## EDITORIAL VIEW

# New markers in sepsis

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## ABSTRACT

Sepsis is a complex disease associated with high morbidity and mortality. Early diagnosis, administration of appropriate antimicrobial therapy and source control are the cornerstones of treatment. The use of biomarkers to guide management of sepsis has been extensively investigated and is well described in the literature. However no single biomarker has been validated for the diagnosis of sepsis, prognostication or to guide antimicrobial prescribing. So their role in clinical practice is still unclear. An approach that integrates data from various combinations of biomarkers with the clinical information available at the bedside shows promise but requires further evaluation.

**Key words:** Biomarkers, sepsis, diagnosis, prognosis, antimicrobial therapy

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**Abbreviations:** C-Reactive Protein (CRP), Lipopolysaccharide binding protein (LPS-LBP), Interleukin (IL), Tumor necrosis factor (TNF), Macrophage migration inhibitory factor (MIF), High mobility group-box 1 protein (HMGB1), chemokine receptor (CCR), Fms-like tyrosine kinase (FLT), Toll like receptor (TLR), soluble triggering receptor expressed on myeloid cells (STREM1), A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMSTS13), Intracellular adhesion molecule (ICAM), Vascular cell adhesion molecule (VCAM), endothelial leukocyte adhesion molecule (ELAM), vascular endothelial growth factor, Von Willebrand Factor (vWF), Platelet derived growth factor (PGDF), vasoactive intestinal peptide (VIP), platelet factor.

Delay in diagnosis or initiation of antimicrobials increases mortality from sepsis.[1] However, antimicrobial stewardship is required to stem the tide of multi-drug resistant organisms. This conflict causes significant challenges in the management of critically ill patients in whom failure to accurately distinguish the systemic inflammatory response syndrome (SIRS) from sepsis (SIRS with a confirmed or presumed infection) can be devastating.

In this ambiguous but life-threatening situation there is considerable interest in the potential role of biomarkers in the early diagnosis and management of sepsis. A biomarker should identify the normal physiological and abnormal pathogenic processes initiated by infection and the responses to the treatment of sepsis as well.[2]

The use of biomarker in clinical medicine is not a novel concept. For example, at least 14 biomarkers are available to guide the diagnosis and prognostication of myocardial infarction; a condition which essentially only affects cardiac myocytes.[3]

In contrast, sepsis is a syndrome that is triggered by an infection and affects almost all cells, tissues and organs. In 1904, William Osler noted "It appears that patients are dying not from their infections but rather their reaction to them." He astutely recognized that although initiated by infection, sepsis is propagated by the host response that we now know activate or disrupt complement, coagulation cascades and endothelial function throughout the body. Moreover, it is not surprising that more than 170 different biomarkers have already been investigated as potential diagnostic or prognostic tools in patients with sepsis.[4]

The morbidity and mortality associated with sepsis is very high. To improve outcomes physicians need reliable tools to enhance their clinical acumen as

**Table 1:[6] Classification of Biomarkers of Sepsis According to their Biochemical Properties**

| Acute-Phase Protein | Cytokine/ Chemokine | Soluble Receptor, Cell Surface, and Other Markers | Biomarkers related to vascular endothelial damage | Biomarkers related to vasodilation | Coagulation biomarker |
|---|---|---|---|---|---|
| CRP, LPS-LBP, Procalcitonin, Pentraxin, Alpha 1 acid glycoprotein, Hepcidin etc. | IL6, IL8, IL12, 13,18, TNFα IL10, MIF, HMGB1 etc. | CCR, FLT1, TLR 2&4, STREM1 etc. | ADAMTS13, Angiopeptin 1,2; ELAM1, ICAM1, PDGF, VCAM1, VEGF, vWF etc. | Neuropeptide, NO, Substance P, VIP etc. | Antithrombin, aPTT, D-dimer, Fibrin, PF etc. |

they wrestle with common but difficult challenges such as distinguishing sepsis from the plethora of causes of SIRS; when and which antimicrobial to start and when to stop antimicrobials.

The parameters of SIRS criteria have limited value, as it is a non-specific response to many non-infectious diseases and non-bacterial infections.[1] Other conventional laboratory investigations used to monitor sepsis, such as neutrophil count with leftward shift, high blood sugar level or lactate, whilst sensitive and easy to measure, are also nonspecific. Unfortunately, causative pathogens are never identified in one-third of septic patients which can mislead the treatment strategy.[5]

To be clinically useful, a sepsis biomarker must complement the information already available at the bedside from the history, physical examination and routine investigations such as the white cell count. It must therefore differentiate sepsis from sterile (i.e. non-infectious) causes of SIRS quickly and accurately. The effectiveness of a biomarker is increased if it can also indicate the type of microorganism causing the infection, severity of infection, prognosticate and reflect the effectiveness of therapy.

Sepsis biomarkers is primarily the biological description of sepsis i.e. the biochemical changes that illustrate the host response to infection. Inflammatory mediators can be classified into different categories (see Table 1).[6]

There is an urgent need for biomarkers of sepsis that can detect infections early in the course of the disease, before the SIRS criteria, physical signs and organ damage become clinically apparent. Such biomarkers could facilitate the earlier initiation of definitive and supportive treatments, perhaps even before SIRS is established, and thereby reduce mortality from infectious diseases. Biomarkers that monitor immune function could guide more advanced management strategies by identifying patients who could benefit from immunomodulatory therapies and excluding those who would not.

Some of the biomarkers that may be useful in clinical practice and recently discussed in literature distinctively are mentioned below:

Procalcitonin (PCT) is acute-phase proteins with both pro-inflammatory and anti-inflammatory effects. It is a secreted from thyroid tissue in healthy individuals and involved in calcium homeostasis. In infectious conditions, PCT is released from many other organs including the lungs, liver etc.[7] It is released in response to endotoxin or mediators secondary to bacterial infections and correlates significantly with the presence and severity of infections.[8]

PCT has specificity of 81% than CRP (specificity 67%) for differentiating bacterial infection in hospitalized patients.[9] Total five meta-analyses have been performed on the diagnostic accuracy of PCT in septic patients. Three of these meta-analyses observed significant association of PCT with clinically or culture proven infection.[9-11] However, one meta-analysis reported only a moderate benefit,[12] and another could not illustrate any significant association.[13] Recent guidelines by different societies recommend the use of PCT as an adjunctive diagnostic marker to differentiate between sterile versus non-sterile SIRS.[14]

The evidence on the use of PCT in systemic fungal infections is still debatable. In recent days, study demonstrated PCT as a useful tool for workup of Candida in critically ill patients. Cortegiani et al[15] observed that PCT has high negative predictive value for the detection of Candida by blood culture or polymerase chain reaction both alone and in a mixed infection with bacteria.

The use of PCT, like any other biomarker should complement a holistic clinical assessment that takes into account all relevant patient- and therapy-related factors that may affect the initial magnitude and the trend of this biomarker.

Cytokines/Chemokines have a role in the activation of innate immune system secondary to injury or infection. TNF and IL-1 both activate endothelial cells that attract circulating leukocytes to the infection site. Fever and other non-specific symptoms are the common and early findings. IL-6 catalyzes the production of the acute phase reactants which stimulates a 'left shift' that helps in the production of neutrophils in the bone marrow.[16]

IL-6 and IL-8 both have inadequate discriminative value as compare to PCT for the detection of infection. These markers have significant role in pathogenesis but their role is ill defined because of non-specific nature.

Soluble triggering receptor expressed on myeloid cells 1 (STREM-1) is a recently discovered member of the immunoglobulin family. The expression of STREM-1 is greatly increased in the presence of bacteria or fungi in cell culture, peritoneal lavage fluid, and tissue samples from patients infected with these microorganisms.[17] The sensitivity and specificity of STREM-1 for the diagnosis of bacterial infection was 0.82 and 0.86 respectively. However, it's sensitivity and specificity is limited for the diagnosis of some infections such as urinary tract infections.[18]

A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS 13) which is also known as vWF-cleaving protease has been studied comprehensively in acquired and congenital thrombotic thrombocytopenic purpura (TTP).[19] Low activity of ADAMTS 13 is associated with platelet aggregation and thrombotic microangiopathy in severe sepsis and septic shock. The imbalance between procoagulant and anticoagulant mechanisms potentiate micro thrombosis in small vessels leading to organ failure. Martin et al[20] observed that the ADAMTS 13 activity was lower in patients with severe sepsis and organ failure than in patients who had developed organ failure from another cause.

ADAMTS 13 may help in prognosticating and therapeutic monitoring in patients with severe sepsis and septic shock. Further studies are warranted to define the role of ADAMTS 13 in septic patients.

The combination of biomarkers has also been discussed in the literature to overcome the limitation of use of single marker for diagnostic purpose of sepsis syndrome. Kofoed et al. studied six markers including CRP, PCT, neutrophil count, immunoassay measured soluble urokinase type plasminogen activator receptor (suPAR), STREM-1, and macrophage migration inhibitory factor (MIF); the result illustrated that combination markers are sensitive and better than relying on a single marker.[21] Despite some limitations this study illuminated a multidimensional approach in sepsis syndrome.

**System Biology and "omic" approach:**

There is a clear need for new strategies to guide the diagnosis and management of sepsis. The classic hypothesis driven selection of biomarkers for investigation is time consuming and has yet to provide any game changing solutions to this problem.

Integrated, system biology approaches such as genomics, transcriptomics, and proteomics provide systemic information on the host-pathogen interaction. This 'blunderbuss,' hypothesis-free approach has rapidly improved our understanding of the pathophysiology of sepsis and systemic inflammation and has facilitated the discovery of many new sepsis biomarkers. It is observed that multiplexed quantitative PCR (q-PCR) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) have capable of overcoming the limitations of single biomarkers. These techniques may help to differentiate between sterile and non-sterile SIRS (sepsis) and it can also benefit to determine the status of the patient's immune system.[22]

## CONCLUSION

The pathophysiology of sepsis is complex and the associated morbidity and mortality remain high. The abilities of the most widely used biomarkers, PCT and CRP, to distinguish sepsis from SIRS, prognosticate and guide management are limited. Although, many advances have been made in the identification of new biomolecules, significant challenges prevent the use of individual biomarkers in the management of sepsis. There is an urgent need for a new approach. Techniques that integrate data from various combinations of biomarkers with information already available at the bedside are promising but require further evaluation.

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