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An Overview on Biomarkers of Sepsis and Septic Shock

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Abstract:

Sepsis is a life-threatening condition characterized by dysregulated host response to infection leading to organ dysfunction. Despite advances in understanding its pathology, sepsis remains a global health concern and remains a major contributor to mortality. Timely identification is crucial for improving clinical outcomes, as delayed treatment significantly impacts survival. Accordingly, biomarkers play a pivotal role in diagnosis, risk stratification, and management.

Keywords: Sepsis, Septic Shock, Diagnosis.

Introduction

Sepsis is a condition of life-threatening organ dysfunction caused by a dysregulated host response to infection. Potentially affecting as many as 20 million individuals globally each year **(1)**.

The consequences of sepsis include prolonged length of stay in ICU , long-term morbidity, and increased short-term and long-term risk of death **(2)**.

Despite many years of active and intense research, no specific interventions have been identified for the treatment of sepsis, and management relies on adequate resuscitation and organ support combined with eradication of the infecting microorganism with antibiotics and source control **(3)**.

The most important aspect of management for patients with sepsis is to institute appropriate measures as soon as possible in the course of the disease. But identifying sepsis can be complicated, especially early in its course when signs and symptoms are nonspecific and present in many individuals without as well as those with sepsis. Moreover, microbiological information may not be available because cultures are still pending or remain negative in part because some patients with suspected sepsis are already receiving antimicrobial therapy and in part because microorganisms are not always present in the blood. Identifying sepsis may also be difficult in specific populations, such as neonates, and in specific circumstances, such as polytrauma or pancreatitis **(4)**.

Because sepsis is a clinical picture corresponding to the effects of organ dysfunction due to an infection, no specific test can identify it. However, the host response associated with infection can be easily quantified. Indeed, as we have begun to discover the pathophysiology and mechanisms of sepsis, some of the multiple molecules involved in the complex systemic response to organisms have been identified and proposed as potential biomarkers or indicators of sepsis. Some of these biomarkers are known to play key roles in the immune response, while others are more innocent bystanders. Either way,their concentrations change as a reflection of the host response, providing an indication of the presence or severity of sepsis **(5)**.

C-Reactive Protein

CRP was first described in the early 1930s, and CRP levels are widely used as a relatively nonspecific marker of inflammation. Many studies have now been published that demonstrated increased CRP levels in patients with sepsis **(6)**.

As an acute phase protein, however, CRP levels are increased to some extent in most conditions associated with inflammation, including rheumatoid arthritis, Crohn's disease, acute myocardial infarction and pancreatitis, to list but a few **(7)**.

As such, CRP is a very nonspecific marker of sepsis. Nevertheless, it is a cheap and widely available test and when levels are raised in a patient with signs suggestive of sepsis, it provides useful supporting evidence. In 112 ICU patients, it was reported that a serum CRP concentration of >8.7 mg/dl had a sensitivity of 93.4% and a specificity of 86.1% for infection;[120] the combination of CRP >8.7 mg/dl and temperature >38.2°C increased the specificity for infection diagnosis to 100% **(8)**.

Because baseline CRP levels are often raised as a result of comorbid chronic inflammatory conditions, changes in concentrations over time are more useful than single values **(8).**

CRP concentrations increased over time in infected patients, but remained unchanged in non-infected patients. A maximum daily CRP variation of greater than 4.1 mg/dl predicted nosocomial infection with a sensitivity of 92.1% and a specificity of 71.4%; moreover, when combined with a CRP concentration greater than 8.7 mg/dl, the sensitivity and specificity increased to 92.1 and 82.1%, respectively.

Similarly, as a prognostic marker, a decrease in CRP level after 48 h was associated with a mortality rate of 15.4%, while an increased CRP level was associated with a mortality rate of 60.9% in patients with CRP concentrations >10 mg/dl on ICU admission **(9)**.

Because CRP levels decrease as sepsis resolves, it has been suggested that levels could be used to guide antimicrobial therapy. In 50 adult ICU patients with sepsis, an increase in CRP of at least 2.2 mg/dl in the first 48 h was associated with ineffective initial antibiotic therapy with a sensitivity of 77% and a specificity of 67%. Similarly, in patients with ventilator-acquired pneumonia, serum CRP levels were significantly lower in patients with appropriate antibiotic treatment than in those with inappropriate empirical treatment at 96 h (10.3 ± 10 mg/dl vs 19.2 ± 14 mg/dl), and in patients with community-acquired pneumonia, a less than 60% decrease in CRP levels by 3 days after admission was associated with an increased risk of having received inappropriate empiric antibiotic treatment. However, use of CRP levels to guide therapy has not been tested prospectively in adult patients with sepsis **(8)**.

Procalcitonin

PCT was described more recently than CRP and is not routinely measured in all hospital laboratories. PCT levels have been shown to be raised in patients with sepsis and may be particularly useful in distinguishing bacterial from other forms of infection **(10)**.

In patients with community-acquired pneumonia, PCT values >0.25 μg/l had a sensitivity of 96% and specificity of 40% for predicting bacteremia. Similarly, in patients with febrile urinary tract infection presenting to the emergency department, PCT values >0.25 μg/l had a sensitivity of 95% and specificity of 50% for a diagnosis of bacteremia **(11)**.

In patients admitted to the emergency department with symptoms of systemic infection, a PCT threshold of 0.15 ng/ml had a sensitivity of 75%, specificity of 79% and negative predictive value of 98% for a diagnosis of bloodstream infection. Several studies have suggested that PCT is a more reliable marker of sepsis than CRP **(8)**.

Higher PCT levels have been associated with increased mortality rates. In ICU patients with sepsis, reported mortality rates of 25.6% in those with PCT less than or equal to 0.85 ng/ml, but 45.3% in those with PCT greater than 0.85 ng/ml. As with CRP, PCT levels are raised in other inflammatory conditions, including pancreatitis, acute myocardial infarction and postcardiac surgery. Trends in concentrations over time are again of more value than single measurements **(12)**.

It was reported that although PCT concentrations did not differ between hospital survivors and nonsurvivors, mortality rates were lower in patients whose PCT concentration decreased by more than 50% in 72

h than in those in whom levels decreased by less than 50% (12.2 vs 29.8%). Nevertheless, the precise role of PCT remains unclear with meta-analyses reporting conflicting findings **(10)**.

Indeed, 'Procalcitonin should be included in diagnostic guidelines for sepsis and in clinical practice in intensive care units' whereas another published a year later noted that 'The findings … do not lend support to the widespread use of the procalcitonin test in critical care settings', although differences in the search criteria and studies included in these meta-analyses may explain these different conclusions. The use of PCT levels to guide antibiotic therapy has been tested in several clinical trials in different groups of infected patients **(13)**.

meta-analysis of 14 trials in patients with acute respiratory infection, that use of PCT to guide initiation and duration of antibiotic treatment was effective in reducing antibiotic exposure in these patients without increasing rates of treatment failure or mortality. Another meta-analysis suggested that although PCT-guided antibiotic therapy was associated with a reduction in antibiotic usage and reduced costs, an associated 7% increase in hospital mortality could not be excluded **(14)**.

Lactate clearance

Lactate can be metabolized by the liver and kidneys either by direct oxidation or as a source of glucose. Generated lactate can be transformed into oxaloacetate or alanine via the pyruvate pathway or can be utilized directly by perioral hepatocytes (60%) to produce glycogen and glucose (neoglycogenesis and neoglucogenesis; Cori cycle). Furthermore, the kidneys participate in 30% of lactate metabolism, with the cortex classically acting as the metabolizer by neoglucogenesis and the medulla as a producer of lactate **(15)**.

Lactate is not only transformed into glucose via the Cori cycle, it is also removed through oxidation. This oxidative compartment which is likely close to the mitochondria is considered responsible for lactate uptake by mono-carboxylate transporter (MCT) into mitochondria and oxidation via pyruvate and the Krebs cycle with adenosine triphosphate (ATP) production. This intracellular lactate shuttle balances the lactate level between producing by glycolysis and clearance by oxidation **(16).**

In sepsis patients whose vital signs were stable, hyperlactatemia might be induced by the dysfunction of hepatic lactate clearance, However, chronic liver disease alone causes only minimal hyperlactatemia, and kidney failure adds to the impairment in lactate clearance **(17)**.

Lactate versus lactate clearance in patients with sepsis and septic shock

Repeated measurements of blood lactate levels after quantitative resuscitation can serve as a surrogate marker of patient's response to therapy and may be more predictive of mortality than the initial lactate value. While the current surviving sepsis guidelines recommended the re-measurement of lactate levels within 6 hours if the initial lactate levels were elevated, no study has yet examined which time point is the most significant prognostic value of lactate from the recognition of shock at the emergency department in patients with septic shock **(15)**.

Several studies also reported about lactate kinetics and clearance. These studies showed that lactate clearance greater than 10%, based on the initial measurement obtained during the first 2 to 6 hours of resuscitation, predicted survival in patients with septic shock , Moreover, it was demonstrated that for every 10% increase in lactate clearance, there was a corresponding 11% decrease in in-hospital mortality **(18)**.

In general, <10% of lactate clearance 6 hours from initial resuscitation was an independent predictor of in-hospital mortality. There was a systemic review and meta-analysis about lactate clearance and mortality in critically ill patients. They show that lactate clearance is strongly associated with all-cause mortality and rapid clearance is a strong predictor of survivor, there is not enough evidence to suggest a specific cutoff value of lactate clearance for resuscitation target goal, because among the recent studies there was a significant heterogeneity such as different time point and severity. Thus, we recommend to the clinicians to follow the current guidelines implementing a guided resuscitation to normalize lactate levels in patients with septic shock, although it supported with weak recommendations and low-quality evidence **(19)**.

Measurement of the lactate levels at time 0 (T0), T6, T12, and T24 and showed that the best predictor of death was the T24 clearance. Similarly, it was investigated the role of 6-, 12-, and 24-h lactate clearance in patients with sepsis and septic shock and showed only the 24-h lactate clearance measurement to be associated with mortality **(20)**.

a delay in lactate clearance measurement 24–48 hours after initial resuscitation and that the median clearance of 31.6% was significantly associated with mortality. Although some changes in lactate kinetics were clearly significant within 6 to 24 hours after resuscitation, it is currently not possible to define the best time interval between lactate measurements **(20)**.

Furthermore, the interesting issue is whether lactate or lactate clearance is more useful in guiding septic shock management. sensitivity and specificity were significantly different when comparing subsequent lactate levels less than the recommended level *vs.* <10% lactate reduction in the non-vasopressor therapy hyperlactatemia group; however, unlike the complete cohort, no statistical difference was found when comparing a <20% lactate reduction to either of the previous metrics **(15)**.

The important management of lactic acidosis is to treat the underlying cause. Thus, sepsis should be treated immediately by early administration of appropriate antibiotics and infection source control **(21)**.

To reduce lactate production, the macro-circulatory oxygen delivery should improve first. The oxygen delivery depends on the patient's cardiac output, hemoglobin, and oxygen saturation. Adequate volume resuscitation using inotropes, red blood cell transfusion, and provision of adequate oxygen supply are essential **(22)**.

The use of catecholamine should be limited as stimulation of β-adrenergic receptors increases glycolytic flux. In patients with septic shock, reduction of the norepinephrine dose by adding a low-dose vasopressin improved survival by 10% in patients initially receiving <15 μg/min norepinephrine in the vasopressin and septic shock trial. To reduce lactate production caused by overstimulation of the respiratory muscles, a mechanical ventilator support is required and sometimes neuromuscular blocker may help too **(23)**.

To increase lactate removal, hepatic function should be preserved and monitored. Evidence of decreased hepatic function should be sought, and reversible contributors to hepatic dysfunction should be treated. In addition, potential hepatotoxins or renal toxins should be avoided. Continuous renal replacement therapy can be performed in critically ill patients with severe lactic acidosis and acute kidney injury **(16)**.

Sodium bicarbonate administration should be avoided; because it increases carbon dioxide production and decreases serum ionized calcium, which may decrease ventricular and vascular contractility **(24)**.

Lactate/albumin ratio

The tissue hypoxia level is important in determining mortality estimation. The measurement of blood lactate levels used to determine tissue hypoxia is rapid, inexpensive and easy **(25)**.

On the other hand, among the limitations of serum lactate measurement; the interaction between the production and elimination of lactate also affects the results. For instance, the lactate levels of a patient with sepsis with hepatic dysfunction might be higher. Because lactate and albumin levels progress differently as the development of sepsis proceeds, a ratio between the two rather than analyzing lactate and albumin alone may be a new and perhaps better indicator for the patient's prognosis **(26)**.

Using lactate/ albumin ratio as a mortality indicator by using both onset lactate and albumin predictive values. Serum albumin levels can be indicator of systemic inflammation several studies have suggested that albumin is a biomarker of mortality and prognosis. The concentration of albumin, a negative acute phase reactant, decreases with sepsis and metabolic disease.

Furthermore, the half-life of albumin (i.e.,~20 days) can be significantly reduced by systemic inflammation, malnutrition, and liver disease , A large population study demonstrated that serum albumin is an important marker of mortality and morbidity **(27)**.

In another study, serum albumin levels were the laboratory finding that was most closely associated with mortality in adult patients with sepsis, a study with 1381 patients in 2020 and found that the albumin values were: 2.58±0.64 g/dl in the group with mortality and 2.95±0.66 g/dl in the group without mortality, and that the difference between the groups was significant ($p<0.001$). and this study was the largest sampled study evaluating the lactate/albumin ratio and the association of sepsis., Serum lactate and albumin levels change during sepsis **(28)**.

it was reported that the combination of lactate and albumin is a better predictor of mortality in critically ill patients Rather than evaluating separately lactate and albumin, which have an important effect on the prognosis of sepsis, combining these factors by using the ratio between lactate and albumin will provide a new and important variable **(29)**.

The lactate/albumin ratio for the first time in an adult ICU setting and proved that it correlated well to the development of multiple-organ dysfunction syndrome and mortality **(30)**.

The study conducted with 1381 patients with sepsis reported that the lactate/albumin ratio was a predictor of in-hospital mortality. the lactate/ albumin ratio the multicenter registry of 10 emergency departments (n = 946). reinforce the finding that the lactate to albumin ratio outperforms lactate alone as a prognostic marker in sepsis **(31)**.

conducted a study with 348 patients with sepsis and found that lactate/albumin ratio was independently related to the mortality in patients with sepsis **(32)**.

lactate/albumin ratio was a better marker than lactate in terms of mortality. These results showed the importance of using lactate/albumin ratio rather than using lactate or albumin values alone **(33)**.

Lipopolysaccharide-binding protein

Lipopolysaccharide-binding protein (LBP) is a 58 kDa protein, acute phase reactant produced at the liver level. Under physiological conditions, it facilitates the binding of bacterial lipopolysaccharide (LPS) to CD14 (cluster of differentiation CD), which is present in monocytes and macrophages, and to the Toll-like receptor 4/MD2 complex caused by the transcription of cytokines and other pro-inflammatory drugs **(34)**.

However, it has been reported that it is not a specific biomarker of inflammatory response and is still unclear if it can help to differentiate between infectious and noninfectious causes of SIRS **(35).**

CD64

CD64 is an immunoglobulin Fcγ receptor (Fcγ-RIII) expressed on monocytes and eosinophils, which mediates phagocytosis of bacteria and other microorganisms. Neutrophils normally have low levels of CD64 antigen on their membrane, but expression (assessed by a FACS [fluorescence-activated cell sorting] analysis) is increased within 4–6 h after activation by inflammatory cytokines, not only in infectious processes but also in many other conditions, including cardiopulmonary bypass **(36).**

In a meta-analysis of eight studies assessing CD64 expression for sepsis diagnosis, sensitivity was 0.76 (95%CI 0.73–0.78) and the pooled specificity was 0.85 (95% CI 0.82–0.87) , Although CD64 expression was a good indicator of disease severity; it was not a good predictor of 28- day mortality **(37).**

Cytokines

Cytokines are immunomodulatory agents produced by almost all nucleated cells; they participate in the inflammatory process of infectious or noninfectious origin, in sepsis both pro- and anti-inflammatory cytokines are produced and secreted simultaneously, which has allowed them to be postulated as biomarkers **(38)**.

IL-6 is produced by monocytes, fibroblasts, endothelial cells, keratinocytes, T lymphocytes, and tumor cells and acts as a differentiation factor for B lymphocytes and a T lymphocyte activation factor.

Following administration of live bacteria, IL-6 is released into the bloodstream for 4–6 h; its levels decrease in the following 24–48 h. IL-8 is produced under the same conditions by macrophages and also by endothelial cells **(39)**.

IL-10 is the key cytokine in the anti-inflammatory response, produced by T2 cells, CD4 +, monocytes, and B cells, in an attempt to control inflammation. This protective role of IL-10 is the result of inhibition of pro-inflammatory mediators including TNF-α and IL-1β, IL- 8 and IL-6, interferon-γ, nitric oxide, and prostaglandin metabolites **(40)**.

Adrenomedullin

Adrenomedullin is a circulating 52-amino acid peptide that is highly conserved across evolution. It is expressed mainly in endothelial and vascular smooth muscle cells and has multiple functions including vasodilatory activity. It has an in vivo half-life of just over 20 min. Concentrations of adrenomedullin increase in patients with sepsis and are independently and strongly associated with mortality **(41)**.

STREM-1

Triggering receptor expressed on myeloid cells-1 (TREM-1), a member of the immunoglobulin superfamily, is involved in the innate immune response. Present on the surface of polymorph nuclear cells and mature monocytes. TREM expression is up regulated during bacterial and fungal infection and soluble TREM (sTREM- 1) released into the bloodstream. Levels are also increased in other body fluids, such as cerebrospinal fluid (CSF) and urine. stream has demonstrated good diagnostic and prognostic ability in some patients with sepsis, although a meta-analysis of nine studies reported only moderate sensitivity and specificity to predict mortality (0.75 [95% CI 0.61–0.86] and 0.66 [95% CI 0.54–0.75], respectively) **(42)**.

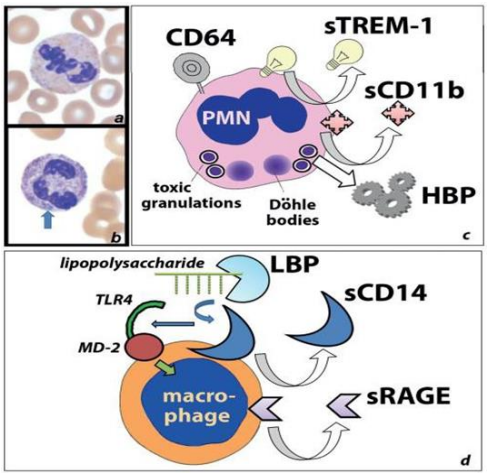

Figure 1: Activated inflammatory cells up-regulate a number of proteins which may be detected as biomarkers of sepsis, either on the cell surface or as soluble forms in plasma. (a) An unstimulated PMN; (b) a stimulated PMN with darker (‘‘toxic’’) granules and a Dohle body (arrow); (c) frequently utilized biomarkers of sepsis related to PMNs include CD64, the soluble forms of TREM-1 and CD11b, and HBP. (d) Frequently utilized biomarkers of sepsis related to macrophages or monocytes include the soluble forms of CD14 (which facilitates recognition of bacterial lipopolysaccharides) and the receptor for RAGE **(43).**

Presepsin

Presepsin (soluble CD14) is a glycoprotein receptor involved in the activation of Toll-like receptor 4 in response to the binding of lipopolysaccharide. Plasma levels of presepsinrise early during sepsis, and it has a half-life of 4–5 h. Presepsin has been shown to have diagnostic and prognostic value in patients with sepsis. In a meta-analysis of eight studies assessing presepsin for the diagnosis of sepsis, the pooled sensitivity and specificity were 0.86 (95% CI 0.79–0.91) and 0.78 (95% CI 0.68–0.85), respectively **(44).**

Application of Sepsis Biomarkers in Clinical Practice:

First Application: Recognition or Exclusion of Infection

Sepsis markers can be used to diagnose infection. As mentioned earlier, this is important because any infection needs prompt therapy with appropriate antibiotics and source control when indicated. Especially in patients with sepsis, any delay in diagnosis retards initiation of appropriate treatment, which is associated with worse outcomes **(45)**.

Importantly, although these biomarkers are referred as sepsis markers, the more correct term is infection markers or even host response markers. Infection typically includes some host response, not only fever and the associated tachycardia but also altered white blood cell count and changes in the concentrations of these "sepsis" markers. However, these markers are very sensitive, so that elevated concentrations reflect not only infection but also other types of host responses to trauma, surgery (which is after all a special form of "programmed" trauma), pancreatitis, etc. Indeed, the sepsis response is essentially triggered by pathogen-associated molecular patterns (PAMPs), molecules, such as endotoxin, lipoteichoic acid, and nucleic acid motifs, which are derived from microorganisms **(46)**.

In 112 ICU patients, it has been reported that a sensitivity of 93.4% and a specificity of 86.1% for infection using a CRP cutoff of >8.7 mg/ dL .In surgical ICU patients, CRP levels increased more in the first few days after major surgery in infected than in non-infected patients **(47).**

Because many, especially elderly, patients will already have a raised CRP concentration prior to ICU admission, an increase in CRP concentrations over time may be more reliable to identify infection. CRP concentrations were measured daily in a small cohort of ICU patients and reported that a maximum daily CRP variation >4.1 mg/dL predicted development of nosocomial infection with a sensitivity of 92.1% and specificity of 71.4% **(7).**

In addition to aiding with diagnosis of infection attempts have been made to use biomarker levels to distinguish between different types of infection. In a recent systematic review of 59 studies that used biomarkers to distinguish between bacterial and nonbacterial infections, none of the markers studied, including CRP and PCT, consistently showed high diagnostic performance. Nevertheless, most studies included in the review reported higher CRP and PCT concentrations in patients with bacterial infections than in those with infections of other, mostly viral, causes. Other biomarkers have been much less widely studied, and it is difficult to draw any conclusions regarding their ability to differentiate between bacterial and nonbacterial infections **(48)**.

Second Application: Evaluation of the Severity of Disease and Prognosis

For many biomarkers, the degree of change in concentration is proportional to the severity of the disease and, therefore, to the risk of death. Biomarkers could therefore potentially provide useful information for patient triage, particularly in terms of need for ICU admission. ICU patients with serum CRP levels >10 mg/dL at ICU admission were more likely to develop organ dysfunction than patients with CRP levels <1 mg/dL and had higher mortality rates (36 vs. 21%, $p < 0.05$) **(49)**.

Importantly, changes in biomarker concentrations over time are again more valuable than single measurements. a decrease in CRP concentration after 48 h in patients with CRP concentrations >10 mg/dL on ICU admission was associated with a mortality rate of 15%, whereas an increase in CRP was associated with a mortality rate of 61% ($p < 0.05$) **(7)**.

In multicenter prospective study across 13 American ICUs, failure to decrease PCT by at least 80% from baseline to day 4 was an independent predictor of 28-day mortality in Cox regression analysis (hazard ratio 1.97 [95% CI, 1.18–3.30; $p < 0.009$]) after adjusting for relevant confounders **(50)**.

Third Application: Therapeutic Guidance

If sepsis markers reflect the development and severity of the host response, then logically they should be expected to provide information regarding patient response to therapy. A persistently raised biomarker concentration could suggest that source control is suboptimal or that the chosen antimicrobial regime is not adequately covering

the causative pathogen(s). Similarly decreasing biomarker concentrations may suggest resolution of infection, enabling antibiotics to be stopped. However, the potential risks associated with this approach include poorer control of infection with increased risk of relapse **(51)**.

Most studies have reported reduced antibiotic duration in patients managed using PCT algorithms to reduce antibiotic usage, with no negative impact on outcomes. However, a recent retrospective analysis suggested that PCT use was associated with increased antibiotic days and incidence of *Clostridium difficult* infection, with no change in mortality **(52)**.

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