CRITICAL CARE

COMMENTARY

Predicting outcome in patients with sepsis: new biomarkers for old expectations

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Abstract

Early prediction of the outcome of patients with sepsis could be helpful in guiding therapies but remains challenging. Presepsin, a new sepsis biomarker whose elevation as early as day 1 is well correlated with 28-day mortality, could be considered to this end.

Predicting prognosis in sepsis is of paramount importance. Clinical assessments and the usual biological surrogates for organ dysfunction are still widely used and help us to provide care for critically ill patients with sepsis in everyday practice. We thus hope to optimize therapies and provide the most appropriate care to our patients by considering every severity endpoint as a danger signal that will trigger the most suitable interventions, in an attempt to improve survival. As suggested in this issue of *Critical Care* by Masson and colleagues [1], sepsis biomarkers and especially newly discovered ones such as presepsin may give us the opportunity to earn time.

As previously shown, the main objective in this setting is clearly to intervene early and in an appropriate manner, especially regarding empirical antibiotic therapy and fluid management [2]. Dampening an overwhelming inflammatory response is also desirable, but so far this objective has remained beyond our reach. Accordingly, sepsis severity is strongly related to the inflammatory response resulting from the ambivalent interaction between innate immunity and pathogens [3]. Physicians thus have to rack their brains to find the best way to assess such imbalances in the host response to infection. The aim is to accurately predict organ failure before it becomes obvious, by which time it is very often too late. This makes sense if interventions likely

to prevent end-organ dysfunction and immunomodulatory therapies could then be implemented, leading in turn to an improved survival.

The challenge is therefore to find biomarkers that give the physician accurate information regarding the risk of a poor outcome within the very first hours of management. This point is especially relevant in the emergency room in order to improve the triage of patients with sepsis since it is known that delayed ICU admission could worsen the outcome.

An additional benefit we could expect from sepsis biomarkers is to assess the efficacy of our management, especially the appropriateness of our first-line antibiotic therapy, which is known to be critical in septic shock [4]. The biomarker's kinetics should be quickly and tightly related to the patient's outcome, thus allowing prompt therapy adjustment if necessary (that is, before any microbiological data are available).

Masson and colleagues [1] present the results of an interesting and timely study that aimed to evaluate the prognostic value of presepsin in septic patients admitted to the ICU [1]. This is an ancillary study of a large randomized controlled trial that compared albumin with crystalloids for the early management of patients with sepsis. The authors showed that, compared with procalcitonin (PCT), presepsin measured on day 1 predicted 90-day mortality in these selected patients more accurately than, and thus independently from, other potential confounders. In addition, presepsin kinetics were also related to the outcome, suggesting a close relationship between the biomarker course and the effectiveness of both host response and the therapies used. This biomarker therefore seems to fulfill the above-mentioned requirements for any sepsis biomarker we would like to use as a marker of prognosis. However, further data are required before stronger conclusions can be drawn.

Moreover, these results illustrate another key point. The 'all-in-one' concept, in fact, does not suit sepsis biomarkers very well, and one should not have too many

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expectations when assaying biomarkers. PCT, in addition to clinical assessment, is considered one of the best diagnosis tools for sepsis. However, as shown in the present study and an earlier study [5], the magnitude of PCT elevation on day 1 does not reliably predict the outcome in patients with sepsis. Taken together, these findings suggest that one given biomarker should not be used to answer more than one given relevant question. Indeed, we have shown that, despite having excellent diagnostic value, some biomarkers, like CD64 neutrophil expression, failed to predict outcome [6]. Conversely, one recently published study showed that PCT performed better as a diagnosis tool than presepsin in patients with suspected sepsis in the emergency room [7]. As a result, these two biomarkers should be used in combination. However, cost and availability issues might compromise such practices.

Sepsis is a dynamic event, and the clinical evolution within the very first days in the ICU is clearly related to survival. To be useful, biomarkers should be able to predict developing or worsening organ failure; if this is not the case, clinical judgment and sequential organ failure assessment (SOFA) score calculation, for instance, will have to be enough. PCT kinetics was shown to be tightly related to clinical outcome and thus better than calculating the SOFA score daily and measuring blood lactate variations [5]. The authors failed to demonstrate such a relationship in the present study, whereas the presepsin time course did seem to correlate nicely with outcome. However, it should be pointed out that PCT concentrations were not measured daily, but only on days 1, 2, and 7. The half-life of presepsin may be longer than that of PCT and the kinetics therefore slower. Nonetheless, further studies are needed before any firm conclusions can be drawn.

One last expectation related to sepsis biomarkers is their ability to customize antibiotic duration. Monitoring PCT has been shown to be effective regarding this point in various clinical conditions, including sepsis and septic shock, without compromising the outcome, at least apparently [8]. The authors suggest that presepsin could be useful to this end since its course is related to the outcome. This issue deserves future investigation, and comparison with PCT is essential.

In conclusion, although many correlations have been established between the net values or kinetics (or both) of some biomarkers and outcomes in patients with sepsis, there is little convincing evidence to support their use as such in everyday practice. Only one trial, the Procalcitonin And Survival Study, was designed to this end, but it failed to demonstrate any improvement in the outcome when PCT elevation beyond an alert value was used as a trigger for the implementation of new antibiotic therapy [9]. However, an effort should be made to design new studies able to test such hypotheses, using existing and new biomarkers such as presepsin. Actually, evidence rather than belief is still required.

Abbreviations
PCT: Procalcitonin; SOFA: Sequential organ failure assessment.

Competing interests

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References
1. Masson S, Caironi P, Spanuth E, Thomae R, Panigada M, Sangiorgi G, Fumagalli R, Mauri T, Isgro S, Fanizza C, Romero M, Tognoni G, Latini R, Gattinoni L: Presepsin (soluble CD14 subtype, sCD14-ST) and procalcitonin for early mortality prediction in severe sepsis and septic shock. A retrospective case–control study from the Albumin Italian Outcome Sepsis (ALBIOS) trial. *Crit Care* 2014, 18:R6.
2. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R, Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup: Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013, 39:165–228.
3. Munford RS, Pugin J: Normal responses to injury prevent systemic inflammation and can be immunosuppressive. *Am J Respir Crit Care Med* 2001, 163:316–321.
4. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, Suppes R, Feinstein D, Zanotti S, Taiberg L, Gurka D, Kumar A, Cheang M: Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006, 34:1589–1596.
5. Charles PE, Tinel C, Barbar S, Aho S, Prin S, Doise JM, Olsson NO, Blettery B, Quenot JP: Procalcitonin kinetics within the first days of sepsis: relationship with the appropriateness of antibiotic therapy and the outcome. *Crit Care* 2009, 13:R38.
6. Gibot S, Béné MC, Noel R, Massin F, Guy J, Cravoisy A, Barraud D, De Carvalho Bittencourt M, Quenot JP, Bollaert PE, Faure G, Charles PE: Combination biomarkers to diagnose sepsis in the critically ill patient. *Am J Respir Crit Care Med* 2012, 186:65–71.
7. Ulla M, Pizzolato E, Lucchiari M, Loiacono M, Soardo F, Forno D, Morello F, Lupia E, Moiraghi C, Mengozzi G, Battista S: Diagnostic and prognostic value of presepsin in the management of sepsis in the emergency department: a multicenter prospective study. *Crit Care* 2013, 17:R168.
8. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, Schortgen F, Lasocki S, Veber B, Dehoux M, Bernard M, Pasquet B, Régnier B, Brun-Buisson C, Chastre J, Wolff M, PRORATA trial group: Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet* 2010, 375:463–474.
9. Jensen JU, Hein L, Lundgren B, Bestle MH, Mohr TT, Andersen MH, Thornberg KJ, Løken J, Steensen M, Fox Z, Tousi H, Søe-Jensen P, Lauritsen AØ, Strange D, Petersen PL, Reiter N, Hestad S, Thormar K, Fjeldborg P, Larsen KM, Drenck NE, Ostergaard C, Kjær J, Grarup J, Lundgren JD, Procalcitonin And Survival Study (PASS) Group: Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: a randomized trial. *Crit Care Med* 2011, 39:2048–2058.