Review Article:

PRESEPSIN: NEW BIOMAKER TO EVALUATE EMPIRICAL ANTIBIOTIC THERAPY OUTCOME IN SEPTIC CONDITION

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ABSTRACT

This review presents key publications from the research field of new biomarker of sepsis and other relevant journals during 2009-2015. The results of these experimental studies and clinical trials are discussed in the context of biomarker for sepsis and the accuracy of presepsin for optimising antibiotic therapy. The discussion highlights and summarises articles on three main topics: diagnostic and prognostic biomarkers, presepsin as new biomarkers, and outcome studies. According to the review, presepsin is specific biomarker for bacterial infections compare with CRP and PCT. It may be useful to evaluate the empirical antibiotic outcome in sepsis condition.

Keywords: Septic condition; antibiotic therapy; biomarker; presepsin; bacterial infection; CRP; PCT

ABSTRAK

Ulasan ini menyajikan publikasi utama dari bidang penelitian biomarker baru sepsis dan jurnal terkait lainnya selama 2009-2015. Hasil penelitian eksperimental dan uji klinis ini dibahas dalam konteks biomarker untuk sepsis dan keakuratan presepsin untuk mengoptimalkan terapi antibiotik. Diskusi menyoroti dan merangkum artikel tentang tiga topik utama: biomarker diagnostik dan prognostik, presepsin sebagai biomarker baru, dan studi hasil. Menurut ulasan, presepsin adalah biomarker spesifik untuk infeksi bakteri dibandingkan dengan CRP dan PCT. Mungkin bermanfaat untuk mengevaluasi hasil antibiotik empiris dalam kondisi sepsis.

Kata kunci: Kondisi septik; terapi antibiotik; biomarker; presepsin; infeksi bakteri; CRP; PCT

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INTRODUCTION

Sepsis is a state caused by microbial invasion from a local infectious source into the blood stream which leads to signs of systemic illness in remote organs. This was the first scientific definition of sepsis proposed by Dr. Schottmuller in 1914. Sepsis, septicemia, and bloodstream infections (bacteremia) were considered to refer to the same clinical condition, and in practice, the terms were often used interchangeably (Camacho 2014).

Sepsis, severe sepsis and septic shock are some of the most common conditions handled in the Emergency Department (ED) and ICU, and, despite modern antibiotic therapy in conjunction with cardiovascular and respiratory support, mortality rates remain between 30% and 60% (Ulla et al 2013). It is a major concern to physicians because of high levels of antibiotic consumption and of the increasing prevalence of antimicrobial resistance. Thus, they lack accuracy to tailor subsequent therapy (Camacho 2014). According to the most recent guidelines, published in 2013 by the Surviving Sepsis Campaign, early recognition of these conditions and the speed and appropriateness of therapy in the initial hours after presentation are likely to influence the outcomes of septic patients (Ulla et al 2013).

The major problem threatening the continued success of antimicrobial drugs is the development of resistant organisms. Microorganisms can adapt to environmental pressures in a variety of effective ways, and their

response to antibiotic pressure is no exception. An inevitable consequence of antimicrobial usage is the selection of resistant microorganisms, perhaps the most obvious example of evolution in action. Overuse and inappropriate use of antibiotics in patients has fueled a major increase in prevalence of multidrug-resistant pathogens. Antibacterial antibiotics are misused by providers in a variety of ways, including use in patients who are unlikely to have bacterial infections, use over unnecessarily prolonged periods, and use of multiple agents or broad spectrum agents when not needed (Katzung et al 2012).

Blood culture is considered as the criteria on standard for diagnosis of sepsis, but it takes several days to obtain the blood culture results. In addition, blood culture has a low sensitivity and a high contamination rate. Therefore, the diagnosis of sepsis generally depends on the physician's experience; furthermore, the nonspecific symptoms of sepsis make it difficult to establish the diagnosis based on clinical findings alone (Kweon et al 2014). Blood cultures to detect bloodstream infections are the mainstay of such attempts when patients do not display localizing signs or symptoms. The presence of SIRS has been shown to increase the likelihood that the blood culture will be positive but blood cultures are often negative in patients with clinical sepsis (Camacho 2014).

More recently, the biomarkers used as diagnostic criteria for sepsis, plasma C-reactive protein (CRP) or procalcitonin (PCT) levels more than 2 standard deviations (SD) above the normal value, are now part of the inflammatory variables which, together with infection, whether documented or suspected, constitute a definition of sepsis (Ulla et al 2013). Various biomarkers such interleukin 6 (IL-6), tumor necrosis factor, and high-sensitivity C-reactive protein (hs-CRP) are used as the diagnostic markers for bacterial sepsis. Among them, PCT is known to have a high specificity for diagnosing sepsis compared with the other biomarkers (Hou et al 2015).

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. In conditions without bacterial infection, such as severe trauma, invasive surgical procedure, and critical burn injuries, PCT levels could increase beyond the reference range, thus resulting in false-positive results (Ulla et al 2013, Yu et al 2017).

Furthermore, biological predictors of mortality are absent, clinical scores appear to be of limited value and the role of PCT as a poor prognostic factor in patients admitted to the emergency department because of sepsis

remains to be proved (Ulla et al 2013). The ideal biomarker should retain high sensitivity and specificity and be cost-effective and promptly available.

Cluster of differentiation 14 (CD14) is a glycoprotein expressed on the membrane surface of monocytes and macrophages and serves as a receptor for lipopolysaccharides (LPSs) and LPS-binding proteins (LPBs). By activating a pro inflammatory signaling cascade on contact with infectious agents, CD14 has a role as a recognition molecule in the innate immune response against microorganisms (Camacho 2014).

During inflammation, plasma protease activity generates soluble CD14 (sCD14) fragments. One of them, called sCD14 subtype (sCD14-ST), or presepsin, is normally present in very low concentrations in the serum of healthy individuals and has been shown to be increased in response to bacterial infections. Plasma levels of presepsin can be measured using an automated chemoluminescent assay (PATHFAST) (Camacho 2014).

Similar to other reported Biomarkers, the distribution of presepsin values is slightly different, with a small overlap between healthy controls (294.2 ± 121.4 pg/ml) and septic patients (817.9 ± 572.7 pg/ml) (Shozushima et al 2011). Moreover, the level of presepsin typically increases within 2 h and reaches the peak in 3 h after infection (Okamura & Yokoi 2011). By using the chemoluminescence enzyme immunoassay as detecting tool, the result can be available in 1.5 h (Shirakawa et al 2011). The above evidence indicates that presepsin might be a better biomarker for sepsis during the early stage of sepsis than in later stages (Wu et al 2017).

No single biomarker of septic condition may be ideal, but many are helpful in terms of evaluate antibiotic therapy outcome in critically ill patients who need close monitoring, so that the antibiotic therapy may be modified or stopped as soon as possible. This review will discuss the accuracy of presepsin as new biomarkers to evaluate empirical antibiotic outcome in sepsis condition.

Biomarker for sepsis

Despite the use of modern antibiotics and bundle treatment, sepsis related mortality remains unacceptably high in modern intensive care medicine. During the previous two decades, biomarkers have been used as early indicators of sepsis and surrogate indicators for severity, response to therapy, and outcomes. However, only a few of these biomarkers are ideal for sepsis (Yu et al 2017).

Sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs. Sepsis occurs in 1-2 % of all hospitalizations, and it is the eading cause of mortality in critically ill patients. However, rapid and accurate diagnosis of sepsis is often difficult in routine clinical practice because the clinical manifestations of this condition can overlap with many non-infectious causes of systemic inflammation, such as pancreatitis, ischemia, multiple trauma, and hemorrhagic shock, which are collectively (Zheng et al 2015).

Many biomarkers can be used in sepsis, but none has sufficient specificity or sensitivity to be routinely employed in clinical practice. PCT and CRP have been most widely used, but even these have limited abilities to distinguish sepsis from other inflammatory conditions or to predict outcome. In view of the complexity of the sepsis response, it is unlikely that a single ideal biomarker will ever be found (Camacho 2014). Although CRP and PCT are the preferred biomarkers to be used in clinical context currently (Julian-Jimenez et al 2014, Kibe et al 2011), some issues for their diagnostic accuracy still remain unsolved, which prevent clinicians from starting or withholding antimicrobial therapy (Wu et al 2017).

CRP is a protein produced in response to infection and/or inflammation and it is widely used in clinical tests to diagnose and manage patients with sepsis. This biomarker is an acute phase reactant whose synthesis in the liver is upregulated by IL-6.The CRP's role during acute inflammation is not entirely clear and it may bind the phospholipid components of microorganisms, facilitating their removal by macrophages. Because the levels of CRP rise significantly during acute inflammation, this biomarker has been used for decades to indicate the presence of significant inflammatory or infectious disease, especially in pediatric (Camacho 2014). Although its low specificity may be its primary drawback as a biomarker of sepsis in adults, it is commonly used to screen for early onset sepsis in neonatology (Hofer et al 2012).

CRP has been tested in various conditions, but only a few of these studies have focused on its use for optimising antibiotic therapy. A single, prospective, randomized, controlled trial performed in the 1990s in children is available. Other studies have compared an intervention group to historical controls. Despite the few available studies confirming its usefulness, CRP measurements are widely used in children to adjust the duration of therapy (Dupuy et al 2013).

Several studies show the usefulness of CRP measurements as an aid to shorten the duration of therapy in adult patients having sepsis, community-acquired pneumonia or exacerbation of chronic obstructive pulmonary disease (COPD). Pending results from these studies, the use of CRP cannot be recommended at present as an aid to the initiation or discontinuation of antibiotics in adults; in children. However, CRP can probably be used to help discontinuing therapy, although the evidence is limited (Dupuy et al 2013). Although CRP is another commonly used biomarker in the clinical context, previous studies revealed that its diagnostic accuracy for sepsis is significantly lower than PCT (Tang et al 2007).

Procalcitonin is a pro hormone (peptide precursor) of calcitonin that is released by parenchymal cells, including liver cells, kidney cells, adipocytes, and muscle cells in response to bacterial toxins, leading to elevated serum levels (up to 5000 - fold) within 2 to 4 hours. In contrast, procalcitonin is down regulated in patients with viral infections (Gilbert 2010). The biological half-life of PCT is 22 to 26 hours, an advantageous time point compared with CRP and other acute-phase reactants (Limper et al 2010). Although elevations of PCT can be observed in noninfectious disorders, especially following trauma (Billeter et al 2009), at present, PCT levels have been used to guide empirical antibacterial therapy in patients with acute exacerbations of chronic bronchitis, community-acquired pneumonia (CAP), and sepsis. Also, PCT levels, along with standard clinical parameters, can assist in determining whether the patient's empirical antibacterial therapy is effective (Schuetz et al 2011). Higher PCT levels have been associated with increased mortality rates and correlated with severity scores (APACHE, SOFA, and SAPS) (Vincent & Beumier 2013). Finally, the most useful application is the use of sequential PCT levels to determine if antibacterial therapy can be stopped (Manian 2012).

Procalcitonin has been more widely tested for optimising antibiotic therapy in both children and adults. In adults presenting with community-acquired lower respiratory tract infections (LRTI), several randomized, controlled trials (RCTs) have tested the use of PCT as an aid to the initiation and/or discontinuation of antibiotics and have been summarised in a recent individual patient meta-analysis (Christ-Crain et al 2006, Briel et al 2008). Four of these studies enrolled more than 900 patients hospitalised in intensive care or high dependency units (Nobre et al 2008, Hochreiter et al 2009, Stolz et al 2009, Bouadma et al 2010). Two well-designed studies have been performed in children: one study included 121 neonates having early sepsis (Stocker et al 2010) and another studied 384 children aged 1 to 36 months with acute fever of undetermined origin (Dupuy et al 2013).

In view of these studies, the inclusion of PCT measurements within decision algorithms of antibiotic management for specific infections is likely appropriate. However, further studies are needed in infections which have been insufficiently examined so far (i.e., most infections other than LRTI) to better define the role of PCT in the antibiotic strategy (Dupuy et al 2013).

Presepsin (formerly CD14), is a glycoprotein receptor occurring at the surface of monocytes/macrophages. CD14 binds to lipopolysaccharide (LPS) complexes and LPS binding protein (LPB), which triggers the activation of toll-like receptor 4 (TLR4), resulting in the production of numerous pro-inflammatory cytokines. Following Presepsin activation by bacterial products, the CD14 complex is released in the circulation as its soluble form (sCD14), which in turn is cleaved by a plasma protease to generate a sCD14 fragment called sCD14-subtype (sCD14-ST). Plasma levels of sCD14 can be measured using an automated chemo-luminescent assay (PATHFAST, Ingen, France) (Dupuy et al 2013).

In a multicenter prospective study (106 patients with suspected sepsis or septic shock were included and 83 SIRS patients without infection), elevated concentrations of presepsin were observed in septic patients compared to control patients (Charles et al 2009). The best diagnostic cutoff for presepsin was 600 pg/mL with sensitivity of 78.95% (95% CI, 69.4 to 86.6) and specificity of 61.90% (95% CI, 50.7 to 72.3). There was no difference between levels of presepsin and sepsis severity. Moreover, the area under the curve (AUC) calculated for PCT was wider, demonstrating a better diagnostic accuracy than presepsin. Although presepsin showed a significant prognostic value and initial values were significantly correlated with in-hospital mortality of patients affected by sepsis, severe sepsis, or septic shock, two recent studies have shown that presepsin is an useful biomarker for early diagnosis of sepsis and evaluation of prognosis in septic patients (sensitivity: 71- 72%, specificity: 70-86%, and NPV: 52-71%) (Masson et al 2014, Liu et al 2013). In the study to evaluate the value of dynamic procalcitonin and presepsin measurements for patients with severe sepsis that was conducted by Yu et al (2017) showed that presepsin in the circulation was superior to that of PCT.

The accuracy of presepsin for optimising antibiotic therapy

Immunity against a microorganism relies primarily on the activity of monocytes and macrophages that recognize pathogen-associated molecular patterns,

partly via cluster-of-differentiation marker protein 14 (CD14), which has an immediate response against lipopolysaccharides (LPS) (Medzhitov & Jr 2000). After LPS binds to CD14 via the LPS-binding protein, a subtype of soluble CD14 (presepsin) is released into the blood (Chenevier-Gobeaux et al 2015). Previous clinical studies demonstrated that presepsin levels performed well for early diagnosis, risk stratification, and prognosis of sepsis (Endo et al 2014, Kweon et al 2014, Zheng et al 2015, Behnes et al 2014, Liu et al 2013). In addition, changes in presepsin levels seem to reflect the appropriateness of antibiotic therapy (Masson et al 2015). A previous comparison of the prognostic value between presepsin and PCT in patients with sepsis was limited to only 7 days (Masson et al 2014). Furthermore, few studies have compared the value of evaluating the severity of severe sepsis over time (Yu et al 2017).

The study was conducted by Yu et al (2017), evaluating therapeutic efficacy and prognostic value of dynamic presepsin and PCT levels for severe sepsis within 12 days. First, the results suggest that presepsin had a better and earlier correlation with SOFA than did PCT. Second, CR (clearance rate) of presepsin had an earlier and better correlation with SOFA than did CR of PCT. Third, PCT levels in both survival and non-survival groups declined synchronously with time. Presepsin levels also declined gradually in the survival group, while they rose in the non-survival group. Fourth, CR of PCT in both survival and non-survival groups rose synchronously. CR of presepsin rose in the survival group and declined in the non-survival group (Yu et al 2017).

Compared with PCT, presepsin is a highly specific diagnostic biomarker for bacterial infections because it is cleaved from the monocyte/macrophage-specific CD14 receptor complex after LPS binds to CD14 (Yu et al 2017). Presepsin tends to increase in patients with positive microbiology findings and inappropriate antibiotic therapy (Masson et al 2015). Therefore, dynamic monitoring for presepsin helps to evaluate the infection.

The release of presepsin is related to recognition of pathogen recognition bymonocytes/macrophages, so persistent high levels or increases of presepsin reflect the continuous existence of infection and interaction between immunity and pathogens. Indeed, more severe sepsis is accompanied by higher presepsin levels, and persistent high levels of presepsin predict a more adverse outcome. Likewise, decreases of presepsin levels could, in a sense, reflect clearance of pathogens. Therefore, both presepsin itself and the CR of presepsin are relatively ideal prognostic biomarkers, and

consistently monitoring presepsin helps to evaluate the prognosis in the whole course of severe sepsis. As a biomarker for evaluating therapy and prognosis, dynamically monitoring presepsin is better than PCT (Yu et al 2017).

In addition, presepsin kinetics were also related to the outcome, suggesting a close relationship between the biomarker course and the effectiveness of both host response and the therapies used (Charles & Gibot 2014). PCT kinetics was shown to be tightly related to clinical outcome and thus better than calculating the SOFA score daily and measuring blood lactate variations (Charles et al 2009). However, it should be pointed out that PCT concentrations were not measured daily, but only on days 1, 2, and 7. The half-life of presepsin may be longer than that of PCT and the kinetics therefore slower (Charles & Gibot 2014).

CONCLUSION

According to the review, presepsin is specific biomarker for bacterial infections compare with CRP and PCT. It may be useful to evaluate the empirical antibiotic outcome in sepsis condition.

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