EDITORIAL

BIOMARKERS OF SEPSIS

“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 is among the most common causes of death in hospitalized patients. Its death toll is in the same range as that of myocardial infarction.¹ Early and reliable diagnosis is imperative, because of the remarkably rapid progression of sepsis into a life-threatening condition.²

Findings in a patient with suspected or proven infection include fever or hypothermia, tachypnea, tachycardia, leukocytosis or leucopenia, acutely altered mental status, thrombocytopenia, an elevated blood lactate level, respiratory alkalosis, or hypotensions.³

Documenting the presence of the pathogenic microorganisms that are clinically significant to sepsis has proven difficult. Causative microorganisms typically are detected by culturing a subject's blood, sputum, urine, wound secretion, in-dwelling line catheter surfaces, etc. Unfortunately, cultures take at least 5 days to obtain results. Causative microorganisms may reside only in certain body microenvironments such that the particular material that is cultured may not contain the microorganisms. Detection may be complicated further by low numbers of microorganisms at the site of infection or by contamination of samples by non-pathogenic microorganisms.² In many cases, blood cultures are negative due to prior antibiotic administration, the presence of slow-growing or fastidious organisms, or the absence of microbial invasion of the bloodstream.³

A need, therefore, exists for a method of diagnosing sepsis, using techniques that are satisfactorily specific and sensitive and fast enough to allow effective intervention and prevention. Various biomarkers have been studied to address this issue. Here the major types of biomarkers of bloodstream infections/sepsis which have been tested in different conditions are discussed.

Acute-Phase Protein Biomarkers

CRP

CRP is an acute phase reactant whose synthesis in the liver is

upregulated by IL-6. CRP's role during acute inflammation is not entirely clear and it may bind the phospholipid components of microorganisms, facilitating their removal by macrophages. This biomarker has been used for decades to indicate the presence of significant inflammatory or infectious disease, especially in pediatrics.² Elevated plasma concentrations of CRP correlate with an increased risk of organ failure and/or death.⁴

Procalcitonin (PCT)

PCT is produced ubiquitously in response to endotoxin or to mediators released in response to bacterial infections (i.e., IL-1, TNF- α , and IL-6) and strongly correlates with the extent and severity of bacterial infections. PCT shows a more favorable kinetic profile than CRP and cytokines: its levels increase within 4 to 12 h upon stimulation. In patients with community-acquired pneumonia and in patients with urinary tract infections, PCT at a cutoff of 0.1 $\mu\text{g/liter}$ had a very high sensitivity to exclude bacteremia.⁴

Lipopolysaccharide-binding protein

Lipopolysaccharide (LPS)-binding protein (LBP) is an acute-phase reactant that binds the LPS of gram-negative bacteria to form an LPS-LBP complex. In humans, LBP is constitutively present in serum at a concentration of 5 to 10 $\mu\text{g/ml}$, and levels increase during the acute-phase reaction, reaching peak levels of up to 20 $\mu\text{g/ml}$.⁴

Pentraxin

Pentraxins are a superfamily of proteins that act as pattern recognition receptors (PRRs). The classic “short” pentraxins include serum amyloid P component (SAP) and C-reactive protein (CRP), which are produced in the liver following inflammatory signals. The “long” pentraxin 3 (PTX3) is secreted by various cells, including leukocytes and endothelial cells and binds to specific patterns of fungi, bacteria, and viruses and induces phagocytosis by its binding to complement component C1q. In patients with severe sepsis and septic shock, persisting high levels of circulating PTX3 over the first days from the onset of sepsis were associated with mortality.⁴

Other acute-phase reactants

Levels of other acute-phase reactants, such as serum amyloid A, ceruloplasmin, alpha-1-acid glycoprotein, and hepcidin have been found to be elevated in sepsis and to be higher in patients with poor outcomes.⁴

Cytokine/Chemokine Biomarkers

Cytokines

Cytokines are immune-modulating agents that may be derived from virtually all nucleated cells. In septic patients, the secretion of both pro- and anti-inflammatory cytokines occurs in a simultaneous manner from the very first moments of infection. Serum levels of the cytokines IL-6 and IL-8 are closely related to the severity and outcome of sepsis in patients.⁴

High-mobility-group box 1

High-mobility-group box 1 (HMGB1) is a 30-kDa nuclear and cytosolic protein known because of its properties as a transcription and growth factor. It is also a cytokine mediator of local inflammation as well as lethal systemic inflammation (e.g., endotoxemia and sepsis). It is released by activated macrophages, and during endotoxemia and sepsis, serum levels increase significantly.⁴

Macrophage migration inhibitory factor

Macrophage migration inhibitory factor (MIF) is a regulator of innate immunity, the level of which is elevated in septic shock. MIF distinguished between survivors and non survivors but failed to differentiate infectious from noninfectious causes of inflammation.⁴

Coagulation Biomarkers

The host response that is induced by severe infections and sepsis is often accompanied by disseminated intravascular coagulation, which is triggered by several proinflammatory cytokines, such as interleukin-6 and TNF- α . It is known that changes in coagulation factors such as thrombocyte counts, antithrombin, protein C and thrombomodulin are appropriate markers to gauge the severity of the host response and that the course of these markers has prognostic implications.⁴

Soluble Receptor, Cell Surface, and Other Markers

sTREM-1

Triggering receptor expressed on myeloid cells 1 (TREM-1) is a recently discovered member of the immunoglobulin superfamily. Many studies suggest that the value of plasma sTREM-1 levels as an indicator of sepsis was superior to

those of CRP and PCT. A meta analysis found that the sensitivity of sTREM-1 for the diagnosis of bacterial infection was 0.82 and that the specificity was 0.86.⁴

suPAR

The soluble form of urokinase-type plasminogen activator receptor (suPAR) is a new biological marker of immunologic activation. During inflammatory stimulation, uPAR is cleaved from the cell surface by proteases to create the soluble form of the receptor, suPAR, which can be detected in blood, urine, and cerebrospinal fluid.¹

Pro-ADM.

Adrenomedullin (ADM) is a 52-amino-acid peptide with immune modulating, metabolic, and vasodilator activity. ADM has a bactericidal activity and could be helpful in the diagnosis and prognosis of sepsis. Prohormone fragments (pro-ADM) are more stable, their levels can be measured in biological fluids by automated methods using the TRACE (Time-Resolved Amplified Cryptate Emission) method after immunocapture. The midregional fragment of proadrenomedullin (MR-pro-ADM), included between amino acids, is the most stable part of the ADM, and it has been detected in plasma of patients with septic shock as a consequence of the ADM active peptide degradation.¹

Polymorphonuclear CD64 index

The CD64 index has been found to be useful for the early detection of sepsis in critically ill neonates. It is an adjunctive marker when combined with more sensitive markers in medical ICU patients, and has high sensitivity and specificity for the detection of infection in unselected ICU patients.⁴

Panels of Biomarkers

- Combinations of biomarkers have been proposed to overcome limitations of single biomolecules. A panel consisting of serum concentrations of sTREM-1 and PCT and the expression of the polymorphonuclear CD64 index in flow cytometry, called the “bioscore,” was higher in patients with sepsis than in all others.⁵
- In critically ill patients, the combination of PCT and BPW increased the specificity of either marker alone for the detection of sepsis.⁶
- In the emergency department, the usefulness of a combination of a multiplex immunoassay measuring suPAR, sTREM-1, and MIF in parallel with standard

measurements of CRP, PCT, and neutrophils was significantly greater than that of any single marker.⁷

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Dr. Bashir Ahmad Fomda
Professor Department of Microbiology
Sher-i-Kashmir Institute of Medical Sciences