Biomarkers in Sepsis: Value of Procalcitonin in Diagnosis and Prognostication

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Abstract

Sepsis is the most common way of death in critical patients. The mortality rate of septic shock (SS) lies between 20% and 40% in developed countries, although varies substantially from center to center. The definitions of Sepsis were revised in the conference held by The European Society of Intensive Care Medicine (ESICM) and Society of Critical Care Medicine (SCCM) in 2016 Sepsis-3 as "life-threatening organ dysfunction caused by a deregulated host response to infection".

Keywords: Biomarker; Sepsis; Procalcitonin; Diagnosis; Diagnostic value; Outcome

Introduction

The most important predictors of mortality in septic patients are early recognition of deterioration to SS and expedient treatment with antibiotics. The diagnosis can be overlooked in the early phases of sepsis much more commonly than most other diseases. New proposals point out new criteria for the diagnosis of sepsis cases "life-threatening organ dysfunction associated with proven infectious process". In the new proposals, health community disregarded definitions such as "severe sepsis" and "Systemic Inflammatory Response Syndrome" (SIRS) criteria in the diagnosis and management of the entity [1-4].

Biomarkers in Sepsis: When and How to use Procalcitonin in Sepsis and Septic Shock?

Lactate and procalcitonin (PCT) are among the most commonly cited biomarkers in the septic process. A recent Australian study disclosed that hyperlactatemia was proven to be more accurate in predicting mortality when compared to hypotension unresponsive to fluid replacement [5]. Shetty et al. indicated that lactate levels >2 mmol/L in ED patients who were suspected to have sepsis are to be viewed as a risk predictor [6]. Also, these high levels of lactate was associated with in-hospital mortality rates greater than 10 percent and stay times in ICU longer than 72 hours in patients with respiratory and abdominal infectious foci in this study.

PCT

Meta-analytic data involving 16514 patients demonstrated that PCT levels with a cut-off of 0.5 mmol/L had a sensitivity of 76% and a specificity of 69% to rule out bacteremia in those with bloodstream infections [7]. Nishikawa et al. used the same cut-off level and found that the area under curve of PCT in diagnosing bacteremia was larger than that of CRP (0.79 *vs* 0.66, respectively) [8]. Cha et al. indicated that PCT levels should not be used as a sole diagnostic for sepsis without blood cultures, evidenced by inability to rule out one-fourth of

those with nosocomial sepsis when a PCT cut-off level of 0.27 ng/mL was used [9].

On the other hand, researchers cited that PCT and neutrophil/lymphocyte count ratio could be used in the diagnosis of SS and AUC was found to be higher when these two markers are used together [10].

Six studies' meta-analysis disclosed that PCT had a high sensitivity for ICU patients (0.84), but a low specificity (0.64) for identifying secondary bacterial infections among patients with influenza [11]. It can be used to rule-out influenza pneumonia for its negative likelihood ratio was reasonably low (LR=0.26; 95% CI: 0.17–0.40).

There is data claiming that the level of PCT over the first 24 hours regardless of the initial severity classification accurately predicts mortality in sepsis patients in the critical care unit [12]. More interestingly, an 80% decrease in PCT level over 72 h carried a 90% NPV for mortality.

Porfyridis et al. evaluated the diagnostic value of clinical pulmonary infection score (CPIS), CRP, and PCT and to compare the accuracy of pneumonia severity scores (confusion, urea nitrogen, breathing frequency, blood pressure, >65 y of age [CURB-65]; pneumonia severity index; nursing home acquired pneumonia (NHAP) index; systolic blood pressure, multilobar involvement, albumin, breathing frequency, tachycardia, confusion, oxygen, arterial pH [SMART-COP]; and systolic blood pressure, oxygen, age > 65 y, breathing frequency [SOAR]) in predicting inpatient mortality from NHAP [13]. Patients with Gram (+) pneumonia had significantly higher CRP and PCT levels. PCT levels averaged 4.6+-5.4 ng/mL in mortal patients, while survivors had an average of 0.8+-0.9 ng/mL (p<0.001). CPIS, PCT and CRP proved to have high accuracy in diagnosis of pneumonia, while PCT and CURB-65 was stronger in predicting in-hospital mortality when compared to other tools. Nosocomial bloodstream infections increased in accord with renal failure (0.12 ng/mL with estimated glomerular filtration rate [eGFR] $\geq$ 60 mL/min/1.73 m^2; 0.84 ng/mL with 30 $\leq$ eGFR<60 mL/min/1.73 m^2; 1.71 ng/mL with eGFR<30 mL/min/1.73 m^2). The evidence that the cutoff value of PCT for identifying sepsis was higher in patients with impaired renal function, are consistent with some other studies [14]. PCT cut-off levels in

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patients with kidney failure should be higher than healthy controls [15].

Use in Elderly Patients

PCT was also proven useful in elderly patients suspected for having bacteremia. Lee et al. reported that PCT was not inferior to other adults in diagnosing bacterial infection [16]. However, the imperfect accuracy of the test withheld recommendations on the use of the test in isolation. In a more recent study on elderly sepsis patients, PCT, IL-10, IL-6, and IL-5 were found useful in predicting ICU admission, but were not effective in predicting the death [17].

H1N1 and PCT

In the era of H1N1 pandemic of 2009, ICU patients with bacterial pneumonia had higher PCT levels than those having only H1N1 infection (average 6.2 mcg/L and 0.56 mcg/L) [18]. The test had 80% sensitivity and 73.2% NPV in predicting bacterial pneumonia with the cut-off level taken as 0.5 mcg/L.

Conclusion

PCT is the most commonly investigated sepsis-specific biomarker *via* well-designed, prospective, randomized trials in different samples to establish an easy-to-use diagnostic tool which can help expedient patient care in the acute setting. Specifically, PCT was found superior to most other acute phase reactants and indicators, including CRP as a predictor of bacteremia and sepsis.

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