



ORIGINAL RESEARCH PAPER

Pediatrics

Role of C reactive protein in occult paediatric bacterial infection

KEY WORDS: C-reactive protein. Occult paediatric bacterial infection.

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ABSTRACT

Objectives: To determine The usefulness of C-Reactive protein in clinically undetectable serious bacterial infection in febrile children 1-36 months of age.. Comparison of C-Reactive protein with total white blood cell count and absolute neutrophil count in predicting occult serious bacterial infection.
Materials and methods : Study Design : Descriptive Study. Study Place : Institute of Child Health and Hospital for Children, Egmore, Chennai. Study Period : October 2007 to September 2008. Inclusion Criteria a) Children aged 1-36 months. b) Fever more than 12 hrs up to 7 days .c) Without obvious focus of infection on clinical examination. Sample Size : 140. Exclusion Criteria: Children who have received prior antibiotics and vaccines and children with underlying immunological disease.
Results. Total no of children studied – 140.Children with serious bacterial infection- 30. Children without serious bacterial infection- 110. All were subjected to sepsis screening tests like CRP, total White Blood Cell count, ESR, absolute neutrophil count and other investigations as appropriate. These children were divided into SBI and no SBI. The clinical features and laboratory results of babies with SBI and non SBI were then studied. If duration of fever is more than 24 hours more CRP positive cases seen . If Age less than 12 months more CRP positive cases seen . Temperature between 38.5 to 40 more CRP positive cases seen . 9 Cases of CRP positive associated with WBC more than 15,000. **Conclusion:** CRP concentration measured from blood, results readily available the test is inexpensive .With recent availability of rapid CRP tests we can readily use in emergency settings. 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

Background:

C Reactive Protein is an acute phase reactant. Other acute phase reactants include serum ceruloplasmin, alpha1 antitrypsin, haptoglobin, procalcitonin etc. Measurement of C-reactive protein, an acute phase protein synthesised by hepatocytes is valuable measure in distinguishing systemic bacterial and viral in both immunocompetent and immunodeficient hosts.¹ After the onset of inflammation or acute tissue injury, CRP synthesis increases within 4 to 6 hours ,doubling every 8 hours thereafter, peaks by 36 hours after the onset of inflammation. The kinetics of CRP metabolism seem to closely parallel the degree of injury and repair, there by supporting its value as an acute measure of disease activity. CRP estimation is simple and rapid test and does not require expertise. It is less expensive and results will be available within short time. It is normally present in trace amounts in blood of healthy individual. Its level increases within hours of acute injury or onset of inflammation and reaches peak within 24 to 48hours.In serum it is found in association with very low density lipoproteins. Its activity resembles those of an antibiotic .CRP is elevated in all bacterial infections in acute stages The relationship between acute infectious disease and WBC, absolute neutrophil count (ANC) and band neutrophils has been recognized for many years. ANC more accurate than total WBC in predicting bacteremia.² More than 10,000 cell /cumm indicates sepsis. Bacterial sepsis may be one of the cause for neutropaenia less than 1500 cells /cumm. CRP has high positive predictive value, negative predictive value ,sensitivity and specificity We sought to prospectively study the diagnostic properties of quantitative CRP in comparison with other clinical and laboratory predictors of occult SBI. **OBJECTIVES:** i. To determine ii.The usefulness of C-Reactive protein in clinically undetectable serious bacterial infection in febrile children 1-36 months of age. Iii.Usefulness of semi-quantitative C-Reactive protein in diagnosing serious bacterial infection. iv.Comparison of C-Reactive protein with total white blood cell count and absolute neutrophil count in predicting occult serious bacterial infection. **MATERIALS AND METHODS :** Study Design : Descriptive Study Evaluation Of A Diagnostic Test. Study Place :Institute of Child Health and Hospital for Children, Egmore, Chennai. Outpatient and Inpatient Departments/Wards. Study Period : October 2007 toSeptember 2008. Inclusion Criteria a) Children aged 1-36 months.b) Fever more than 12 hrs up to 7 days .c) Without obvious focus of infection on clinical examination. Sample Size : 140.Exclusion Criteria)Children who have received prior antibiotics

and vaccines. B. Children with underlying immunological disease. Febrile children presenting to outpatient department and inpatient department with ages 1-36 months are screened for temperature >39.5C rectal temperature more than 39.5C or axillary temperature more than 38.5C.Fever up to 7 days are subjected to enrolled in the study. Informed consent is obtained from parents or guardian & clearance of Institutional Ethical Committee Review Board. Patients are reviewed thereafter at 3rd, 7th and 10th day. Blood samples are taken for total WBC count, ANC and CRP and at the same time samples for blood culture and urine analysis, urine culture and Chest X-Ray (CXR) are done. Qualitative method: CRP done by slide agglutination method. Semi quantitative CRP-Agglutination in highest serum dilution will corresponds to amount of CRP in mg/dl. **RESULTS:** Total no of children studied – 140.Children with serious bacterial infection- 30.Children without serious bacterial infection- 110. **OBSERVATIONS:** 140 children aged 1-36 months were enrolled in the study. All children under went thorough clinical examination. They were all subjected to sepsis screening tests like CRP, total White Blood Cell count, ESR, absolute neutrophil count and other investigations as appropriate. These children were divided into SBI and no SBI. The clinical features and laboratory results of babies with SBI and non SBI were then studied. If duration of fever is more than 24 hours CRP becomes more positive. If Age less than 12 months more CRP positive. Temperature between 38.5 to 40 more CRP positive cases. 9 Cases of CRP positive associated with WB Cmorethan 15,000.

Characteristic	O.R.	95% C.I.	p-value	DURATION OF FEVER	CRP + cases	AGE IN MONTHS	NO. CRP POSITIVE CASES
ANC >10000 <=10000	5.3 1.0	1.0 , 26.5 Reference	0.04	□ 24 HOURS	2	1-12	12
CRP Positive Negative	43.7 1.0	13.5 , 141.5 Reference	0.00	24-72 HOURS	24	13-24	8
				□ 72HOURS	5	25-36	10

No of Culture Positive Cases	Median CRP Concentration In Mg/Dl
Blood Culture-9	12
Urine Culture-6	12
Xray –Pneumonia-11	12

	Sensitivity (95% C.I.)	Specificity (95% C.I.)	Likelihood Ratio (95% C.I.)	PPV (95% C.I.)	NPV (95% C.I.)	TEMPERATURE	NO. CRP POSITIVE CASES
WBC	30 (14.6, 46.4)	88 (82.2, 94.2)	2.5 (1.2, 5.4)	41 (20.4, 61.5)	82 (75.3, 89.1)	38.5-39	15
ESR	53 (4.2, 35.5)	85 (3.0, 78.9)	3.7 (2.1, 6.4)	50 (3.3, 67.3)	87 (80.7, 93.4)	39.1-40	13
ANC	30 (13.6, 46.4)	95 (90.3, 98.8)	5.5 (2.1, 14.0)	60 (35.2, 84.8)	83 (76.7, 89.8)	40	2
CRP	77 (61.5, 91.8)	94 (89.1, 98.2)	12.0 (5.7, 25.0)	77 (61.5, 91.8)	94 (89.1, 98.2)		

Characteristics	Patient with SBI (N=30)		Patient without SBI (N=110)		p-value
	n	%	n	%	
Age (in months), mean ± SD	18.5 ± 10.0		18.3 ± 9.4		0.94@
Sex					
Male	15	21.1	56	78.9	1.00#
Female	15	21.7	54	78.3	
Temperature, mean ± SD	39.3 ± 0.8		39.2 ± 0.7		0.19@
Duration of fever, median (range), h	48 (24, 120)		48 (24, 168)		0.47^
WBC (thousand/mm ³), mean ± SD	13.5 ± 5.1		10.9 ± 4.0		0.02@
WBC >15000	9	40.9	13	59.1	0.02#
WBC ≤15000	21	17.8	97	82.2	
ESR, median (range)	16 (7, 45)		9 (4, 60)		0.00^
ESR >15	16	50.0	16	50.087.	0.00#
ESR ≤15	14	13.0	94	0	
ANC (thousand/mm ³), mean ± SD	8.4 ± 4.1		4.9 ± 2.8		0.00@
ANC >10000	9	60.0	6	40.0	0.00#
ANC ≤10000	21	16.8	104	83.2	
CRP Positive	23	76.7	7	23.3	0.00#
CRP Negative	7	6.4	103	93.6	
Urine culture Positive	11	100.0	-	-	0.00#
Urine culture Negative	19	14.7	110	85.3	
Blood culture Positive	11	100.0	-	-	0.00#
Blood culture Negative	18	14.1	110	85.9	
X-ray Abnormal	12	100.0	-	-	0.00#
X-ray Normal	18	14.1	110	85.9	

Characteristics	CRP Positive (N=30)		CRP Negative (N=110)		p-value#
	n	%	n	%	
Age (months)					0.10
≤12	12	24.0	38	76.0	
13 – 24	8	13.6	51	86.4	
25 - 36	10	32.3	21	67.7	
Temperature					0.19
38.5 – 39.0	15	17.9	69	82.1	
39.1 – 40.0	13	31.0	29	69.0	
>40.0	2	14.3	12	85.7	
Duration of fever (hours)					0.70
≤24	1	11.1	8	88.9	
25 – 72	24	21.6	87	78.4	
>72	5	25.0	15	75.0	
WBC					0.02
>15000	9	40.9	13	59.1	
≤15000	21	17.8	97	82.2	
ESR					0.00
>15	16	50.0	16	50.0	
≤15	14	13.0	94	87.0	
ANC					0.004
>10000	8	53.3	7	46.7	
≤10000	22	17.6	103	82.4	
Urine culture					0.01
Positive	6	54.5	5	45.5	
Negative	24	18.6	105	81.4	
Blood culture					0.00
Positive	9	81.8	2	18.2	
Negative	21	16.3	108	83.7	
X-ray					0.00
Abnormal	11	91.7	1	8.3	
Normal	19	14.8	109	85.2	

S.NO	CRP CONC in mg /dl	TOTAL WBC incumm
1	12	17.9
2	24	24.3
3	12	13.9
4	6	8.6
5	12	17
6	6	14
7	12	11.5
8	12	18
9	24	9.6
10	12	7.2
11	24	13.8
12	6	7.4
13	12	11.2
14	6	22.2
15	12	9.6
16	48	21.9
17	6	18
18	6	7.4
19	12	12.8
20	6	13
21	12	20
22	6	7.9
23	6	13.9
24	6	15.3
25	6	11.5
26	24	14.1
27	6	8.5
28	6	12.4
29	6	14.6
30	12	10.5

Discussion:

CRP estimation is both sensitive and specific than WBC and ANC . CRP and ANC are significant predictor of occult serious bacterial infection. The management of febrile young children without apparent source of infection remains controversial, because there

has been no test available with adequate sensitivity and specificity required to distinguish which children are at risk for bacterial infection. Total WBC is the most commonly used laboratory test used in this clinical situation. As a screening test for occult bacteremia, the total WBC has sensitivity 80% and specificity of 69%.³In this study WBC has a sensitivity 30% and specificity 88%. Although the total WBC is less sensitive and somewhat specific, because of the low incidence of occult bacteremia, the test has a negative predictive value (NPV) 82% and positive predictive value (PPV) of 44%. In this study 66% of children with WBC more than or equal to 15,000 will not have occult bacteremia. Using a level of more than or equal to 15,000 did not significantly differ between children with SBI and Non SBI. Recent studies investigating the utility of WBC indices conclude that ANC is better test for detecting pneumococcal bacteremia than WBC, with an approximate cutoff value of 109 cells/L.³ ANC is used as a screening test for occult bacteremia. In this study ANC has sensitivity 30%, specificity 95%, NPV 83%, PPV 60% and likelihood 60%. Erythrocyte sedimentation rate has a sensitivity 53%, specificity 85%, NPV 87%, PPV 50% and likelihood ratio 3.7%. CRP has been evaluated as predictors of bacterial illness in febrile children. Recent prospective studies of febrile young children have found CRP to be a more sensitive and specific predictor of serious bacterial infection compared WBC. CRP also has been found valuable in the diagnosis bacterial meningitis. Although there are few tests available with 100% sensitivity, but they are too costly. This study demonstrates CRP is both more sensitive and specific in distinguishing children with occult serious bacterial infection from those without bacterial illness. Although CRP concentration of more than 6mg% that maximizes the sensitivity and specificity. It may not necessarily be the clinically most useful value. A CRP concentration more than 6mg/dl is helpful than total WBC of more than or equal to 15,000.⁴Our study has demonstrated CRP concentration dependent on the duration of fever, suggesting that CRP is more reliable as an indicator of bacterial infection if fever has been present for more than 12 hours. CRP is one of the early markers for sepsis. Latest studies show that other early markers available are procalcitonin, IL-6, TNF α or combination is more effective.^{5,6}In our study out of 140 cases observed 9 cases were both CRP & blood culture positive, 4 cases of *S. Pneumoniae*, 4 cases of *H. influenzae* and 1 case of *Klebsiella* were isolated. 6 cases were positive for both CRP and urine culture positive 1 case *Klebsiella*, 4 cases of *E. coli*, 1 case of *H. influenzae* were found in our study. 11 cases were chest x ray positive. *S. Pneumoniae* is now the predominant cause of occult bacteremia.³Limitation of our study was all children CRP was not quantified, 140 children population which is a minimum study group. In this study, CRP in predicting which children had occult serious bacterial infection but not limited to occult bacteremia...Urinary tract infection remains common occult bacterial infection confirmed by culture and colony count. The results of the urine culture are delayed by 24 to 48 hours. Similarly, the diagnosis of occult bacteremia by blood culture is delayed by mean 15 to 16 hours and up to 48 hours.^{7,8}

Conclusion:

Quantitative CRP concentration is a useful laboratory test in the evaluation of children less than 3 years who are at risk for occult bacteremia and serious bacterial infection. Semi-quantitative CRP is useful in predicting occult serious bacterial infection in children between 1 month to 36 months. CRP is considered to be a better predictive test than total white blood cell count and absolute neutrophil count. CRP determines a more selective strategy for children with SBI for additional diagnostic studies and antibiotic therapy.

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