C - Reactive protein and other Hematological parameters for diagnosis of Neonatal Sepsis

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Abstract

Background: Sepsis is one of the most common causes of morbidity and mortality in the newborn. Early diagnosis and treatment is vital to improve outcome. The present study was therefore carried out to determine the usefulness of C-reactive protein (CRP) for evaluation of neonatal sepsis in teaching hospital of central India. **Method:** 82 neonates with clinical suspicion of sepsis were prospectively studied over a 12 month period. Blood was obtained from each subject recruited for the qualitative estimation of CRP. Blood culture was used as gold standard for diagnosis of NNS. **Results:** Of 82 neonates studied, 67 (81.7%) had positive CRP while 58 (70.73%) had positive blood culture. The sensitivity, specificity, positive and negative predictive values and diagnostic accuracy of CRP were 81.7%, 88.0%, 95.7%, 59.5% and 83.2%. respectively. **Conclusion**: The qualitative method of estimating CRP which is cheap and rapid has moderate sensitivity, specificity and negative predictive value. It is a good diagnostic test and can identify the infection in neonates at the time of initial assessment.

Keywords: Neonatal sepsis, C-reactive protein, Sepsis screen

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Introduction

Sepsis is one of the major problems in neonates. It remains a significant cause of morbidity and mortality in newborn. Globally, sepsis accounts for 26% of all neonatal deaths [1] with 98% of these deaths occurring in developing countries [2]. Malnutrition, poor socio-economic status, unhygienic delivery conditions, poor medical set-up and some traditional and cultural practices in community are important causes of such a high mortality in developing countries.

On the basis of clinical criteria alone, it is very difficult to diagnose neonatal sepsis because of non-specific and variable sign and symptoms [3]. As the clinical signs of neonatal sepsis are often non-specific; empiric antibiotic therapy may result in the treatment of as many as 30 unin-fected neonates for everyone who is eventually diagnosed to be infected [4,5,6]. The current practice of starting empirical antibiotic therapy in all neonates showing infection-like symptoms, results in their exposure to adverse drug effects, nosocomial complications, and in the emergence of resistant strains

[7]. Adequate and timely diagnosis of neonatal sepsis remains an important challenge to the pediatrician. Blood culture is the gold standard for definitive diagnosis but it takes at least 48-72 hours by which time the infection may have progressed with important consequences on the morbidity and mortality of the neonate [8], especially if antibiotic treatment is not initiated immediately.

The use of safe and effective antimicrobial therapy has markedly reduced the neonatal mortality [9]. Hence there is need for rapid screening test that can identify infected neonates at the time of initial assessment thus sparing the uninfected ones from unnecessary antibiotic therapy. On contrary, under treatment is also dangerous and at time can lead to serious mortality and morbidity.

We need a laboratory test that is easily available, cost effective and results are readily available. C-reactive protein (CRP) is a screening test that can be used to assess neonatal sepsis.

C-reactive protein was first described in 1930 by Tillet and Francis at Rockefeller University [10]. C-reactive protein is an acute phase and an inflammatory marker that

is synthesized in the liver in response to inflammatory cytokines and plays a major role in innate immunity.

The level of C-reactive protein rises rapidly with a peak level in 6 hours, even up to thousands folds during an acute response. It has a short half-life of 19 hours, so the level falls rapidly once the source is removed [11,12,13].

Thus CRP level is also a useful marker in determining the duration of antibiotic therapy. These features distinguish CRP to other acute phase proteins and with availability of rapid assay method, it has a potential importance in neonatal sepsis.

Unlike blood culture, CRP level is not affected by prior antibiotic therapy [14], so may be particularly useful in developing countries like India, where a significant number of neonates may have been given antibiotics by local unqualified doctors before presentation at the hospital.

CRP passes the placenta only in very low quantities; therefore, any elevation in the neonate always represents endogenous synthesis [15]. De novo hepatic synthesis starts very rapidly after a single stimulus with serum concentrations peaking around 48 hours [16].

CRP level can be assayed by both quantitatively and qualitatively. Quantitative method provide rapid, highly sensitive and specific result but more expensive and required more technical expertise, so it is mostly used in developed countries and well equipped modern hospitals[17].

The qualitative method provide very rapid but less specific result, it has the advantage of being simple and easier to perform and interpret and as such can be performed at the patients bed side or side laboratory [18]. It is also less expensive and requires less skill.

The qualitative method may therefore, be more feasible in resource poor countries and where there may be no laboratory services or trained manpower. In neonates, there is a many non infectious causes where CRP level is elevated, eg- maternal and perinatal distress, maternal fever during labour, stressful delivery, prolonged rupture of membranes, prolonged labor, meconium aspiration syndrome, neonatal hypoxia, intraventricular hemorrhage, pneumothorax, surfactant application and tissue injury. [15, 19, 20, 21, 22]

There are certain other laboratory procedures which are widely used as an indirect indicator of septicemia, eg- WBC count, DLC, immature neutrophils count and their ratio, band cells and blood culture. This study was planned to determine the sensitivity and specificity of C-reactive protein with above mention parameters in diagnosing neonatal sepsis in our set up.

Therefore we have studied role of CRP in the blood as an early marker of neonatal sepsis & correlation among CRP and TLC, DLC, Band Cells & Immature cells.

Material and Methods

This prospective study was conducted over a period of one year, in the department of Pediatric, NSCB Medical College, Jabalpur (MP), India. Ethical approval regarding the study was obtained from ethical committee of medical college.

Cases were selected randomly among the patients admitted in the nursery with suspicion of septicemia. 82 neonates (age ≤ 28 days, whether term or preterm) who were clinically suspected of septicemia were included in this study.

Clinical suspicion of neonatal septicemia based on profile suggested by Avery (1981). Following investigation were performed on all patients-
1. Total leucocyte counts
2. Differential leucocyte count including ration of immature neutrophils (Band Cells) to mature neutrophils
3. Blood culture
4. C-reactive proteins
5. Other investigation like hemoglobin, serum bilirubin, lumber puncture for CSF study, urine examination, stool examination, umbilical swab culture, pus swab culture, X-ray chest were done as and when required.

Results

A total 82 neonate with clinical suspicion of septicemia selected according to selection criteria, over a period of 12 months.

Table No 1: Age, sex, weight and Gestational age wise distribution of neonates

S. No	Chrono-logical Age	No of Cases			Birth Wt (Kg)	No of Cases			Gestational Age	No. of cases (%)
		Male (%)	Female (%)	Total (%)		Male (%)	Female (%)	Total (%)		
01	<24 Hrs	01 (02.1)	02 (05.9)	03 (03.9)	≤1.0	01 (02.1)	01 (02.9)	02 (02.4)	Pre-term	52 (63.4)
02	1-3 days	07 (14.6)	03 (08.8)	10 (09.8)	1.0-1.5	12 (25.0)	05 (14.7)	17 (20.7)	Term	26 (31.8)
03	4-7 days	16 (33.3)	16 (47.1)	32 (39.1)	1.5-2.5	29 (60.4)	25 (73.5)	54 (65.8)	Post-term	04 (04.8)
04	8-28 days	24 (50.0)	13 (38.2)	37 (45.2)	>2.5	06 (12.5)	03 (08.8)	09 (10.9)	-	-
	Total	48	34	82		48	34	82		82
	Mean ±SD	08.79 ±5.95	08.78 ± 6.71							

Table No-01 depicts that maximum number of patients belong to age group 8-28 days, this is also same for male patients, where 50% (24 patients) belong to 8-28 days category, but 47.1% (16 patients) female patients belong to 4-7 days group. Only 03 (3.85%) neonates admitted within 24 hours of birth. Average age of newborn was 8.79±5.95 days for male and 8.78±6.71 days for female neonates. There was clustering of cases in weight group 1.5-2.5kg, total 54 (65.8%) belong to this group. Total 60.4% (29 patients) male and 73.5% (25 patients) female patients belong to same category. Only 2.4% patients belong to ≤1kg category. Most of the patient were pre-term (63.4%) and only 04.8% neonates were post-term.

Table No 2: Clinical profile (Signs & Symptoms) of Neonates suspected Sepsis

S No.	Symptoms	No. of cases	%	Signs	No. of cases	%
01	Lethargy	72	87.80	Vacant stare	24	29.27
02	Refusal of feed	68	82.93	Seizure	20	24.39
03	Temperature instability	54	65.85	Bulging anterior fontanel	09	10.97
04	Abdominal distension	12	14.63	Periumblical erythema	08	09.76
05	Bleeding/ DIC	06	07.32	Scleroderma	05	06.10

Table No-02 shows that lethargy (87.80%), refusal of feed (82.93%) and temperature instability (65.85%) were most common presenting symptoms and vacant stare (29.27%) and seizure (24.39%) were most common sings. Bulging anterior fontanel (10.97%) and periumblical erythema (09.76%) were other common presenting signs.

Table No 3: Total Leucocyte Count (TLC), Band Cell: TLC Ratio (I/T Ratio), C- Reactive Protein (CRP) and Blood Culture distribution in Septicemic Neonates

S No	Parameter	Result	No. of cases	%	Total
01	Total Leucocyte Count	<5000 /mm^3	28	34.14	82
		5000-15000 /mm^3	49	59.76	
		>15000 /mm^3	05	06.10	
02	Immature: Total Leucocyte Count Ratio (I/T Ratio)	Positive (>0.2)	52	63.41	82
		Negative (<0.2)	30	36.58	
03	C-reactive Protein	Positive	67	81.70	82
		Negative	15	18.29	
04	Blood culture	Positive	58	70.73	82
		Negative	24	29.27	

Table No-03 shows that total leucocyte count was <5000/mm^3 in 34.14% neonates and between 5000-15000/ mm^3 in 59.76% cases. Only 06.1% patients have counts >15000/ mm^3. Mean ± SD of TLC was 8592.68 ±3869.43. In our study 63.41% neonates shown positive (>0.2) I/T ratio (Band Cell/ Total Leucocyte Ratio) and 36.58% negative. CRP was positive

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in 81.70% cases and in only 18.29% cases it was negative. Similar 70.73% septic neonates were positive for blood culture and only 29.27% cases blood culture was negative. Most common organism grown in culture were Klebsiella (35.36%), E. Coli (18.29%), Streptococci (14.63%) and Pseudomonas (02.44%). In 29.27% cases culture was sterile.

Table No 4: Clinical suspicion of septicemia and CRP status

S No.	Group	Features	No of cases	%	Positive CRP	
					No. of cases	%
01	A	Clinical evidence of sepsis + Positive blood culture	58	70.73	58	100
02	B	Clinical evidence of sepsis + ancillary evidence of infection (Negative blood culture)	18	21.95	09	50
03	C	Only Clinical evidence of sepsis	06	07.31	00	00

Table No-4 depicts that CRP is 100% positive in Group-A (which was having positive blood culture), while 50% in Group-B (in which blood culture is negative)

Table No 5: Sensitivity and Specificity of various investigation alone and in combination

S No.	Test	Sensitivity	Specificity	Positive Predictive Value (PPV)	Negative Predictive Value (NPV)	Diagnostic Accuracy (DA)
01	Blood Culture	70.7	100	100	51.0	77.6
02	CRP	81.7	88	95.7	59.5	83.2
03	TLC	40.2	92	94.3	31.9	52.3
04	I/T Ratio	63.4	92	96.3	43.4	70.0
05	CRP + TLC	47.8	100	100	30.0	57.3
06	CRP + I/T Ratio	77.6	100	100	50.0	81.7

Various tests were analyzed alone and in combination in table No-05. Blood culture was sensitive in 70.7% cases but 100% specific; CRP estimation is 81.7% sensitive and 88% specific. Sensitivity of TLC is only 40.2% but specificity is high (92%). When CRP was combine with TLC and I/T Ratio, through sensitivity decreased (47.8% and &&.6% Vs 81.7% respectively) but specificity improved (100% and 100% Vs 88% respectively). Diagnostic accuracy was highest with CRP (83.2%) followed by blood culture (77.6%). Positive predictive value was highest with blood culture (100%) and negative predictive value was highest with CRP (59.5%)

Table No 6: Multivariate Linear Regression Analysis

Coefficient of Correlation

Model	R	R Square	Adjusted R Square	Standard Error of Estimation
1	0.901 (a)	0.812	0.801	0.191

a Predictor: (Constant), ABDD, BCR, TEMP, CRP.

ANOVA

Model	Sum of Square	df	Mean Square	F	Significance
Regression	15.473	06	2.579	70.694	0.000 (a)
Residual	03.575	98	0.036		
Total	19.048	104			

a. Predictor: (Constant), ABDD, BCR, TEMP, CRP, LETH, RFEED

b. Dependent variable: Septicemia

Coefficients (a)

	Un-standardized Coefficients		Standardized Coefficients		
	B	Std. Error	Beta		
(Constant)	0.121	0.037		3.311	0.001
BCR*	0.138	0.046	0.162	3.036	0.003
CRP*	0.180	0.047	0.202	3.805	0.000
RFEED*	0.156	0.058	0.179	2.705	0.008
LETH*	0.368	0.058	0.408	6.301	0.000
TEMP*	0.179	0.042	0.210	4.216	0.000
ABDD*	0.133	0.059	0.100	2.257	0.026

a Dependent Variable: Septicemia   * Significant

We carried out a multivariate analysis considering septicemia as an outcome on various dependent variable on BCR (blood culture), CRP (C-reactive protein), REFFD (refusal of feed), LETH (lethargy), TEMP (temperature instability), ABDD (abdominal distension). The value of correlation coefficient was found to be positive and significant association with development of septicemia. CRP, lethargy and temperature instability were highly significant, refusal to feed and positive blood culture were significant and abdominal distension was considerably significant. This lead to establish that septicemia is directly dependent of several factor studied.

Discussion

Neonatal sepsis is a serious and potentially life threatening condition. In developing countries like India, neonatal sepsis is major cause of morbidity and mortality in newborn. Risk is increased very much again because of unclear delivery and poor postnatal follow-up. However early diagnosis and treatment is vital for favorable outcome. Early diagnosis is difficult task and based mainly on clinical suspician. No doubt, blood culture is still the gold standard but because of its non-availability in most peripheral setups, high cost, more chances of contamination and delayed results, a need more convenient, cost effective and whose results are available in time. C-reactive protein can fill up this time gap, as this is important indirect test to diagnose neonatal sepsis. C-reactive protein has some practical advantages: it can be done in all those neonates who are on prior anti-microbial therapy. Despite all this still it is recommended to rely on both clinical correlations and laboratory findings for confirm diagnosis.

This study showed that C-reactive protein was positive in 81.7 % (67 of 82) of neonates. 86.56% (54 of 67) neonates were having confirmed sepsis. This shows that C-reactive protein was best single marker to diagnose neonatal sepsis in resource limited countries. Our results are comparable with the study done by WE Benitz et al in 1998, that shows C-reactive protein had higher sensitivity 92.9% and 85% for proven and probable in early onset sepsis and 78.9% and 84.4% for proven and probable sepsis in late onset episodes [33]. Sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of C-reactive protein was

81.7%, 88%, 95.7%, 59.5% and 83.2% respectively. We can compare our result with the study done by Jan AZ et al in 2012, that shows that C-reactive protein was positive with the Sensitivity, specificity, negative and positive predictive values of 94.01%, 69.17%, 79.29%, 90.19% respectively and diagnostic accuracy of CRP was 83.0% [34]. The marked difference of result among studies evaluating C-reactive protein as useful marker, can be explained by non-availability of universally acceptable definition of neonatal sepsis, difference in reference range values and environmental influence on the results in different setups. A negative CRP, however can be more useful in making the decision to discontinue antibiotics especially if the neonate has no clinical feature of sepsis. Kashabi et al. in 2004 also demonstrated that CRP can be a useful guide in making a decision to discontinue antibiotic therapy, thus facilitating early discharge, significantly reduced cost, complications of treatment, misuse of antibiotics and family anxiety [35].

In this study prevalence of blood culture proven neonatal sepsis was 70.73% (58 patients). This is higher than studies done previously, eg- Chako et al (2005) 41.7%, Roy et al (2002) 47.5%, Ahmed Z et al (2005) 28%, Manucha V et at (2002) only 14% and 10.7% by Ugochukwu et al in 2003 [23-27]. The higher prevalence observed in this study could be attributed to poor obstetric and neonatal care, unhygienic living and delivery conditions in remote areas and being a tertiary care center most of the patients reach to hospital in advances stage and taking some home remedies, which increase the risk of infection . The knowledge of

etiological organism and antimicrobial sensitivity is necessary effective therapeutic intervention. The commonest organism isolated was klebsiella pneumoniae (35.36%) followed by E. Coli (18.29%) and Streptococci (14.63%). Klebsiella pneumoniae (50% in preterm and 65.5% in term) and staphylococcus aureus (21.2% in preterm and 19% in term) were most common organism in study conducted by West BA et al in 2012 [28]. One Indian study, conducted by Roy et al in 2002 also shows similar type results [29].

Studies from other developing countries showing that Klebsiella pneumoniae was most common organism of neonatal sepsis [30,31]. The differences in common organism in different studies may be because of different geographic location and replacement of one organism or a group of organisms with another organism or group of organism [32].

Elevated I/T ratio was found to be quite reliable hematological indicator of neonatal sepsis with sensitivity 63.4%, specificity 92% and PPV 96.3%. Various other studies like those done by Ghosh et al (2001) and Manisha Makkar et al (2013) also shows that immature PMN count and I:T PMN ratio was also a very sensitive indicator of neonatal sepsis[36,37].

Presence of toxic granules indicates the production of unusual PMNs during infection and stress induced leucopoiesis. They are never seen in healthy babies. I:T PMN ratio and degenerative changes were the most reliable tests for diagnosing sepsis. An abnormal I:M PMN ratio was highly sensitive in identifying sepsis. Degenerative changes in neutrophils were not found to be a very sensitive indicator of sepsis [38]. Different studies also shows that thrombocytopenia is associated with poor prognosis [39, 40].

Conclusion

 Although blood culture is a "gold standard" test in diagnosing sepsis but its main limitation is its delayed result, more chances of contamination, high cost and non-availability in most peripheral setups in our country. Estimation of CRP is useful test in the early diagnosis of neonatal sepsis. Quantitative CRP assays is sensitive, precise, accurate and available commercially.

Unfortunately quantitative CRP assay required expertise and automated instruments and hence not suitable for bedside or for remote areas. Alternatively qualitative method of CRP estimation (eg-slide latex agglutination) is rapid, inexpensive, simple to perform, easy to interpret and being a non instrumental test it is ideal to assess neonatal sepsis. The C-reactive protein may therefore, help in the early detection of neonatal sepsis while awaiting blood culture results. CRP may also be invaluable in the management of neonatal sepsis in resource poor counties where facilities for blood culture may not be readily available. Our study suggests that CRP should be used as a preferred marker in evaluating a neonate for sepsis. Despite the high sensitivity C-reactive protein, we would still stress upon clinical correlation and laboratory findings should be used simultaneously for the diagnosis of neonatal sepsis.

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