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Original Research Article

Relative importance of inflammatory markers in deciding infection versus inflammation

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ABSTRACT

Background: Fever is the commonest presentation of pediatric patients attending emergency departments of all children's hospital. The cause of fever may be acute bacterial infections or primary vasculitic disorders like Kawasaki disease or inflammation due to non-bacterial infections. The objective was to compare the performance of the four biomarkers ESR, CRP, Procalcitonin and IL-6 in predicting a diagnosis of sepsis/infection and find out a definite cut off value for the statistically most significant one.
Methods: The authors conducted this prospective observational study at the indoors of a pediatric tertiary care referral center in India to find out a biomarker which can differentiate between infection and inflammation (vasculitis) in children admitted with fever and finally diagnosed as infection or inflammation (vasculitis).
Results: Among ESR, CRP, Procalcitonin and Interleukin-6, only IL-6 showed statistical significance in differentiating infection from inflammation (vasculitis) analysed using the Receiver Operating Characteristic (ROC) curve and Mann-Whitney U test, sensitivity and specificity.
Conclusions: IL-6 level 27 pg/mL or less at the time of admission indicates an infectious etiology while level more than this indicates towards a vasculitic cause.

Keywords: Biomarkers, C-reactive protein, ESR, Interleukin-6, Infection, Procalcitonin

INTRODUCTION

Bacterial sepsis can be difficult to distinguish from other non-bacterial infections and non-infectious conditions in patients presenting with clinical signs of acute inflammation (mainly fever) to the emergency department. The rates of non-infectious etiologies misdiagnosed as bacterial sepsis ranges from 14-18% in patients presenting with fever as a chief complaint.[1,2] This issue is of paramount importance given that therapies and outcomes greatly differ between patients with those with and without bacterial sepsis. Till date, no single clinical or biological indicator of bacterial sepsis has gained unanimous acceptance. This paper is a continuation of our efforts to look for a laboratory marker that will help to say that the fever is of inflammatory origin (vasculitis) and not sepsis. The authors initially chose Kawasaki disease as a model for this purpose and studied procalcitonin as a marker for the same.[3] Subsequently, it was felt that procalcitonin (PCT) has limitations so Interleukin-6 (IL-6) was chosen. Both PCT and IL-6 levels have extensively been used in critical care medicine to establish or to exclude sepsis.

It has to be appreciated that such a laboratory marker will be of immense clinical importance as a clinician facing a PUO (Pyrexia of Unknown Origin) is often in a dilemma as to the cause of fever i.e. inflammatory or infective. The concept is to relieve the patients of inflammatory disorders from unnecessary use of antibiotics.

METHODS

This prospective observational study, as a pilot project, was conducted at the indoors of Institute of Child Health, Kolkata, a pediatric tertiary care hospital in Eastern India between April 2016 to June 2017.

Inclusion criteria

- 42 children in the age group 1 month to 18 years were included
- patients without any previous treatment history outside our institution diagnosed as culture-positive bacterial sepsis and clinically diagnosed non-bacterial infection or vasculitis with/without supportive laboratory markers.

Exclusion criteria

- Patients were excluded if they had culture negative sepsis, clinical vasculitis without rise in inflammatory biomarkers or if they were participating in an ongoing clinical trial.

A formal Institutional Ethical Committee clearance was obtained before commencement of the study.

Data collection

Following informed consent, parents/guardians of the patient completed a questionnaire about demographic factors and medical history. Biological specimens i.e., blood cultures and cultures of other sites were collected maintaining proper asepsis as ordered by treating physicians. Other baseline measurements included complete blood counts, blood chemistries, urinalysis and radiography were ordered to reach a provisional diagnosis. Researchers of this study themselves reviewed and abstracted vital signs, microbiology, laboratory, and imaging results obtained during the Emergency Department encounter.

Sample processing

Upon collection of blood within 8 hours of admission through ED, samples for biomarker level determination were frozen. They were later thawed at room temperature, gently mixed, and analyzed within eight hours. PCT and IL-6 were measured by electrochemiluminescent immunoassay (ECLIA) [sandwich ELISA]. CRP was quantified using a chemiluminescent (CLIA) immunoassay. ESR was measured with Wintrobe's tube method.

Statistical analysis

Subjects were divided into 2 groups: Infective condition (sepsis group) and Inflammatory conditions (Vasculitis group). All 4 biomarkers were measured in all the patients of both groups and performance of each biomarker as a sepsis diagnostic was analysed using the Receiver Operating Characteristic (ROC) curve and Mann-Whitney U test, specificity, likelihood ratio and sensitivity.

RESULTS

Patients were divided into two groups - infective and inflammatory disease. Under the "infective" group typhoid fever, urinary tract infections, respiratory tract infections with culture positivity, acute streptococcal tonsillopharyngitis, meningococcal septicaemia, staphylococcal sepsis etc. were included. Under "inflammatory" heading Kawasaki disease, juvenile idiopathic arthritis, systemic lupus erythematosus (SLE), Henoch-Schonlein Purpura (HSP), urticaria, systemic sclerosis, reactive arthritis, dengue fever, viral fever etc. were clubbed.

Out of 42 patients 22 were in infective and 20 were in inflammatory condition group. It has been observed that 4 biomarkers (PCT, CRP, IL-6 and ESR) were increased from the normal baseline range in infective as well as inflammatory conditions. IL6 was comparatively more increased in inflammatory conditions.

All the four biomarkers (PCT, CRP, IL-6 and ESR) in two group infective and inflammatory condition were analysed by Receiver Operating Characteristic (ROC) curve (Figure 1) and Mann-Whitney U test, specificity, likelihood ratio and sensitivity.

It was generally observed that procalcitonin rises more in infective conditions, but only negligible rise was noticed in inflammatory conditions, the only exception being SLE. ESR was observed to rise in both the groups equally. CRP was more increased in infective conditions. IL-6 was more increased in inflammatory conditions as observed in our study.

But during statistical analysis interestingly among the four markers others showed no significant difference except IL-6 which showed statistically significant difference (p-value= 0.01) with sensitivity 75% (95%CI 50.9-91.3) and specificity 72.73% (95% CI 48.8-89.5). AUC [Area Under Curve] - 0.732 [95% CI-0.573 to 0.857], Z statistics-2.857, significant level p (area 0.5) 0.005. IL-6 value 27 pg/ml or less showed the potential to predict infective condition.

Figure 1 shows Receiver Operating Curve (ROC) ["100-Specificity" in X-axis and "Sensitivity" in Y-axis] for IL-6 with an Area Under Curve (AUC) of 0.732 (95% CI – 0.573 to 0.857).

Among the study population (n=42), 31 (73.81%) were male and 11 (26.19%) were female. No statistically significant difference has been noted regarding any of the four biomarkers between the two genders.

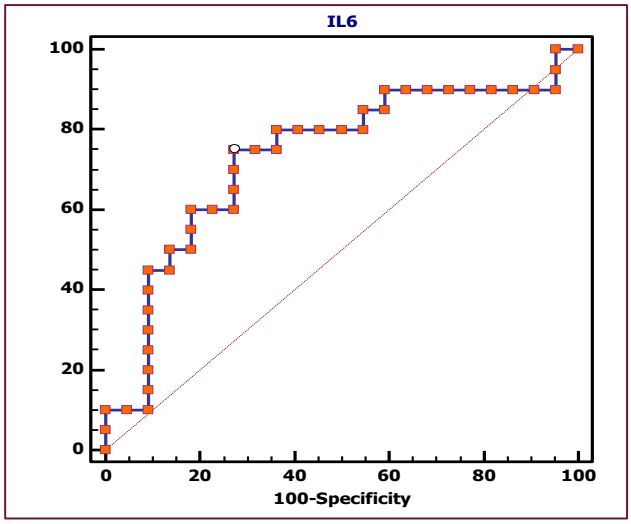

Figure 1: Receiver Operating Curve (ROC) ["100-Specificity" in X-axis and "Sensitivity" in Y-axis] for IL-6 with an area under curve (AUC) of 0.732 (95% CI – 0.573 to 0.857).

DISCUSSION

Diagnosis of sepsis is very challenging to clinicians as clinical diagnostic criteria for sepsis lacks specificity and sensitivity and no laboratory test is available which can differentiate sepsis (infection) and inflammation (vasculitis). Infections and inflammatory conditions often overlap in their clinical pictures and initial routine investigation results. As sepsis is associated with high mortality, any delay in initiation of antibiotic therapy could be catastrophic. On the other hand, unnecessary use of antibiotics in inflammatory conditions mimicking sepsis is associated with untoward drug adverse effects as well as increase in socio-economic burden.[4,5]

Several biomarkers have been studied so far but studies in pediatric population are scarce in number. We compared only 4 biomarkers: ESR, CRP, Procalcitonin and Interleukin-6 (IL-6). ESR has long been used as a nonspecific marker for acute inflammation. In present study ESR was increased in both infection as well as inflammatory conditions and statistical analysis showed no significant difference between the two groups.

CRP, an acute phase reactant produced from hepatocytes by cytokines like IL-6, TNF alpha etc. rise during inflammation. Several studies in adults as well as children observed CRP to predict bacterial infections more accurately than other markers like studies conducted by Bilavsky et al, Zarkesh et al etc.[6,7] Andreola et al showed that overall CRP may be the most convenient marker of infections in children due to its better sensitivity and feasibility.[8] But in our study, we observed low levels of CRP in patients with UTI and pertussis despite bacterial infection and high levels in inflammatory conditions like Kawasaki disease and HSP. It should be remembered that CRP level may remain normal in SLE though it is a vasculitis/ inflammatory disorder. Statistical analysis also showed no significant difference between the infective and inflammatory groups. Perhaps it is correctly said that the continuous trend of CRP levels is thus more important in guiding antibiotic policies rather than one single value.[9]

Procalcitonin (PCT), a precursor peptide form of human calcitonin, is known to rise in response to pro-inflammatory conditions. Unlike our study which excluded ICU patients, most of the previous studies on PCT were conducted on critically sick patients and observed in ICU settings. PCT yielded highest discriminative value for differentiating sepsis from SIRS due to inflammatory conditions in several studies.[10,11] Four meta-analyses have analysed effectiveness of PCT in the diagnosis of sepsis or bacteremia. Two suggested that PCT is superior to other markers such as CRP and supported its use in sepsis diagnosis whereas the others found it not so effective to identify sepsis in critically ill patients.[12-15] Subsequently after publishing the first study on PCT, the authors observed that PCT values often become erroneous after 1st week of illness. In this study also, PCT didn't show statistically significant difference between the two groups. Interestingly, PCT was found in lower ranges in infective conditions like pneumonia, UTI and typhoid fever. This effect might be due to the fact that in this part of the world before coming to ED of a tertiary care center children usually receive antibiotics prescribed by primary care physicians and as we know PCT starts decreasing after patient receives antibiotics, a lower range of PCT level was observed during admission despite definitive proof of infection.

Among the interleukins, IL-6, a pleotropic cytokine which has a wide variety of actions in numerous systems including the immune, nervous, and endocrine systems, is being extensively studied as biomarker for sepsis and inflammatory diseases over last couple of decades.[16] Besides being an endogenous pyrogen, it initiates acute phase protein synthesis in the liver and stimulates antibody production.[17,18]

Large-sample multicenter study or meta-analysis on IL-6 on sepsis diagnosis is still lacking. A recent meta-analysis from China concluded that IL-6 has sensitivity of 80% and specificity of 75% for detection of early sepsis according to previous studies and accepted that further extensive studies and continuous re-evaluation of the results in clinical settings are required.[19] Studies have observed increased levels of IL-6 in inflammatory disorders like rheumatoid arthritis, systemic juvenile idiopathic arthritis, Castleman disease, Crohn's disease etc. and also observed effective management of these conditions by targeting IL-6 by monoclonal antibodies.[20] Calandra et al observed IL-6 levels to be detectable in only 18% of the patients with sepsis on day 1 and also they observed that concentrations of IL-6 usually peaked near the onset of shock.[21].

In present study, authors found elevated IL-6 levels in UTI and febrile illnesses later proven to be culture positive sepsis and lower levels in meningitis, pneumonia, rickettsial infection, typhoid fever among the infective group. On the other hand, apart from urticaria and reactive arthritis, higher levels of IL-6 were observed in all other febrile conditions in inflammatory disease group (Kawasaki disease, SLE, dengue, systemic onset juvenile idiopathic arthritis, scleroderma, HSP). Among the 4 biomarkers studied, only IL-6 showed statistically significant difference with sensitivity of 75% (95% CI 50.9-91.3), specificity of 72.73% (95% CI 48.8-89.3) and AUC in ROC- 0.732 (95% CI 0.573-0.857). According to our study findings, a cut-off level of IL-6 of less than or equal to 27 pg/ml suggest infective disease. Levels above 27 pg/ml would point towards fever due to non-infective etiology/vasculitis.

The limitation of this study was its small (n=42) study population. Actually, this was a pilot study among the non-ICU febrile patients admitted in general pediatric wards through ED and on the basis of the study findings, we are going to conduct a larger study on predictive accuracy of IL-6 in same kind of patient population in future.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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