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Serial and panel analyses of biomarkers do not improve the prediction of bacteremia compared to one procalcitonin measurement

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Summary *Objectives:* We evaluated the value of a single biomarker, biomarker panels, biomarkers combined with clinical signs of sepsis, and serial determinations of biomarkers in the prediction of bacteremia in patients with sepsis.
Methods: Adult patients visiting the emergency department because of a suspected infection with at least two of the following symptoms: temperature >38.3 °C or <36 °C, heart rate >90/min, respiratory rate >20/min, chills, altered mental status, systolic blood pressure <90 mmHg, MAP <65 mmHg, and hyperglycemia in the absence of diabetes mellitus were included. Procalcitonin (PCT), interleukin-6 (IL-6), lipopolysaccharide-binding protein (LBP), C-reactive protein (CRP) were measured, and two blood cultures were taken. The analyses included: (1) determination of the biomarker with the highest predictive value for bacteremia and to examine the predictive value of this biomarker in combination with other biomarkers; (2) analysis of the best biomarker data in combination with clinical signs of sepsis; and (3) analysis of serial determinations of the best biomarker.
Results: Of 342 included patients, PCT had the best predictive value for bacteremia with an area under the curve of 0.80, sensitivity 89%, specificity 58%. The predictive value of a combination of PCT plus a panel of other biomarkers, clinical signs, or analysis of serial PCT levels did not lead to a significant improvement of the predictive value of PCT alone.

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Conclusions: The ability of PCT to predict bacteremia in patients with sepsis does not further improve when combined with IL-6, LBP, CRP, clinical signs, or serial measurements. Naturally, this does not exclude that a panel of other biomarkers may lead to different results.

Introduction

It is becoming increasingly clear that early identification of patients with sepsis is important but difficult because signs of systemic inflammation response syndrome (SIRS) are not specific[1,2] and the predictive value of single biomarkers is limited.[3] Although blood cultures are considered the gold standard for the detection of bacteremia, delays between blood sampling and information returned to the clinician is an important disadvantage, but no alternatives are currently available.[4]

To improve survival in patients with sepsis and septic shock, early initiation of appropriate empirical antimicrobial therapy is essential.[5–9] The choice of the empirical antimicrobial therapy in sepsis mainly depends on the suspected site of infection and the antimicrobial susceptibility of the expected pathogens. To include more resistant but often less prevalent pathogens, the empirical therapy of a severe infection is usually broad-spectrum.[5,10] The downside of this strategy is that the prescribed antibiotics are often more broad-spectrum than necessary[11] or even are used in the absence of a bacterial infection.[12,13] This may have potentially deleterious consequences such as anaphylactic reactions, antibiotic resistance, and high costs. Rapid tests that provide insight in the etiology of infection may guide appropriate use of antibiotics and are urgently needed.

To improve diagnosis and management of sepsis, the usefulness of single biomarkers (e.g., C-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6), and lipopolysaccharide-binding protein (LBP)) is described in many studies.[3,11–28] Of many biomarkers tested, some appear to have a sensitivity and specificity value above 90%.[3] Although PCT and CRP have been most widely used,[14] these biomarkers have limited abilities to distinguish sepsis from other inflammatory conditions or to predict outcome. In patients with sepsis admitted to the emergency department (ED), PCT had a sensitivity of 0.62–0.71, and specificity 0.67–0.88.[19,20,22] Therefore, further evaluation of a combination of different sepsis biomarkers is recommended.[19,20,22]

In patients with sepsis, only a few studies have examined the usefulness of biomarker panels.[29–33] Beneficial effects of a panel to predict organ dysfunction, septic shock, and in-hospital mortality[29] and the differentiation between bacterial and viral lower respiratory tract infections[30] have been reported. Also, chills[31] and increasing values during repeated PCT measurements,[32] predict the presence of a positive blood culture.

In view of the absence of a reliable biomarker to predict bacteremia,[4] we evaluated the predictive value of four single biomarkers (PCT, IL-6, LBP, and CRP), the combination of the best performing biomarker with one up to three other biomarkers (panels), the combination of the best performing biomarker with clinical signs of the patient and conventional laboratory parameters, and serial determinations of the best performing biomarker in predicting bacteremia in ED patients with sepsis. We selected bacteremia to have a less disputable diagnosis of infection and aimed to find a reliable (panel of) marker(s) to predict the presence or absence of bacteremia, which may lead to a reduction of the number of blood cultures that needs to be taken.

Because PCT and CRP are the most widely used single biomarkers, the value of IL-6 and LBP for the diagnosis and management of sepsis were frequently evaluated in earlier studies, and PCT, IL-6, LBP, and CRP are commercially available, we included these biomarkers in our panel analyses.

Materials and methods

Study design

The present study was a prospective single centre study, performed at the ED of a 953-bed university hospital in the Netherlands. Each year approximately 20,000 patients visit the ED and 3–4% is admitted because of sepsis, severe sepsis or septic shock. During the 8-month study period, medical policy at the ED and the nursing wards was solely based on the clinical chemistry test results in combination with a physical examination and additional diagnostic procedures and not on the results of the inflammatory markers described in this manuscript. Prior to the conduct of this study, the local Medical Ethics Committee was informed. Although they waived the need for a written informed consent, patients were informed about the study and the acquisition of supplementary plasma.

Study population

Inclusion criteria were: patients (≥16 years old) visiting the ED because of a suspected infection, who had at least two of the following clinical signs of sepsis[1,34,35]: temperature >38.3 °C or <36 °C, heart rate >90/min, respiratory rate >20/min, chills, altered mental status, systolic blood pressure <90 mmHg, MAP <65 mmHg, and hyperglycemia in the absence of diabetes mellitus. For the analysis of serial (3 days) biomarker data, all hospitalized patients admitted to one of the departments of internal medicine (internal medicine, rheumatology, hematology, nephrology, gastroenterology, oncology, and intensive care), were included. The final confirmed diagnosis at discharge, as described in Table 1, was based on a combination of clinical signs and symptoms of sepsis, the presence/absence of an infiltrate on chest X-ray, laboratory parameters, and culture results (e.g., blood, urine, sputum, and wound) obtained during the first 24 h following ED admission.