EDITORIAL

Interleukin-6 in Sepsis—Promising but Yet to Be Proven

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Introduction

Sepsis and associated organ failure impose a tremendous burden on healthcare systems and despite advancements in diagnosis and therapy, it remains a leading cause of death worldwide. Sepsis results from the complex interactions between the pathogen and host immune system. Cytokines play an important role in the regulation of the host immune response and their altered expression is often involved in the inter-individual susceptibility as well as the severity of sepsis in individuals.[1]

Establishing an early diagnosis is one of the pivotal priorities in sepsis. However, signs and symptoms may be non-specific, and microbiological diagnosis may take several days to be established thereby delaying initiation of aggressive therapeutic interventions leading to increased risk of organ dysfunction as well as mortality.[2]

Biomarkers in Sepsis

Several biomarkers have been evaluated in different aspects of management in sepsis scenarios including diagnosis, prognostication, and offering therapeutic guidance. C-reactive protein (CRP) and procalcitonin (PCT) have been most frequently studied followed by interleukin-6 (IL-6), presepsin, and CD64 among more than 250 biomarkers currently available.[3] Several of these have been evaluated either in isolation or combined with other biomarkers or severity of illness scores. However, the utility and choice of the biomarkers at the bedside remain undefined.

Interleukin-6

Interleukin-6 is a pleiotropic interleukin that has the unique property of functioning both as a pro-inflammatory as well as an anti-inflammatory cytokine. It is secreted from T cells and macrophages to stimulate an immune response to burns, and trauma, and in response to certain microbial molecules termed pathogen-associated molecular patterns (PAMPs). Interleukin-6 levels are elevated in a myriad of disease processes including cardiovascular diseases, autoimmune disorders, malignancy as well as in sepsis.[4–6]

Interleukin-6 in Sepsis Diagnosis

The number of studies evaluating biomarkers has been increasing. However, most of them have included a small number of patients. Of the several biomarkers tested for the diagnosis of sepsis in studies including over 300 patients, 6 of them were evaluated using a receiver operating characteristic curve (ROC) analysis. Out of more than 250 biomarkers evaluated, only IL-6[7] along with only 2 other biomarkers namely CD64[8] and inter-alfa inhibitor[9] proteins have shown an area under curve (AUC) of >0.8.

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In this issue of the Journal, Reddy et al. conducted a prospective observational study to assess the diagnostic potential of IL-6 to predict bacteremia and to determine its association with the severity of sepsis and outcomes in 118 patients admitted to the ICU.[10] It was found that 60 out of the 108 (55.6%) patients analyzed had bacteremia. The AUC OF IL-6 using a cut-off value of 223 pg/mL was 0.512 with a sensitivity of 50% and specificity of 54% thereby concluding that IL-6 was not a reliable predictor of bacteremia in this study population.

The authors also compared the performance of IL-6 with other biomarkers such as CRP, PCT, and lactate as well as disease severity scores such as acute physiology and chronic health evaluation (APACHE II) and sequential organ failure (SOFA) scores. Multivariate analysis found that CRP and APACHE II scores performed better than IL-6 and were found to be independent predictors of bacteremia in this study population. Although there have been several studies in which IL-6 has been a diagnostic marker in neonatal sepsis, a Cochrane review was performed addressing the diagnostic accuracy of plasma IL-6 concentration in identifying bacterial sepsis in critically ill adults. Note that 23 studies (n = 4,912) were included. There was a high level of heterogeneity in the studies and the authors concluded that further studies applying rigorous methodology were required to ascertain the diagnostic accuracy of IL-6 in sepsis diagnosis.[11]

A recent study conducted in the emergency department of a hospital in China attempted to explore the diagnostic and prognostic performance of IL-6 in patients with sepsis. Interleukin-6 by itself was found to be an independent predictor of sepsis diagnosis but the combination with blood urea nitrogen (BUN) and mean arterial pressure (MAP) demonstrated a better diagnostic efficacy.[12]

Interleukin-6 in Assessing Response to Therapy

The relatively slow dynamics of conventional biomarkers, such as CRP and PCT, warrants the search for an alternative that could

hasten the assessment of response to therapy especially in critically ill septic patients. Serum IL-6 level rises within minutes after a stimulus (infection, trauma, or any inflammatory process) and has a short half-life of about an hour. It also correlates with the severity of inflammation, the extent of organ damage, and mortality.[13] Rate of decrease in IL-6 in septic patients has been shown to indicate therapeutic response and correlate with improved survival in several studies. Weidhase et al. compared the trend of IL-6 to CRP and PCT in 328 patients with sepsis and septic shock and found that IL-6 was better in predicting treatment success in non-surgical sepsis within 48–72 hours.[14]

Prognostic Significance of Interleukin-6

In sepsis, the response to the invading pathogen includes inflammatory and anti-inflammatory processes, humoral and cellular interactions, and circulatory abnormalities. Interleukin-6 levels are shown to be elevated in sepsis and the magnitude of rise is higher in patients with shock as compared to those who are not.[15] Higher IL-6 levels as well as IL-6/IL-10 ratios have also been shown to affect mortality as the levels in non-survivors have been significantly higher than in survivors.[16]

Similar results regarding prognostic performance and outcome prediction have also been demonstrated in the study by Reddy et al. The median values of IL-6 in the group of patients with septic shock [461 pg/mL (77.00–1207.00)] were significantly higher than in those in patients without shock [101 pg/mL (28.50–204.00)], ($p < 0.001$). Also, the median IL-6 values between non-survivors 294 pg/mL (138.00–1079.00) and survivors 112 pg/mL (37.50–351.50) ($p = 0.002$) showed a significant difference.[10] The AUC for IL-6 to differentiate between sepsis and septic shock was 0.724 (95% CI, 0.625–0.823; $p < 0.001$). At a threshold of 145 pg/mL for IL-6, the ROC curve exhibited a sensitivity and specificity of 66% and 67%, respectively, which was found to be statistically significant. Additionally, they found that using a cut-off point of 176 pg/mL for IL-6, demonstrated a sensitivity and specificity of 71% and 68%, respectively in predicting mortality.[10]

How Does Interleukin-6 Fare in Comparison with Other Biomarkers and Scoring Systems?

Several studies have assessed the value of combining IL-6 with other cytokines, biomarkers such as CRP, PCT, and lactate, and other scores such as Glasgow Coma Score (GCS), SOFA, and APACHE II scores in predicting outcomes. It has been shown in most of them that a combination of biomarkers and clinical parameters along with the severity of illness scores often performed better than those assessed individually.[16,17]

Reddy et al. found that CRP and APACHE II scores were better predictors of bacteremia as compared to IL-6. In terms of prediction of sepsis severity, although lactate, PCT, IL-6, and APACHE II were identified, only lactate and APACHE II score remained significant in multivariate analysis. Similarly, only PCT, SOFA score, and APACHE II score were found to be independent predictors of mortality.[10]

In contrast to these findings, other studies have reported the superiority of one or more biomarkers in isolation or combination in the prediction of bacteremia, sepsis severity, and outcomes. These discrepancies in findings could be attributed to differences in the study population, severity of sepsis, timing of measurement of biomarkers at different stages of sepsis, and non-uniformity of sepsis definitions included in studies over the years.

Conclusion

Despite many biomarkers are available, their precise role in sepsis is still unclear. Most of the studies have evaluated different combinations of biomarkers and there is a huge diversity among study populations, stages of sepsis as well as outcomes which makes it impossible to draw reliable conclusions and identify the "most promising" candidates. Hence the way ahead would mean applying more rigorous means to evaluate and identify the ones that will stand the test of time and make a difference in influencing sepsis diagnosis, and therapy and reliably predict outcomes.

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