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Review Article

Sepsis Biomarkers: A Brief Review

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Abstract

Sepsis is a prevalent issue in critically ill patients, both as a cause of admission to critical care units and also as a healthcare-associated infection. Sepsis is a significant cause of mortality in critically ill patients across age groups. Effective early antibiotic therapy decreases both morbidity and mortality. However, differentiating sepsis from the Systemic Inflammatory Response Syndrome (SIRS) has become one of the holy grails of medicine. To improve outcomes, early diagnosis and monitoring of monitoring are of utmost importance. Many biomarkers have been proposed to differentiate Sepsis from SIRS. The usefulness of a biomarker is enhanced if it also provides information on the effectiveness of therapy. In this mini-review, we discuss conventional and newer biomarkers for sepsis diagnosis. The challenge will be to identify the most cost-effective markers and how to incorporate such a panel into daily clinical practice. Procalcitonin and CRP are commonly used, but both have significant limitations in application. A combined panel of novel and traditional markers reflecting different aspects of the human body's response to infection is an attractive proposition and warrants further investigation.

Keywords: Sepsis; Biomarkers; SIRS; Procalcitonin

Introduction

Sepsis is a prevalent issue in critically ill patients, concerning both admission to the critical care unit and also as a significant problem with healthcare-associated infection following admission. Early initiation of antibiotics is shown to reduce the morbidity and mortality in patients with sepsis. However, a substantial number of critically ill patients have Systemic Inflammatory Response Syndrome (SIRS) and thus, distinguishing between SIRS and Sepsis has become one of the holy grails of medicine.

To be clinically useful, a sepsis biomarker needs to provide information additional to that already available from established clinical assessments and investigations. To achieve this, the biomarker must accurately differentiate Sepsis from SIRS, predict prognosis and be available in a timely, cost-effective manner. The utility of a biomarker can be further enhanced if it serves as a guide to therapy effectiveness. We discuss a few of the newer biomarkers and a few conventional markers in this mini-review.

Procalcitonin

Procalcitonin (PCT) is a precursor of the hormone calcitonin and is synthesized physiologically by thyroid C cells. In normal conditions, PCT levels in the serum are low (<0.1 ng/mL). However, in bacterial infection, PCT is synthesized in various extra-thyroidal neuroendocrine tissues. Bacterial infections cause the greatest increases in PCT, with lower or negligible elevations in localized, viral and intracellular infections (e.g., *Mycoplasma pneumoniae*) [1]. There is evidence that Gram-negative bacteremia causes higher PCT rises than Gram-positive bacteremia. PCT levels begin to rise four hours after the onset of systemic infection and peak between 8 and 24 hours. Reflecting this, the American College of Critical Care Medicine and the Infectious Diseases

Society of America have recommended using serum PCT as an adjunctive diagnostic tool to discriminate between infection as the cause of fever and sepsis [1]. Given that PCT can be elevated in certain non-infective conditions, it is probably better used to rule out than rule in systemic bacterial infection.

Serum PCT levels have also been noted to increase with increasing severity of sepsis and organ dysfunction [2]. It is found that a high maximum PCT and also an increase in PCT value from a baseline of >1.0 ng/mL were both independent predictors of 90-day mortality. The relative risk of mortality increases with each day the PCT value continues to rise after the first reading >1.0 ng/mL: 1.8 for 1 day, 2.2 for 2 days and 2.8 for 3 days.

The use of PCT has also been extended for antimicrobial stewardship. With serial PCT measurements, antibiotics can be safely discontinued once the PCT level falls below a predefined cut-off. PCT variations between Day 2 and Day 3 are shown to be critical, as a significantly greater PCT decline during this period was expected in patients with appropriate empirical antibiotic therapy. As a result, it was suggested that patient management might be reassessed if PCT does not decrease by 30% between Day 2 and Day 3 [3].

Serum Oestradiol

Sexual dimorphism has been widely considered important in the outcome of patients with sepsis. In critical illness, serum estradiol concentrations are elevated [4]. The estrogens are produced in many peripheral tissues (primarily adipose tissue), where the aromatase enzyme catalyzes the conversion of androgens to estrogens. Whereas the stress and inflammation in response to critical illness inhibit the central production of estrogens, peripheral biosynthesis is stimulated. Although it is inferior to APACHE II, serum estradiol concentration at 48 h is a useful single-variable predictor of death. Estradiol concentrations above 50 pg/mL are 48% sensitive and 80% specific for predicting death.

Eosinopenia

Eosinopenia is an attractive potential biomarker in sepsis, as eosinophil counts are already serially measured in routine clinical practice. A study found an AUROC of 0.89 for an eosinophil count cut-off of 50 cells/mm^3 in differentiating between non-infected and infected patients in a medical intensive care unit. Although this is promising, other studies have found that CRP (>70 mg/L) and PCT (>1.5 ng/mL) outperformed eosinopenia as markers of sepsis (negative predictive values of 94%, 87% and 80%, respectively) [5].

Biomarkers of Coagulation

Changes in coagulation biomarkers have also been demonstrated in severe sepsis, with activated Partial Thromboplastin Time (aPTT) waveform analysis showing considerable clinical potential [6]. The aPTT time is correlated with the Multi-Organ Failure (MOF) score in patients with Sepsis and Disseminated Intravascular Coagulation (DIC) and has a high negative predictive value. Another study showed an aPTT biphasic waveform to be more useful than PCT or CRP in distinguishing severe sepsis and septic shock, being significantly higher during days 1-3 in those who died of sepsis compared with those who did not or those who died of non-sepsis causes.

Many other coagulation factors have also been studied as biomarkers of sepsis, like Antithrombin, D-dimer, Thrombin-antithrombin complex, Prothrombin Time, Fibrin, Platelet Factor-4, Plasminogen activator inhibitor (PAI)-1, Protein C and S, Thrombomodulin, which help in predicting the development of MOF and mortality, DIC and response to therapy.

Serum Lactate

Hyperlactatemia is associated with increased morbidity and mortality in critically ill patients. Even hemodynamically stable patients with raised lactate levels, a condition referred to as compensated shock, are at increased risk of dying. Even in patients with normotension, those with increased blood lactate levels (>4.0 mmol/l) had ten times higher mortality rate compared to those with normal lactate levels [7]. In addition to the anaerobic response to tissue hypoxia, aerobic processes can also raise lactate levels in critically ill patients. First, increased aerobic glycolysis can lead to pyruvate production exceeding the capacity of the Pyruvate Dehydrogenase Enzyme complex (PDH). Secondly, sepsis-induced dysfunction of Pyruvate Dehydrogenase has also been reported. Thirdly, lactate is also produced by the lung, which could probably reflect inflammation-induced metabolic adaptations. Impaired lactate clearance in sepsis has also been associated with hyperlactatemia. Lactate clearance is defined as

the percentage decrease in lactate over the initial 6-hour evaluation and treatment period. It is shown that higher lactate clearance is associated with lower mortality. In fact, mortality was reduced by approximately 11% for each 10% increase in lactate clearance. Patients with a lactate clearance >10% had a greater improvement in APACHE II scores and lower 60-day mortality [8].

Serum Cholesterol

Serum cholesterol levels are altered during sepsis and low cholesterol levels are associated with increased mortality. It is not clear whether low concentrations are due to the inflammatory response or whether low lipoprotein levels predispose patients to infection. Epidemiologic studies have identified a relationship between hypocholesterolaemia below 130 mg/dL and increased mortality from all causes [9]. It is also found that low levels of High-Density Lipoprotein (HDL) cholesterol on admission are associated with increased mortality in sepsis. Overall mortality, sepsis-related mortality, risk of prolonged ICU stay and rate of hospital-acquired infection are increased in patients who have HDL cholesterol levels of less than 20 mg/dL and apolipoprotein A-I levels of less than 100 mg/dL. There are many reasons suggested for the hypocholesterolaemia seen in critically ill patients. Still, the one that seems pertinent for patients with sepsis concerns the ability of lipids and Lipoproteins to bind to and neutralize bacterial endotoxin (LPS) from gram-negative microorganisms, as well as lipoteichoic acid from gram-positive microorganisms [10,11]. Thus, it can be presumed that hypocholesterolaemia in these patients might have contributed to inflammation by impairing LPS neutralization.

Serum Uric Acid

Serum Uric Acid (UA) is a potent free-radical scavenger and increases in response to acute oxidative stress. There is a significant increase in serum UA in patients with severe sepsis and septic shock. Serum UA is an essential contributor to serum total antioxidant capacity. The mechanism for hyperuricemia in sepsis and septic shock is not clearly elucidated. Sepsis can cause both increased production and decreased excretion of UA. Severe sepsis and septic shock may induce ischemia or hypoxia in multiple organs, further increasing the conversion of xanthine/hypoxanthine to UA by activating xanthine oxidase in microvascular endothelium [12]. On the other hand, renal dysfunction induced by septic shock may reduce the secretion of UA from the kidneys, which may increase serum UA. The studies indicate that hyperuricemia might be associated with poorer clinical outcomes in sepsis.

Presepsin

Presepsin is the soluble subtype of Cluster of Differentiation 14 (CD14) glycoprotein. CD 14 is a cell surface receptor on macrophages and monocytes for the binding of lipopolysaccharides (LPS) and associated binding proteins. During sepsis, presepsin levels increase significantly and can be used to differentiate bacterial from non-bacterial infections. Presepsin levels are very low in healthy individuals and rise rapidly within 2 hours in patients with sepsis, correlating with sepsis severity [13]. A diagnostic cut-off of 400-600 pg/ml has been suggested for the diagnosis of sepsis [14,15].

Ulla, et al., conducted a prospective multicenter study on 106 patients suspected of having sepsis and septic shock and on 83 patients with SIRS. They found that presepsin levels were more elevated in patients with sepsis and a cut-off value of 600 pg/mL had a specificity of 61.90% (95% CI, 50.7 to 72.3) and a sensitivity of 78.95% (95% CI, 69.4 to 86.6) [15]. However, the levels did not correlate with the severity of sepsis. Also, they suggested that PCT showed greater accuracy in diagnosing sepsis than presepsin. Presepsin is also found to be elevated in patients with kidney disease, due to reduced glomerular filtration and decreased catabolism in the proximal tubule. Hence, the significance of elevated presepsin levels in renal failure needs to be better evaluated [16,17].

Actin

Actin is present in monomeric or polymeric form in all eukaryotic cells. It plays an essential role in many cellular functions, including cytoskeletal formation, cell division, cell motility and sarcomere contraction [18]. It is released from the cells when there is a massive cellular injury and has many toxic effects, including platelet activation, endothelial dysfunction, small-vessel occlusion, etc and may lead to multi-organ dysfunction [19,20]. The released actin is removed by the actin scavenger system, which mainly comprises the proteins Gelsolin and Gc-globulin. However, during sepsis, this scavenger system is overwhelmed due to the massive release of actin [21].

In view of this, it was presumed that circulating actin levels could be used to assess disease severity. The serum levels of actin were, however, found to be only non-significantly higher in sepsis compared to controls [3.5 (1.6-6.1) mg/L vs 3.0 (2.1-3.7) mg/L, respectively] [22].

On the other hand, urine levels of actin showed significantly higher levels in patients with sepsis-induced Acute Kidney Injury (AKI) compared to septic patients without AKI [8.17 (2.09-45.53) ng/mL vs. 4.03 (091-10.21) ng/mL, respectively]. Patients needing dialysis had further increased urinary levels [36.02 (4.7-176.56) ng/ml]. Urinary actin levels correlated significantly with serum creatinine ($p<0.01$), whereas serum actin levels did not [23]. Therefore, urinary actin levels could be an early biomarker for the diagnosis of sepsis-induced AKI.

Gelsolin

Gelsolin (GSN) is a member of the actin-scavenging system, which breaks down actin filaments and depolymerizes them. GSN has also been found to bind other molecules, such as platelet-activating factor, fibronectin, LPS and other inflammatory mediators. GSN has been shown to have significant accuracy in differentiating sepsis from controls and other inflammatory states and also in outcome prediction of sepsis, with levels being lower in sepsis nonsurvivors [22,24-26]. Also, serum actin/Gelsolin ratio has also been proposed and shown to have similar prognostic accuracy for ICU mortality as APACHE II scores [22].

GC-Globulin

GC- Globulin is another member of the actin scavenger system and is produced predominantly by the liver. It is also an acute phase reactant and acts as Vitamin D binding protein, modulates T cell activity, increases chemotaxis of neutrophils, etc. [27]. It has been shown that plasma Gc-globulin levels below 134 mg/L at admission are associated with pulmonary or hematologic dysfunction [28]. It is also shown that levels of Gc-globulin and Vitamin D (25-hydroxy) are reduced in patients with critical illness [29].

Orosomucoid

Orosomucoid (ORM) is another acute phase reactant with important immune modulating activity, including inhibition of apoptosis, inhibiting neutrophil or complement activity, platelet aggregation, etc. [30,31]. Serum levels of ORM rise during any inflammatory state, with a higher rise during sepsis. When combined with the SOFA score, serum ORM levels at admission had good accuracy for predicting sepsis outcome (AUROC: 0.878) [32,33]. Urinary ORM has also generated significant interest and is suggested to be another marker for sepsis diagnosis. The urine levels are found to be elevated up to 10 times in patients with SIRS, while they are about 100 times elevated in patients with sepsis [34]. A ratio of urinary ORM and urine creatinine at a cut-off of 6.75 mg/mmol had a sensitivity of 94.7% with a specificity of 90.0% for sepsis diagnosis. Urinary ORM appears to be a better sepsis biomarker compared to serum ORM.

Pro-Adrenomedullin

Adrenomedullin is a peptide with bactericidal activity, an immunomodulator and a vasodilator and can be helpful for diagnosing sepsis and prognosticating its course [35]. ADM is unstable and therefore, the levels of fragments of its prohormone (pro-ADM) are assessed in body fluids. Among pro-ADM fragments, the mid-region fragment between 45 and 92 amino acids (MR pro-ADM) is more stable and has been studied in patients with septic shock [36]. The ratio of pro-ADM and the precursor of endothelin-1 had higher prognostic accuracy than CRP and was comparable to the APACHE II score [37].

Suberviola, et al., conducted a single-centre study in a Spanish ICU involving 137 patients. They showed that pro-ADM was a stronger predictor of in-hospital mortality (OR = 3.00, 95% CI 1.06-8.46) than CRP or PCT. However, the prognostic accuracy of APACHE II and SOFA was better than that of the biomarkers [38]. Angeletti, et al., compared PCT and MR pro-ADM for the diagnosis of sepsis. They found that at a cut-off of 1 nmol/L, MR pro-ADM had an AUC of 0.977. The combination of MR pro-ADM with PCT gave a significant post-test probability of 0.998 in patients with sepsis [39].

Interleukin (IL)-27

IL-27 is secreted by antigen-presenting cells in response to antigenic stimulation and has been suggested as a marker for the diagnosis of sepsis in children [40-42]. Hanna, et al., found that IL-27 could be a valuable marker for the diagnosis of bloodstream

infections in children and could be particularly helpful even in immunocompromised children [43]. The AUCs for IL-27 and PCT were 0.64 (0.59 to 0.68) and 0.61 (0.56 to 0.65), respectively. In analyzing blood culture-proven sepsis, the AUCs for IL-27 and PCT improved to 0.75 (0.68 to 0.81) and 0.64 (0.57 to 0.71), respectively. IL-27 had a specificity of 95% (92% to 97%) for the diagnosis of bloodstream infections at a predetermined cut-off of 5.0 ng/mL.

Metabolome

The metabolomes of patients at hospital admittance who would die differed markedly from those who would survive. They differed consistently across several sets of patients and diverged further as death approached. Given the consistency of metabolomic changes between sepsis survivors and nonsurvivors, a biomarker panel was developed and assessed for its utility in predicting sepsis outcomes upon arrival at the emergency room. Seven biomarkers were selected for the panel. These were 4-cis-decenoylcarnitine, 2-methylbutyroylcarnitine, butyroylcarnitine, hexanoylcarnitine, lactate, age and haematocrit. The biomarker panel had strong predictive discrimination between sepsis survival and death.

Carnitine esters with medium- or short-chain fatty acids and branched-chain amino acids were the most pronounced biochemical groups that differed between the sepsis nonsurvivor group and the survivor group. Carnitine plays an essential role in facilitating the transport of medium- and long-chain fatty acids from the cytosol into mitochondria for β-oxidation and energy generation and in preventing the accumulation of toxic acyl-CoA compounds.

Plasma acyl-carnitine levels across all fatty acid lengths were elevated in sepsis nonsurvivors [44]. It's suggested that there is a profound defect in fatty acid β-oxidation in sepsis nonsurvivors, which is absent in sepsis survivors. Chronic conditions, including kidney diseases, diabetes mellitus, heart failure, cirrhosis and critical settings such as trauma, have also been associated with carnitine deficiency [45]. A logistic regression model using carnitine esters and clinical variables consistently categorized survivors with greater than 85% accuracy, while sepsis nonsurvivors were accurately predicted with 45 to 55% accuracy across most test sets. This model performed better than capillary lactate, SOFA or APACHE II scores. It should be noted that prognostic performance increased as time-to-death decreased.

Furthermore, PPARα expression is decreased in septic shock and correlates with severity [46]. While clinically untested, these results suggest that treatment of selected patients with PPAR agonists may improve sepsis outcomes through increased β-oxidation in heart, liver and kidney tissues.

A significant negative finding is that the plasma metabolome did not differ between sepsis survivors, severe sepsis survivors and septic shock survivors. Sepsis survivors may represent a molecular continuum, irrespective of progression to severe sepsis or septic shock or class of infective agent.

Pro-Atrial Natriuretic Peptide

Pro-ANP (Atrial Natriuretic Peptide), measured on admission, also significantly predicted mortality and performed similarly to the APACHE II score and PCT. Pro-ANP was also found to predict mortality when measured on days 0 and 4 in patients with VAP. Plasma brain natriuretic peptide level measured on day 2 has also been shown to have potentially useful prognostic value in septic shock [37]. Resistin has also been shown to be significantly elevated during the first 2 weeks following admission in severe sepsis and septic shock patients compared with healthy controls. Resistin correlated well with APACHE II and SOFA scores [47,48].

Conclusion

The above studies, whilst not an exhaustive review of biomarkers in sepsis, demonstrate the wide range of potentially clinically useful biomarkers currently under investigation. The challenge will be to identify the most cost-effective markers and how to incorporate such a panel into daily clinical practice. PCT and CRP are commonly used, but both have significant limitations in application. Thus, a panel of biomarkers could be proposed to improve the diagnostic and prognostic accuracy. The combined panel of novel and traditional markers, reflecting different aspects of the human body's response to infection, is an attractive proposition and warrants further investigation.

Conflict of Interest
The authors have declared that no conflict of interest exists.

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Ethical Approval
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Author Contributions
All authors contributed to the study conception and design. HN, HA, SSAB and VKB performed material preparation, data collection and analysis. SSAB wrote the first draft of the manuscript and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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