.7% NPV = 92.2%
 Specificity = 77% P value = 0.000
 PPV = 63.2%

Table-5: Sensitivity and specificity of CRP in neonates of age group 11 to 15 days (n = 24)

			Neonatal sepsis on CRP		Total
			Positive	Negative	
Neonatal sepsis on blood culture	Positive	Within neonatal sepsis on blood culture	8 (100%)	0 (0%)	8 (100%)
		Within neonatal sepsis on CRP	72.7%	0%	33.3%
	Negative	Within neonatal sepsis on blood culture	3 (18.8%)	13 (81.2%)	16 (100%)
		Within neonatal sepsis on CRP	27.3%	100%	66.7%
Total			100%	100%	100%

Sensitivity = 100% NPV = 100%
 Specificity = 81.2% P value = 0.000
 PPV = 72.7%

Table-6: Sensitivity and specificity of CRP in neonates of age group 16 to 20 days (n = 3)

			Neonatal sepsis on CRP		Total
			Positive	Negative	
Neonatal sepsis on blood culture	Positive	Within neonatal sepsis on blood culture	1 (100%)	0 (0%)	1 (100%)
		Within neonatal sepsis on CRP	100%	0%	33.3%
	Negative	Within neonatal sepsis on blood culture	0 (0%)	2 (100%)	2 (100%)
		Within neonatal sepsis on CRP	0%	100%	66.7%
Total			100%	100%	100%

Sensitivity = 100% NPV = 100%
 Specificity = 100% P value = 0.083
 PPV = 100%

Table-7: Sensitivity and specificity of CRP in neonates of age group 21 days and above (n = 53)

			Neonatal sepsis on CRP		Total
			Positive	Negative	
Neonatal sepsis on blood culture	Positive	Within neonatal sepsis on blood culture	21 (91.3%)	2 (8.7%)	23 (100%)
		Within neonatal sepsis on CRP	67.7%	9.1%	43.4%
	Negative	Within neonatal sepsis on blood culture	10 (33.3%)	20 (66.7%)	30 (100%)
		Within neonatal sepsis on CRP	32.3%	90.9%	56.6%
Total			100%	100%	100%

Sensitivity = 91.3% NPV = 90.9%
 Specificity = 66.7% P value = 0.000
 PPV = 67.7%

DISCUSSION

Despite advancements in neonatal medicine, early neonatal sepsis is still a leading cause of mortality with the rate ranging from 1.5% in term up to 40% for babies of very low birth weight.^{20,21} The signs and symptoms associated with neonatal sepsis are often nonspecific and subtle. Because they are indistinguishable from certain noninfectious conditions including maladaptation and respiratory distress syndrome. Commencement of empirical antibiotic treatment is current practice for all neonates displaying infection-like symptoms, but this results in their exposure to adverse drug effects, the emergence of resistant strains and nosocomial complications.²² Correct and rapid diagnosis of sepsis in neonates is therefore vital for both protecting the newborn from bacterial invasion consequences and preventing harm from redundant antibiotic use. A definitive diagnosis for sepsis relies on a positive blood culture, which requires a minimum period of 48-72 hours, and provides a positive result from only 10-60% of cases.²³ This process is time consuming in most hospital settings, so there is a desire for identifying suitable alternatives, hence the reason for our present study.

Early detection of neonatal sepsis is mainly based on clinical judgment. However, laboratory investigations requires a microbiological and clinical correlation. Many neonates were empirically prescribed with antibiotics for several days while awaiting the confirmation of suspected infection through bacteriologic culture. In our study, 35.3% of neonates were proved to have sepsis by the blood culture test, but the suspected sepsis group was 64.7%. All of the additional neonates with suspected sepsis cannot be disregarded, because fatal infection has been testified by other studies even following a negative blood culture test.²⁴ Other studies have reported neonatal sepsis rates of 42%²⁵, 20%²⁶ and 42.1%.²⁷ Diagnosis of neonatal sepsis is still a significant challenge and no single hematological parameter is superior for predicting its presence. Our study used a cut off score of >3 and we observed a specificity of 74.5%, sensitivity of 90%, PPV of 65.9% and NPV of 93.2%. The results of this study were consistent with other studies.^{24,29-31}

Ghosh et al³⁰ and Narasimha et al³² observed that the I:T PMN ratio and immature PMN count were also useful indicators of neonatal sepsis. In this study a deteriorating change in the PMN count had no significant effect on the diagnosis. Furthermore, the detection of toxic granules points toward PMNs during infectious process and stress induced leucopenia.

These changes are not manifested in healthy babies. The presence of these granules always indicates sepsis, but their count is not always enhanced.^{31,32}

CRP is a reliable and widely documented laboratory test for neonatal sepsis. The CRP test does have limited sensitivity during the initial phases of infection, especially at early presentation, but it does provide very high NPVs. It is therefore useful for recognizing babies that are unlikely to be infected or for monitoring their responses to various treatments.³³⁻³⁶ There is evidence that CRP-related characteristics may not be as suitable for use in preterm babies as in term babies, however.³⁷⁻³⁹ The CRP test in neonatal sepsis is also complicated by a nonspecific increase occurring just after birth.^{40,41} Because CRP crosses the placenta poorly, elevated serum levels in neonates always indicates endogenous synthesis.⁴² Following a single stimulus, De novo hepatic synthesis of CRP begins very quickly with serum concentrations becoming higher than 5 mg/l by 4-6 hours, becoming abnormal by 24 hours and maximizes by 48 hours.⁴³

For diagnosing early onset sepsis, sensitivity is more important than specificity. This is because there are fewer potential complications from giving unnecessary treatment to an uninfected baby than from not treating an infected baby. Irrespective of the gestational and postnatal age of the neonate, a CRP cut-off value of 10 mg/l is most commonly used. Given the CRP physiologic dynamics during the initial days following birth and the effect of gestational age on CRP response to infection it is sensible to reconsider the static cut-off value of 10 mg/l and assess the potential benefits from introducing dynamic reference values.⁴⁴ There is little published evidence for recommending this approach in clinical practice, however. During the early phases of sepsis, diagnosis is most accurate when the CRP test result matches that from another infection marker, such as IL-6, IL-8 or PCT. Certain other parameters could be tested, but they have not yet been examined sufficiently in clinical practice. The CRP test is especially beneficial for monitoring responses to antibiotic therapy and for preventing further infection. Following the initiation of antibiotic therapy, frequent measurement of CRP levels at 24 to 48 hours carries a 99% NPV in precisely identifying uninfected neonates. It should be recognized that three days following birth, there is a physiologic increase in CRP level.^{41,42} These physiologic subtleties in addition to perinatal and maternal factors can influence CRP levels in healthy neonates. Furthermore, various reports recommend that non-infectious confounders, including perinatal maternal risk conditions and meconium aspiration syndrome,

can increase CRP levels in symptomatic or at-risk neonates and this can misperceive interpretation of CRP values in diagnosing neonatal sepsis.³⁷

CONCLUSION

Neonatal sepsis is a lethal condition but it is also treatable if early action is taken. Non-infectious ailments can present similar hematological changes to those seen with infection, therefore justifying the specificity and PPVs of the screening tests. Based on our study at a paediatric hospital in Peshawar, it was concluded that determination of CRP is a valuable test to differentiate non-infected from infected babies. For early diagnosis of neonatal sepsis the CRP test is a quick, simple, readily available and cost effective tool with high sensitivity and affordable specificity. The CRP test is therefore valuable for making decisions about use of life-saving antibiotic therapy in neonates. This delivers early treatment, reduced mortality, shorter hospital stay, and also minimizes the risk of emergence of resistant organisms due to misuse of antibiotics.

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