Biomarkers: Diagnosis and Risk Assessment in Sepsis

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KEYWORDS

• Sepsis • Biomarkers • Diagnosis • Risk assessment

The challenges of diagnosing and treating sepsis only seem more daunting as incidence increases, patients become older and sicker, and pathogenic organisms evolve.[1,2] New understanding of inflammatory mediators and pathways, immunity, and genetic variability in this disease state suggests that the current definitions of systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock are oversimplified.[3] Evidence supports early intervention[4] and diagnosis in sepsis and that the failure to intervene results in significant morbidity and mortality.[5] Early and appropriate antibiotic therapy is critical.[6] Likewise, limiting exposure when infection is absent will become exceedingly important as drug resistance increases.

These complexities have led to the search for the ''troponin'' of sepsis, a biomarker or set of biomarkers with compelling sensitivity and specificity for effectively identifying the disease, patients at risk for untoward outcomes, and reliably guiding treatment. Countless potential markers have been evaluated in published literature, a detailed discussion of which is beyond the scope of this article. The most relevant biomarkers are highlighted, including interleukin (IL)-6, C-reactive protein (CRP), procalcitonin (PCT), and triggering receptor expressed on myeloid cells (TREM)-1, as are composite markers or biomarker panels. A more comprehensive list of potential markers of interest is included in **Table 1**.

DEFINITIONS AND CRITERIA

Biomarkers are an appealing addition to the care of patients who have sepsis because they are noninvasive, ideally rapidly available, and may be followed over a patient's course. They may ultimately serve as potential targets for therapy and large-scale randomized control trials. Assay reliability, the establishment of cut-offs, and timely, affordable processing must be considered and addressed before the widespread adoption of a given marker.

A biomarker is defined as ''a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.''[7] Before the widespread use of a marker of interest, it must endure *validation* (ie, have known characteristics, be well standardized, and be accurate) and *qualification* (ie, be integral to the disease process and clinical end points).[8] Depending on the intended use, the validation and qualification process may be more or less rigorous (known as the ''fit-for-purpose'' paradigm in drug development[9]) (**Table 2**).

A recently convened consensus panel put forth important distinctions between sepsis *measures*, *markers*, and *mediators* to address the need for a more systematic approach to clinical research in sepsis.[10] Currently, the literature is filled with countless measures and markers in various stages of preclinical, translational, and clinical

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Table 1
Potential biomarkers of interest

Cell Surface Markers	Cytokines	Apoptosis	Coagulation	Soluble Receptors	Miscellaneous	Acute Phase Proteins
CD13-HLADR[122]	TNF-α[123]	Fas/Apo-1[124]	vWF[125,126]	sIL-2R[127]	NT-proBNP[127,128]	PTX3[129]
HLA-G5[130]	IL-8[23,127]	Gas6[131]	PAI-1[132–134]	sCD163[135]	pro-ADM[136,137]	ET-1[123]
HLA-DR[138,139]	IL-12[140]	TNFRI[141]	Thrombopoietin[142]	s-TNF-R[32]	MBL[143]	—
—	IL-10[139]	Fas/FasL[141]	aPTT waveform analysis[144]	TNF-R p55[145]	HDL[146]	—
—	—	—	AT[59,147]	—	Gc-globulin[148]	—
—	—	—	—	—	Copeptin[149]	—
—	—	—	—	—	ICAM-1[150]	—

Abbreviations: aPTT waveform analysis, activated partial thromboplastin time; AT, antithrombin; CD13-HLADR, CD13-class II histocompatibility antigen; ET-1, endothelin-1; FasL, Fas ligand; Gas6, growth-arrest-specific protein 6; HDL, high-density lipoprotein; HLA-G5, human leukocyte antigen-G5; ICAM-1, intercellular adhesion molecule-1; MBL, mannan-binding lectin; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAI-1, plasminogen activator inhibitor type 1; pro-ADM, pro-adrenomedullin; PTX3, pentraxin3; sIL-2R, soluble IL-2 receptor; s-TNF-R, soluble TNF-α receptor; TNF-R p55, tumor necrosis factor receptor p55; TNFRI, tumor necrosis factor type-I receptor; vWF, von Willebrand factor.

investigation. Sample sizes remain small, variable assays and cut-offs abound, and study populations vary widely, however. It is not surprising that myriad randomized control trials based on a perceived understanding of sepsis mediators have been negative.[11–17]

While we are searching for the biomarker "holy grail," clinicians at the bedside remain charged with the difficult task of diagnosing and assessing risk in sepsis. With this article, we hope to offer clinicians a summary of the current biomarker literature and identify the markers most likely to prove useful in clinical practice. Ideally, a useful biomarker should be accurate and available, enhance clinical assessment, and aid in decision making for patient care.

SELECTED BIOMARKERS

Interleukin-6

The release of inflammatory cytokines, such as tumor necrosis factor (TNF)-α, IL-1β, IL-8, and IL-6, in response to infectious pathogens and host injury leads to SIRS and multiple organ dysfunction syndrome.[18] IL-6 is induced by TNF-α and has a longer half-life, which can be measured reliably in the blood after insult to the host.[19] IL-6 is an important mediator in septic shock and has long been acknowledged to predict severity and outcome in this disease.[20–25] As a marker of infection, it is relatively nonspecific, however, and is elevated in a variety of inflammatory states.[25–31] As one of the initial cytokines released in inflammation, IL-6 may be an early predictor of more downstream effects, such as organ dysfunction. This concept has been supported by recent work in sepsis-induced acute kidney injury.[32,33] A retrospective study of the placebo arm of the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial correlated serum IL-6 levels independently with the development of acute kidney injury on multivariate analysis.[33]

As a diagnostic and prognostic tool, some evidence suggests that IL-6 performs reasonably well, although not as well as PCT.[23,34–36] Harbarth and colleagues[23] reported IL-6's moderate ability to distinguish SIRS from sepsis (area under the curve [AUC] 0.75, 95% CI 0.63-0.87). For risk assessment, they demonstrated levels of more than 1000 ng/mL to be highly predictive of sepsis-related death. A single study demonstrated IL-6 levels on day 2 of intensive care unit (ICU) admission had comparable discriminative power to day 2 PCT and Acute Physiology and Chronic Health Evaluation (APACHE II) scores in predicting hospital mortality.[24] Several studies have shown that the diagnostic and prognostic accuracy of IL-6 may