

Presepsin: A Promising Biomarker for Sepsis

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ABSTRACT

Sepsis is the most common cause of mortality in non-cardiac ICUs. The quest for early diagnosis and treatment has led to the discovery of many biomarkers. In this issue, Abdelshafey et al. have evaluated presepsin, a novel biomarker for early detection of sepsis. Presepsin is formed by cleavage of N-terminal of soluble CD14 (sCD14) which is a member of the Toll-like receptors (TLRs). Studies have found a higher level of presepsin in septic patients and values above 946 ng/L correlated well with gram-negative bacterial sepsis.

Keywords: Biomarkers, Presepsin, Sepsis.

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OVERVIEW

Sepsis is a life-threatening entity causing millions of deaths worldwide, with variable clinical manifestations and poses difficulty in diagnosis and treatment. Early recognition of sepsis not only helps in the optimization of treatment but also improves the overall outcome.¹ Blood cultures continue to be the gold standard for diagnosing sepsis, though associated with some limitations. They have a low yield in patients who are receiving antibiotics or have been previously treated with antibiotics.² Moreover, despite advancements in microbiological techniques the results may be obtained over several days. This delay may contribute to further worsening of critically ill septic patients thereby increasing morbidity and mortality. Sepsis triggers a systemic host response releasing several mediators that have the potential to be used as biomarkers for diagnosing sepsis and can also be of prognostic utility. In this issue, Abdelshafey et al. have evaluated presepsin as a biomarker for sepsis and compared it with SIRS and qSOFA.³ Biomarkers play a role in decision tools for managing sepsis and also play a vital role in antibiotic stewardship which is extremely essential in this era of increasing antibiotic resistance. Literature review on biomarkers in sepsis suggests that nearly 258 biomarkers have been evaluated in different clinical settings of sepsis.⁴ Amongst these biomarkers, some of them have established themselves over a period of time while some biomarkers continue to be in various stages of evolution. Procalcitonin (PCT) and C-reactive protein (CRP) are acute-phase proteins that are being most commonly utilized to diagnose bacterial sepsis and also to guide antibiotic therapy.⁵ Limitations associated with them include that their levels can get elevated in a variety of inflammatory conditions. Hence, the search is still on for a novel biomarker that holds promise as a tool for evaluating sepsis either as an individual or in combination with other biomarkers to improve the overall sensitivity and specificity for diagnosing and prognosticating bacterial infections.

Innate immune system has the unique characteristic of providing an immediate protective response to invasive pathogens. CD14 is a co-receptor present on the surface of the monocyte/macrophage. It is a member of the Toll-like receptors (TLRs), with an ability to identify groups of ligands of both gram-positive and gram-negative pathogens.⁶ Lipopolysaccharide (LPS) which is competent of the gram-negative bacterial cell wall is one of the best-studied ligands. CD14 presents LPS to TLR and then

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contributes to intracellular signals promoting the expression of genes responsible for the immune response. CD14 exists in two forms namely membrane-bound (mCD14) and a soluble form (sCD14). The sCD14 has different subtypes that get released in circulation and acted upon by proteases and cathepsin D. The N-terminal fragment of the sCD14-ST subtype is called presepsin. Of late presepsin has aroused interest among the researchers but its utility is still under investigation.

PRESEPSIN FOR SEPSIS DIAGNOSIS AND PROGNOSIS

Presepsin levels are not only helpful in differentiating between sepsis and systemic inflammatory response syndrome (SIRS) but also act as a prognostic tool in bacterial sepsis.⁷ sCD14-ST was first studied in 2005 to differentiate patients with sepsis from healthy controls and patients in SIRS.⁸ The level of sCD14-ST in subjects with sepsis was much higher than the levels in subjects with SIRS and healthy controls. They reported a receiver operating characteristic (ROC) curve of 0.817 for diagnosing sepsis. A meta-analysis on presepsin has shown that it has a higher sensitivity and specificity when used as a biomarker for diagnosing sepsis.⁹ Although another systematic review suggested that it should not be studied in isolation for diagnosis of bacterial infections and expressed a word of caution.¹⁰ Using it in combination with other biomarkers would be more useful to differentiate sepsis from the systemic inflammatory response.

The study by Abdelshafey et al. is an observational exploratory study because the sample size was not calculated. Though it is limited by its inadequate randomization, it does highlight the role of presepsin as a biomarker for sepsis patients.

Several multicentric and prospective trials have shown that presepsin levels are significantly higher in patients with bacterial infections. Sensitivity has ranged from 70 to 87% and specificity from 63 to 81% when cutoff values have ranged from 600 to 864 ng/L.⁷ A cutoff value of 600 ng/L failed to differentiate between gram-positive and gram-negative infections. However, levels above 946 ng/L correlated well with gram-negative bacterial infections.

Single elevated values of presepsin levels at ICU admission have correlated with acute kidney injury, need for renal replacement therapy, longer ICU stay, longer days of mechanical ventilation, and more days on vasopressor. Serial monitoring of presepsin levels would prove more useful for clinicians at the bedside to monitor the appropriateness of antibiotic therapy and thereby influencing the overall outcome. Studies suggest that reduction in presepsin levels on Day 7 strongly correlates with the efficacy of antibiotic therapy.¹¹

The different performance efficiency values in the literature may be due to the heterogeneity in the included studies, variations in sepsis criteria, and even the type of sample used (plasma, serum, or whole blood) for measurement of presepsin. Further prospective studies with larger and more diverse populations are required to establish the cutoff values for presepsin for the diagnosis and prognosis of bacterial infections.

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