CRITICAL CARE

COMMENTARY

Cell-free DNA and outcome in sepsis

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See related research by Dwivedi *et al.*, http://ccforum.com/content/16/4/R151/abstract

Abstract

Severe sepsis can be a catastrophic condition that is often associated with poor outcomes. The early diagnosis and management of the condition are vital in order to improve the chances of survival. However, owing to the syndromal nature of its definition and the lack of a biomarker able to accurately confirm the condition, the diagnosis of sepsis is challenging. Even more challenging is the prediction of how these patients will respond to the therapy and whether they will survive the intensive care and the hospital admission.

The search for a biochemical marker that can be used to confirm infection and sepsis – much like troponin is used to diagnose myocardial injury [1] – has been the source of a great deal of work. Many different compounds have been assessed either to diagnose the condition or to prognosticate between a good and a poor outcome in patients in whom the problem has already been diagnosed. These include acute-phase proteins such as C-reactive protein [2], procalcitonin, inflammatory (pro- and anti-) cytokines, cell surface proteins (adhesion molecules, for instance), and markers of coagulation and apoptosis [3].

The ideal biomarker should possess a number of properties: it should have a high sensitivity for the disease process being detected, it should be very specific (that is, it should not be present if the disease is absent), its levels should reflect the severity of the condition, it should have a time course that allows the clinical evolution of the disease to be detected early, it should have a half-life that enables raised levels to remain in a clinically useful time frame and then decrease to enable tracking of severity, it should provide independent information on outcome, and it should be reproducible and, of course, cheap and easy to measure. Very few of the available biomarkers possess all of these qualities. If an ideal biomarker were found, however, we would have a tool that would help us to diagnose sepsis early and, in turn, enable us to direct evidence-based interventions directly toward the appropriate groups. In addition, this biomarker would enable clinical trials to be performed on homogenous patient groups of a comparable risk severity and, in turn, improve patient selection and therefore hopefully increase the likelihood of positive (or negative) results.

In recent years, free circulating nucleic acids in plasma and serum have been studied as biomarkers [4]. Free circulating DNA – cell-free DNA (cfDNA) – is released from a number of cells, including neutrophils, eosinophils, and macrophages, as a result of either apoptosis or other forms of cellular damage [5]. A couple of important considerations have to be made in order to understand the possible clinical impact of this biomarker. First, levels of cfDNA are detectable in healthy individuals; second, raised levels are not specific to a single disease. Nevertheless, raised levels of cfDNA have been shown, in a number of studies, to be extremely sensitive and specific for poor outcomes. cfDNA has been shown to have prognostic relevance in many conditions, including trauma [6], stroke [7], cancer, diabetes mellitus, sickle cell disease, organ transplantation [4], and critical illness [8-10].

In the previous issue of *Critical Care*, Dwivedi *et al.* [11] confirmed the prognostic abilities of cfDNA in severe sepsis. In a retrospective observational study of 80 patients with severe sepsis, the authors were able to show that cfDNA at baseline had a remarkable discriminatory power to predict intensive care mortality and, to a lesser (though still impressive) extent, hospital mortality. cfDNA performed a lot better than any of the available severity of illness or organ dysfunction scoring systems and also a lot better than interleukin-6, thrombin, and protein C. Indeed, the addition of these other markers added very little to the overall results. A cutoff level of cfDNA at baseline of 2.35 ng/μL had a sensitivity of 88% and a specificity of 94% for predicting intensive care unit mortality.

At least in terms of prediction in intensive care, these results are very similar to those of studies by Rhodes *et*

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al. [8], Butt *et al*. [9], and Saukkonen *et al*. [10] in mixed critical illness and sepsis and by Lo *et al*. [6] in trauma. In each of these studies, the presence of increased levels of this marker had very significant abilities to predict overall outcome from the disease being treated. Another thing these studies have in common, however, is that they are all on relatively small samples of patients, and it is gratifying to see that Dwivedi *et al*. already have a grant to complete a larger confirmatory study. We await the results eagerly.

Several questions do need to be considered, however. Raised levels have been detected in a number of different diseases [12] and interventions (for instance, hemodialysis [13]) that are all too often present in patients with sepsis. Which of the two are leading to the raised levels or the sepsis per se: the underpinning diseases or the interventions? In addition, what is the additive effect of the interventions on a complicated patient requiring multiple organ supports? In a separate issue, the fact that the results suggest that outcome can be predicted at baseline does raise an important concern. Does this mean that, if cfDNA is already elevated when we start to treat these patients, the chances of survival will not be affected by our treatment? Or even worse, does it mean that some patients already have a predetermined outcome when they present to us for treatment? If so, what is the effect of our current managements and supports? If this is the case, then the implications for how the information would be used are profound.

In the studies performed to date, circulating cell-free nucleic acids seem to be among the more promising prognostic markers that could be used in severe sepsis. The studies do need replicating, however, and the assays need standardizing and would need to be made more user-friendly. Only then could we consider measuring this as a routine in our patients, and even then, we would need some careful thoughts about how to act upon the information obtained. This new information would enable better selection for clinical trials but also may have a far wider potential as a routine part of our clinical investigation and management.

Abbreviation
cfDNA, cell-free DNA.

Competing interests
The authors declare that they have no competing interests.

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