Serum Biomarkers for Sepsis

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Editorial

Sepsis is defined as the presence of a serious infection that correlates with systemic and uncontrolled immune activation [1]. It is associated with high mortality, largely due to multi-organ failure [2,3]. Sepsis could be extremely dangerous in infants, elderly population, immuno-compromised and critically ill patients [4]. Early diagnosis and prompt appropriate intervention is essential to halt the progression of sepsis and improve survival. A positive blood culture is the commonly used assay in sepsis diagnosis. However, this diagnostic tool has its limitations as culture is time dependent resulting in delay. Furthermore, positive blood cultures may not be present in many patients with sepsis [5].

In recent years, serum lactate testing in sepsis has become popular and it is being used in many centres to expedite early treatment and to monitor response of the therapy [6]. Researchers have been working for quite some time to indentify a "perfect biomarker" for early diagnosis of sepsis. Nearly 200 biomarkers have been assessed for potential use in sepsis, more for prognosis than for diagnosis [7]. A "perfect biomarker" should be measured accurately and results should be reproducible. The biomarkers may be used as a diagnostic tool as well as help in determining sepsis severity, prognosis, and response to intervention.

C-reactive protein (CRP) is found in blood plasma and synthesized by the liver. CRP production is a part of the non specific acute phase response to inflammation, infection, and various form of tissue damage [8]. Currently, CRP is used as a serum biomarker to assess the presence of infection. High sensitivity and specificity of CRP for the diagnosis of sepsis has been reported [9]. Additionally, it can differentiate between viral and bacterial infections [10]. However, due to its non-specific nature, this is not regarded as a "perfect biomarker" for sepsis. Serum Procalcitonin (PCT) is a precursor of the hormone calcitonin and is synthesized (physiologically) by thyroid C cells (normal serum level 0.1 ng/mL). However in bacterial infection, PCT is synthesized in various extra-thyroidal neuro-endocrine tissues hence resulting in high serum concentration of PCT [11,12]. As a serum biomarker for sepsis, PCT is an improvement on CRP and other conventional biomarkers, but it lacks the necessary accuracy to be used without clinical judgement [13]. Although, higher PCT levels suggest a systemic bacterial infection but serum PCT concentrations do not correlate with the severity of sepsis or with mortality [12]. Serum PCT levels are particularly valuable in patients who present early in the course of sepsis or have focal infection and in surgical patients in whom various cut-off points have been identified for different diagnoses [13]. Moreover, repeated measurements of PCT level may be better employed to rule out systemic sepsis in intensive care settings [13]. So far, PCT's value as a biomarker in the diagnosis and prognosis of sepsis hangs in balance [14]. The diagnostic value of serum PCT levels to differentiate systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock is remained to be established by definitive scientific evidence. It is observed that the initial PCT levels are not reliable as a diagnostic biomarker, however, serial PCT measurements may have role in monitoring sepsis outcomes [12]. At present, PCT role is solely investigational with regard to determining the timing and suitability of escalation of antimicrobial therapy in septic patients. Nevertheless, it may have a role in determining the de-escalation of antibiotic therapy [12]. Cytokine levels (e.g. IL-6 and IL-8) are closely related to the severity and outcome in septic individuals [15]. Additionally, in sever sepsis, the higher levels of TNF-α and IL-10 are also associated with adverse outcomes [15]. However, sensitivity and specificity of these cytokines relative to diagnosis of sepsis and prognosis is not well supported by robust evidence to allow wider acceptability of these as biomarkers.

Angiopoietins (Ang-1 and Ang-2) are antagonistic factors in endothelial cell activation. They have been associated with inflammation and their levels have been studied as a potential prognostic biomarker in sepsis [16] Ricciuto et al. demonstrated that, in septic patients, low Ang-1 levels at admission were associated with poor outcome while Ang-2 levels correlated with disease severity along with organ damage [17]. Cell surface receptors such as CD64 (a leukocyte surface antigen) are also investigated as biomarkers for sepsis [18]. Expression of CD64 is on neutrophils is usually low levels in the absence of infection but increased during infection/sepsis. In particular, it has a highest diagnostic accuracy to differentiate bacterial sepsis and SIRS in children [19]. Furthermore, during sepsis, CD64 index has higher sensitivity and specificity than CRP, white blood cell count, neutrophilic and eosinophilic granulocyte counts, or erythrocyte sedimentation rate in adults [20]. Regulatory T cells (Tregs), a lymphocyte sub-population, plays a pivotal role in preventing autoimmunity [21]. Circulating levels of CD39+ Tregs can increase significantly in septic patients and are associated with poor prognosis [22]. Similarly, CD4+CD25+ Tregs count may increase in circulation during sepsis and results in poor outcome [23].

Many other serum agents (e.g. serum amyloid A, Mannan, IFN-γ etc.) have been investigated and can potentially be used as biomarker for sepsis but their utility is yet to be proved. So far, no single biomarker has acceptable specificity or sensitivity to merit their use in routine clinical practice. PCT and CRP have been most widely used and investigated, however, these have limited ability to predict outcomes and lack accuracy to distinguish sepsis from other inflammatory conditions. Available data of the biomarkers of sepsis is encouraging however demands further research before a "perfect biomarker" is available for clinicians.

Perhaps a more realistic alternative approach is to combine multiple biomarkers and determine steps to improve accuracy and eliminate

existing flaws. The combination of several biomarkers is likely to overcome the limitations of sensitivity and specificity of a single biomarker. Future research requires multicentre studies, method standardization, rigorous assays and improved technology input (e.g. development of a multiplex point of care testing kits for quick and accurate detection). The perfect biomarkers should have ability to be implemented easily in clinical setting and should be cost-effective to allow widely utility in any health care system. Additionally, useful sepsis biomarkers can have potential to be not used as a sole diagnostic tool but also help to guide appropriate therapy and monitor response. With ongoing research and enthusiasm among the researchers, it is possible that such biomarkers will soon be part of routine paradigm in sepsis management.

References

1. Moreira J. Severe sepsis and septic shock. N Engl J Med 369: 2063.

2. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, et al. (2001) Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 29: 1303-1310.

3. Gaieski DF, Edwards JM, Kallan MJ, Carr BG (2013) Benchmarking the incidence and mortality of severe sepsis in the United States. Crit Care Med 41: 1167-1174.

4. Cardelli P, Ferraironi M, Amodeo R, Tabacco F, De Blasi RA, et al. (2008) Evaluation of neutrophil CD64 expression and procalcitonin as useful markers in early diagnosis of sepsis. Int J Immunopathol Pharmacol 21: 43-49.

5. Calandra T, Cohen J (2005) The international sepsis forum consensus conference on definitions of infection in the intensive care unit. Crit Care Med 33: 1538-1548.

6. Rhee C, Murphy MV, Li L, Platt R, Klompas M, et al. (2015) Lactate Testing in Suspected Sepsis: Trends and Predictors of Failure to Measure Levels. Crit Care Med. 43:1669-1676.

7. Pierrakos C, Vincent JL (2010) Sepsis biomarkers: a review. Crit Care 14: R15.

8. Wiwanitkit V. C reactive protein in sepsis. J Vet Emerg Crit Care (San Antonio). 20: 1.

9. Póvoa P, Almeida E, Moreira P, Fernandes A, Mealha R, et al. (1998) C-reactive protein as an indicator of sepsis. Intensive Care Med 24:1052-1056.

10. Shaw AC (1991) Serum C-reactive protein and neopterin concentrations in patients with viral or bacterial infection. J Clin Pathol 44: 596-599.

11. Dahaba AA, Metzler H (2009) Procalcitonin's role in the sepsis cascade. Is procalcitonin a sepsis marker or mediator? Minerva Anestesiol 75: 447-452.

12. Sridharan P, Chamberlain RS. The efficacy of procalcitonin as a biomarker in the management of sepsis: slaying dragons or tilting at windmills? Surg Infect (Larchmt) 14: 489-511.

13. Kibe S, Adams K and Barlow G. Diagnostic and prognostic biomarkers of sepsis in critical care. J Antimicrob Chemother 2: ii33-40.

14. Reinhart K, Bauer M, Riedemann NC, Hartog CS (2012) New approaches to sepsis: molecular diagnostics and biomarkers. Clin Microbiol Rev. 25: 609-634.

15. Gogos CA, Drosou E, Bassaris HP, Skoutelis A (2000) Pro- versus anti-inflammatory cytokine profile in patients with severe sepsis: a marker for prognosis and future therapeutic options. J Infect Dis 181: 176-180.

16. Elhefny RA, Shaban MM, Shaker OG (2015) Prognostic value of pro-inflammatory cytokine and pro-angiogenesis factor in differentiating malignant from benign exudative effusion. Clin Respir J.

17. Ricciuto DR, dos Santos CC, Hawkes M, Toltl LJ, Conroy AL, et al. (2011) Angiopoietin-1 and angiopoietin-2 as clinically informative prognostic biomarkers of morbidity and mortality in severe sepsis. Crit Care Med 39: 702-710.

18. Chen Q, Shi J, Fei A, Wang F, Pan S, et al. (2014) Neutrophil CD64 expression is a predictor of mortality for patients in the intensive care unit. Int J Clin Exp Pathol 7: 7806-7813.

19. Groselj-Grenc M, Ihan A, Pavcnik-Arnol M, Kopitar AN, Gmeiner-Stopar T, et al. (2009) Neutrophil and monocyte CD64 indexes, lipopolysaccharide-binding protein, procalcitonin and C-reactive protein in sepsis of critically ill neonates and children. Intensive Care Med 35: 1950-1958.

20. Gerrits JH, McLaughlin PM, Nienhuis BN, Smit JW, Loef B (2013) Polymorphic mononuclear neutrophils CD64 index for diagnosis of sepsis in postoperative surgical patients and critically ill patients. Clin Chem Lab Med 51: 897-905.

21. Kessel A, Bamberger E, Masalha M, Toubi E (2009) The role of T regulatory cells in human sepsis. J Autoimmun 32: 211-215.

22. Huang H, Xu R, Lin F, Bao C, Wang S, et al. High circulating CD39(+) regulatory T cells predict poor survival for sepsis patients. Int J Infect Dis 30: 57-63.

23. Chen K, Qiu-xiang Z, Hong-wei S, Wen-fang L, Zhao-fen L (2015) Prognostic value of CD4(+), CD25(+) Tregs as a valuable biomarker for patients with sepsis in ICU. World J Emerg Med 6: 40-43.