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Biomarkers of sepsis and their potential value in diagnosis, prognosis and treatment

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Abstract

Biomarkers have great potential to improve the diagnosis and treatment of sepsis. The available literature supports the potential utility of sTREM-1, IL-27, suPAR, neutrophil CD64, presepsin, cfDNA and miRNAs as novel diagnostic, prognostic and treatment response biomarkers. The future of sepsis biomarkers lies in extensive validation studies of such novel biomarkers across heterogeneous populations and exploration of their power in combination. Furthermore, the use of a companion diagnostics model may augment the ability of investigators to identify novel sepsis biomarkers and develop specific therapeutic strategies based on biomarker information.

Keywords

biomarker; cfDNA; combination biomarkers; companion diagnostics; IL-27; miRNA; neutrophil CD64; presepsin; sepsis; suPAR; TREM-1

Biomarkers: definition & utility

In 2011, NIH defined a biomarker as 'a characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathological processes or pharmacological responses to a therapeutic intervention' [1]. Based on this broad consensus definition, biomarkers are utilized daily by all medical practitioners in the diagnosis and treatment of patients in the form of routine laboratory tests. However, most practitioners consider biomarkers to be novel laboratory evaluations that provide clinicians with information otherwise not part of the routine diagnostic workup or monitoring evaluation [2]. For the purpose of this article, the discussion will focus on such biomarkers.

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Several authors have proposed four functional classes of biomarkers [2–4]. *Diagnostic* biomarkers confirm the presence or absence of a disease and emphasis is placed on specificity for clinical utility as tests to 'rule in' a disease of interest. Alternatively, when considering diagnostic biomarkers as screening tools, the emphasis is placed on sensitivity (i.e., a 'rule out' test). *Monitoring* biomarkers are indicators of the effectiveness of therapy for the purpose of titration. *Surrogate* biomarkers provide a readout that correlates with a clinical outcome of interest in the setting of a therapeutic intervention. *Stratification* or *staging* biomarkers classify diseases based on outcome probability, thereby potentially limiting exposure to unnecessary therapies for low-risk patients and identifying those at high risk for poor outcome as candidates for more aggressive therapies.

According to the expert panel review of Dupuy *et al*., in clinical practice, two types of biomarkers can be identified: those used independently from therapy (i.e., a diagnostic or prognostic test) and those used as an adjunct to treatment (i.e., to identify those who may benefit most from a specific therapy or to predict efficacy or toxicity early in the course of treatment) [5].

Regardless of classification, the demand for new and accurate biomarkers of sepsis is high. Clinicians now seek to expand their management of sepsis beyond the traditional diagnosis and treatment, tailoring therapy for individual patients not only from prognostic information, but also in response to treatment efficacy.

Biomarkers in sepsis

Sepsis is a heterogeneous syndrome resulting from the response of the immune system to invasive infection. When accompanied by organ system dysfunction or cardiovascular shock, severe sepsis or septic shock occur and are a leading cause of morbidity and mortality in critically ill patients [6,7]. Given the importance of timely initiation of appropriate antibiotics to optimize sepsis outcomes [8], clinicians must achieve a diagnosis of infection quickly in a setting where standard microbiologic cultures can lack sensitivity and there is an inherent delay between obtaining microbiologic cultures and generating clinically actionable data. Furthermore, once a diagnosis of sepsis is made and standard therapies initiated, it is often difficult to differentiate those patients most likely to achieve positive versus negative outcomes. Here, bio-markers have the potential to serve a crucial role by providing adjunctive information to guide clinicians to rapid diagnosis and extension of treatment beyond the standard therapy.

In 2010, Pierrakos and Vincent estimated that at least 178 different sepsis biomarkers have been reported in the literature [9]. Four years later, that number is likely higher. Thus, a genuine systematic review of the subject is beyond the scope of the authors' intent. Based on their informed opinion, the authors selected a group of biomarkers that the authors believe have the most biological plausibility and potential as sepsis bio-markers. The authors also highlight the concepts of combination biomarkers and companion diagnostics. By compiling these select biomarkers and concepts into their review, the authors hope to provide readers with a concise reference that can serve as a source for further research and development to address important gaps in the field of sepsis.

Triggering receptor expressed on myeloid cells-1

Triggering receptor expressed on myeloid cells-1 (TREM-1) is an immunoglobulin whose signaling induces the production of cytokines, chemokines and reactive oxygen species, all of which contribute to the inflammatory response. Furthermore, TREM-1 signaling leads to degranulation of neutrophils and increased phagocytosis. A soluble form of TREM-1 (sTREM-1) can be measured in body fluids and has potential as a sepsis diagnostic biomarker.

A recent review and meta-analysis by Jiyong *et al*. showed that elevated sTREM-1, sampled and measured from the location of infection, is highly predictive of bacterial infection [10]. However, it demonstrates low sensitivity as a biological marker of infection in the urinary tract. It was proposed by these authors that the utility of sTREM-1 is when a low level is obtained, thereby providing support to the clinician to withhold antibiotics while awaiting culture data (i.e., a ‘rule-out’ test).

Although sTREM-1 may prove a useful adjunct for a correct sepsis diagnosis, further validation studies are necessary before sTREM-1 may be utilized clinically. Furthermore, the studies of sTREM-1 have included assays from body fluids not limited to blood sampling (cerebrospinal fluid [CSF], pleural fluid, urine), which may decrease its utility as a diagnostic biomarker given a potential delay in obtaining such site-specific samples.

IL-27

IL-27 is a heterodimeric cytokine produced by antigen-presenting cells upon exposure to microbial products and inflammatory stimuli [11,12]. IL-27 regulates T-cell function and has both pro- and anti-inflammatory effects [13,14]. Ablation of IL-27 activity by either genetic deletion or soluble decoy receptor confers a survival advantage in a murine model of sepsis [15].

IL-27 was identified as a candidate sepsis diagnostic bio-marker through transcriptomic studies involving children with septic shock [16]. In these studies, Epstein–Barr virus-induced gene-3 mRNA expression demonstrated the greatest predictive capacity to differentiate critically ill children with systemic inflammatory response syndrome (SIRS) secondary to bacterial infection from critically ill children with SIRS from non-infectious causes. Because Epstein–Barr virus-induced gene-3 is a subunit of IL-27, subsequent studies focused on IL-27 serum protein concentrations as a sepsis diagnostic biomarker. These initial studies demonstrated that an IL-27 serum concentration >5 ng/ml had >90% specificity and positive predictive value for identifying critically ill children with laboratory-confirmed bacterial infection. Furthermore, IL-27 outperformed procalcitonin (PCT) in this cohort, and a decision tree combining IL-27 and PCT performed better than either biomarker alone.

Two subsequent studies tested the diagnostic utility of IL-27 in critically ill adults with sepsis [17,18]. In these studies, IL-27 did not perform as well as it did in critically ill children. However, a combination of IL-27 and PCT improved the ability of both biomarkers to identify patients with a non-pulmonary source of sepsis. Interestingly, these

studies also demonstrated that critically ill children with sepsis have a greater capacity to produce IL-27 than their adult counterparts. Consistent with this observation, Krumbiegel *et al*. previously demonstrated that monocyte-derived dendritic cells from neonates express greater amounts of IL-27 p28 mRNA compared with that of adults, when stimulated with Toll-like receptor ligands [19]. Accordingly, these studies suggest that IL-27 may turn out to be a more useful sepsis diagnostic biomarker in the pediatric population and illustrate the importance of testing biomarker performance in multiple patient populations.

Soluble urokinase-type plasminogen activator receptor

Soluble urokinase-type plasminogen activator receptor (suPAR) has recently been proposed as a potential biomarker of immune activation. Urokinase-type plasminogen activator is present on many cell types including monocytes and macrophages and is involved in the migration of inflammatory cells from the bloodstream into tissues. It is cleaved from the cell surface during periods of inflammation, producing its soluble form, suPAR, which can be measured in blood, urine and CSF. Increased inflammation secondary to activation of the immune system thereby produces increased concentrations of suPAR in body fluids.

Levels of suPAR are increased in acutely ill patients, but this increase is not specific for sepsis. Therefore, suPAR is not particularly useful as a diagnostic biomarker. Alternatively, however, suPAR has been demonstrated in multiple recent studies to have prognostic utility and is a promising biomarker in this category.

Initially, Eugen-Olsen *et al*. demonstrated that high serum suPAR concentrations correlated with mortality in patients with active tuberculosis [20]. Furthermore, suPAR levels were found to be highest in those patients with mycobacterium identified via direct microscopy when compared with patients who were only culture positive. The authors of this investigation thereby concluded that elevated suPAR might be indicative of disease severity.

In a 2004 study measuring suPAR levels in the CSF of patients with suspected meningitis, those with bacterial meningitis had significantly higher suPAR levels than those with aseptic meningitis or without meningitis [21]. More notably, of those patients with purulent meningitis, higher CSF suPAR levels correlated with mortality.

In a 2014 prospective study, serial serum suPAR concentrations were found to be higher in adult ICU patients with end-organ dysfunction, specifically those who required vasopressor support or mechanical ventilation [22]. This study also demonstrated significantly higher admission suPAR levels in non-survivors compared with survivors, providing further support for the prognostic utility of suPAR. These investigators concluded that the best admission cutoff value to predict ICU and 28-day mortality was 6.2 ng/ml in the total population and 10.2 ng/ml in patients with sepsis.

In 2004, Wittenhagen *et al*. demonstrated that patients with *Streptococcus pneumoniae* bacteremia had significantly higher serum suPAR levels when compared with healthy controls and that higher levels correlated with mortality [23]. In 2011, Molkanen *et al*. produced similar results for patients with *Staphylococcus aureus* bacteremia, concluding that 9.3 ng/ml was the optimal cut-off value to predict 28-day mortality [24]. In 2011, Huttunen

et al. broadened the scope of these results by measuring serum suPAR levels in a prospective group of bacteremic patients and concluded that suPAR was both a sensitive and specific prognostic biomarker in patients with *Staphylococcus aureus, Streptococcus pneumonia, Escherichia coli* or β-hemolytic *Streptococcus* bacteremia [25]. These investigators found that median suPAR values measured on days 1 through 4 post-blood culture were significantly higher in non-survivors compared with survivors and concluded that a level of 11 ng/ml could be used as a cut-off value to predict fatal disease (sensitivity 83%, specificity 76%).

Studies conflict regarding the use of serial suPAR measurements to assess response to antibiotic treatment. After 8 months of appropriate treatment, patients with active tuberculosis had a decrease in suPAR levels comparable with patients without disease [20]. However, a recent study by Donadello *et al*. did not demonstrate a correlation between suPAR levels and response to therapy in ICU patients with sepsis, although the follow-up period was a much shorter 14 days [22].

Neutrophil CD64

Expressed on neutrophils and monocytes, CD64 is the high-affinity immunoglobulin Fcγ receptor I and mediates phagocytosis of bacteria. CD64 expression is low at baseline, but when activated by proinflammatory cytokines, it is rapidly upregulated up to 10-fold higher levels [26,27]. CD64 has potential both as a diagnostic and prognostic sepsis biomarker.

Several studies have demonstrated that CD64 expression is relatively specific for bacterial infection and may therefore have diagnostic utility for sepsis. A recent meta-analysis by Cid *et al*. reported that the overall pooled sensitivity of CD64 as a sepsis diagnostic biomarker was 79% and specificity was 91% [28]. The authors did note, however, a high degree of variability in the literature and concluded that the methodological quality of the included studies was suboptimal.

In 2006, Livaditi *et al*. prospectively enrolled adult ICU patients with sepsis and measured neutrophil CD64 levels (in addition to other potential biomarkers) within 24 h of the onset of sepsis [29]. These investigators found that CD64 expression was significantly increased when compared with healthy controls and that higher levels correlated with worsening severity of sepsis as determined by clinicians upon enrollment and via Acute Physiology and Chronic Health Evaluation (APACHE-II) scoring. Furthermore, 28-day mortality was significantly associated with increased CD64 expression. Although the literature on the prognostic utility of neutrophil CD64 is not extensive, CD64 remains a promising candidate given its potential to serve both diagnostic and prognostic roles.

Presepsin

CD14 is a glycoprotein expressed on monocytes and macrophages, serving as a receptor for lipopolysaccharides and thereby playing a role in the innate immune system by activating a proinflammatory signaling cascade upon contact with pathogens [30]. During inflammatory stress, soluble CD14 fragments are cleaved, one of which has been identified as presepsin

(sCD14-ST), which is readily measured using a chemiluminescent enzyme immunoassay. Presepsin has potential both as a diagnostic and prognostic sepsis biomarker.

In 2013, Ulla *et al*. performed a multicenter study that prospectively enrolled adult patients presenting to the emergency department with SIRS [30]. Serum samples were collected at presentation, 24 and 72 h after admission and presepsin levels were later correlated with a final diagnosis of SIRS without infection, sepsis, severe sepsis and septic shock. These investigators found that presepsin levels were significantly lower in non-infected patients, and although increased levels of presepsin trended with increased sepsis severity, the difference between groups was not significant. They further concluded that presepsin levels were highest in infected patients at the earliest time point measured, making it an ideal candidate as a diagnostic biomarker. A higher level of presepsin at presentation was also found to correlate with 60-day mortality. Similarly, Romualdo *et al*. demonstrated that increased presepsin correlated to an ultimate finding of bacteremia in patients presenting to the emergency department with SIRS [31].

In 2014, Masson *et al*. released retrospective results of the Albumin Italian Outcome Sepsis trial in which the prognostic potential of presepsin was further investigated. The authors found that presepsin measured at presentation in patients with severe sepsis or septic shock was higher in non-survivors when compared with survivors [32]. The evolution of presepsin levels over the course of illness was also different in survivors compared with non-survivors: presepsin levels remained significantly higher on days 2 and 7 in non-survivors when compared with survivors. Presepsin was independently associated with ICU and 28-day mortality, even after correction for key variables related to resuscitation (mean arterial pressure, serum lactate and central venous oxygen saturation).

Also in 2014, Endo *et al*. demonstrated that presepsin levels correlated with the severity of sepsis when compared with other common sepsis biomarkers (IL-6, C-reactive protein, PCT) [33]. Adult emergency department and ICU patients with sepsis were prospectively enrolled, serial serum samples of presepsin and other biomarkers were monitored and patients were grouped into favorable and unfavorable prognosis groups (based on Sequential Organ Failure Assessment and APACHE-II scores). The investigators found that while all tested bio-markers decreased over 7 days in the favorable prognosis group, only presepsin did not decrease over time in the unfavorable prognosis group, again indicating its utility as a prognostic biomarker.

Cell-free DNA

Cell-free plasma DNA (cfDNA) consists of short-lived fragments of DNA that are likely released because of cell necrosis or apoptosis and can be quantified from the blood. Given that cell death is a common occurrence during sepsis, although not sepsis-specific, cfDNA has recently been explored as a prognostic biomarker for sepsis.

In 2006, Rhodes *et al*. demonstrated that ICU patients had higher cfDNA concentrations than healthy controls. Furthermore, patients who developed sepsis or subsequently died had significantly higher levels of cfDNA when compared with other disease processes and patients who survived [34].

In 2008, a large study by Saukkonen *et al*. demonstrated that admission cfDNA in adults with sepsis or septic shock was significantly higher in non-survivors when compared with survivors [35]. However, the study indicated that admission cfDNA was only moderately predictive of ICU mortality based on receiver operating characteristic analysis, comparable to standard clinical scoring systems (multiple organ dysfunction, Sequential Organ Failure Assessment, APACHE-II).

In 2012, Dwivedi *et al*. demonstrated that cfDNA provides high prognostic accuracy in patients with severe sepsis when measured via a UV-absorbance method at 260 nm, rather than the previously utilized PCR method for the β-globin housekeeping gene [36]. Day 1 levels of serum cfDNA were markedly higher in adult non-survivors of severe sepsis when compared with survivors. Furthermore, cfDNA had the strongest predictive power for ICU mortality (area under the curve [AUC] value 0.97) compared with the modest predictive value of the clinical scoring systems (multiple organ dysfunction: AUC value 0.63, APACHE-II: AUC value 0.64). These investigators concluded that a cut-off value of 2.35 ng/μl should be considered, as their data yielded both high sensitivity (88%) and specificity (94%) for ICU mortality. Furthermore, non-survivors had persistently high cfDNA levels compared with survivors who had persistently low levels.

In 2014, a group of Finnish investigators prospectively enrolled adult patients with *Staphylococcus aureus* bacteremia and monitored plasma cfDNA levels at days 3 and 5 following blood culture collection as well as up to 90-day mortality [37]. They demonstrated that cfDNA levels were higher in patients requiring ICU admission. Furthermore, they found a sensitivity of 67% and a specificity of 77% for mortality using a cfDNA level of >1.99 μg/ml on day 3. However, cfDNA on day 5 was not found to predict fatal outcome, indicating the lower prognostic value of cfDNA later in the course of illness.

miRNA

miRNAs are a newly identified class of biomarkers that may serve a diagnostic or prognostic role in various human pathologic conditions, including sepsis. miRNAs are short sequences of endogenous RNAs that are involved in translational gene regulation [38]. The process for identification of potential miRNAs involved in sepsis is unique when compared with other biomarkers and varies among the investigators exploring their potential. Some investigational strategies identify the target genes of previously identified miRNAs (often identified as involved in sepsis via wide genome screening or from prior animal studies) and monitor serum levels of the target proteins [39]. Other studies directly measure serum levels of the miRNA themselves [40,41]. Several miRNAs and/or their target proteins have been identified as indicative of disease or severity for sepsis, but further studies are needed to validate such findings [39–41].

Combination biomarkers

In 2012, Gibot *et al*. performed a robust study measuring several biomarkers (PCT, sTREM-1 and CD64) in unselected ICU patients and combined the results into a ‘bioscore’, which proved highly diagnostic for sepsis [42]. The investigators established individual cut-off values for PCT, sTREM-1 and neutrophil CD64 index based on receiver operating

characteristic analyses and demonstrated improved diagnostic accuracy when combined into a bioscore. Importantly, the diagnostic performance of the bioscore was validated in an independent prospective cohort of ICU patients from another center. The combination bioscore demonstrated an AUC of 0.95 and was useful in >80% of patients regarding an immediate diagnosis of sepsis or non-sepsis, demonstrative of its clinical prowess.

Similarly, in 2012, Dwivedi *et al*. combined cfDNA levels with multiple organ dysfunction scores and protein C levels and produced improved predictive power for mortality in patients with septic shock compared with the individual markers alone [36]. These studies provide a rationale for investigators to consider examining other, or broader, combinations of biomarkers that may improve the clinician's real-time diagnostic and prognostic capabilities.

In keeping with this line of investigation, transcriptomic studies have identified a group of genes having predictive capacity for mortality in children with septic shock [2]. This gene list facilitated the discovery of serum protein biomarkers for developing the Pediatric Sepsis Biomarker Risk Model (PERSEVERE) [43]. PERSEVERE consists of a decision tree incorporating five stratification biomarkers and age to assign a mortality probability for children with septic shock. Recently, the prognostic accuracy of PERSEVERE was prospectively validated in an independent cohort [44]. A temporal version of PERSEVERE has been derived and validated, which considers biomarker changes over time to assign a reliable probability of poor outcome [45]. This version of PERSEVERE has the potential to serve as an adjunct monitor for therapeutic effectiveness. PERSEVERE has also been adapted for adults with septic shock [46]. Both the pediatric and adult versions of PERSEVERE outperform commonly used prognostic scoring systems based on laboratory and physiological parameters. A comparison of the two models may provide some insight regarding the influence of age and development on the biology of sepsis [47].

Companion diagnostics

Companion diagnostics is an approach that holds great potential to advance the discovery of novel biomarkers in sepsis and to provide an avenue for identification of new treatment strategies. Companion diagnostics has been defined as a diagnostic assay developed in parallel to a targeted drug and used to guide treatment [48]. This investigational strategy has been employed primarily in the oncology field and has been highly successful. For example, the development of an immunohistochemistry assay for HER2-positive breast cancer has led the way for better selection of patients for treatment with trastuzumab (Herceptin®) [48].

The utility of companion diagnostics lies in its unique ability to identify patients most likely to benefit from a particular therapy and to employ that therapy only in cases where patients are likely to respond. The field of biomarker and treatment discovery using a companion diagnostics model is relatively underdeveloped for sepsis and offers a highly productive opportunity for investigators in this arena. Meisel *et al*. performed what can be considered the first, genuine biomarker-guided immunostimulatory trial in sepsis. These investigators administered granulocyte-macrophage colony-stimulating factor to patients with sepsis as a means of reversing sepsis-associated immunosupression. Notably, the patients were selected

based on monocyte HLA-DR expression, which served as a biomarker for sepsis-associated immunosupression [49]. The EUPHRATES clinical trial is currently enrolling patients with septic shock to evaluate the efficacy of polymyxin B hemoperfusion, and one of the inclusion criteria is an endotoxin activity assay value of ≥0.6 endotoxin activity assay units [50].

Expert commentary

The identification of relevant and useful sepsis biomarkers presents many challenges. Most importantly, sepsis is a heterogeneous illness without a reliable gold standard. Given the low sensitivity of a positive blood culture, many cases are diagnosed based on a relatively subjective clinical milieu, which provides variability among diagnosticians and contributes to a lack of homogeneity among studies investigating novel sepsis biomarkers.

Extensive clinical validation in multiple independent cohorts is required before a biomarker can be determined efficacious. The candidate biomarkers described in this review, albeit promising, are not ready for immediate use and require further investigation to confirm their utility and cut-off values. Furthermore, clinical laboratory assays are not widely available to measure such novel markers. Related to this, clinical assays for sepsis biomarkers need a rapid turnaround time given the time-sensitive needs of patients with sepsis.

The identification of new and useful biomarkers that serve diagnostic and prognostic roles in sepsis has great potential to improve the bedside management of the disease. While PCT and C-reactive protein are commonly used in current practice, their implementation into routine clinical practice has revealed the ongoing need for the development of additional diagnostic and prognostic biomarkers for sepsis. Although the biomarkers discussed in this review require further investigation and validation, there is promise that these biomarkers, singly or more likely in combination, may be able to identify patients with sepsis and at high risk for poor outcomes with improved accuracy. Table 1 summarizes the novel biomarkers detailed in this review and indicates their potential roles in the clinical realm of sepsis.

The use of combination biomarkers provides a means of improving sensitivity and specificity for both diagnostic and prognostic agendas in sepsis. Combination biomarkers are also appealing from a mechanistic standpoint. Sepsis is a tremendously complex and heterogeneous biological syndrome, so it makes sense that a combination of biomarkers is more likely to account for this heterogeneity than a single biomarker. As demonstrated by Gibot *et al*., the combination of PCT, sTREM-1 and CD64 was highly diagnostic for sepsis [42]. The potential for an even more robust test is evident, given the number of potential biomarkers discussed in this review and the myriad of unexplored combinations that could provide improved accuracy. PERSEVERE, based on a translational genomic approach, has demonstrated superior prognostic utility of combination biomarkers in sepsis [43,44] and provides incentive for investigators to explore combinations through traditional and more novel investigational methods. The cost of multiple analyses, of course, will ultimately factor into a final product used regularly at the bedside, although the statistical potential of using multiple biomarkers may prove best for the patient.

Companion diagnostics, while not widely used as an investigational method in sepsis, offers a major step towards the highly desired concept of personalized medicine. The management of sepsis, as a leading cause of morbidity and mortality, could achieve rapid advancement should investigators utilize such a strategy for identifying diagnostic and therapeutic targets. The trial by Meisel *et al*. involving HLA-DR expression and granulocyte-macrophage colony-stimulating factor [49], and the EUPHRATES trial, are excellent examples of this approach and the results of these trials may ultimately bring the concept of companion diagnostics to the bedside of patients with sepsis.

Five-year view

The future of sepsis biomarkers, including those discussed here, lies in extensive validation studies and further exploration of biomarker combinations that may augment the diagnostic and prognostic capabilities of clinicians at the bedside. As sepsis is a complex and heterogeneous syndrome, validation of sepsis bio-markers and combinations of biomarkers demand exploration across heterogeneous populations (e.g., children vs adults, medical vs surgical patients, oncologic patients, etc.). It is important to recognize that biomarkers that are highly useful in one population may not have the same test characteristics in another population and, therefore, validation studies must be highly critical to optimize the right test for the right patient. In addition, future studies should adhere to the STAndards for the Reporting of Diagnostic accuracy (STARD) study guidelines for the conduct and reporting of sepsis diagnostic biomarkers [51].

As previously stated, the lack of a reliable gold standard for sepsis presents an ongoing challenge in establishing appropriate diagnosis and treatment, and further results in significant heterogeneity among studies investigating sepsis biomarkers. In response, there is a growing field of molecular diagnostics that relies on detection of bacterial DNA in the bloodstream for identification of sepsis rather than the traditional low-sensitivity blood culture. This novel technology may swing the pendulum in the opposite direction, proving too sensitive by perhaps falsely identifying positive cases from transient bacteremia with unknown clinical or biological significance. This information may ultimately confound the clinical picture, resulting in antibiotic courses for well-appearing patients without true infection. In this situation, biomarkers may serve as an adjunct to molecular diagnostics by providing clinicians with more information to judge whether the presence of bacterial DNA in the bloodstream is indicative of true infection.

Regardless of the standard upon which sepsis is judged, bio-marker investigation, validation and clinical integration remains vital to improving the care provided for the patient with sepsis. The availability of high-throughput technologies such as transcriptomics, proteomics and metabolomics provide robust frameworks for the discovery and development of novel biomarkers [52–54].

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Key issues

- Sepsis biomarkers have potential to alter the timeliness of diagnosis and improve management by providing prognostic information to clinicians in real-time.
- Soluble form of triggering receptor expressed on myeloid cells-1 has diagnostic potential as a sepsis biomarker, but further validation studies are necessary before regular use. Exploration comparing serum versus site-specific levels may be useful to improve bedside utility.
- IL-27 may be useful diagnostic sepsis biomarker in pediatric patients, but does not produce similar general results in adult studies.
- Soluble urokinase-type plasminogen activator receptor is a useful prognostic sepsis biomarker, but further studies to validate cutoff levels to predict mortality are needed.
- Neutrophil CD64 is a promising diagnostic and prognostic sepsis biomarker, but more studies that are robust would be useful to further evaluate its potential.
- Presepsin is a promising sepsis biomarker with a sound body of research to confirm its diagnostic and prognostic utility. Further studies are needed to validate cut-off values before it can be clinically utilized.
- Cell-free plasma DNA and miRNAs are largely unexplored targets that may offer a new realm of sepsis biomarker investigation.
- Combination biomarkers have perhaps the best potential to provide highly sensitive and specific real-time results to influence bedside diagnostic and therapeutic decisions.
- Companion diagnostics offer a previously unutilized method for identifying sepsis biomarkers and developing therapeutic strategies based on biomarker information.

Table 1

Novel biomarkers and their potential utility in diagnosis, prognosis and treatment response in sepsis based on current literature.

	Diagnostic utility	Prognostic utility	Treatment response	Areas of future investigation
Soluble form of triggering receptor expressed on myeloid cells-1	Yes			Low sensitivity in the urinary tract Levels sampled from site of infection rather than serum
IL-27	Yes			Higher utility in pediatric patients than adults
Soluble urokinase-type plasminogen activator receptor		Yes	Possibly	Variable cut-off values to indicate high mortality in literature Inconsistent results regarding therapy effectiveness
Neutrophil CD64	Yes	Yes		Limited studies to date
Presepsin	Yes	Yes		
Cell-free plasma DNA		Yes		High variability of results using different assays (ultraviolet-absorbance vs PCR method)
miRNA	Yes	Yes		Inconsistent methods of investigation