Sepsis Biomarkers

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Abstract

Sepsis-related biomarkers have a variety of potential applications. The most well-known application is to differentiate patients with signs of systemic inflammation caused by infection, from those with systemic inflammation due to a non-infectious cause. This application is important for timely and judicious prescription of antibiotics. Apart from diagnostic applications, biomarkers can also be used to identify patients with sepsis who are at risk for poor outcome and to subgroup patients with sepsis based on biological commonalities. The latter two applications embody the concepts of prognostic and predictive enrichment, which are fundamental to precision medicine. This review will elaborate on these concepts, provide relevant examples, and discuss important considerations in the process of biomarkers discovery and development.

Keywords
- biomarkers
- sepsis
- diagnostic

Introduction

Biomarkers are broadly defined as characteristics that can be measured objectively and serve as indicators of normal biological processes, pathological processes, or response to a therapeutic intervention.[1] Classically, there are four broad classes of biomarkers.[2] *Diagnostic* biomarkers serve to establish the presence or absence of a disease or clinical condition. This is the most common class of biomarkers when considering sepsis, wherein there is substantial interest in developing biomarkers that can distinguish between infection and noninfectious systemic inflammation. *Monitoring* biomarkers provide information regarding the effectiveness of a given therapy for the purpose of titration, for example, measuring glucose to guide insulin therapy. *Surrogate* biomarkers provide information regarding the effectiveness of a given therapy, but for the purpose of predicting a clinical outcome. For example, trials of lipid-lowering therapies use lipid levels as surrogates for the outcome of interest, such as cardiovascular disease. *Stratification* biomarkers serve to stage or subclassify diseases based on outcome risk, severity, or biological mechanism.

Stratification biomarkers are important for the concept of *enrichment*, defined as the selection of a patient cohort that is more likely to respond to a therapeutic intervention, compared with an unselected cohort.[3] *Prognostic* enrichment selects a patient cohort that is more likely to have a disease-related event, such as mortality. *Predictive* enrichment selects a patient cohort that is more likely to respond to a therapeutic intervention based on a biological mechanism. Prognostic and predictive enrichment strategies, via either biomarkers or some other approach, are fundamental for embracing precision medicine.

Sepsis Diagnostic Biomarkers

Early recognition and prompt antibiotic prescription are fundamental initial steps in the treatment of bacterial sepsis. Providing a timely distinction between patients with non-infectious systemic inflammation and those with infection, and between viral and bacterial infections, are monumental challenges in clinical medicine. Traditional microbiological cultures obtained from blood or other body fluids remain the gold standard. While specific, they can lack sensitivity and there is typically a significant delay between obtaining

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cultures and generating actionable data. Consequently, broad-spectrum antibiotics are often prescribed absent the necessary data to ensure that patients with bacterial infection receive prompt treatment. However, this exposes a great number of patients without bacterial infection to unnecessary antibiotics with the consequent risks of developing antibiotic resistance, antibiotic-mediated toxicity, and increases in health care costs. These issues are greatly intensified among critically ill patients. Biomarkers that provide a reliable, early estimate of the likelihood of bacterial infection well before culture results are available would obviate the risk of treatment.

Procalcitonin (PCT) is the only sepsis diagnostic biomarker currently having Food and Drug Administration approval.[4,5] Its diagnostic accuracy appears to depend on the population being tested, with a recent meta-analysis indicating modest performance among critically ill patients.[6] Recently, Lautz et al[7] evaluated the utility of PCT among children in the pediatric intensive care unit, and concluded that PCT was not superior to C-reactive protein for differentiating bacterial infection from viral illness or noninfectious systemic inflammation.[4,7] As a sepsis diagnostic biomarker, PCT has been incorporated into clinical decision algorithms to guide both initiation and discontinuation of antibiotics. This reflects the important concept of antibiotic stewardship. In this regard, PCT-guided algorithms have yielded inconsistent results, depending on the nuances of the algorithms and the test population.[8–16]

Despite variable performance, PCT is approved for clinical use as a sepsis diagnostic biomarker and is being increasingly incorporated into clinical practice. Accordingly, future studies evaluating alternative sepsis diagnostic biomarkers should incorporate comparisons to PCT performance into the study design.

Interleukin-27 (IL-27) was recently evaluated as a sepsis diagnostic biomarker among critically ill children. It was identified as a candidate biomarker through discovery-oriented transcriptomics, and in the initial study was found to be superior to PCT for differentiating between critically ill children with culture-confirmed bacterial sepsis and those with culture-negative systemic inflammatory response syndrome.[17] In a follow-up study, its performance was less robust when including critically ill patients with negative cultures, but with a high clinical suspicion for bacterial infection.[18] A secondary analysis suggested improved performance among patients with congenital or acquired immune suppression.[18] Interestingly, IL-27 does not seem to perform as well among adults with suspected sepsis.[19,20] This might reflect that children with infection produce significantly greater amounts of IL-27,[19] compared with adults with sepsis, and further illustrates the need to evaluate sepsis diagnostic biomarkers within specific age groups. Further work is required to evaluate IL-27 as a sepsis diagnostic biomarker.

There are multiple other candidate sepsis diagnostic biomarkers. Some of the more notable ones include the soluble fragment of CD14 (sCD14-ST or presepsin), neutrophil CD64, cell free deoxyribonucleic acid (cfDNA), soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), and soluble urokinase-type plasminogen activator receptor, as recently reviewed.[15,16] This raises the possibility that a combination of biomarkers can improve diagnostic performance relative to single biomarkers. Indeed, Gibot et al reported a "bioScore" combining PCT, sTREM-1, and neutrophil CD64.[21] The bioScore had superior diagnostic performance relative to the individual biomarkers and was validated in an external, independent cohort.

All of the aforementioned biomarkers, except for cfDNA, reflect proteins in the blood compartment. Recently, investigators evaluated the ability of transcriptomic signatures reflecting whole blood-derived messenger ribonucleic acid (mRNA) as candidate sepsis diagnostic biomarkers. Sweeney and colleagues identified two gene sets that are diagnostic for bacterial infection.[22–24] Their multicohort analyses of 17 publicly available gene expression data sets included 1,089 pediatric and adult patients from the emergency department, general ward, and intensive care unit, representing the broad clinical heterogeneity of sepsis. An 11-gene Sepsis MetaScore reliably distinguished between noninfectious inflammation and infection, while a separate set of 7 genes reliably differentiated between bacterial and viral infection. A combination of these 18 genes produced an "integrated antibiotics decision model" with a pooled sensitivity and specificity of 94 and 60% for bacterial infection across 24 independent, public cohorts representing 1,040 patients. The negative likelihood ratio of 0.1 indicates clinical utility for identifying patients with a very low likelihood of bacterial infection and therefore candidates for safely withholding of antibiotics.

In another study based on mRNA expression, Mahajan et al reported on an expression signature to identify febrile infants with bacterial infection in the emergency department.[25] Similarly, Herberg et al reported on a two-gene expression signature to distinguish children with bacterial infection from those with viral infection.[26]

Stratification of Biomarkers for Estimating Mortality Risk

The development of biomarkers to estimate mortality risk is predicated on the concept that knowing baseline risk is fundamental to clinical practice and research. Knowing baseline risk can inform decision making, serve as a benchmark to evaluate outcomes, enable stratified analyses of clinical data, and ultimately can serve to inform enrollment into clinical trials. The latter reflects the concept of prognostic enrichment.

Interleukin-8 (IL8) has high sensitivity and negative predictive value for estimating the risk of 28-day mortality among children with septic shock.[27] Interestingly, it does not perform as well among adults with septic shock,[28] again reflecting the influence of developmental age on the host response to sepsis and the need to develop biomarkers and biomarker-based decision rules that are age appropriate.[29–31]

The Pediatric Sepsis Biomarker Risk Model (PERSEVERE) uses a panel of protein biomarkers measured during the first 24 hours of a septic shock diagnosis and a decision tree to estimate baseline risk of mortality among children with septic shock.[32] The PERSEVERE biomarkers were identified through discovery-oriented transcriptomic studies, further informed by mechanistic and feasibility considerations.[33] PERSEVERE has been validated prospectively,[34] and recently updated to provide improved performance across septic shock phenotypes reflecting different patterns of multiple organ failure.[35] A temporal version of PERSEVERE measures how the biomarkers change over time and how the changes reflect changing mortality risk.[36,37] While this temporal version of PERSEVERE requires further validation, it has the potential to serve as a monitoring tool to evaluate therapeutic efficacy.

The ability of PERSEVERE to inform decision making or clinical trial enrollment depends on the development of a rapid assay platform that can generate reliable biomarker data for individual patients. Pending this development, PERSEVERE has been tested in post hoc stratified analyses of clinical data. One study demonstrated that a positive fluid balance was associated with increased risk of poor outcome from septic shock among patients with a low PERSEVERE-based mortality risk, but not in those with an intermediate or high PERSEVERE-based mortality risk.[38] Another study tested the hypothesis that the benefits of corticosteroids among children with septic shock are dependent on baseline mortality risk, as measured by PERSEVERE.[39] The study could not find any benefits associated with corticosteroids among any of the PERSEVERE-based mortality risk strata.

Stratification of Biomarkers for Identifying Septic Shock Endotypes

An endotype is a subclass of a disease based on a biological mechanism or process. Whole genome expression profiling, followed by unsupervised hierarchical clustering enabled the identification of gene expression-based subclasses of both pediatric and adult septic shock.[40,41] Importantly, in both children and adults, the gene expression-based subclasses have important clinical differences with respect to illness severity, organ failure burden, and mortality.

In children, the subclass-defining genes were subsequently distilled to a 100-gene signature reflecting adaptive immunity and the glucocorticoid receptor signaling pathway.[42,43] These links to biological pathways and function suggest that the subclasses reflect endotypes of pediatric septic shock. This assertion, is further strengthened by the growing interest in enhancing adaptive immunity as a therapeutic strategy in sepsis,[44] and the ongoing controversies regarding the role of adjunctive corticosteroids in septic shock.[45]

A subsequent prospective study validated the existence of pediatric septic shock endotypes "A" and "B," based on the 100-gene expression signature.[46] These genes were repressed among the endotype A subjects, relative to the endotype B subjects. Importantly, allocation to endotype A was independently associated with increased risk of mortality, after adjusting for illness severity, age, and comorbidity burden. In addition, corticosteroids were independently associated with increased risk of mortality among endotype A subjects, but not endotype B subjects. The most recent study in this area reduced the endotype-defining gene signature to a decision tree consisting of just four genes.[47] This provides an opportunity to develop a clinical test to rapidly endotype children with septic shock in the clinical setting.

Because the endotype-defining genes reflect adaptive immunity and glucocorticoid receptor signaling, endotyping could serve as a predictive enrichment strategy. In support of this assertion, a recent study combined prognostic enrichment based on PERSEVERE, with predictive enrichment based on endotyping, in an attempt to identify children with septic shock who might be more likely to benefit from corticosteroids.[48] This post hoc analysis revealed that among endotype A subjects with an intermediate to high PERSEVERE-based mortality risk, prescription of corticosteroids was independently associated with a more than 10-fold reduction in the risk for poor outcome. This combination of prognostic and predictive enrichment strategies for pediatric septic shock and corticosteroid responsiveness requires prospective validation combined with standardized corticosteroid prescription.

Analogous to the concept of pediatric septic shock endotypes, Alder et al recently investigated the role of olfactomedin-4 (OLFM4) among children with septic shock.[49] OLFM4 was first cloned from the neuroepithelium of the bullfrog olfactory bulb, hence its name.[50,51] The OLFM4 protein is a secreted glycoprotein known to facilitate cell adhesion, but relatively little else is known about its biological function. It is expressed in the intestine, colon, and prostate, as well as in intestinal and gastric tumors.[52] OLFM4 is also expressed in a subset of neutrophils; approximately 25 to 35% of neutrophils from healthy subjects are OLFM4 + .[53] As such, OLFM4 may be identifying a subset of neutrophils. The functional significance of this putative subset is unknown. In critically ill patients with acute respiratory distress syndrome and respiratory syncytial virus bronchiolitis, OLFM4 expression is associated with illness severity.[54,55] OLFM4 is also a candidate biomarker for sepsis-associated acute kidney injury.[56,57] OLFM4 null mice have increased resistance to bacterial challenge.[58–60] Thus, OLFM4 appears to have a role in a variety of critical illnesses triggered by infection and inflammation.

In the study by Alder et al, OLFM4 was the highest expressed gene among children who did not survive septic shock, and the percentage of OLFM4+ neutrophils was independently associated with increased risk for poor outcome.[49] Collectively, these data indicate that OLFM4 might serve as a biomarker to identify a subset of pathogenic neutrophils in children with septic shock. Beyond serving as a biomarker, these data also raise the possibility of selectively targeting pathogenic OLFM4+ neutrophils as a novel therapeutic strategy for sepsis.

Current State of Sepsis Biomarker Research

Biomarkers hold the promise of improving our clinical approach to pediatric sepsis at multiple levels. These include enhancing sepsis diagnosis, monitoring therapeutic efficacy, and developing prognostic and predictive enrichment tools to enable precision medicine within pediatric sepsis. However, there is a major discrepancy between the large amount of research focused on sepsis biomarkers, and the actual number of biomarkers that are in use clinically.[61] Among the many candidate biomarkers in the literature, only PCT has reached the bedside of children as a clinical test. The clinical experience thus far is that PCT is imperfect, indicating the need to develop additional biomarkers. These challenging issues provide an opportunity to reflect on the arduous process of identifying, developing, evaluating, and validating sepsis-related biomarkers.

There are two broad approaches to biomarker identification.[33,62] The knowledge-based approach relies on the traditional scientific method wherein a candidate biomarker is identified based on existing knowledge. The strengths of this approach are that it is hypothesis driven and focused. The weakness, however, is that the approach is inherently biased because it is limited by current knowledge. An alternative approach is discovery-oriented, relying on high-throughput technologies such as proteomics or transcriptomics. The strengths of this approach are that it is unbiased and provides an opportunity to identify previously unconsidered candidates. The weaknesses of this approach are that they can be costly and prone to false positive findings. An alternative to these two extremes is a hybrid approach, wherein initial discovery employs high-throughput screening, followed by final selection of candidates based on biology and mechanistic considerations. The selection of the PERSEVERE biomarkers reflects this hybrid approach.[33]

Clinicians seek biomarkers that provide a dichotomous readout. For example, the ideal sepsis diagnostic biomarker provides an unambiguous "yes" or "no" answer to the presence of infection. This is probably an unrealistic expectation. A more realistic expectation might be that a sepsis diagnostic biomarker provides a probability of infection, and this information is then integrated with the clinical context. Similarly, it is unrealistic to expect that prognostic biomarkers have a high specificity for predicting mortality, because this implies that outcome from sepsis is predetermined and not modifiable by therapeutic interventions. PERSEVERE illustrates this point in that it is highly sensitive for mortality, but also generates several false positive predictions, thus leading to modest specificity. However, the PERSEVERE-based false positive subjects have higher organ failure burden and illness severity, compared with the PERSEVERE-based true negatives subjects.[32] This suggests that PERSEVERE can indeed identify patients who are at high risk of mortality, but that risk can be modified by therapeutic interventions.

Novel sepsis biomarkers are useful if they improve upon existing tools or provide new information. Thus, it is imperative that the performance of new biomarkers be rigorously compared with existing tools. As indicated earlier, PCT is now the reference criterion for sepsis diagnostic biomarkers, so it is important to compare the performance of new sepsis diagnostic biomarkers to that of PCT. Similarly, prognostic biomarkers should be compared with existing tools for estimating mortality risk and assessed for the possibility of providing additional biological information.

Biomarker performance is often dependent on the population in which it is tested, given the nuances of disease prevalence and severity. For example, a sepsis diagnostic biomarker will likely have different test characteristics among a population of children presenting to an outpatient setting, compared with a population of children in the intensive care unit.[17,18,63] Similarly, a prognostic biomarker will likely show low specificity when evaluated in a population in which the outcome of interest has a low prevalence, but will have high sensitivity if the prevalence is high. Thus, it is important to evaluate biomarker performance in diverse settings and interpret data in the appropriate context.

Finally, timing is a major, but often forgotten, consideration when developing sepsis biomarkers.[64] Biomarker data related to sepsis requires a rapid turnaround time to be actionable. Thus, sepsis biomarkers should be developed with this concept in mind, wherein they require sample preparation procedures and analyses that are congruent with time-sensitive decision making inherent to children with sepsis.

Conflict of Interest
The author and Cincinnati Children's Hospital Medical Center hold United States patents for the PERSEVERE biomarkers and the endotyping strategy described in this manuscript.

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