

## Mini Review

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# Role of presepsin for the evaluation of sepsis in the emergency department

**Abstract:** Sepsis, severe sepsis and septic shock are among the most common conditions handled in the emergency department (ED). According to new Sepsis Guidelines, early diagnosis and treatment are the keys to improve survival. Plasma C-reactive protein (CRP) and procalcitonin (PCT) levels, when associated with documented or suspected infection, are now part of the definitions of sepsis. Blood culture is the gold standard method for detecting microorganisms but it requires too much time for results to be known. Sensitive biomarkers are required for early diagnosis and as indexes of prognosis sepsis. CRP is one of the acute phase proteins synthesized by the liver: it has a great sensitivity but a very poor specificity for bacterial infections. Moreover, the evolution of sepsis does not correlate with CRP plasma changes. In recent years PCT has been widely used for sepsis differential diagnosis, because of its close correlation with infections, but it still retains some limitations and false positivity (such as in multiple trauma and burns). Soluble CD14 subtype (sCD14-ST), also known as presepsin, is a novel and promising biomarker that has been shown to increase significantly in patients with sepsis, in comparison to the healthy population. Studies pointed out the capability of this biomarker for diagnosing sepsis, assessing the severity of the disease and providing a prognostic evaluation of patient outcome. In this mini review we mainly focused on presepsin: we evaluate its diagnostic and prognostic roles in patients presenting to the ED with systemic inflammatory response syndrome (SIRS), suspected sepsis or septic shock.

**Keywords:** Emergency Department; presepsin; sepsis.

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## Introduction

Sepsis, severe sepsis and septic shock are unquestionably some of the major healthcare problems, affecting millions of people each year worldwide, responsible for one death every four, and increasing in incidence [1–3]. Prompt diagnosis and treatment with appropriate antimicrobial chemotherapy is of utmost importance in reducing morbidity and mortality associated with sepsis [4]. Sepsis is a systemic deleterious host response to infection, possibly leading to severe sepsis (acute organ dysfunction secondary to documented or suspected infection) or septic shock (severe sepsis plus hypotension not reversed with fluid resuscitation). According to the most recent guidelines, published by the Surviving Sepsis Campaign [5], early recognition of these conditions and speed and appropriateness of therapy in the initial hours after presentation considerably influence the outcomes of septic patients. Plasma C-reactive protein (CRP) and procalcitonin (PCT) values more than two standard deviations (SD) above the normal levels, if associated with infection documented or only suspected, are now part of the definition of sepsis [5, 6].

Blood culture is the gold standard method for detecting the presence of microorganism in the bloodstream. However, it has limited usefulness for early detection of infection because it usually requires several days for results to be known [7]. Blood culture may also be plagued by some false negative cases, especially in patients undergoing antibiotic therapy. This can lead to a delay in antibiotic administration and consequently to increased mortality. Moreover, sepsis can be suspected in the absence of an obvious infectious source, particularly in elderly people who often present with non-specific signs (weakness, confusion, dyspnea and organ dysfunction, such as acute renal failure and acute coronary syndrome). In conclusion,

sensitive biomarkers are needed for diagnosis and prognosis of sepsis, severe sepsis and septic shock, particularly in such cases of atypical presentations [8].

## Selection of studies

We analyzed the most recent and important studies that reported results about presepsin: we systematically searched PubMed, Ovid and Scopus databases in a time period from July 1995 to February 2014 using the term “presepsin”. Retrospective, prospective studies and reviews were taken into account, avoiding unpublished literature and papers published only in abstract form.

The area under the curve (AUC) was used to show diagnostic and prognostic accuracy. A  $p$ -value  $<0.05$  was considered to be significant.

## Traditional biomarkers

CRP is one of the acute phase inflammation proteins synthesized by the liver; CRP levels increase 6 h after interleukin 6 (IL-6) stimulation and has a half-life of 20–24 h [8]. Its main advantage is its great sensitivity as soon as an inflammatory process affects the human body, but unfortunately it is weakly specific for bacterial infections; moreover, the evolution of sepsis is poorly correlated with changes in serum CRP level [9].

PCT is the pro-hormone of calcitonin: it is synthesized by thyroid cells. During any pro-inflammatory stimuli, many tissue and immune cells attain the ability to produce PCT [10, 11]. This biomarker increases within 4 h from the start of the innate immunity cascade, peaking within 6–8 h [9]. Although PCT has an established role as a biomarker in septic patients and has been shown to correlate closely with infection, it has some limitations: it rises transiently in patients with non-septic conditions and systemic inflammatory response syndromes (SIRS) (e.g., trauma, surgery, heatstroke).

However, PCT can be used as an index of progression to septic shock and multi-organ failure [12]. Two recent studies tried to establish a PCT-algorithm useful to manage sepsis antimicrobial therapy based on plasma PCT levels changes with conflicting results. Bouadma and colleagues showed that this algorithm could reduce antibiotic exposure without apparent adverse outcomes [13], while Jansen et al. showed a prolonged admission to the intensive care units without any improvement in the survival rate [14].

## sCD14-ST or presepsin

Cluster of differentiation 14 (CD14) is a glycoprotein expressed on the membrane surface of monocytes and macrophages (mCD14) and serves as a high-affinity receptor for complexes of lipopolysaccharides (LPSs), a compound from the outer cell wall of Gram-negative bacteria, and LPS-binding proteins (LPBs). CD14 activates the toll-like receptor 4 (TLR4)-specific proinflammatory signaling cascade in order to start the inflammatory reaction against microorganisms [7, 15]. The soluble form of CD14 (sCD14) is directly secreted by hepatocytes: during inflammation plasma proteases activate a cleavage of sCD14 in order to generate a truncated form named sCD14-subtype (sCD14-ST), well known as presepsin.

Membrane CD14 may also function as a receptor for peptidoglycan, a cell wall component of Gram-positive and some Gram-negative bacteria [7].

Presepsin is normally present in very low concentrations in the serum of healthy individuals and has been shown to increase in response to bacterial infections, according to the severity of the disease [16]; however, information about presepsin concentrations in specific populations are very poor. A French study pointed out that presepsin concentrations increase with age and kidney dysfunction in the absence of any infectious sign. Then, an adapted threshold may be necessary in the elderly population and in the case of kidney impairment since the interpretation of presepsin levels could be misleading in these situations [17].

More recent studies confirmed presepsin as a promising biomarker in the diagnosis of sepsis, as well as for assessing the severity and predicting the outcome in septic patients [16, 18–21]. Furthermore, a rapid assay, based on the chemiluminescence enzyme immunoassay principle (called PATHFAST® Presepsin assay, Mitsubishi Chemical Medience Corporation, Tokyo, Japan), is now available and can be used on a point-of-care testing basis [22], thus allowing the emergency physician (EP) to get presepsin values in a short time from whole blood samples [23].

## Diagnostic role and diagnostic accuracy

Several studies compared presepsin diagnostic power to that of PCT in detecting sepsis in patients presenting at the emergency department (ED) with a documented or suspected infection. Endo and colleagues demonstrated similar AUCs for presepsin and for PCT, 0.908 and 0.905,

respectively, in their ability to differentiate between patients with bacterial and non-bacterial infections [21]. In another study the AUC of presepsin was lower than PCT (0.70 vs. 0.87) in a cohort of septic patients [20], even if presepsin was able to significantly differentiate sepsis from SIRS ( $p=0.02$ ), and severe sepsis/septic shock from SIRS ( $p<0.001$ ). In contrast to the latter study, Liu et al. reported that presepsin is a very powerful biomarker, superior to PCT for the diagnosis of sepsis and severe sepsis (AUC for presepsin and PCT were 0.82 and 0.72, respectively, in the case of sepsis and 0.84 and 0.74 in the case of severe sepsis) [19].

Few studies evaluated the role of presepsin in predicting the presence of bacteremia. An Italian study evaluated this relationship in a surgical population (cadaveric-donor organ transplant recipients and abdominal surgery patients). Novelli et al. showed that high presepsin concentrations could indicate the presence of an infection despite clinical absence of septic signs and symptoms when a blood test for presepsin was performed. The presence of infection was confirmed days after study enrollment by positive blood cultures [24]. Some authors found that CRP, PCT and presepsin serum values were significantly higher in the bacteremic population without any differences among the blood culture-positive, -negative and mixed flora groups [7]. In a pediatric oncology population with febrile neutropenia, PCT levels were significantly higher in the sepsis/bacteremia group (where infections were further confirmed with positive blood cultures) compared to the fever of unknown origin (FUO) group (with negative blood cultures) whereas presepsin concentrations did not differ between the two groups [25].

Recent studies compared presepsin values to Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Health Evaluation (APACHE) II scores in patients with sepsis, finding a close correlation between plasma biomarker levels and the severity of the scores [16]. Endo and colleagues confirmed previous studies: presepsin levels correlated with the sepsis diagnosis at hospital admission and with the monitoring of sepsis during the follow-up. During follow-up, marker serum levels were associated with the decreasing trend in SOFA and APACHE II, while other tested biomarkers (such as PCT and CRP) were not [26]. Ulla et al. found a significant correlation only between presepsin values at the first medical evaluation in ED and SOFA scores [20].

The potential influence of presepsin in sepsis-induced disseminated intravascular coagulation (DIC) was studied by considering 11 variables [antithrombin activity, coagulative protein C, thrombomodulin, platelet counts, prothrombin time-international normalized ratio, D-dimer, presepsin, PCT, IL-6, CRP and white blood cell (WBC

count]: presepsin and coagulative protein C (PC) was the best association to predict the severity of sepsis-induced DIC. The AUCs for the combination of presepsin and PC in the patients with and without sepsis and DIC were 0.913 and 0.880, respectively [27].

Few studies evaluated the usefulness of presepsin in the surgical environment. Popov et al. defined the biomarker's ability in predicting clinical complications in cardiac surgical patients (acquired heart valvular diseases with cardiopulmonary bypass) during perioperative period: increased postoperative levels of presepsin were associated with a major risk of infection complications and untoward outcomes [28]. Some authors evaluated presepsin in preoperative diagnosing of abdominal sepsis: the AUC to discriminate SIRS from sepsis was 0.996. Presepsin showed a better diagnostic accuracy when compared to PCT, CRP and WBC count [29].

Cakir Madenci et al. underlined the significant diagnostic role of presepsin in diagnosis and follow-up of sepsis in burn patients. The AUC for detecting sepsis was 0.834, very similar to that of already known biomarkers like PCT and CRP (0.847 and 0.819, respectively) [30].

Diagnostic performance of presepsin was also evaluated in the detection of sepsis-related fatalities using post-mortem femoral blood compared to PCT and CRP. Results indicated that postmortem serum PCT, CRP and presepsin levels allowed septic cases to be identified (AUCs were 0.89, 0.96 and 0.84, respectively). Postmortem biochemical investigations failed in identifying underlying bacterial infections and hidden sepsis status in the control group: none of the subjects included in this group had a documented, clinical diagnosis of sepsis *in vivo* and none had been admitted to the hospital prior to death [31].

## Prognostic role and prognostic accuracy

Recent studies correlated presepsin serum values with mortality: Ulla et al. demonstrated a significant correlation ( $p=0.04$ ) between high presepsin values at the first medical evaluation in ED and 60-day in hospital mortality, data not confirmed with PCT levels [20]. According to Masson and colleagues, high biomarker values, withdrawn at 1, 2 and 7 days after study enrollment, were independently associated with the negative outcome during the hospital stay, on days 28 and 90 after study enrollment, while PCT concentrations were not (AUCs of 0.69, 0.70 and 0.74, respectively, on days 1, 2 and 7; vs. 0.56, 0.55 and 0.64, respectively, for PCT) [32]. Presepsin prognostic

power has also been studied in the context of burns: non-survivors people had significant higher presepsin levels when compared to survivors ( $p < 0.0001$ ). In these studies, PCT and CRP reached equivalent results ( $p < 0.0210$  and  $p < 0.0008$ , respectively) [30].

## Presepsin in neonatology

Despite every year almost one million newborns dying from infections, there are very few studies about presepsin in the neonatology population [9]. A great effort to reduce the neonatal mortality rate is put into looking for new biochemical markers. Nowadays PCT and CRP are used to manage critically ill newborns with sepsis: although they have good diagnostic and monitoring performances, they show very limited values for stratification and in predicting outcomes. Among biomarkers, presepsin could be one of the most interesting and reliable candidates for sepsis management [9], specifically for early diagnosis, the classification into severity degrees, the prediction of complications and death [33]. Mussap et al. studied a group of critically preterm ill newborns with gestational age between 26 and 36 weeks, admitted for various severe diseases in the absence of documented sepsis: no correlation was found between presepsin values and gestational age. Thus it seems reasonable to adopt a unique reference range for preterm population [34].

## Conclusions

Sepsis represents a continuum from an inciting infectious event and the consequent host-pathogen interaction, possibly leading to hemodynamic consequences caused by pro-inflammatory, anti-inflammatory, and apoptotic mediators [35]. In some cases sepsis can evolve into severe sepsis, when documented or suspected infection is associated with multiorgan involvement and failure, or even into septic shock, when hypotension becomes unresponsive to fluid therapy and vasopressors are required. Sepsis, severe sepsis and septic shock are common conditions, very frequently recognized and handled (at least initially) in the ED: strong evidence suggests that early identification and prompt therapeutical intervention are beneficial in affecting outcome [36]. Early recognition of sepsis is not always straightforward and clinical signs at presentation can be misleading and very heterogeneous in the population, especially in patients presenting to the ED, due to frequent comorbidities or variable

demographic characteristics (age, sex, ethnic group). In the emergency setting therefore an urgent need for a reliable diagnostic procedure, allowing early discrimination between SIRS and sepsis, exists. Biomarkers, such as CRP and PCT, recently introduced among the diagnostic criteria of sepsis [5], could contribute to promptly identify patients affected by sepsis, severe sepsis and septic shock who could benefit from quick and appropriate therapy.

CRP demonstrated high sensitivity but very low specificity: it rises as soon as any inflammation process affects the human body but it has limited specificity for bacterial infections. PCT has gained a significant diagnostic role in this field, but this biomarker still retains some important limitations: it tends to rise transiently in non-septic conditions and SIRS, e.g., invasive trauma, surgery, heatstroke and physical exercise [37].

Presepsin is a novel biomarker with high sensitivity and good specificity for sepsis, is readily available in the ED and significantly correlated to in-hospital mortality of patients with severe sepsis and septic shock. Preliminary findings provide a solid basis for its future application even if more insights are needed concerning the pathophysiological conditions associated with presepsin release and a more extensive evaluation of presepsin as a biomarker for severe sepsis and septic shock is advisable. The added value of this biomarker for clinical decision-making in terms of diagnosis, risk stratification and therapy monitoring should also be clarified [32]. There are few studies on the impact of this new biomarker on the antibiotic management of patients and larger studies are required in this field [38].

## Key message

Due to the complexity of sepsis response, it is unlikely that a single biomarker will be sufficient for use in clinical practice. A combination of several sepsis biomarkers may be more effective, but this requires further investigations both on the clinical outcome and cost effectiveness of traditional markers associated with new markers [30]. The availability of easy and fast commercial methods for the automated measurement of sCD14-ST represents a challenge for the evaluation of a new reliable marker of sepsis in all age groups [33].

## Conflict of interest statement

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