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Original Research Article

Role of C- Reactive Protein in Fever without Focus in Children between 1 to 36 Months of Age

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ABSTRACT

Background: Fever without any source (FWS) of infection is one of the most common complaints seen in emergency departments in children <36 months of age. In spite of modern medical technologies, prevalence and cause of fever is unclear. Set of evaluation tests are available but no single test is Gold standard.
Aims: Our study aimed in using CRP as a marker to differentiate contaminated vs. true positive blood culture, compare it with other diagnostic tests WBC, ANC, ESR.
Methodology: A descriptive study was done with 140 specimens obtained from febrile children between 1-36 months of age. This study was carried out from 2014 to 2015, in the department of paediatrics at a medical college and hospital and tested for total WBC count, ANC, ESR and CRP. Blood culture, Urine analysis, urine culture, colony count, chest radiograph were done. CSF analysis was done for selected cases. CRP was done by slide agglutination method followed by Semi-quantitative CRP was performed.
Results: Out of 140 of children, children with serious bacterial infection are 40, and children without serious bacterial infection are 100. These children were divided into with and without Serial Bacterial Infection (SBI). Results analyzed using simple statistical proportions and ROC curve. CRP had sensitivity of 77 %, specificity of 89% PPV of 74%, NPV of 91% and likelihood ratio of 9.6% in the present study. While using CRP and WBC combination, over all sensitivity increased to 57%, specificity increased to 97%, PPV increased to 86% and NPV increased to 91%.
Discussion and Conclusions: Fever in children requires rapid treatment and management. So, test with adequate sensitivity and specificity to is very much essential. This study demonstrates CRP is both more sensitive and specific in distinguishing children with occult serious bacterial infection from those without bacterial illness. Our current study reveals that CRP along with WBC count concentration is better than other tests in predicting serious bacterial infection in febrile young children.

Keywords: C-reactive protein, bacteraemia, Serial Bacterial Infection, White Blood Cell Count

INTRODUCTION

Fever without any source (FWS) of infection is accompanied by temperature 38^{o}C or higher in children <36 months and may be without signs or symptoms. [1,2] It is most recurrent complaints seen in patients

of paediatric age; which accounts for approximately 25% of the emergency department visits. [3] Infant < 29 days that appears toxic should go through sepsis work-up whereas, non-toxic-appearing children one to 36 months of age without fever with no apparent source and who have received the vaccinations, could should go through laboratory screening test. [4]

Many diseases depending upon geographical region and time are responsible for Fever of unknown origin (FUO). [5] Any fever > 3 weeks and remains undiagnosed even after 1 week of inpatient evaluation are of FUO. [6, 7] Discriminating FUO and FWS is important and is based on duration of fever. FWS can progress to FUO if no cause is elicited after 1 week of fever. [6]

In spite of modern medical technologies, prevalence of pediatric FUO remain unclear. Many overlapping conditions such as collection of symptoms and insidious disease courses are found to be cause of FUO. Evaluation tests for diagnosis is based on patient presentation, geographic location, associated symptoms, environmental exposures, physician experience.[6] Gold standard diagnostic test for the detection of FUO is still not available with any set of "routine" investigations. [5-8] These febrile patients are associated with increased risk of bacterial infections especially in children < 3 months compared to 3 months to 36 months age group along with non-infectious inflammatory disease (NIID), and malignancy.[7] Approximately 10-15% of children with temperature > 39^0c is because serious bacterial infection. [8, 9]

Previous studies have found that children 3 to 36 months of age with FUO are at risk for occult bacteremia (1.6% to 7%). [10-12] *Streptococcus pneumoniae* cause 90% of occult bacteremias, after the introduction of the *Haemophilus influenzae* conjugate vaccine. [10,11] Rate of pneumococcal bacteremia has decreased because of polysaccharide vaccine. Therefore increased incidence of bacteremia in young children may be due to part of maturational immune deficiency in production of opsonic IgG antibodies to polysaccharide antigens present on encapsulated bacteria. [11]

The bacterial etiological agents responsible for infections in children aged <1 month are group B streptococcus, *Escherichia coli*, *Listeria monocytogenes*, *S. pneumoniae*, *H. influenzae*, *Staphylococcus aureus*, *Neisseria meningitides*, and *Salmonella* spp. In case of children >3 months of age most bacterial infections are caused by *Streptococcus pneumoniae* (in non-immunised children), *Neisseria meningitidis*, or *Salmonella* spp. [11-13] Bacterial infections are often transient, which facilitates recovery of patients without the aid of antimicrobials. Rarely for these children, meningitis / septic shock occur as a part of systemic or focal infections. Most febrile infants under 1 month of age and all those more than 7 days should be admitted to hospital, treated with antimicrobials; however, observation in hospital without antimicrobials or outpatient management is an option in selected low risk cases. [13, 14]

Till date there exists no recommended or published standard advanced diagnostic methodology for the detection of FUO. Newer Diagnostics techniques and reported shift in the pattern of disease has changed the etiological agents causing FUO. [15,16] The routine diagnostic tests includes white blood cell count and differential erythrocyte sedimentation rate, urine analysis, C reactive protein, morphological changes in peripheral neutrophils, microscopic examination of buffy coat, and quantitative blood cultures. [13]

CRP is the prototype acute-phase protein which is originally found to precipitate with the C-polysaccharide fraction of the pneumococcus. CRP is unique human acute-phase proteins, as it is usually present in lower quantities nanogram-per-milliliter concentrations and

increases significantly and rapidly to hundreds of micrograms per milliliter within 3 days. CRP elevates and decreases more rapidly on resolution of the infectious process when compared to the erythrocyte sedimentation rate. [17-19] Concentration of CRP rises 103-fold in response to injury or infection and it is quick, reliable and easily measured in clinical laboratory. [20]

Few Indian studies are available on the role of CRP in diagnosis of serious bacterial infection in febrile children between 1-36 months of age. Therefore the study is aimed in using CRP as a marker to differentiate contaminated vs. true positive blood culture, compare it with other diagnostic tests WBC, ANC, ESR which will aid in fastening the discharge, avoid unnecessary admissions and unnecessary use of antibiotics.

METHODOLOGY

A descriptive study was done with 140 specimens obtained from febrile children between 1-36 months of age. This study was carried out from 2014 to 2015, in the department of paediatrics at a medical college and hospital. The study protocol was approved by the institutional ethics sub-committee (IRB) after which the study was initiated. Informed verbal consent was taken from the patient's parents / guardian before including into the study.

Children aged 1-36 months presenting with fever for more than Fever more than 12 hours up to 7 days without obvious focus of infection on clinical examination were screened for temperature >39°C and who satisfied inclusion criteria were included in the study. Temperatures were recorded either in the axillary or rectal areas. Children who have received prior antibiotics and vaccines, children with underlying immunological disease are excluded from the study. Blood samples were taken for total WBC count, ANC, ESR and CRP and for blood culture. Blood cultured in various media incubated overnight and colony morphology was read. Urine analysis, urine culture, colony count, chest radiograph were done. CSF analysis was done for selected cases. CRP was done by slide agglutination method. Qualitative CRP followed by Semi-quantitative CRP was performed.

RESULTS

Total numbers of children aged 1-36 months studied were 140 of which, children with serious bacterial infection are 40, and children without serious bacterial infection are 100. All children under went thorough clinical examination, were all subjected to CRP, Total WBC count, ESR, ANC and other investigations as appropriate. These children were divided into SBI and no SBI. The results analyzed using simple statistical proportions. Sensitivity, Specificity, Positive predictive value and Negative predictive value for all tests were compared with gold standards.

WBC ≥15000 was observed in 15 cases of children who had SBI giving rise to sensitivity of 30%, 89 children who did not have SBI have WBC <15000 giving a specificity of 89%. Among 26 cases with WBC >15000 only 15 (58%) cases had SBI giving PPV of 58%.Among 114 cases of WBC <15000 89 (78.1%) cases did not have SBI giving a NPV of 78%.

ESR ≥ 15mm was observed in 22 cases who had SBI giving rise to sensitivity of 55%, 83 children who did not have SBI have ESR <15mm giving a specificity of 83%. Among 39 cases, ESR > 15mm, only 22 cases had SBI giving PPV of 56%. Among 101 cases, 83 were ESR<15mm did not have SBI giving NPV of 82%

ANC ≥10000 was observed in 15 cases who had SBI giving rise to sensitivity of 38%, 93 children who did not have SBI have ANC <10000 giving a specificity of 93%. Among 22 cases ANC > 10000 only 22 cases had SBI giving PPV of 68%.Among 118 cases of ANC <10000, 93cases did not have SBI giving a NPV of 78% .

CRP ≥ 6mg/dl was observed in 31cases of children who had SBI giving rise to sensitivity of 78%, 89 children who did

not have SBI have CRP <6mg/dl giving a specificity of 89%. Among 42cases with CRP more than 6mg/dl only 31 cases had SBI giving PPV of 74%.Among 98 cases of CRP <6mg/dl 89 cases did not have SBI giving a NPV of 91%.

Using CRP and WBC combination, compared to WBC alone as a predictive test, sensitivity increased to 57%, specificity increased to 97%, PPV increased to 86% and NPV increased to 91%. CRP and ANC combination, when used than isolated ANC for predicting, SBI sensitivity is increased to 57% but little less than isolated CRP. Specificity increased to 98%, PPV increased to100% and NPV increased to 92%. WBC and ANC combination, when used the sensitivity, specificity, 38 PPV, NPV remained to be the same. When CRP & WBC & ANC combination was used sensitivity remained to be same as that of CRP and WBC, CRP and ANC .The specificity increased to 98%, PPV increased to 100% and NPV increased to 92%. The results were shown in Table 1 Predictors of SBI.

Table 1: Predictors of SBI

	Sensitivity (95% C.I.)	Specificity (95% C.I.)	PPV (95% C.I.)	NPV (95% C.I.)	Likelihood Ratio (95% C.I)
WBC	30 (12.3, 48.8)	89 (78.9, 97.4)	58 (19.7, 69.5)	78 (70.4,95.7)	2.9 (0.8, 4.9)
ESR	55 (3.3, 58.8)	83 (10.3, 86.8)	56 (8.6, 61.4)	82 (75.1, 96.5)	3.3 (1.3, 5.8)
ANC	38 (16, 48.6)	93 (89.3, 97.6)	68 (33.6, 78.8)	78 (72.4, 92.4)	4.1 (1.6, 12.2)
CRP	78 (60.8, 93.5)	89 (81.1, 99.2)	74 (64.7, 94.6)	91 (81.8, 99.7)	9.6 (4.7, 24.1)
CRP &WBC	57 (59.4, 89.7)	97 (94.8, 100.0)	86 (63.1, 100.0)	91 (88.9,98.9)	48.4 (15.6, 64.4)
CRP & ANC	57 (49.4, 89.7)	98 (92.5, 100.0)	100 (93.3, 100.0)	92 (88.9, 98.9)	-
WBC & ANC	34 (16.3, 45.8)	94 (89.6, 100.0)	68 (56.3, 71.0)	78 (68.5, 91.9)	4.8 (1.6, 21.7)
CRP & WBC & ANC	58 (49.4, 89.7)	98 (92.5, 100.0)	100 (93.3, 100.0)	92 (88.9, 98.9)	-

When fever was more 24 hours duration CRP was positive in 28 (20%) cases when compared to 112 cases (80%) across CRP negative. However duration of fever is insignificant p value is 0.89. The results were shown in Table 2 Comparison of characteristics of CRP Positive and Negative. Among age more than 12 months 29 (31.18%) cases were CRP positive, when compared to 64 (68.81%) across CRP negative. p value is insignificant. (0.45) as shown in table 2 and table 3.

Table 2 Comparison of characteristics of CRP Positive and Negative

Duration of fever	CRP Positive (%)	CRP Negative (%)	Total	P value
≤ 24 hours	2(28.57)	5(71.4)	7	0.89
24-72 hours	22(19)	94(81)	116	
≥72hours	4(23.5)	13(76.5)	17	
Total	28(20)	112(80)	140	

Table 3: Comparison of CRP Positive and Negative in higher age group

S.No.	Age - months	CRP		Total	P value
		Positive n (%)	Negative n (%)		
1	1-12	11(23.4)	36(76.59)	47	0.45
2	13-24	16(24.61)	49(75.38)	65	
3	26-36	13(46.4)	15(53.5)	28	
Total		40	100	140	

Based on the ROC curve, cut off point is fixed for each variable. For WBC the cut off is 12.4 thousands per cu mm. At this cut off point sensitivity increased to two fold (58%). The cut off point for ANC is 6.2thousands per cu mm. The sensitivity

goes up by two and a half fold. Cut off point for ESR is 12.4 mm and CRP is 4.9 mg /dl. The cut offs for each variable, along with p value, Sensitivity, Specificity, PPV, NPV. Likelihood ratios are shown in the table 4.

To further explore the diagnostic utility of CRP concentration, multilevel likelihood ratios were calculated for a range of CRP concentration. A CRP concentration of ≤ 5mg/dl had a likelihood ratio of SBI of 0.39 corresponding to a NPV of 93%. A CRP concentration of > 15 mg/dl had a likelihood ratio of SBI 16.75, corresponding to PPV of 75% and shown in Table 5.

Table 4: Predictors of SBI (based on ROC curve)

	Cut off *Point*	Sensitivity (95% C.I.)	Specificity (95% C.I.)	Likelihood Ratio (95% C.I.)	PPV (95% C.I.)	NPV (95% C.I.)
WBC	12.4	58 (40.1,.80.4)	64.7 52.9,69.1)	1.9 (23.6,39.4)	29 (19.4, 38.4)	87 (78.1,90,12)
ESR	12.4	74 (580.1, 80.4)	64.7 52.9,69.1)	1.9 (23.6,39.4	29 (19.4, 38.4)	87 78.1,90,12
ANC	6.2	58 (40.1,.80.4)	64.7 52.9,69.1)	1.9 (23.6,39.4	29 (19.4, 38.4)	87 78.1,90,12
CRP	4.9	88 (40.1,.80.4)	64.7 52.9,69.1)	1.9 (23.6,39.4	29 (19.4, 38.4)	87 78.1,90,12

Table 5: Multilevel Likelihood Ratios for CRP Concentration

CRP concentration	SBI	No SBI	Likelihood Ratio (95% C.I.)	Post test probability of SBI
>15	6	3	16.75 (1.4,140.89)	84
10-15	17	5	11.35 (4.89, 40,78)	72.4
6-10	9	13	7.8 (2.37, 21.84)	63.75
<6	8	79	0.39 (0.14,0.79)	4.8
Total	**40**	**100**		

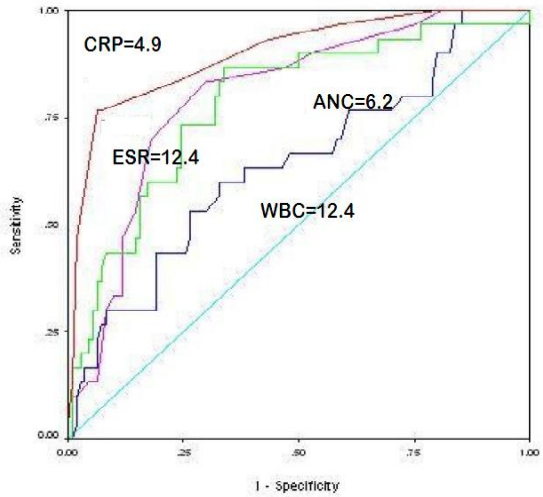

Fig 1. ROC for variables associated with SBI. Area under the curve for CRP 0.798 (95% CI: 0.672, 0.984); for ESR 0.701 (95% CI: 0.423,0.575); for ANC 0.483 (95% CI: 0.868, 0.179); and for WBC 0.819 (95%CI: 0.223, 0.355).

Statistical analysis

Patients with and without SBI were compared using the 2-tailed t test or Mann-Whitney U test or variables expressed as mean values according to their parametric distribution. $\chi 2$ analysis was used to access the association between variables expressed as percentages and SBI. The variables that gave the best fit was included in the final mode. ROC curve was done to determine the best cut off point for predictor of SBI. The cut-off was obtained from the value that maximized the sensitivity and specificity. For each variable, patients were dichotomized into 2groups based on the cut off value. Sensitivity, specificity, likelihood ratio, positive predictive value and negative predictive value of each of the predictors of SBI were determined at the cut off points. Multilevel likelihood ratios for CRP were determined. Statistical analyses were performed using the SPSS statistical software package, version 11.0 for Windows (SPSS, Inc, Chicago, IL). Statistical significance was determined at 5%.

DISCUSSION

Fever in children is one of the most common presenting complaints to emergency departments and pediatricians. Although their fever, distinguishing the

child with a serious bacterial infection (SBI), such as bacteremia, urinary tract infection, meningitis, and pneumonia is important and can be difficult. [21] All febrile children under 3 years old who have toxic manifestations should be admitted to hospital, be fully investigated for sepsis and meningitis, and receive antimicrobial treatment. [13]

Treatment and management of febrile young children without apparent source of infection is essential. A test with adequate sensitivity and specificity to distinguish what type of children are at risk for bacterial infection is very much essential. Occult bacteremia, urinary tract infection and pneumonia are considered as serious bacterial infection in children (SBI). [21, 22]

Among 140 cases included in the study, 40 cases were CRP positive, among them 29 cases of SBI were identified. 9 cases were occult bacteremia (both CRP and blood culture positive), 4 cases of S. *pneumoniae*, 4 cases of *H. influenzae* and 1 case of *Klebsiella* were isolated. 6 cases of urinary tract infection were identified (both CRP and urine culture positive) 1 case of *Klebsiella*, 4 cases of *E. coli*, 1 case of *H.influenzae* were found in this study. 11 cases were diagnosed as pneumonia (both CRP and chest x ray positive). Incidence of occult bacteremia found is 26.82%.

CRP has been evaluated as predictors of bacterial illness in febrile children. CRP was found to be having a sensitivity of 77 %, specificity of 89% PPV of 74%, NPV of 91% and likelihood ratio of 9.6% in the present study.

In the present study WBC has a sensitivity of 30% and specificity of 89% Although the total WBC is less sensitive and specific, because of the low incidence of occult bacteremia, the test has a NPV 78%, PPV of 58% and likely hood ratio 2.9% In this study, 11 children with WBC more than or equal to 15,000 did not have occult bacteremia. Using a level of more than or equal to 15,000 did not significantly differentiate between children with SBI and Non SBI.

ANC is another test done for predicting bacterial illness. [23, 24] Using ANC as a screening test it has a sensitivity of 30% and specificity of 93%, NPV of 78%, PPV of 68% and likelihood ratio of 4.1%. Based on our observation it is slightly better than Total WBC. Recent studies concluded that ANC is a better test for detecting pneumococcal bacteremia than WBC, with approximate cut off value of 10^9 cells/L. [25]

Erythrocyte sedimentation rate has been evaluated as predictors of bacterial illness in febrile children. Our observation was that it has a sensitivity of 55 %, specificity of 83%, NPV of 82%, PPV of 56% and likelihood ratio of 3.3%. Based on these results we consider ESR is better than WBC. CRP & WBC combination when used as predictive test, sensitivity increases from 30% to 57%, specificity increases from 88% to 97%, PPV increased to 86%, PPV increased to 91% and likelihood ratio of 48.4%. CRP & ANC combination when used as predictive test, sensitivity increases from 38% to 57%, increases specificity from 93% to 98%, PPV increased to 100%, NPV increased to 92%. WBC and ANC combination is found to have increased specificity however; combination of tests is more useful than isolated test except for CRP alone. As screening test CRP and ANC combination is better than isolated ANC and as a specific test CRP & WBC & ANC combination is more useful.

Receiver operating characteristic curves (ROC) for CRP, ESR, ANC, and WBC were constructed. Based on the curve, cut off values for each variable was determined that simultaneously maximizes the sensitivity and specificity. For each variable, patients were dichotomized into 2 groups based on the cut off value and x^2 analysis was done to assess the association between the dichotomized variables and the presence of SBI. Multilevel likelihood ratios and CRP concentration were calculated.

Cut off value fixed at 4.9 mg for CRP, sensitivity increases from 77% to 88%. For WBC cut off fixed at 12.4 cells per cu mm, which increases sensitivity from 38 % to 58%. ANC has a cutoff point fixed at 6.2 cells/cu mm which increases sensitivity from 55% to 74%. ESR has a cutoff point 12.4 mm which increases sensitivity from 55% to 74%.

Multilevel likelihood ratios and CRP conc. were calculated. A CRP concentration of ≤ 6mg/dl had a likelihood ratio of SBI of 0.39 corresponding to a NPV of 94%. A CRP of > 15 mg/dl had a likelihood ratio of SBI 16.75, corresponding to PPV of 84%. Likelihood Ratios are a powerful clinical tool because a clinician may estimate pre test probability of the presence of disease in particular patients.

This study demonstrates CRP is both more sensitive and specific in distinguishing children with occult serious bacterial infection from those without bacterial illness. Based on curve results, CRP of > 4.9 mg% maximizes the sensitivity. A CRP concentration > 6mg/dl is helpful rather than total WBC of more than or equal to 15,000. [21,26] CRP is dependent on the duration of fever, [27] suggesting that CRP is more reliable as an indicator of bacterial infection if fever has been present for >24 hours. [28, 29] However significant numbers of cases were also negative for CRP in this study.

CRP is one of the early markers for sepsis. [29,30] *S. pneumoniae* is now the predominant cause of occult bacteremia. [10,11,31] The use of conjugate pneumococcal vaccine decreases the risk of occult bacteremia. However, the vaccine is only 90% effective in preventing invasive disease; therefore, even vaccinated children will be at risk of invasive pneumococcal disease. [32] For *H.influenzae* effective vaccine is also available. But it comes under optional vaccine list; in countries like India still many children remain unvaccinated with optional vaccines.

In the clinical setting of febrile young child with no apparent source of fever, the child is at risk for serious bacterial infection in addition to invasive pneumococcal disease. [33] there will remain a need for a rapid screening test for serious bacterial infection even after the use of conjugate pneumococcal vaccine and HiB vaccine.

Urinary tract infection remains common occult bacterial infection confirmed by culture and colony count. The results of urine culture are delayed by 24 to 48 hours. Similarly, the diagnosis of occult bacteremia by blood culture is delayed by a mean of 15 to 16 hours and up to 48 hours. [34] Blood cultures are positive in 3 to 5% of febrile young children with pneumonia. Children who received a chest radiograph, true prevalence remains unclear. [35] More over it is very difficult to differentiate viral from bacterial pneumonias based on the chest radiograph alone.

CRP concentration measured from blood is a readily available [27] inexpensive test. With recent availability of rapid CRP tests we can readily use in emergency settings. [19, 27] CRP may become valuable diagnostic tool in the initial evaluation of febrile young children for occult serious bacterial infection and determine which children need additional diagnostic tests and antibiotic therapy. Our current study reveals that CRP along with WBC count concentration is better than other tests in predicting serious bacterial infection in febrile young children.

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