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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

tests in the diagnosis of sepsis; moreover, it has been shown to correlate with the extent and severity of microbial invasion. The dual function of PCT, as a precursor peptide of the hormone calcitonin and as a mediator that is elevated on systemic bacterial infections, along with other cytokines, has resulted in the term ''hormokine'' being coined.[25] In a systematic review and meta-analysis, PCT was found to be more specific (specificity 81% [95% CI: 67–90%]) than CRP (67% [95% CI: 56–77%]) for differentiating bacterial infection among hospitalized patients. The cut-off median PCT value in this meta-analysis was 1.1 ng/mL (interquartile range: 0.5–2.0 ng/mL).[26] PCT levels are also elevated after surgery, cardiogenic shock, heat shock, acute graft-versus-host disease, and immunotherapy, such as granulocyte transfusion, which could limit its usefulness as a sepsis biomarker.

1.2.4. *sTREM-1*

Soluble triggering receptor expressed on myeloid cells-1 (TREM-1) is a recently discovered member of the immunoglobulin superfamily of receptors that is expressed on polymorphonuclear granulocytes and mature monocytes. A soluble form of TREM-1 (sTREM-1) can be found in body fluids, such as plasma, pleural fluid, bronchoalveolar lavage fluid, urine, and cerebrospinal fluid, where it can be assayed by ELISA using commercial immunoassay kits.[27] A meta-analysis of 11 studies (1795 patients included) showed a pooled sensitivity and specificity of 79% (95% confidence interval (CI), 65–89) and 80% (95% CI: 69–88), respectively with ROC curve of 0.87 (95% CI: 0.84–0.89). In this meta-analysis, for a prevalence of 62% of sepsis, the negative predictive value (NPV) was 0.7 and the positive predictive value (PPV) is 0.86. Finally, plasma sTREM-1 had a moderate diagnostic performance in differentiating sepsis from SIRS and was not sufficient for sepsis diagnosis in systemic inflammatory patients.[28]

1.2.5. *suPAR*

The soluble form of urokinase-type plasminogen activator receptor (suPAR) is a new biological marker of immunologic activation.[29] 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.[30] Measurements can be obtained from commercial ELISA kits; suPAR measurements also are included in multiplex assays together with cytokines. Some studies have showed that suPAR levels were elevated in acutely ill patients but their diagnostic value was not superior to other biomarkers, such as CRP, PCT, or sTREM-1. Recently, two studies evaluating diagnostic accuracy of suPAR have shown specificity from 64% to 77%.[31]

1.2.6. *Presepsin*

Presepsin or sCD14 subtype (sCD14-ST) is normally present in very low concentrations in the serum of healthy individuals and has been shown to be increased in response to bacterial infections.[32] Plasma levels of presepsin can be measured using an automated chemoluminescent assay (PATHFAST). Although presepsin showed a significant prognostic value and initial values were significantly correlated with in-hospital mortality of patients affected by sepsis, severe sepsis, or septic shock, two recent studies have shown that presepsin is an useful biomarker for early diagnosis of sepsis and evaluation of prognosis in septic patients (sensitivity: 71–72%, specificity: 70–86%, and NPV: 52–71%).[33]

1.2.7. *Pro-ADM*

Adrenomedullin (ADM) is a 52-amino-acid peptide with immune modulating, metabolic, and vasodilator activity. Prohormone fragments (pro-ADM) are more stable than the complete peptide and 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 45–92, 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.[34] In an Italian study comparing PCT and MR-pro-ADM in 200 septic patients, 90 patients with SIRS, and 30 healthy individuals, the pro-ADM distinguished septic patients. Moreover, the combined use of PCT and MR-pro-ADM gave a post-test probability of 0.998 in the cohort of all septic patients. The combination of biomarkers may substantially improve the early diagnosis of sepsis.[35]

2. Conclusion

More than 170 different biomarkers have been assessed for potential use in sepsis, more for prognosis than for diagnosis. None has 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.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. Reinhart K, Bauer M, Riedemann NC, Hartog CS. New approaches to sepsis: molecular diagnostics and biomarkers. *Clin Microbiol Rev*. 2012;25(4):609–634.
2. Vincent JL, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med*. 2006;34(2):344–353.
3. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29:1303–1310.
4. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. *N Engl J Med*. 2003;348:138–150.

5. Gullo A, Bianco N, Berlot G. Management of severe sepsis and septic shock: challenges and recommendations. *Crit Care Clin*. 2006;22:489–501.
6. Levy MM, Dellinger RP, Townsend SR, et al. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. *Intensive Care Med*. 2010;36:222–231.
7. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther*. 2001;69:89–95.
8. Marshall JC, Reinhart K. Biomarkers of sepsis. *Crit Care Med*. 2009;37:2290–2298.
9. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med*. 2008;36:296–327.
10. Ranieri VM, Thompson BT, Barie PS, et al. PROWESS-SHOCK Study Group. Drotrecogin alfa (activated) in adults with septic shock. *N Engl J Med*. 2012;366:2055–2064.
11. Vincent JL. The rise and fall of drotrecogin alfa (activated). *Lancet Infect Dis*. 2012;12:649–651.
12. Guntupalli K, Dean N, Morris PE, et al. TLF LF-0801 Investigator Group. A phase 2 randomized, double-blind, placebo-controlled study of the safety and efficacy of talactoferrin in patients with severe sepsis. *Crit Care Med*. 2013;41:706–716.
13. McCulloh R, Opal SM. Human recombinant lactoferrin for sepsis: too good to be true? *Crit Care Med*. 2013;41:908–909.
14. Opal SM, Laterre PF, Francois B, et al. ACCESS Study Group. Effect of eritoran, an antagonist of MD2-TLR4, on mortality in patients with severe sepsis: the ACCESS randomized trial. *JAMA*. 2013;309:1154–1162.
15. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup, Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013;41:580–637.
16. Choi JH. Recent evidences of sepsis treatment. *Infect Chemother*. 2008;40:67–75.
17. Hotchkiss RS, Monneret G, Payen D. Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach. *Lancet Infect Dis*. 2013;13:260–268.
18. Unsinger J, McGlynn M, Kasten KR, et al. IL-7 promotes T cell viability, trafficking, and functionality and improves survival in sepsis. *J Immunol*. 2010;184:3768–3779.
19. Tang BL, Kumar R. Biomarkers of mild cognitive impairment and Alzheimer's disease. *Ann Acad Med Singap*. 2008;37:406–410.
20. Marshall JC, Vincent JL, Fink MP, et al. Measures, markers, and mediators: toward a staging system for clinical sepsis. A report of the Fifth Toronto Sepsis Roundtable, Toronto, Ontario, Canada, October 25–26, 2000. *Crit Care Med*. 2003;31:1560–1567.
21. Cho SY, Choi JH. Biomarkers of sepsis. *Infect Chemother*. 2014;46(1):1–12.
22. Shapiro NI, Howell MD, Talmor D, et al. Serum lactate as a predictor of mortality in emergency department patients with infection. *Ann Emerg Med*. 2005;45:524–528.
23. Jaye DL, Waites KB. Clinical applications of C-reactive protein in pediatrics. *Pediatr Infect Dis J*. 1997;16(8):735–747.
24. Hofer N, Zacharias E, Müller W, Resch B. An update on the use of C-reactive protein in early-onset neonatal sepsis: current insights and new tasks. *Neonatology*. 2012;102 (1):25–36.
25. Muller B, Becker KL. Procalcitonin: how a hormone became a marker and mediator of sepsis. *Swiss Med Wkly*. 2001;131:595–602.
26. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. *Clin Infect Dis*. 2004;39:206–217.
27. Lee H. Procalcitonin as a biomarker of infectious diseases. *Korean J Intern Med*. 2013;28(3):285–291.
28. Bopp C, Hofer S, Bouchon A, Zimmermann JB, Martin E, Weigand MA. Soluble TREM-1 is not suitable for distinguishing between systemic inflammatory response syndrome and sepsis survivors and nonsurvivors in the early stage of acute inflammation. *Eur J Anaesthesiol*. 2009;26 (6):504–507.
29. Backes Y, Sluijs KV, Mackie D, et al. Usefulness of suPAR as a biological marker in patients with systemic inflammation or infection: a systematic review. *Intensive Care Med*. 2012;38 (9):1418–1428.
30. Thuno M, MacHo B, Eugen-Olsen J. SuPAR: the molecular crystal ball. *Dis Markers*. 2009;27(3–4):157–172.
31. Loonen AJ, Jager CP, Tosserams J, et al. Biomarkers and molecular analysis to improve bloodstream infection diagnostics in an emergency care unit. *PLOS ONE*. 2014;9(1). Article ID: e87315.
32. Endo S, Suzuki Y, Takahashi G, et al. Usefulness of presepsin in the diagnosis of sepsis in a multicenter prospective study. *J Infect Chemother*. 2012;18(6):891–897.
33. Liu B, Chen YX, Yin Q, Zhao YZ, Li CS. Diagnostic value and prognostic evaluation of Presepsin for sepsis in an emergency department. *Crit Care*. 2013;17(5).
34. Struck J, Tao C, Morgenthaler NG, Bergmann A. Identification of an adrenomedullin precursor fragment in plasma of sepsis patients. *Peptides*. 2004;25(8):1369–1372.
35. Angeletti S, Battistoni F, Fioravanti M, Bernardini S, Dicuonzo G. Procalcitonin and mid-regional pro-adrenomedullin test combination in sepsis diagnosis. *Clin Chem Lab Med*. 2013;51(5):1059–1067.