Original Article

The Role of C Reactive Protein in Fever without Focus among Children Aged Between 1 – 3 Years

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Abstract

Background: The incidence of invasive pneumococcal disease in children has come down because of polysaccharide vaccine. The increased incidence of bacteremia among young children may be due to part of maturational immune deficiency in the production of opsonic Ig Ganti bodies to the polysaccharide antigens present on en capsulated bacteria. Fever is a common present in gsymp to min paediatric out patient practice and in children less 3 years of age. Approximately 20%to30% of the children may have no identifiable cause off ever after history and physical examination. **Subjects and Methods:** Children in the age group of 1-3 years presenting to the outpatient department 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. Informed consent was obtained from parents or guardian & clearance of Institutional Ethical Committee Review Board. Blood samples were taken for total WBC count, ANC, ESR and CRP and at the same time samples for blood culture. Blood cultured in various media incubated overnight and colony morphology was read. **Results:** CRP >6mg/d1 was observed in 25 cases of children who had SBI giving rise to sensitivity of 75.8%, 46 children who did not have SBI have CRP <6mg/d1 giving a specificity of 39.3%. Among 96 cases with CRP more than 6mg/d1 only 25 (26%) cases had SBI giving PPV of 26%. Among 54 cases of CRP <6mg/d1 46(85%) cases did not have SBI giving a NPV of 85.2%. **Conclusion:** CRP determines more selective strategy for children with SBI for additional diagnostic studies and appropriate antibiotic therapy.

Keywords: C reactive Protein, Fever, Children.

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Introduction

Fever without localizing sign sorsymptoms, usually of acute on set and present for less than one week. It is more common in children less than 36 months of age. Children with fever in whom cause could not be identified after 3 week of evaluation asan out patient or after 1 week of evaluation in hospital.[1]

Fever is a common manifestation of infectious diseases but is not predictive of severity. Many common viral and bacterial infections are-usually benign in normal hosts and respond well to appropriate anti microbial or supportive therapy. Other infections such assepsis, meningitis, pneumonia, osteoarticular infections, pyelonephritis, ifuntreated, may have significant morbidity ormortality. They are considered to be serious bacterial infections.

Most febrile episodes in a normal host can be diagnosed by a careful history and physical examination and require few if any laboratory tests. Febrile patients at increased risk for serious bacterial infections are neonates, infants less than three months children between 3 months to 36 months, children with hyperpyrexia 3 and immune-compromised patients. Approximately 30% off ebrile children between 1 yr to 3 years have no localizing sign sofinfection.[2]

The incidence of invasive pneumococcal disease in children has come down because of polysaccharide vaccine. The increased incidence of bacteremia among young children may be dueto part of maturational immune deficiency in the production of opsonic Ig Ganti bodies to the poly saccharide antigens present on encapsulated bacteria.[3]

Fever is a common presenting symptom min paediatric out patient practice and in children less 3 years of age. Approximately 20% to 30% of the children may have no identifiable cause off ever after history and physical examination.

Although most of these children will have a benign viral illness. Children less than 3 years of age area increased risk of clinically undetectableerious bacterial infection (SBI). The incidence of serious bacterial infection is roughly about 10-15%ofpreviously healthy children presenting with rectal temperature more than39°C. Approximately2-

3%of these children have Occult Bacteremia(OB) 2-8% have UTI depending on the age and gender. Other causes of serious bacterial infection include occult bacterial pneumoniain 3% of children less than 3 yrs, 5% will have other infections such as bone and joint infection, meningitis, soft tissue infection or bacterial enteritis. Although anti biotictreatment is necessary for children with serious bacterial infection it is also important to limit therapy in those children at greatest risk.[4]

Common etiological agents in less than 3 yrs: Group B Streptococci and List eriamonocytogens, Salmonella, E.coli, Neisseria etc. Fever is a controlled increase in body temperature over the normal values for an individual. Body temperature is regulated bythermo-sensitive neurons located in the pre opticoranteri or hypothalamus that respond to changes in blood temperature as well as to directneural connections with cold and warmreceptors located in sk in and muscle.[5]

Thermoregulatory responses include ere directing blood to or from cutaneous vascular beds, increased or decreased sweating, extra cellular fluid volume regulation(via Argininevaso press in) and behavioral responses, such as seeking awarmeror cooler environmental temperature. Normal body temperature also varies in a regular pattern each day. This circadian temperature rhythm, or diurnal variation, results in lowerbody temperature in early morning and temperatures approximately higher in the late afternoon and early evening.[6]

Subjects and Methods

Study Design: Descriptive Study Evaluation of a Diagnostic Test
Study Population: lyr to 3 yrs
Sample Size: 150 .
Inclusion Criteria:

- Children aged 1 yr to 3 yrs
- Fever more than 12 hours up to 7 days 1
- Without obvious focus of infection on clinical examination.
- Exclusion Criteria
- Children who have received prior antibiotics and vaccines.
- Children with underlying immunological disease.

Manoeuvre

Children in the age group of 1-3 years presenting to the outpatient department 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. Informed consent was obtained from parents or guardian & clearance of Institutional Ethical Committee Review Board. Blood samples were taken for total WBC count, ANC, ESR and CRP and at the same time samples 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. Patients were reviewed thereafter. CRP was done by slide agglutination method. Qualitative CRP followed by Semiquantitative CRP was performed. CRP-Agglutination in highest serum dilution corresponds to amount of CRP in mg/dl. The

findings were recorded in a prescribed data entry form (Annexure). CRP Estimation: It is based on the principle of agglutination. One drop of test specimen is placed on a slide after centrifugation using a disposable pipette to which a drop of CRP reagent is added. Both test specimen and the reagent to be uniformly mixed over the entire circle, using a mixing stick.

Results

CRP >6mg/d1 was observed in 25 cases of children who had SBI giving rise to sensitivity of 75.8%, 46 children who did not have SBI have CRP <6mg/d1 giving a specificity of 39.3%. Among 96 cases with CRP more than 6mg/d1 only 25 (26%) cases had SBI giving PPV of 26%. Among 54 cases of CRP <6mg/d1 46(85%) cases did not have SBI giving a NPV of 85.2%.

Table 1: Comparison of characteristics of CRP positive and negative

Duration of fever	CRP			P-value
	Total	Positive (%)	Negative (%)	
< 24 Hours	21	9	1²	0.0614
24 - 72 Hours	115	76	39	
> 72 Hours	14	11	3	
Total	150	96	54	

When fever was more 24 hours duration CRP was positive in 87(90.67%) cases when compared to 42 cases (77.7%) across CRP negative. However duration of fever is insignificant. p value is 0.0614

Table 1(ii): Comparison of characteristics of CRP positive and negative

Age Group	CRP			P value
	Total	Positive (%)	Negative (%)	
1-2 years	61	37	24	0.4799
2-3 years	89	59	30	
Total	150	96	54	

Among age more than 24 months 59 (61.5%) cases were CRP positive, when compared to 30 (55.5%) across CRP negative. p value is insignificant. (0.4799).

ROC for variables associated with SBI. Area under the curve for CRP 0.575 (95% CI: 0.468, 0.682); for ESR 0.555 (95% CI: 0.457, 0.660); for ANC 0.689 (95% CI: 0.581,0.796); and for WBC 0.911 (95% CI: 0.859, 0.962).

Table 2: Predictors of SBI (based on ROC curve)

	CUTOFF	Sensitive	Specificity	P red Value Positive	P red value Negative	Likelihood Ratio
WBC	13.4	81.8 (68.7, 95)	82.1 (75.1, 89)	56.3 (42.2, 70.3)	94.1 (89.6,98 7)	45.6 (30, 69.3)
ANC	19.3	63.8 (50.1, 77.6)	97.1 (93.8, 100.3)	90.9 (81.1, 100.7)	85.5 (79.1, 91.9)	219.1 (70.4, 682.2)
ECR	17.1	54.5 (37.6,	55.6 (46.6,64.6)	25.7 15.5,	81.3 (72.7,	12.3 (8.5, 17.8)

		71.5)		36)	89.8)	
CRP	6.9	75.8 (61.1, 90.4)	39.3 (30.5, 48.2)	26 17.3, 34.8)	85.2 (75.7, 94 7)	12.5 (9.8, 15.9)

Based on the ROC curve, cutoff point is fixed for each variable. For WBC the cutoff is 13.4 thousands per cu.mm. At this cutoff point sensitivity increased to (81.8%). The cutoff point for ANC is 19.3 thousands per cu.mm. The sensitivity goes up by two and a half fold. Cutoff point for ESR is 17.1 mm. The cutoffs for each variable, along with p value, Sensitivity, Specificity, PPV, NPV, Likelihood ratio.

Discussion

150 cases were included in the study. Out of 150 cases 96 cases were CRP positive, among them 25cases 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). CRP has been evaluated as predictors of bacterial illness in febrile children. CRP was found to be having a sensitivity of 75.8%, specificity of 39.3% PPV of 26%, NPV of 85% and likelihood ratio of 12.5% in the present study.

The sensitivity of the present study correlates with Issacman and Pullium study but specificity is slightly higher than the Issacman study. Inpullium study only 77 children were included, the sample size was small. In Issacman study sample size is higher than the present study. Probably the sample size would have altered the sensitivity. The likelihood ratio is also increased when compared to other studies. CRP was found to be a useful screening test for occult bacterial infection.[7]

Receiver operating characteristic curves (ROC) for CRP, ESR.ANC, WBC were constructed. Based on the curve, cutoff 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 cutoff value and c2 analysis was done to assess the association between the dichotomized variables and the presence of SBI. For WBC cutoff fixed at 13.4 cells per cu.mm, which increases sensitivity from 60.6 % to 81.8%. ANC has a cutoff point fixed at 19.3 cells/cu.mm which increases sensitivity from 33.3% to 63.8%. ESR has a cutoff point.[8]

Multilevel likelihood ratios and CRP concentration were calculated. A CRP concentration of < 5mg/d1 had a likelihood ratio of SBI of 0.25 corresponding to a NPV of 94%. A CRP concentration of >15 mg/di had a likelihood ratio of SBI 14.6, corresponding to PPV of 80%. Likelihood Ratios are a powerful clinical tool because a clinician may estimate the pretest probability of the presence of disease in a particular patients.

This study demonstrates CRP is both more sensitive and specific Indistinguishing children with occult serious bacterial infection from those without bacterial illness. Based on the curve CRP concentration of more than 4.5mg% that maximizes the sensitivity. A CRP concentration more than 6mg/dl is helpful rather than total WBC of more than or equal to 15,000.[9]

CRP concentration is dependent on the duration of fever suggesting that CRP is more reliable as an indicator of bacterial infectionif fever has been present for more than 24hours[10].However significant number of cases were also negative for CRP in this study.

predicting children with occult serious bacterial infection because when a febrile young child with no identifiable source of fever presents the clinician is faced with the dilemma for workup and antibiotic therapy.

The most useful test would predict children at risk of bacterial infection and therefore need workup and possible antibiotic therapy. 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. Blood culture are positive in 3 to 5% of febrile young children with pneumonia. Children who received a chest radiograph, true prevalence remains unclear. 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 inexpensive test. 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.

Conclusion

- Semiquantitative CRP is useful in predicting occult serious bacterial infection in children between 1 — 3 yrs.
- CRP is considered to be better predictive test than total white blood cell count and absolute neutrophil count.
- CRP and ANC or CRP, ANC &WBC combination is more useful than isolated CRP concentration.

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