Original Research Article

Role of C-reactive protein as an early indicator of blood culture positivity 1- 5 year old febrile children

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Abstract

Background: Blood culture remains the gold standard in detecting bacteremia, but are not the best choice to there low predictive value like these patients suggestive of acute phase reactants like C-reactive protein helpful in detecting bacterial infections early diagnosis. **Materials and methods**: The present study was undertaken to evaluate the role of C-reactive protein as an early indicator of blood culture positivity. 100 patients were enrolled in the study in the age group of 1 to 5 years. **Results**: Of the 100 patients, 9 patients showed culture positive, 91 were culture negative patients. Acinetobacter, staphylococcus aureus, streptococcus pyogenes, salmonella typhi, and pseudomonas were found in the blood culture. A sensitivity of 88.89% (95%CI:0.5175-0.9972), A specificity of 67.03% (95% CI: 0.5639-0.7653), a likelihood ratio of 2.69% positive predictive value test 0.2105 (95% CI: 0.0955-0.3732) and negative predictive value test 0.9839 (95%CI:0.9134-0.9996) were demonstrated in the study. **Conclusions:** CRP appears to be useful in the early detection of serious bacterial infection.

Keywords: Blood culture, C-reactive protein, Bacteremia.

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Received Date: 14/07/2017 Revised Date: 24/08/2017 Accepted Date: 06/09/2017
DOI: https://doi.org/10.26611/1014333

Access this article online	
Quick Response Code:	Website: www.medpulse.in
	Accessed Date: 12 September 2017

INTRODUCTION

Fever is a common presenting symptom in pediatric practice and emergency rooms, particularly in children under 5 years age. Approximately 15 to 20 % of these children have no identifiable source of fever after history and physical examination although most of children might have a begin viral illness, children under 5 years of age are at increased risk of clinically undetectable serious bacterial infection. Bacterima occurs in 3 to 11 percent of febrile children under 5 years of age. Approximately 2% to 3% of these children have occult bacterima while 2% to 8% have urinary tract infection, depending on the age and gender, other causes of serious bacterial infection (SBI) include occult bacterial pneumonia (3%) and meningitis.[1] Although antibiotic treatment is necessary for children with SBI, it is also important to limit therapy to those children at greatest risk. Because majority of febrile young children do not have SBI, laboratory tests and expectant anyibiotic therapy of these children adds to cost, discomfort and parental anxiety and may contribute to antibiotic resistance. Clinical observations alone lack the necessary sensitivity and specificity in detecting occult bacterial infections. Because it is clinically difficult to identify children with SBI, a number of diagnostic and management strategies have been suggested. Although, blood culture remains the gold standard in detecting bacteremia, the average time for detecting of positive culture is about 15-16 hours and may be as long 24 to 48 hours and therefore increases the risk of complications. Total white blood cells and absolute neutrophil counts are most commonly used screening occult bacterima but are not the best choice to there low predictive value in situations like these , studies have suggested that acute phase reactants including c-reactive

protein may be helpful in detecting bacterial infections early. Their use minimizes delay in therapy, is less expensive and less time consuming. If the C-reactive protein is negative, the unnecessary use of antibiotics may be stopped so as to minimize unnecessary expenditure to the patient.[2] We sought to prospectively study the diagnostic properties of quantitative CRP in comparison with blood culture in 1 to 5 year old febrile children with and without focus of infection. To study the role of C-reactive protein as an early indicator of blood culture positivity 1 to 5 year old febrile children.

MATERIALS AND METHODS

The prospective study comprised of 100 children in the age group of one year to five years with axilary temperature of more than 100 fahrenheit lasting more than one-day. The study was conducted at the pediatric inpatient department of children's medical center from January 2013 to September 2014. Inclusion criteria: Children with evidence of focal infections (otitis media, meningitis, pneumonia, URTI), Fever without focus. Exclusion criteria: Children already on antibiotic treatment, Immunodeficiency and Children already under chronic steroid treatment. Detailed history is taken from the parents, which includes the clinical parameters like age, gender and weight. Axillary temperature is recorded with a digital thermometer in all cases, along with a through clinical examination. They are then subjected to laboratory parameters like complete blood picture, c-reactive protein, blood culture and sensitivity, complete urine examination and serum electrolytes. They are subjected to chest radiograph, parasite falciparam and vivax and widal test depending on the necessity. Blood culture characterized as true pathogens include all cultures yielding streptococcus pneumonia, staphylococcus aureus, haemophilus influenza, nesseria meningitides, group-a streptococcus and salmonella species. In the present study particle enhanced immune turbidimetric test is selected as the methodology for testing c-reactive protein. The assay is based on photometric measurement of antigen and antibody reaction. In this kit, c-reactive protein present in patients sample is reacted against anti C-reactive protein coated micro latex and values are measured photometrically. Fresh serum preferred (or) samples stored at 2-8 °C used for 8 days (or) 3 months at -20 °C used. Centrifuge samples showing visible particles. Hemolysed or lipemic samples should not be used. BacT/ALERT 3D method was used for the blood culture study. 4ml of whole blood was collected into the pediatric blood culture collection kits. Strict technique was maintained during the collection. Descriptive (mean, median and mode), frequencies, correlation and chi-square tests were carried out for statically analysis.

RESULTS

One hundred children were enrolled in the present study, in the age group of one to five years with mean age, 2.79 years for males and 2.67 years for female. From of total of 100 patients , 38 were CRP positive and were CRP negative.

Table 1: Blood culture positivity

	Frequency	Percentage
Positive	9	9.0
Negative	91	91.0
Total	**100**	**100.0**

Of the 100 children who were studied, 38 were CRP positive and 9 of these 38 children showed blood culture positivity.

Table 2: Diseases and percentage of organisms in culture positive serious bacterial infections

Diseases presented with culture positivity	Acute broncho pneumonia	Enteric fever	Occult sepsis	Pyogenic meningitis	Urinary tract infection	Acute gastro enteritis
Total no of patients culture positive	3	2	1	1	1	1
% of organism obtained from culture positive patients	33.33%	22.22%	11.11%	11.11%	11.11%	11.11%

Nine patients (9%) had culture proven bacterial infection (serious bacterial infection). Ninety-one patients (91%) had no serious bacterial infection.

Table 3: Disease, type of organism, distribution and CRP concentration in culture positive serious bacterial infection

Disease	Organism isolated	No. of children	CRP mg/L
Acute broncho pneumonia	Pseudomonas	1	5.82
	Staphylococcus aureus	1	2.21
	Streptococcus pyogenes	1	4.43
Occult sepsis	Acinetobacter	1	10.5
Pyogenic meningitis	Acinetobacter	1	30.0
Urinary tract infection	Acinetobacter	1	12.2
Enteric fever	Salmonella typhi	1	11.43
	Salmonella typhi	1	7.38
Acute gastroententeritis	Acinetobarcter	1	15.6

Acinetobacter was isolated from the blood culture in patients presented with occult sepsis, pyogenic meningitis, urinary tract infection and acute gastroenteritis. Staphylococcus aureus, pseudomonas, streptococcus pyogenes were isolated from the blood culture in three patients presented with acute bronchopneumonia. Salmonella typhi was isolated from the blood culture of patients presented with enteric fever. All above organisms had grown in cultures where the CRP levels were more than 4mg/l. Of the nine patients with serious bacterial infection, three were having acute broncenteric feverho pneumonia, two were having enteric fever and of the remaining four children one had occult sepsis, one had pyogenic meningitis, one had urinary tract infection and one had acute gastroenteritis.

Table 4: Relation of CRP with duration of fever

	No.	Minimum	Maximum	Mean	Median	SD
CRP	100	.01	30.00	3.35	1.89	4.10
Duration of fever (days)	100	2.00	7.00	3.32	2.00	1.73

An attempt was made to correlate height of temperature with frequency of bacteria. It was observed that frequency of positive blood culture increased significantly as temperature increased from a minimum of 100 F to a maximum of 103F. As the duration of fever increases from 2 days to 7 days, the CRP levels increased from 0.01 mg/1 to 30 mg/1.

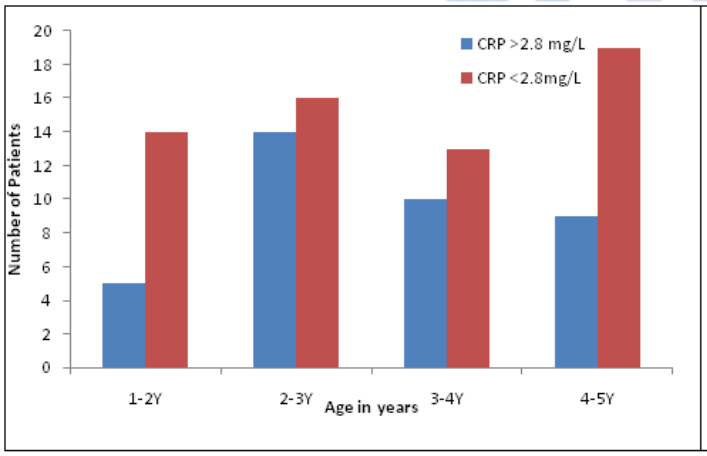

Figure 1: Relation of CRP with age

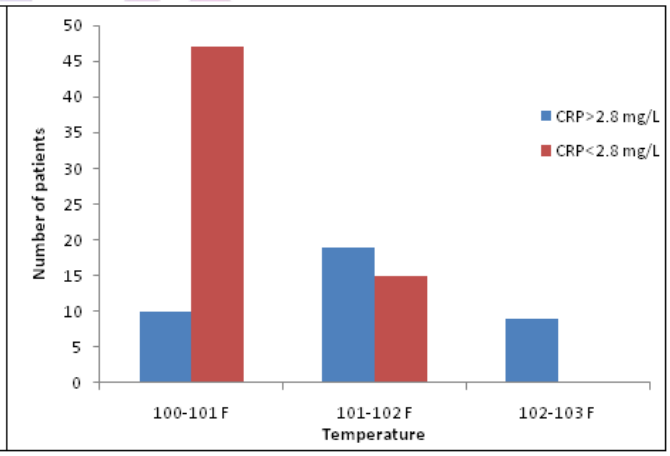

Figure 2: Relation of CRP with Temperature

Table 5: Correlations in study

Correlations		C.R.P	Duration of fever(days)	Temperature
C.R.P	Pearson correlation	1	,229(*)	.475(**)
	Sig.(2-tailed)		.022	.00
Duration of fever (days)	Pearson correlation	.229(*)	1	.246(*)
	Sig.(2-tailed)	.022		.014

Correlation is significant at the 0.05 level (2-tailed); ** Correlation is significant at the 0.01(2-tailed); The sensitivity of serum CRP >2.8 mg/l, for diagnosis of occult bacteremia was 88.89 (95% CI: 0.5175-0.9972); The specificity 67.03%(95% CI: 05639-0.7653) and Likelihood ratio of positive test =2.6963,(95%CI: 1.8567-3.9156); Likelihood ratio of negative test =6.0330,(95%CI: 0.9453-38.5024); Positive predictive value test =0.2105, (95% CI: 0.0955-0.3732);Negitive predictive value test = 0.9839, (95%CI: 0.9134-0.9996)

DISCUSSION

In the present study, the usefulness of C-reactive protein was evaluated in the early diagnosis of serious bacterial infections in febrile children. Blood culture positivity, percentage of organisms, type of organisms, correlation of organisms with CRP levels, age group related to culture positivity, relation of CRP with age, relation of CRP with the degree of temperature and duration of fever were included. The management of febrile young children with and without an apparent source of infection remains controversial and challenging, Limited tests are available with adequate sensitivity and specificity to identify febrile children, who are at risk for bacterial infection.

Blood culture is the gold standard to detect occult bacteremia; however, results are not available quickly. Various other tests like total white blood cell count, absolute neutrophil count showed some usefulness, but have very low sensitivity and specificity in detecting bacterial infections when applied individually. Recent serum procalcitonin levels showed positive results in peripheral hospitals, primary health care centers, time factor (at least two days to get the results) and its prohibitive cost, this test is not much of practical use.

Our study demonstrated that, CRP estimation have some value in early diagnosis of occult bacteremia in children. Moreover, this test has many advantages like advantages like of easy availability, less time and also cost effectiveness.

A total of 100 patients were enrolled in the study in the age group of 1 to 5 years with and without a source of bacterial infection. Temperature between 100 F and 103 F, duration of fever between 2 to 7 days, c-reactive protein levels and relation between the CRP and temperature, a cut off value of 2.8mg/l of CRP were included in the study.

Of the 100 patients , 9 patients shown culture positive and 91 patients were culture negative. *Acinetobacter*, staphylococcus aureus, streptococcus pyogenes, salmonella typhi, and pseudomonas were found in the blood culture. Acinetobacter was the bacteria which was isolated from most patients followed by the salmonella typhi. With increasing CRP levels the blood culture showed increase in the growth of organisms. The growth of organisms had significantly increased when the temperature was increased from 101 F to 103F.

The present study demonstrated a good sensitivity of 88.89 (95%CI:0.5175-0.9972), specificity of 67.03% (95% CI:05639-0.7653), Positive likelihood ratio 2.6963, (95%CI:1.8567-3.915)and likelihood ratio of negative 6.0330, (95% CI:0.9453-38.5024), and negative predictive value test =0.9839, (95% CI:0.91340.9996).An attempt was made to correlate height of temperature with frequency of blood culture positivity. It was observed that frequency of positive blood culture increased significantly as the temperature increases from a minimum of 100 F to a maximum of 103 F. As the duration of fever increased from 2 days to 7 days, the CRP levels also increased from 0.01mg/l to 30mg/l.

The results of the present study coincide with studies conducted by Kholi *et al* [3] , where they found 95% of sensitivity, 86% of specifity and a likelihood ratio of 6.8. Pulliam ea al [4], sensitivity of 79% and specificity of 91% Galetto-Lacour *et al* [5], sensitivity of 76% (95% ci 60-92), specificity of 79% (67-88) and likehood ratio of 3.8 (1.8-76).

Kholi *et al*[3], had done a comparative study on CRP, total and differential leukocyte count and ESR in children with laboratory or radiographically proven bacterial illness and non-bacterial illness and found better sensitivity, specifity and likelihood ratio of CRP than its counterparts and he concluded that CRP is very useful test in the early diagnosis of SBI.

Benitz *et al* [6], conducted a study on serial serum c-reactive protein levels in the diagnosis of neonatal infections and stated that, the sensitivity and specificity of CRP levels in older children has been poor compared to the neonates.

Thayyil S[7] conducted a study on comparision of procalcitonin with CRP in diagnosis of various infections include viral infection, localized bacterial infection, bacterial meningitis and septic shock and found better results with procalcitonin. The ROC curve was 0.96 for procalcitonin and0.83 for CRP and they concluded that, in critically ill children procalcitonin concentration is better diagnostic marker of infection than c-reactive protein.

Isaac man *et al*[8] (2000), conducted a comparative study on CRP and absolute neutrophil count for detection of occult bacterial infection in 256 children with a mean temperature of 40 c and median length of illness was 24 hours and found 69% of ANC sensitivity and 79% of CRP and they stated that, we did not find any advantage in using this test in lieu of the ANC. The sensitivity, specificity and PPV and NPV profiles of these tests are extremely similar. While the addition of CRP testing to that of WBC or ANC provides a slightly better screening profile for ruling out occilt bacterial infection, this comes at the cost of decrease in specificity.

Pulliam *et al*[4] (2001), had done a study on CRP, WBC, absolute neutrophil count ANC), band count in children with laboratory or radiographically proven serious bacterial infections and conducted that CRP had better predictive value than WBC or ANC. Galetto-Lacour *et al*[9], conducted a study on the effectiveness of CRP with procalcitonin, IL-6 and WBC with differential count and found better sensitivity, specificity and likelihood ratio of CRP than procalcitonin, IL-6 and WBC. Andreola B[10] (2007), conducted a prospective cohort study to assess the value of procalcitonin and c-reactive protein, compared with the total white blood cell count in predicting severe bacterial infection. A total of 408 children between the group of 1 week to 36 months were assessed using the ROC method. Serious bacterial infection was diagnosed in 94 children (23,1%) with better sensitivity and specificity in procalcitonin and c-reactive protein than WBC and ANC and they concluded that both procalcitonin and CRP are valuable markers in predicting SBI in children and that they performed better than WBC and ANC. Limitations of the present study include the age group, the fact that there were CRP positive cases in neonates and infants 40%-50%, when compared to 10%-12% in 1 to 5 years age group indicates that the value of CRP is declining as the age advances. The CRP values were taken only once in the study period, serial recording of CRP values would have been more reliable. Patients with 100 F of fever of one day duration and patients without acute illness were also enrolled in the study, this could be the reason for less percentage of culture positivity. After observation and analysis of the present study, CRP appears to be useful in the early detection of serious bacterial infection.

CONCLUSIONS

The present study was undertaken to evaluate the role of C-reactive protein as an early indicator of blood culture positivity. CRP levels estimation have some value in early diagnosis of serious bacterial infection in the children, allowing for a more selective strategy for determining which children need additional diagnostic studies and antibiotic therapy. CRP has a high negative predictive value, than positive predictive value. The CRP testing procedure is less time consuming and results can be obtained within 1 hour after admission of patient. Additional research is needed to validate using CRP as a single screening tool.

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Source of Support: None Declared
Conflict of Interest: None Declared