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Novel biomarkers for sepsis: A narrative review

Frederik Fruergaard Larsen [a], J. Asger Petersen [b,*]

[a] Department of Internal medicine, Amager Hospital, Italiensvej 1, 2300 Copenhagen, Denmark
[b] Department of Day Surgery, Hvidovre Hospital, Kettegaards Alle 30, 2650 Hvidovre, Denmark

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ABSTRACT

Background: Sepsis is a prevalent condition among hospitalized patients that carries a high risk of morbidity and mortality. Rapid recognition of sepsis as the cause of deterioration is desirable, so effective treatment can be initiated rapidly. Traditionally, diagnosis was based on presence of two or more positive SIRS criteria due to infection. However, recently published sepsis-3 criteria put more emphasis on organ dysfunction caused by infection in the definition of sepsis. Regardless of this, no gold standard for diagnosis exist, and clinicians still rely on a number of traditional and novel biomarkers to discriminate between patients with and without infection, as the cause of deterioration.
Method: Narrative review of current literature.
Results: A number of the most promising biomarkers for diagnoses and prognostication of sepsis are presented.
Conclusion: Procalcitonin, presepsin, CD64, suPAR, and sTREM-1 are the best evaluated biomarkers for diagnosis and prognostication of sepsis to date. All have limitations in differentiation between infected and non-infected patients with SIRS, and their future role in diagnosis needs to be evaluated. It is important to test utility, performance, and validity of future biomarkers before implementing them in routine clinical care.

1. Introduction

Sepsis is a major cause of morbidity and mortality among hospitalized patients worldwide, often requiring supportive treatment in the ICU due to multiple organ involvement. Accordingly, much research on sepsis has focused on ICU patients, although 20–80% of all cases are found among patients on general hospital wards [1]. Diagnosis relies on unspecific and ubiquitous symptoms caused by a wide variety of infectious and non-infectious stimuli. Until recently sepsis was defined, as the presence of two or more positive systemic inflammatory response syndrome (SIRS) criteria (Table 1) and confirmed or suspected infection, as the underlying cause. If signs of organ dysfunction were present, the diagnosis of severe sepsis was assigned [2]. Newly revised sepsis definitions aim to emphasize the role of organ dysfunction, and the term sepsis is now reserved for cases where infection is severe enough to cause organ dysfunction, defined as a rise in the sequential organ failure assessment (SOFA) score of two or more (Table 2) [3]. To facilitate detection of septic patients outside the ICU, the quick SOFA (qSOFA) score has been introduced concomitantly (Table 3). This score, based on readily available measures of mentation, respiratory rate, and blood pressure, is less specific than SIRS criteria but performed well in predicting in-hospital mortality in a population of non-ICU patient with suspected infection [4]. Despite many efforts, a diagnostic gold standard for sepsis remains elusive, and diagnosis continues to depend on clinical vigilance. Specifically, discrimination between infectious and non-infectious causes of deterioration continues to be a major clinical challenge. This is unfortunate, since improved outcomes for sepsis depend on timely treatment with antibiotics, fluid resuscitation, and source control [5]. Furthermore, non-infectious causes of deterioration often need to be addressed equally urgent, so rapid methods to establish a definitive diagnosis are desirable. The diagnosis of infection is usually based on positive cultures or biomarkers of inflammation. However, microbiology results take several days to obtain and are negative in up to one-third of cases, especially if antibiotics have been administered prior to culture [6]. C-reactive protein (CRP) is the traditional marker of inflammation; it is elevated in a number of conditions besides infection, i.e. trauma, burns, and pancreatitis. CRP synthesis in the liver is induced by interleukins and elevated levels are found within 6–8 h of introduction of a pathogen, with peaks after 36–50 h [7]. However, as mortality in sepsis rises with every hour effective treatment is delayed, there is great need for better early biomarkers.

Presently, a plethora of promising biomarkers is emerging, but validity and clinical utility has only been tested for very few of them [8]. The aim of this narrative review is to give an introduction to the most well assessed markers that can help informed decision making in patients with sepsis.

* Corresponding author.
E-mail address: john.asger.petersen.01@regionh.dk (J.A. Petersen).

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Table 1
SIRS criteria.

SIRS criteria, two or more of:
Temperature > 38 °C OR < 36 °C
Heart rate > 90/min
Respiratory rate > 20/min OR $PaCO_2$ < 4.3 kPa
Leukocyte count > 12 mia/mL OR < 4 mia/mL OR > 10% immature bands

Table 3
qSOFA score.

Respiratory rate ≥ 22 per min
Systolic blood pressure ≤ 100 mm Hg
Altered mentation

2. Methods

In this narrative review studies were identified by searching PubMed for English language articles published within the last ten years (May 2007 to May 2017) using the following keywords: (sepsis OR sepsis syndrome) AND biomarkers. The two authors critically reviewed the most relevant studies and found supplementary studies in the reference list of selected studies.

3. Pathophysiology of sepsis

Sepsis is an incompletely understood clinical syndrome with heterogeneous disease courses. It is characterized by a dysregulated response to infection, initiated by recognition of pathogen associated molecular patterns (PAMPs) from invasive microorganisms by the innate immune system. PAMPs are highly conserved antigens, typically of bacterial or fungal origin, and they are recognized by four classes of receptors: Toll-like receptors, C-type lectin receptors, retinoic acid inducible gene 1-like receptors and nucleotide-binding oligomerization domain-like receptors [9]. The resulting inflammatory response activates a number of complex intra- and extracellular cascades that among other things causes cell lysis and spillover of intracellular molecules to the extracellular space. These damage associated molecular patterns (DAMPs) are also released after extensive tissue trauma, and act very much like PAMPS on the host immune system, with the risk of inducing an escalating state of inflammation [10,11]. Concomitantly, the body initiates a compensatory anti-inflammatory reaction (CARS) that is mediated through a number of pathways, resulting in an increased release of glucocorticoid, a strong inducer of anti-inflammatory cytokines, including IL-10 [12]. The net result of the inflammatory pathway is an increased capillary permeability and vasodilation leading to hypotension and resulting in tissue hypo-perfusion that is further compromised by coagulation abnormalities. In sepsis, there is an upregulation of tissue factor resulting in a downregulation of anti-thrombin and a subsequent increase in plasma thrombin. At the same time, there is a decreased production of protein C and upregulation of plasminogen activator inhibitor type 1 that further inhibits fibrinolysis. Collectively, these changes induce a hypercoagulable state. Increased coagulation and hypotension in sepsis can lead to multi organ failure, the most severe and life threatening consequence of sepsis [2]. A large number of molecular mechanisms are involved in the inflammatory cascade during sepsis, and many of these have been investigated for their clinical utility.

4. Role of biomarkers for sepsis

Biomarkers can be 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", and they can be used in four overlapping domains [13]:

- as a diagnostic tool
- as a tool for staging of disease severity
- as an indicator of prognosis
- for prediction and monitoring of clinical response to an intervention

The outcome of sepsis is determined by the interaction of the inciting microorganism and characteristics of the host (immune) response. This relationship is conceptualized in the PIRO model (predisposition, infection, response, and organ dysfunction) for staging of sepsis [14]. Biomarkers for sepsis hold the promise of individualized therapy, for example by screening the host for genetic polymorphism that can have influence on the disease course, e.g. mutations in the promoter region of TNF-α [15]. Also, they can contribute to characterize the infection by rapid identification of the causative agent, including resistance to antibiotics, and site of infection. Other biomarkers could aid in daily care by monitoring the effect of interventions, surveillance of organ function, and prognostication of outcomes. Moreover, biomarkers could have a role in triage, by screening patient cohorts for risk factors and prognosis, and help to direct resources appropriately to the most vulnerable patients. Over 100 potential sepsis markers have emerged, and the advent of high throughput techniques for analyzing thousands of molecules of the transcriptome and metabolome simultaneously, has opened up for a genome wide screening [8]. However, the overwhelming amount of data put great demands on bioinformatics to extract useful information. Furthermore, the usefulness of emerging biomarkers or combination of biomarkers must be validated rigorously in clinical trials before applied in routine clinical use. This should include evaluation the test's ability to discriminate between afflicted and non-afflicted patients in a population with true diagnostic uncertainty, and not merely in diseased vs. healthy populations [6]. Ideally, the biomarkers should also be validated in sufficiently powered, prospective, randomized trials to show beneficiary effects on disease course. Furthermore, they should provide additional information to other, routinely available examinations, preferably quickly and inexpensively. Some of the best validated biomarkers will be introduced in the following, with special emphasis on markers for infection.

Table 2
The Sequential Organ Failure Assessment (SOFA) score. MAP, mean arterial pressure; SaO2, peripheral arterial oxygen saturation.

SOFA score	1	2	3	4
PaO2/FIO2 (mm Hg)	<400	<300	<220	<100
SaO2/FIO2	221–301	142–220	67–141	<67
Platelets × 103/mm^3	<150	<100	<50	<20
Bilirubin (mg/dL)	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Hypotension[a]	MAP < 70	Dopamine ≤ 5 or dobutamine (any)	Dopamine > 5 or norepinephrine ≤ 0.1	Dopamine > 15 or norepinephrine > 0.1
Glasgow Coma score	13–14	10–12	6–9	<6
Creatinine (mg/dL)	1.2–1.9	2.0–3.4	3.5–4.9	>5.0
Urine output (mL/d)			<500 mL	<200 mL

[a] Vasoactive mediations administered for at least 1 h (dopamine and norepinephrine μmg/kg/min).