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Review Article

Biomarkers of sepsis: Recent advancements

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ABSTRACT

"Sepsis is a state caused by microbial invasion from a local infectious source into the bloodstream which leads to signs of systemic illness in remote organs," this was the first scientific definition of sepsis proposed by Dr. Schottmuller in 1914. More than 170 different biomarkers have been assessed for potential use in sepsis, more for prognosis than for diagnosis. None have sufficient specificity or sensitivity to be routinely employed in clinical practice. The search for new biomarkers for assessing the severity of sepsis patients and predicting prognosis is very important, interesting, and challenging, providing new insights to confront sepsis. New biomarkers will revolutionize the manner in which sepsis is managed, in terms of early recognition, targeting and titration of therapy, and prognostication. Combinations of several biomarkers may be more effective than single biomarkers, but this requires further evaluation.

1. Introduction

"Sepsis is a state caused by microbial invasion from a local infectious source into the bloodstream which leads to signs of systemic illness in remote organs," this was the first scientific definition of sepsis proposed by Dr. Schottmuller in 1914.[1] Thus, bloodstream infection or bacteremia was a condition in the diagnosis of sepsis and this definition did not change significantly over the years. Sepsis, septicemia, and bloodstream infections (bacteremia) were considered to refer to the same clinical condition, and, in practice, the terms were often used interchangeably. Now, we know that less than one-half of the patients who have signs and symptoms of sepsis have positive blood culture or other microbiological proof of an infectious focus.[2] Sepsis is a leading cause of death in critically ill patients despite the use of modern antibiotics and resuscitation therapies.[3] The septic response is an extremely complex chain of events involving inflammatory and anti-inflammatory processes, humoral and cellular reactions, and circulatory abnormalities.[4,5]

Severe sepsis and septic shock are leading causes of death, representing 30–50% of hospital-reported mortality.[6] Biomarkers can have an important place in this process because they can indicate the presence or absence or severity of sepsis,[7,8] and can differentiate bacterial infection from viral and fungal infections, and systemic sepsis from local infection. Other potential uses of biomarker include roles in prognostication, guiding antibiotic therapy, evaluating the response to therapy and recovery from sepsis, differentiating Gram-positive from

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Gram-negative microorganisms as the cause of sepsis, predicting sepsis complications, and the development of organ dysfunction (heart, kidneys, liver, or multiple organ dysfunction). However, the exact role of biomarkers in the management of septic patients remains undefined.[9]

We have seen the rise and fall of recombinant human activated protein C (drotrecogin alfa) for the treatment of severe sepsis, and the disappointing results might be explained by statistical insignificance stemming from the relatively lower mortality rate (25%) in the Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study.[10,11] In addition to activated protein C, treatments with agents, such as toll-like receptor (TLR) 4-blocker (eritoran) and human recombinant lactoferrin (talactoferrin), are also viewed with skepticism.[12–14] Complexity of pathogenesis of sepsis is such that any new drug targeting a single immunological event may not improve the outcome. Practically, ''bundled care'' for sepsis, with early administration of appropriate antibiotics and supportive care based on SSC (Surviving Sepsis Campaign) guidelines, improves outcome.[15,16]

With this background, this review article highlights the recent advancements in sepsis prognostication and role of newer biomarkers in it.

1.1. *Pathophysiology*

Sepsis has traditionally been considered as a result of uncontrolled inflammatory response, a ''cytokine storm'' that results in shock or organ dysfunction. More than 30 clinical trials have focused on blocking these inflammatory cascades, such as steroids, tumor necrosis factor (TNF)-α antagonist, and antiendotoxin. However, the paradigm of sepsis understanding and treatment has shifted toward its immunosuppressive effects. Such immunosuppression is now considered a key pathogenesis associated with sepsis mortality.[17] Several clinical trials have shown that immune-enhancing therapies, such as recombinant human interleukin (IL)-7 and granulocyte-macrophage colony-stimulating factor, may have beneficial effects.[18]

1.2. *Biomarkers in sepsis*

A multitude of biomarkers have been proposed in the field of sepsis, many more than in other disease processes; for example, a study of patients with myocardial infarction revealed 14 biomarkers suitable for diagnosis and determination of prognosis, and in patients with Alzheimer's disease, just 8 biomarkers were identified.[19] This large difference in the numbers of biomarkers for sepsis is likely to be related to the very complex pathophysiology of sepsis, which involves not only many mediators of inflammation, but also other pathophysiological mechanisms. Coagulation, complement, contact system activation, inflammation, and apoptosis are all involved in the sepsis process, and separate markers for each (part of each) system have been proposed and identified in the literature search (Table 1).[20]

The traditional sepsis model is the immune response activated when TLR expressed on the macrophage recognizes LPS in cell walls of gram-negative bacteria. This is an example of pattern recognition receptors (PRR) and pathogen-associated molecular patterns (PAMP). This recognition stimulates secretion of proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6.[21] The important biomarkers are as follows.

1.2.1. *Lactate*

Elevated lactate levels and lactate-to-pyruvate ratios result mostly from increased glycolysis and lactate production, as well as limited tissue oxygenation. In a large study of 1278 patients with infections, those with lactate levels above 4 mmol/L had higher in-hospital mortality rates than patients with lactate levels less than 2.5 mmol/L (28.4% vs. 4.9%) and early lactate clearance was associated with improved outcomes in patients with severe sepsis and septic shock.[22] Therefore, lactate screening and monitoring may be a valuable tool for risk stratification and to predict sepsis outcome.[21]

1.2.2. *C-reactive protein*

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 pediatrics.[23] 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.[24]

1.2.3. *Procalcitonin*

PCT has been demonstrated to be most clinically useful, and superior to commonly used clinical variables and laboratory

Table 1 – Various biomarkers of sepsis.

Sr.	Biomarker category	Examples
1	Cytokines/chemokines	IL-1, 2, 4, 6, 8, 10; GRO alpha; MIP-1, 2; TNF
2	Cell markers	CD-10, 11b, 11c, 14, 18
3	Receptors	CCR (Chemokine receptors) 2,3; TLR (Toll-like receptors) 2,4; TREM-1
4	Coagulation biomarkers	Antithrombin, aPTT, Fibrin, Thrombomodulin
5	Biomarkers related to vascular endothelial damage	ADAMTS-13, Endothelial leukocyte adhesion molecule (ELAM)-1 (cellular and soluble)
6	Biomarkers related to vaosdilation	Adrenomedullin and proadrenomedullin, Copeptin
7	Biomarkers of organ dysfunction	Atrial natriuretic peptide (ANP), Brain natriuretic peptide (BNP), Carbomyl phosphate synthase (CPS)-1
8	Acute phase proteins	Serum amyloid A (SAA), Cerulospasmin, Ferritin, Hepcidin
9	Other biomarkers	Alpha2 macroglobulin, Dipeptidylpeptidase