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Procalcitonin as a rapid diagnostic biomarker to differentiate between culture-negative bacterial sepsis and systemic inflammatory response syndrome: A prospective, observational, cohort study☆

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ABSTRACT

Purpose: Differentiation between culture-negative sepsis and noninfectious systemic inflammatory response syndrome (SIRS) remains a diagnostic challenge for clinicians, both conditions having similar clinical presentations. Therefore, a swift accurate diagnostic tool, which helps differentiate these 2 conditions would immensely aid appropriate therapeutic continuum. This prospective study was conducted to evaluate the potential diagnostic role of biomarkers, procalcitonin (PCT) and interleukin 6 (IL-6), in culture-negative sepsis patients.
Methods: Enrolled patients (208) included 46 noninfectious SIRS, 90 culture-negative sepsis, and 72 culture-positive sepsis. Culture, PCT, and IL-6 estimations were performed on day 1 of intensive care unit admission.
Results: Procalcitonin and IL-6 levels were significantly higher ($P < .001$) in both culture-negative and culture-positive groups as compared with SIRS group. Procalcitonin was a better predictor of sepsis in both culture-negative (area under curves 0.892 vs 0.636) and culture-positive (area under curves 0.959 vs 0.784) groups as compared with IL-6. In culture-negative group, the best cutoff point for PCT was at 1.43 ng/mL (92% sensitivity; 83% negative predictive value), best cutoff point for IL-6 was at 219.85 pg/mL (47% sensitivity and 42% negative predictive value).
Conclusions: Procalcitonin can accurately differentiate culture-negative sepsis from noninfectious SIRS and thereby contribute to early diagnosis and effective management of these conditions.

1. Introduction

Across the world, various epidemiological studies have revealed an increase in the incidence of sepsis during the last decade [1-3]. In the United States, the hospitalization rate due to sepsis as principal diagnosis has increased by more than 2-fold, extending from 11.6 to 24.0 per 10 000 population between the years 2001 and 2008 [4]. In recent years, improved sepsis management has decreased the case fatality rate in sepsis patients, but owing to the increase in number of cases, the overall mortality is on the rise [5].

Conceptually, *sepsis* is defined as a systemic inflammatory host response to infection and characterized by alterations in physiologic parameters such as temperature, heart rate, respiratory rate, etc [6]. In clinical practice, such changes in physiologic parameters are nonspecific, and may manifest in the other noninfectious systemic inflammatory response (SIRS) conditions such as trauma, burns, pancreatitis, etc [7,8]. According to the currently used definition of sepsis, the presence of documented or suspected infection is the key demarcating characteristic between sepsis and other noninfectious SIRS conditions. The major challenge, however, is to diagnose infection in sepsis patients. Although, microbiological culture is considered as the criterion standard for the diagnosis of infection, the major concern is lack of sensitivity, specificity, and delay in reporting of culture results. The Sepsis Occurrence in Acutely Ill Patients study revealed that approximately 40% of the sepsis patients remain culture negative [9]. The Extended Prevalence of Infection in the intensive care unit (ICU) study has also reported a prevalence of culture-negative infection at 30% of overall infections [10]. Most of these clinically suspected sepsis patients who remain culture-negative pose a challenge in the decision making of antibiotic administration. Hence, it is of utmost importance to differentiate these patients from those with noninfectious SIRS, as both disease conditions require different therapeutic regimens. According to the Surviving Sepsis Campaign recommendation, antibiotics should be administered within 1 hour of septic shock onset [11]. Every hour of delay in antibiotic administration demonstrated an increase in mortality of 7.6% in septic shock [12]. Therefore, early empirical antibiotic administration is crucial for improving outcome in sepsis. This may get delayed due to misdiagnosis of culture-negative sepsis

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patients as SIRS. On the other hand, noninfectious SIRS patients misdiagnosed as sepsis might get inappropriately treated with broad spectrum antibiotics, which may contribute to the emergence of antibiotic resistance—a growing health problem [13]. Thus, a specific biomarker with high sensitivity and negative predictive value (NPV), which can diagnose or exclude suspected sepsis early (within 1 hour of sampling) in culture-negative patients would be of vital importance for timely institution of antibiotic treatment or avoidance thereof.

Inflammatory mediators in the serum, which are altered in septic conditions, have been studied for their potential in diagnosis or prognosis of sepsis. Among these, procalcitonin (PCT) and interleukin 6 (IL-6) have been investigated widely in relation to severity and organ failure in sepsis patients [14-16]. Various studies, including several meta-analyses have assessed the usefulness of PCT as a diagnostic tool in differentiating sepsis from noninfectious SIRS [17-22]. Although PCT has been regarded as a sensitive marker for the prediction of sepsis in culture-positive patients, its role in culture-negative sepsis is scarcely known. To the best of our knowledge, no study in the past has focused on the diagnostic accuracy of PCT and IL-6 in culture-negative sepsis, and therefore, no optimal cutoff value has been proposed for differentiating culture-negative sepsis from noninfectious SIRS. The current prospective observational study sought to investigate the diagnostic accuracy of serum PCT and IL-6 to differentiate between culture-negative sepsis and noninfectious SIRS. We also studied their diagnostic efficacy in culture-positive sepsis.

2. Materials and methods

The study protocol was approved by institutional ethics committee; and the prospective, observational, single-center study was conducted at a 675-bedded superspeciality hospital in New Delhi (India) over a period of 1 year and 5 months (January 2013 to May 2014). Informed consent was taken from each patient or their next of kin if patient was unconscious or not in a state to give consent.

Our inclusion criteria were as follows: adult patients (aged >18 years) admitted from the community to the ICU were screened; and patients diagnosed with noninfectious SIRS, sepsis, severe sepsis, or septic shock (according to the established consensus sepsis definition) were enrolled in this study [23]. Exclusion criteria were patients who had received prior antibiotics (last 3 months), transferred from other ICUs; having conditions, which were considered lethal in the next 24 hours; postoperative; immunocompromised; and with malignancy were not included in the study. Patients with bilateral pneumonia (suspected viral infection) and diagnosed tropical diseases such as malaria, dengue, *Leptospira*, and rickettesiae were also excluded.

Patient's demographics, principal diagnosis, and all clinical parameters were recorded at the time of enrollment. Initial severity of illness was determined using the Acute Physiology and Chronic Health evaluation score (APACHE II) at 24 hours in all patients. Patients were followed up for 28 days to observe survival or mortality.

2.1. Sample collection and processing

Blood samples were assayed for microbiological culture and biomarkers on the day of ICU admission. Two sets of blood cultures, urine culture, sputum culture (in nonintubated patients), endotracheal culture (in intubated patients), and high vaginal swab culture (where puerperal sepsis was suspected) were sent before the commencement of antibiotic therapy. For blood cultures, samples were obtained in both aerobic and anaerobic BacT/Alert bottles and performed by BacT/Alert method (BioMerieux, Marcy l' Etiole, France). Urine and sputum specimen were procured in sterile containers. For endotracheal and vaginal swab cultures, specimens were collected in mucus trap and swab container, respectively. Positive cultures were further processed for the identification of organisms using standard laboratory methods.

Blood samples for PCT and IL-6 estimation were obtained in serum-evacuated separator tubes and centrifuged for the separation of serum and processed on the same day. Procalcitonin estimation was done with time-resolved amplified cryptate emission technology by measuring the signal that is emitted from an immunocomplex with time delay (Kryptor PCT; BRAHMS, Henningsdorf, Germany). The assay time of this estimation takes less than half an hour. Interleukin 6 estimation was done by solid-phase Chemiluminescent Access Immunoassay System (Beckman Coulter, Inc, Brea, California, USA).

2.2. Classification of patient groups

Enrolled patients were classified into SIRS and suspected sepsis at the time of enrollment based on clinical presentation by 4 clinicians (also coauthors). Culture-negative and culture-positive groups were defined, once the microbiological results were available.

(i) Group I (noninfectious systemic inflammatory response group): Included patients with 2 or more signs of SIRS with recent onset pancreatitis and trauma (within 24 hours) without any evidence of infection.

(ii) Group II (culture-negative sepsis group): Patients with 2 or more signs of SIRS and clinical suspicion of infection with negative culture results.
The diagnosis of bacterial infection in these patients was done based on findings of a clinical focus of infection. Intraabdominal infection was diagnosed in case of exudative ascitic tap with increased polymorphonuclear cell count. Bacterial pneumonia was confirmed by x-ray showing lobar infiltrate. Urosepsis was suspected with signs of urinary tract infection and with a raised leukocyte count in the urine (>10 pus cells/high-power field) and signs of pyelonephritis by ultrasonography. Cellulitis was diagnosed by the skin signs, that is, lesions. Puerperal sepsis was suspected in peripartum patients with signs of pelvic pain and abnormal or foul smelling vaginal discharge (presence of pus).

(iii) Group III (culture-positive sepsis group): This group consisted of the patients who had microbiologically documented source of infection with 2 or more of the SIRS criteria.
A blood culture was considered positive if any significant pathogenic bacterial organism was grown from twin cultures taken from different sites. Respiratory secretions were considered positive for infection if many polymorpohonuclear cells were present along with colony count more than 10^5. Urine culture was considered positive if there were more than 10 pus cells/high-power field, along with single organism cultured with more than 10^5 colony-forming units/mL.

2.3. Statistical analysis

Statistical analyses were performed using SPSS, version 17.0 (SPSS, Chicago, IL). Continuous variables are presented as mean (range) or median (interquartile range) as appropriate. Categorical variables are presented as absolute numbers and percentage. For multiple group comparisons, one-way analysis of variance with post hoc comparison or nonparametric Kruskal-Wallis with Mann-Whitney *U* test was used. Categorical variables were analyzed using the χ^2 statistic. The diagnostic performance of biomarkers was demonstrated with receiver operating characteristics (ROC) analysis. The Youden index with highest sum of sensitivity and specificity was used to determine the optimal cutoff values [24]. Positive predictive value, NPV, positive likelihood ratio, and negative likelihood ratios were calculated. For all statistical tests, a P value < .05 was considered significant.

3. Results

The study was conducted in a total of 208 patients prospectively. As defined in methodology, enrolled patients were classified into following