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EDITORIAL

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Biomarkers of sepsis: is procalcitonin ready for prime time?

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New definitions of the human sepsis syndrome were proposed a decade ago [1]. These definitions were needed in order for clinicians to speak the same language, as well as to identify and compare patient populations in clinical trials. The nature and the importance of the host response to the infectious process were central to these new definitions and contrasted with previous definitions, which were more microbiologically-oriented. The 1992 ACCP/SCCM definitions were adopted by the majority of clinical investigators and allowed the stratification of patients with various risks of death. However, many physicians would admit that the definitions remain imperfect and are not widely used at the bedside. Firstly, the concept of the systemic inflammatory response syndrome (SIRS) has been challenged because of its poor specificity and also because some patients may have clinical sepsis and yet lack two SIRS criteria [2, 3]. SIRS is also the addition of a restricted number of signs that may not be relevant to an inflammatory process. Finally, a systemic pro-inflammatory response has been difficult to demonstrate in septic patients [4]. Secondly, the definition of the sepsis syndrome relies on the documentation of an infection, which is not often readily available at the time of admission to the emergency room or to the ICU. Thirdly, in contrast with many acute and severe diseases such as myocardial infarction, pancreatitis, renal and liver failure, etc., sepsis lacks (a) specific biomarker(s). A useful biological marker of sepsis should show a high diagnostic yield, be predictive for outcome, easy to determine, robust and cheap. Similarly to other 'syndromes' such as the acute respiratory distress syndrome, an important difficulty to identify and study biomarkers in sepsis is the heterogeneity of the patient population and the lack of a clear-cut gold standard.

Several biomarkers of sepsis have been proposed, including, for example, the percentage of circulating nonsegmented neutrophils (band forms), acute phase proteins such as C-reactive protein and neopterin, cytokines (TNF, IL-6) and chemokines (IL-8) [5, 6]. Whereas all of these markers have shown some utility in detecting "septic events," they all lack specificity due to a significant overlap with levels measured in other systemic inflammatory diseases. The challenge is to identify a biomarker of host response that would be specific for (severe) infection or for infection inducing organ dysfunction and/or shock. Elevated levels of procalcitonin were first described in 1993 in "septic" pediatric patients [7]. In this seminal study, the authors were able to differentiate children with sepsis from those with localized bacterial infections or with severe viral infections using plasma procalcitonin measurements [7]. Since then, nearly 100 investigations have evaluated the diagnostic and prognostic yield of plasma procalcitonin in different settings, including patients with neutropenia, renal and hepatic failure, patients from the emergency room and the ICU. The exact cellular and organ source for the pro-hormone, its regulation and its relationship with bacteria and bacterial products remain largely unknown.

In this issue of *Intensive Care Medicine*, Giamarollos-Bourboulis et al. confirm the usefulness of measuring plasma procalcitonin in identifying patients with severe sepsis and septic shock [8]. Together with other investigators [9], they however raise concerns as to whether this marker is able to clearly differentiate SIRS patients from those with sepsis. Differentiating these two patient populations is certainly the most challenging task. As indicated above, the diagnosis of sepsis relies on the documentation of an infection in patients presenting with nonspecific systemic signs such as tachycardia, tachypnea, leukocytosis or fever. The

potential risk for a misclassification of septic patients as being "SIRS patients" because of unrecognized infections or of patients as belonging to the "sepsis patient" group because of colonization rather than true infection is important. The overlap of values of an infectious biomarker in this situation is therefore very likely. This raises the possibility that procalcitonin may actually be a more reliable marker of sepsis that the ACCP/SCCM consensus conference criteria. The other possible explanation for these findings is that procalcitonin reacts as an acute phase protein in situations such as multiple trauma or cardiac surgery and could explain higher "basal levels" in these patients. Severe bacterial infection may only boost procalcitonin levels in these patients "primed" with a systemic inflammatory disorder. The diagnostic yield of such a marker is also highly dependent on the pre-test probability. The best yields will be obtained in a population with a high incidence of sepsis, and the lowest if the marker is used as a "screening test" in a group of patients with a low incidence. Many authors would now admit that a "gray zone" exists where procalcitonin levels falling in the range between 0.5 and 2 ng/ml are difficult to interpret. Levels above 2 ng/ml are usually indicative of a bacterial infection with a systemic inflammatory response, whereas levels below 0.5 ng/ml generally rule out a bacterial infection as the process responsible for signs of SIRS. It is important here to stress that procalcitonin should not be used as the sole marker in case of suspicion of sepsis, but rather be integrated in the complex evaluation of the septic patient together with clinical, radiological and laboratory data.

Giamarollos-Bourboulis et al. make another crucial point in the study presented in this issue [8]. They show that the evolution of plasma procalcitonin levels with time carries an important prognostic information. This has been reported in several recent studies and may well represent the "niche" for procalcitonin measurements in our intensive care units [6, 10]. Like many other investigators, they found that the initial procalcitonin level poorly predicted the final outcome and loosely correlated with the severity of the sepsis syndrome and the development of multiple organ dysfunction. However, patients who do well have a sharp decrease in their plasma procalcitonin levels, usually crossing the 1 ng/ml threshold value within 4 to 7 days [6]. In contrast, patients with an ultimately fatal outcome show either a slow decrease or even an increase in their plasma procalcitonin levels over the first few days in the ICU. The prognostic value of daily measurements of plasma procalcitonin appears superior to that of C-reactive protein [10]. In the clinical arena, daily measurement of procalcitonin may be used as a "red flag" marker that the patient is not clearing the infection process properly. Persistently elevated levels therefore may trigger further investigations (bronchoalveolar lavage, laparotomy, pleural tap, etc.) and possibly an adaptation of therapy (surgery, antimicrobial therapy, etc.).

Laboratory measurements should only be performed if they help in making decisions in patients and/or are useful to follow the patient's evolution. Despite abundant literature on procalcitonin, studies of the direct impact of its measurement on the outcome of patients unfortunately are lacking. For example, studies could be designed in which patients with a fast decrease in procalcitonin levels receive a shorter duration of antibiotic therapy, or even have the antibiotics stopped if procalcitonin is two times below a threshold value. Alternatively, it could be studied whether the knowledge of procalcitonin levels can influence the clinician to trigger new investigations. Sepsis definitions are currently being rediscussed in a new consensus conference. A major issue will be whether or not to introduce (a) biomarker(s) in the new set of definitions. Clearly, additional fundamental and clinical investigations are needed in order to convince clinicians to use procalcitonin plasma levels on a regular basis as an aid for the care of the critically ill patient presenting with a suspicion of sepsis.

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