

Presepsin: Hope in the Quest for the Holy Grail

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With one person dying every 2.8 seconds from it worldwide, sepsis is a major public health problem and a leading cause of hospitalization and mortality in infants and children.^{1,2} Being a clinical syndrome rather than a disease *per se*, sepsis significantly contributes to preventable mortality and morbidity across different diseases. Fighting sepsis is an indispensable component of realizing several targets of the health-related sustainable development goal 3, especially those concerning reduction of maternal, child, and neonatal mortality.³ Early detection and timely, appropriate antimicrobial therapy are paramount for improving outcomes. These in turn involve several crucial processes like screening, diagnosis, prognosis (risk stratification), monitoring of therapeutic response, and the determination of optimal duration of antimicrobial therapy where clinical judgment alone may not yield right and timely answers.

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) defines sepsis as a life-threatening organ dysfunction caused by dysregulated host response to an infection.⁴ This revolutionary definition underlines the primary role of the nonhomeostatic host response to microorganisms rather than the infection *per se*. A new bedside index, called the quick Sequential Organ Failure Assessment (qSOFA), has also been introduced. The poor sensitivity of the qSOFA score makes it useful as a risk stratification tool alone and unsuitable for diagnosing sepsis. These new developments are hence not without criticism, as poor diagnostic sensitivity and specificity, by further complicating clinical reasoning, can be dangerous, especially in critically overcrowded environments such as the emergency department.⁵ Clinical presentation itself is often heterogeneous and nonspecific as the causative pathogen(s) and affected organ(s) both are varied. Many patients still remain microbiologically undiagnosed, leading to indiscriminate and irrational usage of antimicrobial therapy, adding to cost, adverse effects and antimicrobial resistance (AMR).

Given the complexity of the syndrome, wide variety of triggers, and variable host response, the intense and relentless search for biomarkers is not surprising. However, ideal biomarkers have remained the Holy Grail in sepsis. Additional issues like feasibility and cost, especially in low- to middle-income countries, further complicate, and often hinder, the bench to bedside journey of novel biomarkers. Compared to adults and neonates, studies on biomarkers in the pediatric age-group are still limited.

C-reactive protein (CRP) and procalcitonin (PCT) remain the commonly used biomarkers in children despite several drawbacks. C-reactive protein (CRP), given its low cost, wide availability, and easy interpretation, represents a well-established diagnostic biomarker. In contrast to PCT, it is little affected by renal dysfunction and immunosuppression. Being the most

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commonly used marker in the emergency department and outpatient clinics, it is also often misused. C-reactive protein (CRP) cannot differentiate infection from inflammation or identify specific infectious agents and needs serial values for meaningful decision-making.

Procalcitonin (PCT), though expensive and not widely available, is an extensively evaluated biomarker and could be more accurate and useful than CRP.⁶ PCT is more reliable in differentiating sepsis from noninfectious systemic inflammatory response syndrome. Levels usually rise earlier during the course of infection than that of CRP. Serial PCT measurements may be a good indicator to safely discontinue antimicrobials and have been seen to correlate with disease severity, multiple organ failure, and mortality.⁷ Some studies show PCT to be a better indicator of sepsis and bacteremia in children with cancer and febrile neutropenia than CRP.⁷ Though acute respiratory distress syndrome (ARDS) and acute kidney injury (AKI) are the major complications of sepsis, few biomarkers have been studied in these specific groups. The accuracy of blood culture, the traditional gold standard, remains limited due to low diagnostic sensitivity and high false negative rates in patients on antimicrobial therapy, or with severe localized infections. Any new biomarker is hence pitted against CRP and PCT.

One of the novel biomarkers which has thrown its hat into the ring just about a decade ago, but is rapidly gaining ground, is presepsin. Presepsin, a glycoprotein expressed on the surface of cells of the myelomonocytic lineage, is a cleavage product of the CD14 membrane co-receptor involved in pathogen recognition.⁵ It is released into circulation after binding with lipopolysaccharide, peptidoglycan, and other microorganism surface molecules. Like PCT, elevated presepsin in blood reflects both a direct effect of bloodborne pathogens as well as host response to the microorganism. It is a rapidly responding biomarker for bacterial and fungal infections.

Despite being a relatively new kid on the block, results have been consistently encouraging. Baseline levels have been shown to correlate with disease severity and predict mortality.⁸ It has been seen to be useful in the diagnosis of sepsis including shock or especially sepsis without shock versus nonsepsis in patients with a change in SOFA score of 2 or more.⁹

After the initial reports in 2011, several meta-analyses on its role in adults, children, and neonates, have been published over the past decade. Wu et al. in a meta-analysis of 18 studies on 3,470 patients showed cumulative sensitivity and specificity of 0.84 (95% CI, 0.80–0.87) and 0.76 (95% CI, 0.67–0.84), respectively, and AUC of 0.88 (95% CI, 0.85–0.90), figures similar to those of PCT.¹⁰ Yang et al., in another recent meta-analysis on 10 studies in 1,617 patients, showed higher presepsin values to be significantly associated with enhanced mortality.¹¹ The latest one in 2019 by Yoon et al. included four studies with 308 patients and showed a pooled diagnostic sensitivity and specificity of 0.94 [95% confidence interval (CI): 0.74–0.99] and 0.71 (95% CI: 0.35–0.92), respectively.¹² The pooled sensitivity was higher than that of CRP (0.51) and PCT (0.76), but overall specificity was lower [CRP (0.81) and PCT (0.76)]. Though the AUC (0.925) was higher than that of CRP (0.715) and PCT (0.820), caution was advised as the studies were small in number and statistically heterogeneous.

Presepsin levels have also been shown to be more sustainably increased in patients with fungal sepsis than PCT, with stronger correlation with SOFA score.¹³ Presepsin-guided antimicrobial therapy may also help reducing unnecessary or inappropriate usage of antimicrobials.¹⁴ More recently in pandemic times, elevated presepsin levels predicted poor outcomes in hospitalized patients with COVID-19 pneumonia and were associated with in-hospital mortality.¹⁵

In this backdrop, the study by Khara et al. in the current issue of the journal is a valuable addition to the growing body of evidence on presepsin as a biomarker in pediatric sepsis. Khara et al. evaluated the utility of presepsin in pediatric sepsis defined according to sepsis-3 guidelines. There are not many studies on sepsis biomarkers using the new definition.¹⁶ They report that elevated presepsin levels may indicate greater severity of sepsis, especially shock, but lack the ability to diagnose sepsis early and have a limited role in predicting mortality. Drawbacks include a small sample size of 54 children and the absence of healthy controls which precluded the evaluation of the diagnostic accuracy of presepsin in sepsis.

While multiple biomarkers exist but none of them optimal individually, will they work better in unison? Severity scoring systems using multiple parameters include the mortality risk model for pediatric sepsis by Chen et al. with six variables [brain natriuretic peptide (BNP), albumin, lactate, D-dimer, mechanical ventilation in 24 hours] and pediatric sepsis biomarker risk model (PERSEVERE) score which uses age and a panel of protein biomarkers measured during the first 24 hours of septic shock to estimate mortality risk.¹⁷ Its revision, incorporating platelet count, and validation of its temporal version, assessing how biomarkers change over time and how the changes affect mortality risk, can represent critical monitoring tools in the future.^{18–20} Hur et al. developed another multi-biomarker approach where BNP, PCT, and NGAL have been proposed as a useful diagnostic and prognostic tool for critically ill patients of all age-groups with suspected sepsis.²¹

Inappropriate usage of antimicrobials contributes to AMR which is predicted to be the single largest killer surpassing all diseases.

Developing tools and strategies for rational diagnosis and therapy is the need of the hour. A holistic approach, with clinical signs and symptoms, sepsis biomarkers, and microbiological tests (cultures and molecular biology) can improve diagnostic management of patients with possible sepsis. Multi-biomarker model appears to be more realistic and efficient though promising genomic tools could establish a unique personalized and dynamic disease management in the future.

Overall, presepsin seems to be a promising biomarker which merits further study to delineate its specific area of utility. High-quality prospective research with larger, diverse populations with an eye on specific subgroups is warranted. Studies seeking to identify the best combinations of clinical parameters and biomarkers may be more yielding.

Any research on changing definitions and novel biomarkers will achieve its true purpose when it can impact the outcome of a child with sepsis and septic shock in a remote rural area of a developing country. This question throws many more challenges than that meet the eye. Sir William Osler, in a lesson delivered in 1904 at the Yale University, affirmed that “except on few occasions, the patient appears to die from the body’s response to infection rather than from it.”^{22,23} Like presepsin, many potential solutions for survival too, may also come from the body’s response rather than the infection triggering it.

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