Mini Review **Open Access**

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Can biomarkers help us to better diagnose and manage sepsis?

Abstract: The recognition over 25 years ago that the host response plays an exquisite role in sepsis, led to the today still-standard sepsis definition. Unfortunately, the inflammatory response syndrome (SIRS) criteria turned out to be less useful than anticipated, lacking sensitivity, specificity and ease of clinical application. Had novel host-response biomarkers been available by that time, it arguably would have been preferable to white blood cell count as an unspecific and not-sensitive laboratory-based SIRS criterion. Several novel markers have been put forward as sepsis markers with better diagnostic and/or prognostic potential in sepsis including inflammatory markers such as procalcitonin (PCT), presepsin, proadrenomedullin (ProADM), endothelial dysfunction markers such as P-selectin, E-selectin, intercellular cell adhesion molecule [ICAM]-1 and vascular cell adhesion molecule [VCAM]-1 and genetic markers among others. The limitations to using clinical parameters and conventional diagnostic markers for patients with clinical suspicion of sepsis may directly lead to both, under treatment of patients with severe disease needing urgent antibiotic and fluid therapy, and unnecessary and prolonged exposure to antimicrobial agents adversely affecting patient outcomes and increasing antibiotic resistance. The aim of this review is to summarize the current evidence for emerging diagnostic, prognostic, and therapeutic-response sepsis biomarkers in different infections and clinical settings, and discuss the reliability, potential benefit and limitations of these marker when used in clinical routine for sepsis management.

Keywords: biomarker; C-reactive protein; procalcitonin; screening; sepsis; SIRS.

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Introduction

Historical perspective

The term "sepsis" derives from the Greek verb sepo [σηπω] (meaning decay or putrefaction) and refers to the disseminated inflammatory response elicited by microbial infections. This condition is the culmination of complex interactions between the infecting microorganism and the host immune, inflammatory, and coagulation responses [1]. Although sepsis has been recognized since antiquity [2], it remains a current challenge: it is a common cause of morbidity and mortality, expensive to treat and the underlying pathobiological mechanisms have not been completely delineated [3].

The controversies in sepsis diagnosis

In addition, there is still a lack of agreement regarding how sepsis is diagnosed. In 1991, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) held a consensus conference that produced specific definitions for sepsis, severe sepsis, and septic shock [4]. According to this consensus, sepsis is defined as "a systemic inflammatory response (SIRS) in combination with clinical suspicion or confirmation of infection". Although the ACCP/SCCM conference gave uniformity to clinical and research classification of sepsis, the definitions proposed, particularly for SIRS, were found to be overly sensitive and yet not specific [5]. Because of the lack of specificity, and as a result of advances in sepsis research, the ACCP and SCCM convened a second consensus conference with the European Society of Intensive Care Medicine (ESICM), American Thoracic Society (ATS),

and Surgical Infection Society (SIS) in 2001 with the aim of improving and making more explicit the definitions of sepsis, severe sepsis, and septic shock [6].

However, recently published data suggest that both the 1991 and 2001 sepsis definitions have a high sensitivity but low specificity, and the diagnostic performances of both definitions are suboptimal. The 1991 sepsis definition presents a sensitivity of 94.6% but a specificity of 61.0%, while the 2001 definition has a slightly increased sensitivity (96.9%) but a decreased specificity (58.3%), respectively [7]. A more recently published study shows that Emergency Department (ED) physicians diagnosis of sepsis may disagree with the international definitions such that severe sepsis is underrecognized by clinician judgment alone. The odds ration for disagreement between a physician-designated no sepsis diagnosis and the 1991 definitions was 0.47 (95% confidence interval, 3.01–7.53) and 5.96 (3.78–9.46) between the same physician-designated diagnosis and the 2001 definition. No agreement was found between the physician diagnosis and 1991 consensus sepsis definitions (k=0.11 and 52.2% agreement) or between the physician diagnosis and the 2001 consensus sepsis definitions (k=0.13 and 50.0% agreement) [8].

Worldwide burden of sepsis and need for more personalized sepsis biomarkers

Sepsis is responsible for significant morbidity, mortality, and costs to healthcare systems worldwide. Despite significant advances in research and science, the overall mortality rate for sepsis has only modestly improved over time [9]. Still, enormous resources have been expended on sepsis trials, with more than 10,000 patients enrolled in over 20 placebo-controlled trials [10–13]. Importantly, most of these novel treatments were disappointing and did not reduce mortality in patients with severe sepsis. One explanation for the lack of benefit from various treatments is that these treatments are being applied indiscriminately to heterogeneous groups of patients with sepsis who may or may not have the pathophysiologic defect being targeted. A better understanding of the biology and pathophysiology underlying sepsis is thus a prerequisite for reducing mortality and morbidity associated with this disease and to move to a more personalized sepsis care. Herein, host biomarkers have attracted much interest and may help to identify patients at high risk for adverse outcome, and patients with a specific biopathological mechanism where sepsis treatments are more or less efficient.

Diagnostic, prognostic, and therapeutic-response biomarkers

Biomarkers may improve sepsis management by providing important information about diagnosis, prognosis, and therapeutic-response to treatment [14]. In regard to diagnosis, no true gold standard exists in sepsis with microbiological cultures remaining negative in a majority of patients, and with risk of false positives due to contamination. Studies have therefore used treatment response to antibiotics as a more pragmatic gold standard. Several markers, particularly procalcitonin (PCT) has shown to reduce unnecessary antibiotic treatment arguing for its diagnostic potential. In regard to prognosis, it is often difficult to determine clinically which patients with signs of SIRS/sepsis on initial evaluation have, or will develop, more severe illness and thus have a poor prognosis. Specifically, the development of organ dysfunction portends poor outcome and is a common pathway to death in these patients [15, 16]. Novel strategies that improve a clinician's ability to risk stratify patients with suspected sepsis facilitate early and appropriate therapeutic intervention, improve important triage decisions [e.g., admission to the hospital versus discharge home, or admission to intensive care unit (ICU) versus non-ICU bed], and provide a means to follow response to therapy. Herein, the use of prognostic serum biomarkers has the potential to improve significantly clinicians' ability to diagnose, risk stratify, and treat patients with systemic infections. There is currently no single accepted biomarker or combination of biomarkers for prognostic use in patients with suspected sepsis, but many markers have been proposed and tested [17, 18]. In regard to therapeutic-response biomarkers, several markers mirror specific pathobiological mechanisms that can be targeted by specific medications. Yet, no study has today proven that phenotyping of patients based on such a strategy improves survival in sepsis patients – but this is certainly a promising future approach.

Aim of this review

Herein, the aim of this narrative review is to summarize the current evidence for emerging diagnostic, prognostic, and therapeutic-response sepsis biomarkers in different infections and clinical settings, and discuss the reliability, potential benefit and limitations of these marker when used in clinical routine for sepsis management.

Procalcitonin – a diagnostic marker that improves antibiotic stewardship

PCT is an inflammatory biomarker synthesized in septic conditions mainly from ectopic sources (i.e., from extrathyroidal tissues) that reflects host response to bacterial infection. Thereby it mirrors the risk of having an infection, and the severity of the infection. PCT secretion is up-regulated by microbial toxins and bacterial-specific mediators such as interleukin-1β, tumor necrosis factor-α, interleukin-6. PCT is down-regulated as these substances decrease during recovery but PCT expression is also attenuated by cytokines typically released due to viral infection such as interferon-γ. PCT measurements therefore may further improve diagnosis of systemic bacterial infections, and also may help to determine the necessity and optimal duration of antibiotic therapy.

Initially, several observational studies investigating the accuracy of PCT in diagnosing sepsis have not been conclusive. This may be explained by different confounding factors including (a) use of first generation PCT assays used in some investigations with lower sensitivity; (b) heterogeneity among studies in regard to patient populations, treatments and clinical settings; (c) limitations in sepsis diagnosis because of lack of true diagnostic gold standard [19, 20]. Recently, a meta-analysis including 30 high-quality studies with a total of 3244 patients found that PCT can differentiate effectively between true sepsis and SIRS of noninfectious origin. The area under the receiver operating characteristic curve (AUC) over all these studies was 0.85 (95% confidence interval [CI] 0.81–0.88) [21] with similar results for medical, surgical, or pediatric patients. These results are encouraging showing high accuracy in establishing or refuting a sepsis diagnosis, particularly if values of this biomarker are low, i.e., <0.5 μg/L or high, i.e., >2.0 μg/L.

In addition to diagnosis, PCT has been studied in the setting of antibiotic stewardship. Thereby effective antibiotic therapy is the foundation of sepsis management [22]. Over-exposure to antibiotics subjects patients to the risk of adverse drug reactions without any corresponding therapeutic benefit, and increases the likelihood of development of bacterial resistance [23, 24]. Physicians are often reluctant to not use or early stop antibiotic therapy based on clinical grounds only. Blood biomarkers that indicate the risk of bacterial infection can improve physicians judgment in these situations. PCT in particular has been studied in various settings for its antibiotic stewardship potential [17].

An individual patient data meta-analysis [25] identified 14 randomized controlled trials, that demonstrated the efficacy and safety of PCT-guided decision-making regarding antibiotics. The PCT protocols used were all based on the same concept: empiric antibiotic therapy was given in all high risk patients with suspicion of sepsis, yet PCT encouraged physicians to early stop antibiotic treatment in patients with clinical improvement plus a drop in PCT below a cut-off level or below a relative decrease threshold [26]. PCT cut-offs for sepsis were <0.5 and <0.25 μg/L or relative decreases from peak levels (<80% or <90%). Daily or every-other-day follow-up PCT measurements were recommended. Within this individual patient data meta-analysis pooling data from patients with respiratory infections, effectiveness and safety of using PCT was assessed [27]. Across such patient populations, the PCT algorithms decreased median antibiotic exposure by more than 3 days (median exposure 8 days in PCT-guided patients vs. 12 days in controls, p<0.001), with no differences in 30-day all-cause mortality (19.9% vs. 23.8%, p=0.443) between PCT-guided patients (n=287) and control patients (n=311). Hospital length-of-stay tended to be shorter in PCT patients, although not statistically significantly so (21 vs. 24 days, p=0.393). Table 1 shows the most important sepsis trials in the critical setting with effect sizes in regard to mortality and antibiotic consumption.

Finally, several studies have also documented a prognostic value of PCT, particularly when repeated levels were used to assess the kinetic of PCT [28, 29].

Presepsin

Presepsin is a soluble fragment of the cluster of differentiation marker protein 14 (CD 14) involved in pathogen recognition by innate immunity [30]. Presepsin is emerging as a novel circulating biomarker of sepsis as it should be used for accurate and timely prediction of abnormal host response at an early stage thus allowing a safe treatment of patients and, similar to PCT, may be suited for monitoring appropriate antibiotic therapy [30, 31]. According to recent studies, the measurement of presepsin levels provides independent diagnostic and prognostic information in patients with sepsis and septic shock during the first week of intensive care treatment [32].

In particular, the diagnostic capacity to diagnose severe sepsis and septic shock at days 1, 3 and 8 in patients admitted to an ICU was very high (range of diagnostic area under the curves 0.72–0.84). Also in the long term,

Table 1: Randomized trials looking at PCT for antibiotic stewardship in the critical care sepsis setting (adapted from [26, 27]).

First author, Ref	Inclusion criteria	No. patients	Follow up time	Adherence to PCT algorithm	Mortality (control patients vs PCT group)	Relative reduction in antibiotic exposure
Nobre	Suspected severe sepsis or septic shock	79	1 month	81% adherence	12/40 (30%) vs. 8/39 (20.5%)	Duration: –37%
Schroeder	Severe sepsis following abdominal surgery	27	Hospital stay	Not reported	3/13 (23.1%) vs. 3/14 (21.4%)	Duration: –20%
Hochreiter	Suspected bacterial infections and >1 SIRS criteria	110	Hospital stay	Not reported	14/53 (26.4%) vs. 15/57 (26.3%)	Duration: –25%
Stolz	VAP when intubated for >48 h	101	1 month	Not reported	12/50 (24%) vs. 8/51 (15.7%)	AB-free days alive: 27%; Duration: –33%
Bouadma	Suspected bacterial infections during ICU stay without prior AB (>24 h)	630	2 months	47% adherence	64/314 (20.4%) vs. 65/307 (21.2%)	AB-free days alive: 19%; Duration: –33%

ICU, intensive care unit; PCT, procalcitonin; SIRS, systemic inflammatory response syndrome; VAP, ventilator-associated pneumonia; AB, antibiotic.

presepsin levels provided significant prognostic information for 30 days and 6 months all-cause of mortality [33].

Proadrenomedullin – a prognostic marker that may improve site of care decisions

Acute disease often leads to an inflammatory host response in patients characterized by the release of different active cytokines and hormone-like peptides into the blood stream. Among them, ProADM is the most potent vasodilator and becomes upregulated in inflammatory and infectious conditions. It belongs to the calcitonin peptide superfamily and is ubiquitously expressed in the body including sepsis, respiratory infections and pneumonia, and also heart failure and myocardial infarction [34, 35]. Importantly, ProADM has been shown to improve clinical pneumonia risk scores [36], and in a pilot intervention study, tended to decrease in length of stay without increased risk for readmissions by improving physicians admission and early discharge decisions [37].

Endothelial markers – mirror to the underlying pathophysiological mechanisms?

The endothelium is an important component for the host reaction to acute disease. Endothelial dysfunction during sepsis and its association with adverse outcomes has been found to be an important contributor to sepsis morbidity. Levels of soluble fms-like tyrosine kinase-1 (sFlt-1), plasminogen activator inhibitors-1 (PAI-1), sE-selectin, soluble intercellular adhesion molecule (sICAM-1), and soluble vascular cell adhesion molecule (sVCAM-1) correlated with endothelial dysfunction and increased sepsis mortality [38–41]. Similarly, proendothelin-1 (proET-1) is one of the precursor hormones of endothelin and a potent vasoconstrictor and vasopressor [42]. In pneumonia patients, proET-1 levels on admission and changes from baseline to day 3 were independent predictors for mortality and ICU admission, and significantly improved the clinical risk scores [43].

Other promising genetic sepsis markers

A number of studies in sepsis have found an association between specific DNA polymorphisms and function of the gene products produced in response to pathogenic stimuli [44–46]. These include genes that code for pattern recognition receptors such as CD14, T-ligand receptor (TLR)-4, TLR-2, mannose-binding lectins, Fcγ receptors among others. Also genes coding for inflammation such as tumor necrosis factor [TNF]-α, TNF-β, interleukin (IL)-1, IL-1Ra, IL-6, IL-10, angiotensin converting enzyme or coagulation (PAI-1, protein C) have been described. Such polymorphisms have been implicated in sepsis mortality. For example, an A to G substitution at the –308 position in the TNF-α promoter was associated with elevated TNF-α

expression in vitro and in vivo, and has been shown to confer a 4-fold increased mortality in one study of septic shock [44], 1.5-fold in another [47], and 2.5-fold in meningitis [48]. Although the association between gene polymorphisms and mortality awaits large-scale validation, there is strong support for the inclusion of genotyping as an important consideration when designing sepsis trials [45, 46, 49].

In addition to approaches focusing on DNA polymorphisms, analysis of mRNA has been proposed as a promising approach for better characterization of patients. Multi-gene transcriptional profiling (MGTP) is a novel high-throughput technique using real-time PCR for rapid, precise and sensitive quantification of mRNA copies per cell for each selected gene in a prespecified panel [50, 51]. Since the number of mRNA copies for a gene correlates in a linear fashion with gene activity, MGTP can quantify the gene expression patterns to inflammation. Therefore instead of waiting for the inflammation mediators to be produced and sent into the blood stream, MGTP will detect the production of inflammation mediators as soon as the relevant gene is activated. This is important since Sepsis is a time-sensitive condition. Several studies have shown that an earlier diagnosis and treatment can reduce sepsis mortality by up to 15% [52, 53]. Again, these approaches need validation and proof of clinical significance in regard to improve patient management.

Conclusions and outlook

Biomarkers have high potential to further improve sepsis management in regard to early diagnosis and improved treatment modalities. Emerging bacterial resistance calls for more effective efforts to reduce the unnecessary and prolonged use of antibiotics in sepsis patients [44]. Adding to a thorough clinical evaluation the information derived from measurements of different sepsis biomarkers appears to be a safe and effective approach to improve sepsis care. These markers, however, should be further validated for use in sepsis trials to further understand their benefit and limitations. These biomarkers may further help us to usher in an era of personalized medicine, wherein interventions may be more rapidly and accurately directed to the patients likeliest to benefit.

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