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Use of biomarkers in sepsis: many questions, few answers

Uso de biomarcadores na sepse: muitas perguntas, poucas respostas

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Why do we use biomarkers in sepsis? There are several answers to this question. Some researchers argue that biomarkers are used to assess the prognosis of septic patients,[1] but why should we use a biomarker merely to determine whether a patient has a higher risk of death when currently available interventions are not able to modify the prognosis?[2] As we all know, dozens of randomized controlled clinical trials whose primary objective was to modulate the inflammatory response have been unsuccessful.[3,4] Others researchers argue that biomarkers are used to generate a more complete clinical and laboratory evaluation of a septic patient.[2,5] This additional clinical information can be categorized as triage, diagnosis, risk stratification, monitoring clinical course and antibiotic stewardship.[6]

However, before a biomarker can be used clinically, it has to be rigorously evaluated in a three stage process.[7] The first stage consists of an **analytical validation**, a process that characterizes the laboratory method used to measure the biomarker. The second stage is **qualification**, i.e., an evaluation of the evidence that supports an association between the biomarker and the disease. This evaluation should show what effects a clinical intervention has on both the biomarker and disease progression. Thus, by monitoring the biomarker, it would be possible to predict the effects of an intervention on disease itself. It should be noted that in biomarker qualification, disease-biomarker relationships are frequently probabilistic rather than deterministic. The last stage is **utilization**, i.e., the evaluation of the clinical use of a certain biomarker. Such an analysis of the available evidence should consider the proposed utilization of a specific biomarker, particularly its advantages and limitations.

In this issue of RBTI, Orati et al. provide new clinical information regarding the **utilization** of C-reactive protein (CRP) as a biomarker of sepsis.[8] The authors conducted a retrospective study of 345 critical care patients with pulmonary (N=195) or abdominal (N=150) sepsis and compared the kinetics of CRP levels during the first 5 days following a diagnosis of sepsis. For both the day of diagnosis and the first 5 days of clinical course, the authors found that serum CRP concentrations were significantly higher in patients with abdominal sepsis. The study does not necessarily conclude that CRP should be used to distinguish between pulmonary sepsis and abdominal sepsis, especially considering that the areas under the ROC curve are not very discriminative, but, rather, that there are differences in the CRP kinetics. What are the reasons for such differences?

Classically, CRP and other sepsis markers are not considered to be specific for infection or even specific microbiological agents.[9] However, the results

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of this study, which have now been published, indicate that abdominal sepsis elicits higher CRP concentrations than does pulmonary sepsis. One possible reason for this difference might be related to surgical aggression.[10] After surgery, there is an increase in the concentrations of CRP and other biomarkers, such as procalcitonin, which reach a peak response between 24 and 48 hours following surgery. If there are no complications, the biomarker concentrations gradually decrease starting on day 3 or 4 following surgery.[10] As the authors mentioned in the discussion, some studies disagree with this explanation.[11]

However, there are additional aspects that the authors did not discuss that may explain these differences. One can speculate that the microbial burden due to abdominal sepsis, particularly in the case of gastrointestinal perforation, is greater than that of pulmonary sepsis, and there is evidence that CRP correlates well with the bacterial burden.[12] Furthermore, abdominal sepsis and in particular secondary peritonitis is a polymicrobial infection consisting of Gram-negative, Gram-positive and anaerobic bacteria, whereas pneumonia is usually a monomicrobial infection. Another aspect that was not considered is related to the presence of a secondary bacteremia that, if Gram-negative in nature, would be associated with higher CRP values.[13]

Moreover, monitoring the variation in CRP values over the first 5 days of clinical progression may be more relevant than determining whether the absolute CRP values are different than those at the onset of infection.[14] It has been demonstrated that the severity-adjusted risk of mortality is 32% lower in patients with a 10% mean daily reduction in CRP values[14] and that, in addition, CRP values are not influenced by either steroid[15] or immunosuppressive therapy.[16]

In conclusion, this study by Orati et al.[8] helps us better understand the kinetics of this important biomarker, which has already been routinely incorporated into clinical practice. Once again, it is clearly evident that this biomarker is best applied when dynamically evaluating a patient's therapeutic response and associated prognosis rather than using single measurements. Future studies should evaluate the role of CRP in patients with sepsis, independent of the disease etiology, in guiding the choice and duration of antimicrobial treatment and the need for potential interventions in controlling infection in surgical patients.

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