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DIAGNOSTIC VALUE OF C - REACTIVE PROTEIN (CRP) BY SEMIQUANTITATIVE METHOD IN PREDICTING OCCULT SERIOUS BACTERIAL INFECTION IN FEBRILE CHILDREN BETWEEN 1-36 MONTHS OF AGE

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ABSTRACT

Background: 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 appropriateantimicrobial or supportive therapy.

Objective: To evaluate The diagnostic value of C - reactive protein (CRP) by semiquantitative method in predicting occult serious bacterial infection in febrile children between 1-36 months of age.

Methods: This descriptive study was conducted at Institute of Child Health and Hospital for Children,Egmore, Chennai. Outpatient and Inpatient Departments/Wards.

Results: WBC ≥15000 was observed in 9 cases of children who had SBI giving rise to sensitivity of 30%,97 children who did not have SBI have WBC <15000 giving a specificity of 88%. ESR ≥ 15mm was observed in16 cases of children who had SBI giving rise to sensitivity of 53%, 94 children who did not have SBI have ESR<15mm giving a specificity of 85%. ANC ≥10000 was observed in 9 cases of children who had SBI giving rise to sensitivity of 30%, 104 children who did not have SBI haveANC <10000 giving a specificity of 95%. CRP≥6mg/dl was observed in 23 cases of children who had SBI giving rise to sensitivity of 77%, 103 children who did not have SBI haveCRP<6mg/dl giving a specificity of 94%.

Conclusions: CRP is considered to be better predictive test than total white bloodcell count and absolute neutrophil count. CRP and ANC or CRP, ANC &WBC combination is more usefulthan isolated CRP concentration.

Keywords: C - reactive protein (CRP), Semiquantitative method, Occult serious bacterial infection, febrile children**.**

INTRODUCTION

Most febrile episodes in a normal host can be diagnosed by acareful history and physical examination and require few if any laboratory tests.[1] 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[2] and immunocompromised patients. Approximately 30% of febrile children between 3 months to 3 years have no localizing signs of infection.[1]

The incidence of invasive pneumococcal disease in children has come down because of polysaccharide vaccine. The increased incidenceof bacteremia among young children may be due to part of maturational immune deficiency in the production of opsonic IgG antibodies to the polysaccharide antigens present on encapsulated bacteria.

Fever is a common presenting symptom in paediatric outpatient practice and in children less 3 years of age. Approximately 20% to 30%of the children may have no identifiable cause of fever after history and physical examination.[3,4]

Although most of these children will have a benign viral illness, children less than 3 years of age are at increased risk of clinically undetectable serious bacterial infection (SBI). The incidence of serious bacterial infection is roughly about 10-15% of previously healthy children presenting with rectal temperature more than 39^0c. Approximately 2-3% of these children have Occult Bacteremia (OB)[,5,6,7]

Common etiological agents in less than 3 months: Group B Streptococci and Listeria monocytogens, Salmonella, E.coli, Neisseriaetc.

Fever is a controlled increase in body temperature over the normal values for an individual. Body temperature is regulated by thermo sensitive neurons located in the preoptic or anterior hypothalamus that respond to changes in blood temperature as well as to direct neural connections with cold and warm receptors located in skin and muscle.

Thermoregulatory responses include redirecting blood to or from cutaneous vascular beds, increased or decreased sweating, extra cellular fluid volume regulation (via Arginine vasopressin) and behavioural responses, such as seeking a warmer or cooler environmental temperature. Normal body temperature also varies in a regular pattern each day. This circadian temperature rhythm, or diurnal variation, results in lower body temperature in early morning and temperatures approximately 1^0C higher in the late afternoon and early evening.

MATERIALS AND METHODS

This descriptive study was conducted at Institute of Child Health and Hospital for Children, Egmore, Chennai. Outpatient and Inpatient Departments/Wards. Duration of study was October 2007 to September 2008.

Study Population: 1-36 months.

Sample Size: Total numbers of children studied were: 140.

Children with serious bacterial infection: 30 Children without serious bacterial infection: 110

Inclusion Criteria

a) Children aged 1-36 months

b) Fever more than 12 hours up to 7 days

c) Without obvious focus of infection on clinical examination.

Exclusion Criteria

a) Children who have received prior antibiotics and vaccines.

b) Children with underlying immunological disease.

MANOEUVRE:

Children in the age group of 1-36 months presenting to the outpatient department and in various wards of Institute of Child Health and Hospital for Children, Egmore, Chennai in the period between October 2007 to September 2008 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 takenfor 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 ina prescribed data entry form.

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. The slide is gently rocked to and fro and considered Negative if no agglutination occurs, if positive CRP concentration is more than 0.6 mg /dL.Dilution and semiquantiative test was done for all cases. S x D = mg/dl =Quantitative CRP was calculated for all cases.

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. χ^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. 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%.

RESULTS

140 children aged 1-36 months were enrolled in the study. All children under went thorough clinical examination. They were all subjected to 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 results were tabulated and analyzed using simple statistical proportions. Sensitivity, Specificity, Positive predictive value and Negative predictive value for alltests were compared with gold standards.

Table1: Various diagnostic tests among children with or without SBI

Test	SBI		
	Positive	**Negative**	
WBC≥15000	9	13	22
<15000	21	97	118
Total	30	110	140

WBC ≥15000 was observed in 9 cases of children who had SBI giving rise to sensitivity of 30%, 97 children who did not have SBI have WBC <15000 giving a specificity of 88%. Among 22cases with WBC more than 15000 only 9 (40.9%) cases had SBI giving PPV of 41%. Among 118 cases

of WBC <15000 97 (82.2%) cases did not have SBI giving a NPV of 82%.

Table 2: ESR and SBI

Test	SBI		Total
	Positive	Negative	
ESR≥15mm	16	16	32
<15mm	14	94	108
Total	30	110	140

ESR ≥ 15mm was observed in16 cases of children who had SBI giving rise to sensitivity of 53%, 94 children who did not have SBI have ESR<15mm giving a specificity of 85%. Among 32cases ESR more than 15mm only 16 (50%) cases had SBI giving PPV of 50%.Among 108 cases 94 (87%) of cases ESR<15mm did not have SBI giving a NPV of 87% .

Table 3: ANC and SBI

Test	SBI		Total
	Positive	Negative	
ANC≥10000	9	6	15
<10000	21	104	125
Total	30	110	140

ANC ≥10000 was observed in 9 cases of children who had SBI giving rise to sensitivity of 30%, 104 children who did not have SBI have ANC <10000 giving a specificity of 95%. Among 15 cases ANC more than 10000 only 9 (60%) cases had SBI giving PPV of 60%.Among 125 cases of ANC <10000 104(83%) cases did not have SBI giving a NPV of 83% .

Table 4: CRP and SBI

Test	SBI		Total
	Positive	Negative	
CRP≥6mg/dl	23	7	30

<6mg/dl	7	103	110
Total	30	110	140

CRP≥6mg/dl was observed in 23 cases of children who had SBI giving rise to sensitivity of 77%, 103 children who did not have SBI haveCRP<6mg/dl giving a specificity of 94%. Among 30cases with CRP more than 6mg/dl only 23 (76.7%)cases had SBI giving PPV of 77%.Among 110 cases of CRP <6mg/dl 103(93.6%) cases did not have SBI giving a NPV of 82%.

Using CRP and WBC combination when compared to WBC alone as a predictive test, sensitivity increased to 57%, specificity increased to 99%, PPV increased to 89% and NPV increased to 94%. 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 100%, PPV increased to 100% and NPV increased to 94%. WBC and ANC combination when used the sensitivity, specificity, 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 100%, PPV increased to 100% and NPV increased to 94%.

When fever was more 24 hours duration CRP was positive in 29(21%) cases when compared to 102 cases (73%) across CRP negative. However duration of fever is insignificant. p value is 0.7 Among age more than 12 months 18 (20%) cases were CRP positive, when compared to 72 (80%) across CRP negative. p value is insignificant. (0.1)

Based on the ROC curve, cutoff point is fixed for each variable. For WBC the cutoff is 11.3 thousands per cumm. At this cutoff point sensitivity increased to two fold (60%). The cutoff point for ANC is 5.7 thousands per cumm. The sensitivity goes up by two and a half fold. Cutoff point for ESR is 13mm and CRP is 4.5mg /dl. The cutoffs for each variable, along with p value, Sensitivity, Specificity, PPV, NPV, Likelihood ratio.

To further explore the diagnostic utility of CRP concentration, multilevel likelihood ratios were calculated for a range of CRPconcentration shown in table 8.A CRP concentration of ≤ 5mg/dl had a likelihood ratio of SBI of 0.25 corresponding to a NPV of 94%. A CRP concentration of > 15 mg/dl had a likelihood ratio of SBI 14.6, corresponding to PPV of 80%

DISCUSSION

The management of febrile young children without apparent source of infection remains controversial, we need a test with adequate sensitivity and specificity to distinguish what type of

children are at risk for bacterial infection. Occult bacteremia, urinary tract infection and pneumonia are considered as serious bacterial infection in children (SBI).

Because majority of febrile young children do not have SBI, laboratory tests and expectant antibiotic therapy of these children adds to cost, time, discomfort, parental anxiety and may contribute to antibiotic resistance.

Recent prospective studies of febrile young children have found CRP to be a more sensitive and specific predictor of serious bacterial infection compared to WBC counts[8].

C reactive protein is a classic acute phase reactant. It is a serum protein which is synthesized in the liver. CRP levels are increased in the serum as a result of infection and inflammation. CRP estimation is a rapid diagnostic test. As CRP is easily available, less expensive, less time consuming and a better laboratory test in delineating children with and without SBI[9,10] this study was conducted. The diagnostic utility of semiquantitative CRP is evaluated in this study. 140 cases were included in the study. Out of 140 cases 30 cases were CRP positive, among them 23cases 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).The incidence of occult bacteremia found in this study is 16%.

CRP has been evaluated as predictors of bacterial illness in febrile children. CRP was found to be having a sensitivity of 77 %, specificity of94% PPV of 77%, NPV of 94% and likelihood ratio of 12% in the presentstudy.

The sensitivity of the present study correlates with Issacman and Pullium study but specificity is slightly higher than the Issacman study. In pullium 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.

Total WBC is the most commonly used laboratory test used in this clinical situation. It is one of the screening test for occult bacteremia. In the present study WBC has a sensitivity of 30% and specificity of 88% .Although the total WBC is less sensitive and specific, because of the low incidence of occult bacteremia, the test has a negative predictive value (NPV) 82% , positive predictive value (PPV) of 44% and likely hood ratio 2.5% In this study 13 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[11,12.]Using ANC as a screening test it has a sensitivity of 30% and specificity of 90%, NPV of 83%, PPV of 60% and likelihood ratio of 8.5%. 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 a approximate cutoff value of 10^9 cells/L.[10,13]

Erythrocyte sedimentation rate has been evaluated as predictors of bacterial illness in febrile children. Our observation was that it has a sensitivity of 53 %, specificity of 85%, NPV of 87%, PPV of 50% and likelihood ratio of 3.7%. Based on this results we consider ESR is better than WBC.

When CRP &WBC combination is used as a predictive test sensitivity increases from 30% to 57%, specificity increases from 88% to 99%, Positive predictive value increased to 89%, Negative predictive value increased to 94%and likelihood ratio of 52.6% when compared to WBC alone. When CRP &ANC combination is used as predictive test sensitivity increases from 30% to 57%, increases specificity from 95% to 100%, increases Positive predictive value from 60% to 100%, increases Negative predictive value from 85% to 94%when compared to ANC alone as predictive test .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, 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 2groups based on the cutoff value and $\square^2$ analysis was done to assess the association between the dichotomized variables and the presence of SBI. Multilevel likelihood ratios and CRP concentration were calculated. Cutoff value fixed at 4.5mg for CRP, sensitivity increases from 77% to 83%. For WBC cutoff fixed at 11.3 cells per cumm, which increases sensitivity from 30 % to 60%. ANC has a cutoff point fixed at 5.7 cells/cumm which increases sensitivity from 30% to73.3%. ESR has a cutoff point 13mm which increases sensitivity from 5 3% to 70%.

Multilevel likelihood ratios and CRP concentration were calculated. A CRP concentration of ≤ 5mg/dl had a likelihood ratio of SBI of 0.25 corresponding to aNPV of 94%. A CRP concentration of > 15 mg/dl had a likelihood ratio of SBI 14.6, corresponding to PPV of 80%. Likelihood Ratios are a powerful clinical toolbecause 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 in distinguishing 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.[2,1]

CRP concentration is dependent on the duration of fever [14], suggesting that CRP is more reliable as an indicator of bacterial infectionif fever has been present for more than 24hours[8,15].
However significantnumber of cases were also negative for CRP in this study.

CRP is one of the early marker for sepsis[16]. S. Pneumonia is now the predominant cause of occult bacteremia.[3,6] 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.[17] 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 inaddition to invasive pneumococcal disease.[19] 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.

CONCLUSION

Semiquantitative CRP is useful in predicting occult seriousbacteria infection in children between 1 month to 36 months. CRP is considered to be better predictive test than total white bloodcell count and absolute neutrophil count. CRP and ANC or CRP, ANC &WBC combination is more useful than isolated CRP concentration. CRP determines more selective strategy for children with SBI foradditional diagnostic studies and appropriate antibiotic therapy

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