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Original Research

Assessment of the semiquantitative diagnostic use of C-reactive protein (CRP) in identifying concealed severe bacterial infections in children

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ABSTRACT:

Background: Although fever is often seen in infectious disorders, it is not a reliable indicator of their severity. In healthy individual, a large number of common bacterial and viral illnesses are often benign and respond well to supportive or suitable antibiotic treatment. **Objective:** To assess the semiquantitative diagnostic use of C-reactive protein (CRP) in identifying concealed severe bacterial infections in children with fevers aged 1–36 months. **Methods**: 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. **Results:** 14 children with SBI had ANC ≥10000, resulting in a 31.3% sensitivity; 109 children without SBI had ANC <10000, resulting in a 96.4% specificity. Only nine (61%) of the fifteen patients with ANC greater than 10,000 developed SBI, resulting in a 61.2% PPV. Of the 135 ANC <10000 instances, 109 (84.6%) lacked SBI, resulting in an 84.7% NPV. **Conclusions:** Compared to absolute neutrophil count and total white blood cell count, CRP is thought to be a more accurate prognostic test. The combination of CRP and ANC or CRP, ANC, and WBC is more beneficial than the concentration of CRP alone.

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

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INTRODUCTION

Few, if any, laboratory tests are needed to diagnosis the majority of febrile episodes in a healthy host after a thorough history and physical examination. [1] Neonates, babies less than three months, children aged three to thirty-six months, children with hyperpyrexia,[2] and patients with impaired immune systems are at heightened risk for developing severe bacterial infections. Thirty percent of children aged three months to three years who have a fever do not exhibit any localized symptoms of illness.[1] The polysaccharide vaccination has reduced the prevalence of invasive pneumococcal illness in children. A maturational immunological deficit in the development of opsonic IgG antibodies against the polysaccharide antigens found on encapsulated bacteria may contribute to the higher prevalence of bacteremia in young children. In pediatric outpatient practice, fever is a frequent presenting symptom in children under the age of three. After a history and physical examination, 20% to 30% of the youngsters may have a fever with no apparent explanation.[3, 4] Children under the age of three are more likely to have a clinically undetected severe bacterial infection (SBI), even though the majority of these kids will just have a benign viral sickness. About 10% to 15% of youngsters who were previously healthy but now have a rectal fever higher than 390 degrees Celsius have a dangerous bacterial illness. Two to three percent of these kids develop occult bacteremia (OB),[5,6,7] In less than three months, common etiological agents include Salmonella, E. Coli, Neisseria, Group B Streptococci, and Listeria monocytogens. A regulated rise in body temperature over an individual's typical range is called a fever.[8] The preoptic or anterior hypothalamus contains thermosensitive neurons that control body temperature in response to variations in blood temperature and by establishing neuronal connections with cold and warm sensors in muscle and skin. Redirecting blood to or from cutaneous vascular beds,

sweating more or less, controlling the amount of extracellular fluid (via arginine vasopressin), and behavioral reactions like pursuing a warmer or colder ambient temperature are examples of thermoregulatory responses.[9] A normal body temperature also fluctuates daily according to a predictable schedule. This diurnal oscillation, also known as the circadian temperature rhythm, causes the body temperature to drop in the early morning and rise by around 10 degrees Celsius in the late afternoon and early evening.

MATERIALS AND METHODS

In patient and outpatient wards and departments. Duration of study was January 2010 to December 2012.

Study Population: 1-36 months.

Sample Size: Total numbers of children studied were: 160.
Children with serious bacterial infection: 30 Children without serious bacterial infection: 130

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 Hospital 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

The 2-tailed t test, Mann-Whitney U test, or variables represented as mean values based on their parametric distribution were used to compare patients with and without SBI. The relationship between factors represented as percentages and SBI was examined using $\chi 2$ analysis. The final mode comprised the factors that provided the greatest match. The statistical software program SPSS, version 11.0 for Windows (SPSS, Inc., Chicago, IL), was used to conduct the statistical analyses. At 5%, statistical significance was established.

RESULTS

The research included 160 children between the ages of 1 and 36 months. Every youngster had a comprehensive clinical evaluation. All of them had screening tests, including CRP, ESR, total white blood cell count, and absolute neutrophil count, along with further testing as needed. These kids were split up into SBI and non-SBI groups. Simple statistical proportions were used to assess and tabulate the data. All test results were compared to gold standards for sensitivity, specificity, positive predictive value, and negative predictive value.

Table1: Various diagnostic tests among children with or without SBI

Test	SBI		
	Positive	Negative	
WBC≥15000	14	18	32
<15000	27	102	128
Total	40	120	160

Nine children with SBI had WBC ≥15000, resulting in a 31% sensitivity; 102 children without SBI had WBC <15000, resulting in an 89% specificity. Only 14 (40.9%) of the 27 patients with WBC more than 15000 developed SBI, resulting in a 42% PPV. Of the 128 WBC <15000 instances, 102 (83.1%) lacked SBI, resulting in an 83% NPV.

Table 2: ESR and SBI

Test	SBI		Total
	Positive	Negative	
ESR≥15mm	21	21	42
<15mm	19	99	118
Total	40	120	160

ESR > 15mm was found in 21 instances of children with SBI, resulting in a 54% sensitivity; 99 children without SBI had an ESR <15mm, resulting in an 86%

specificity. Only 21 (51%) of the 42 patients with an ESR greater than 15 mm developed SBI, resulting in a 51% PPV. Of the 118 instances, 99 (88.2%) had an ESR <15 mm without SBI, resulting in an 88.4% NPV.

Table 3: ANC and SBI

Test	SBI		Total
	Positive	Negative	
ANC≥10000	14	11	25
<10000	26	109	135
Total	40	120	160

Nine children with SBI had ANC ≥10000, resulting in a 31.3% sensitivity; 109 children without SBI had ANC <10000, resulting in a 96.4% specificity. Only nine (61%) of the fifteen patients with ANC greater than 10,000 developed SBI, resulting in a 61.2% PPV. Of the 135 ANC <10000 instances, 109 (84.6%) lacked SBI, resulting in an 84.7% NPV.

Table 4: CRP and SBI

Test	SBI		Total
	Positive	Negative	
CRP≥6mg/dl	28	12	40
<6mg/dl	12	108	120
Total	40	120	160

28 children with SBI had CRP≥6 mg/dl, resulting in a 78.4% sensitivity; 108 children without SBI had CRP<6 mg/dl, resulting in a 95.3% specificity. Only 28 (77.3%) of the 40 individuals with CRP more than 11 mg/dl developed SBI, resulting in a 78.2% PPV. Out of 120 instances with CRP <6 mg/dl, 108 (94.2%) lacked SBI, resulting in an 83.5% NPV. When using CRP and WBC together as a predictive test instead of WBC alone, the sensitivity rose to 58.7%, the specificity to 98%, the PPV to 90%, and the NPV to 95%. For predicting SBI sensitivity, the combination of CRP and ANC is somewhat less effective than standalone ANC, although it still increases to 58%. The NPV rose to 95%, the PPV to 100%, and the specificity to 100%. When using a combination of WBC and ANC, the sensitivity, specificity, PPV, and NPV did not change. The sensitivity of CRP and WBC and CRP and ANC was maintained when the CRP&WBC&ANC combination was employed. The NPV rose to 95%, the PPV to 100%, and the specificity to 100%. 30 instances (22%) had a positive CRP when the fever lasted more than 24 hours, while 107 cases (74%) had a negative CRP. The length of the fever, however, is unimportant. The p-value is 0.8.

DISCUSSION

It is still debatable how to treat feverish young children when there is no obvious cause of the illness; a test with sufficient sensitivity and specificity is required to identify the kinds of kids who are susceptible to bacterial infections. Serious bacterial infections in children (SBI) include pneumonia, urinary tract infections, and occult bacteremia. Laboratory testing and anticipated antibiotic medication for febrile young children increase expenses, time, pain, and parental concern, and they may also promote to antibiotic resistance since the majority of these children do not have SBI. CRP is a more sensitive and specific indicator of a severe bacterial infection than WBC counts, according to recent prospective investigations of young children who are feverish. One typical acute phase reactant is C reactive protein. It is a serum protein that the liver produces. Infection and inflammation cause a rise in CRP levels in the blood. One quick diagnostic test is CRP estimation. This investigation was carried out because CRP is a superior laboratory test for distinguishing between children with and without SBI9,[10] and is readily accessible, less costly, less time-consuming. This research assesses the semiquantitative CRP's diagnostic usefulness. The research included 140 patients. Thirty of the 140 patients tested positive for CRP, and 23 of those cases were SBI cases. Occult bacteremia (both CRP and blood culture positive) was present in 9 instances. Four S. pneumoniae cases, four H. influenzae cases, and one Klebsiella case were isolated. Six urinary tract infection cases were found; both CRP and urine culture results were positive. This investigation discovered one case of H. influenzae, four instances of E. coli, and one case of Klebsiella. Eleven patients (both CRP and chest x-ray positive) were diagnosed with pneumonia. According to this research, occult bacteremia occurs 16% of the time. In children with fever, CRP has been tested as a predictor of bacterial disease. It was discovered that CRP has a 77% sensitivity and a 94% specificity. In the current investigation, the PPV was 77%, the NPV was 94%, and the likelihood ratio was 12%. The current study's sensitivity is comparable to that of the Isaacman and Pullium studies, but its specificity is somewhat better. Only 77 youngsters were enrolled in the Pullium trial, making it a limited sample size. The sample size in Isaacman's research is larger than in this one. The sensitivity would most likely have changed depending on the sample size. Comparing one study to others also increases the likelihood ratio. A helpful screening test for occult bacterial infections was discovered to be CRP. The most often used laboratory test in this clinical setting is total WBC. One of the tests used to screen for occult bacteremia is this one. WBC had an 88% specificity and 30% sensitivity in the current investigation. The test has a negative predictive value (NPV) of 82%, a positive predictive value (PPV) of 44%, and a likely hood ratio of 2.5%, despite the fact that total WBC is less sensitive and specific because to the low frequency of occult bacteremia. Thirteen children in this research did not develop occult bacteremia despite having WBCs more than or equal to 15,000. Children with SBI and non-SBI were not substantially distinguished by using a threshold of greater than or equal to 15,000. [11]

Another test used to forecast bacterial infection is called ANC11,[12].When used as a screening test, ANC has a 30% sensitivity, 90% specificity, 83% NPV, 60% PPV, and an 8.5% likelihood ratio. Our observations indicate that it is marginally superior than total WBC. With a threshold value of around 109 cells/L, recent research found that ANC is a more accurate test than WBC for identifying pneumococcal bacteremia.[10,13] In children with fever, the erythrocyte sedimentation rate has been assessed as a predictor of bacterial disease. We found that it had a likelihood ratio of 3.7%, sensitivity of 53%, specificity of 85%, NPV of 87%, and PPV of 50%. We believe that ESR is superior than WBC based on these findings. When compared to WBC alone, the sensitivity of the CRP and WBC combination predictive test rises from 30% to 57%, the specificity from 88% to 99%, the positive predictive value to 89%, the negative predictive value to 94%, and the likelihood ratio to 52.6%. When compared to using ANC alone as a predictive test, the sensitivity of the CRP & ANC combination rises from 30% to 57%, the specificity from 95% to 100%, the positive predictive value from 60% to 100%, and the negative predictive value from 85% to 94%.With the exception of CRP alone, the combination of the WBC and ANC tests is more beneficial than the individual tests, although the combination of the two is shown to have higher specificity.[14] In screening tests, the combination of CRP and ANC is superior than solitary ANC; in particular tests, the combination of CRP and WBC and ANC is more beneficial. For CRP, ESR, ANC, and WBC, receiver operating characteristic curves (ROC) were created. Cutoff values for each variable that concurrently optimize sensitivity and specificity were established based on the curve. Patients were divided into two groups according to the cutoff value for each measure, and an analysis was conducted to see if there was a correlation between the dichotomized variables and the existence of SBI. CRP concentration and multilevel likelihood ratios were computed. Sensitivity rises from 77% to 83%, with the cutoff value for CRP set at 4.5 mg. The sensitivity is increased from 30% to 60% for WBC cutoff, which is set at 11.3 cells per cumm. With an ANC cutoff point set at 5.7 cells/cumm, sensitivity rises from 30% to 73.3%. With a 13mm cutoff point, ESR's sensitivity rises from 5.3 to 70%. CRP concentration and multilevel likelihood ratios were computed. NPV of 94% was associated with a probability ratio of SBI of 0.25 for a CRP value of < 5 mg/dl. A PPV of 80% was associated with a likelihood ratio of SBI 14.6 for a CRP levels greater than 15 mg/dl. Probability Because they allow a physician to evaluate the pretest likelihood of a patient's illness existence, ratios are an effective clinical tool.[15] This research shows that when it comes to differentiating children with occult severe bacterial infections from those without bacterial disease, CRP is more sensitive and specific. According to the curve, the sensitivity is maximized when the CRP concentration is more than 4.5 mg%. Instead of having a total WBC of 15,000 or more, a CRP concentration of more than 6,000 mg/dl is beneficial.2,1 The length of fever 14 affects CRP concentration, indicating that CRP is a more accurate marker of bacterial illness.if fever has been present for more than 24hours.[8,15]. However, a significant portion of the patients in this research also tested negative for CRP. One of the early indicators of sepsis is CRP.[16]. S. Nowadays, the most common cause of occult bacteremia is pneumonia.[3, 6] The risk of occult bacteremia is reduced by conjugate pneumococcal vaccination. Even children who have received vaccinations are susceptible to invasive pneumococcal illness since the vaccine only prevents 90% of invasive diseases.[17] There is also an effective vaccination for H. influenzae. However, it is under the list of optional vaccinations, and many children in nations like India are still not immunized against them. In the clinical context of a young kid who is feverish and has no discernible cause for the fever, the child is susceptible to both invasive pneumococcal illness and a severe bacterial infection.[18] Despite the introduction of conjugate pneumococcal and HiB vaccines, a quick screening test for severe bacterial infections will still be required.

CONCLUSION

For children aged 1 to 36 months, semiquantitative CRP may be used to predict occult severe bacterial infections. Compared to absolute neutrophil count and total white blood cell count, CRP is thought to be a more accurate prognostic test. The combination of CRP and ANC or CRP, ANC, and WBC is more beneficial than CRP concentration alone. For children with SBI, CRP establishes a more focused approach for further diagnostic testing and suitable antibiotic treatment.

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