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Endotoxin activity levels as a prediction tool for risk of deterioration in patients with sepsis not admitted to the intensive care unit: A pilot observational study

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Abstract

Purpose: The aim of this prospective observational study was to evaluate in patients with sepsis not requiring intensive care unit admission the relationship between the levels of endotoxin activity assay (EAA) early after sepsis recognition and the risk of development of organ dysfunction (OD).

Methods: Endotoxin activity assay levels were drawn immediately after sepsis identification (baseline) and at 6, 24, and 48 hours postbaseline in 50 patients with signs of sepsis of a duration of less than 24 hours. An EAA 0.60 units or greater was considered as highly elevated.

Results: Logistic regression showed independent association between EAA levels at baseline and the appearance of new OD (adjusted odd ratio, 2.41; 95% confidence interval, 1.18-4.90; $P < .05$). Fifteen patients (30%) who developed new OD after baseline had at least 1 EAA level 0.60 or greater. The adjusted linear regression analysis showed that across the 4 time points, EAA levels were significantly higher in patients who developed new OD (0.11; 95% confidence interval, 0.01-0.20; $P < .05$).

Conclusions: Endotoxin activity assay levels 0.60 or greater early after sepsis diagnosis in patients not requiring intensive care unit admission predict risk of development of new organ dysfunction. High EAA levels in the first 48 hours of recognition of sepsis are also predictive of risk of deterioration.

1. Introduction

Sepsis represents a continuum of disease severity with most patients with sepsis cared for outside the intensive care

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unit (ICU). Still, the early and appropriate management of patients with severe sepsis is associated with large improvements in survival rate [1]. Most of the attributable mortality from sepsis is from the development of multiple organ dysfunction syndrome [2]. The early identification of septic patients at high risk for rapid worsening could be a key to prevent the development of organ dysfunction and shock, and numerous biological markers have been proposed toward this aim [3].

Endotoxin, a complex lipopolysaccharide, which is the major component of the outer membrane gram-negative bacteria, is believed to be one of the principal mediators of the cardiovascular, pulmonary, and renal organ dysfunction observed in patients with sepsis [4]. High levels of endotoxin have been detected in patients with severe sepsis and septic shock admitted to ICU [5]. Indeed, endotoxemia has been also documented in patients with severe infections caused by gram-positive bacteria and in critically ill patients with other nonseptic pathologies (eg, trauma, cardiac surgery, burns) supporting the hypothesis of an extravascular source of endotoxin, such as translocation from the gastrointestinal tract [6]. Whatever the source, endotoxemia is generally associated with increased organ dysfunction and other bad outcomes and, therefore, may be a useful biomarker for identifying other high-risk population with sepsis not admitted to ICU [7]. Moreover, a recent pilot study including 64 patients indicated that endotoxin removal seems to have beneficial effects on organ dysfunction in patients with septic shock of abdominal origin and high likelihood of endotoxemia [8], and therefore, endotoxemia may be a valid direct therapeutic target.

The measurement of endotoxin levels in vivo has been notoriously problematic, and the most commonly used diagnostic test (ie, the chromogenic limulus amebocyte lysate assay) has low specificity due to interferences by circulating inhibitors of the coagulation cascade and by fungal products [4]. An alternative and easier method for the assessment of endotoxin levels in the blood has been recently proposed and validated [5,9]. This novel method assays the endotoxin activity (EAA) by the chemiluminescence measurement of the enhanced respiratory burst of the neutrophils after priming by complexes of endotoxin and a specific anti-endotoxin antibody. The EAA has been used in recent studies that demonstrated a correlation between high EAA levels and worse outcomes both in adult and pediatric ICU populations [6,10]. The availability of a reliable measurement of endotoxemia in a short time renders the EAA a promising and useful biomarker for the early recognition of septic patients at high risk for clinical worsening. Unfortunately, most studies published on the relationship between EAA levels and clinical consequences in sepsis deal with patients admitted to ICU.

In this pilot observational study, we aimed to define the prevalence of endotoxemia in patient with sepsis not requiring initial ICU admission early after sepsis diagnosis and to evaluate whether high EAA levels are predictive of the development of new organ dysfunction and clinical worsening.

2. Subjects and methods

2.1. Study population

In this prospective pilot study, we enrolled 50 consecutive patients with sepsis and severe sepsis admitted to wards (ie, not requiring ICU admission) of a 780-bed teaching hospital and visited by the sepsis outreach team (see below). Sepsis, severe sepsis, and septic shock were defined according to the 2001 Sepsis Definitions Conference [11]. Patients younger than 18 years; pregnant women; those with neutrophil count less than 1.0×10^9/L, do-not-resuscitate orders, or uncertain diagnosis were excluded. Patients treated with vasopressors or with signs of sepsis and severe sepsis of more than 24 hours duration before sepsis team first visit were also excluded. In our hospital, a specific outreach team (ie, sepsis team) dedicated to patients with sepsis is available 24 hours a day since 2006 [12]. The sepsis team collaborates with the most responsible attending physician and the nursing department staff in providing for each patient with sepsis the interventions recommended by the evidence-based guidelines of the Surviving Sepsis Campaign [13]. This study was reviewed and approved by the Ethical Committee of Modena Province, and informed consent was obtained from all patients.

2.2. EAA measurement and data collection

In each patient, a 2-mL blood sample for EAA was collected at study inclusion (ie, sepsis team first evaluation) (T0) and 6 (T1), 24 (T2), and 48 (T3) hours later. Blood samples were collected in an EDTA tube, and 0.5 mL was processed within 90 minutes as described elsewhere according to the recommendations of the manufacturer (Spectral Diagnostics, Toronto, Canada) [9] by use of a murine immunoglobulin M monoclonal antibody raised against the lipid A of *Escherichia coli* J5. The patient's neutrophil respiratory burst activity stimulated by opsonized zymosan was detected by a chemiluminescence technique (Autolumat LB953; E.G. & G. Berthold; Bad Wildbad; Germany). Endotoxin activity assay levels are expressed in relative units derived from the integral of the basal and stimulated chemiluminescent response and represent the mean of the 2 determinations from the same sample. The EAA assessments were considered consistent if the coefficient of variation between duplicates was lower than 15% and 30% for EAA levels below and above 0.2, respectively.

For each stage of analysis, we also collected clinical and laboratory data needed for the calculation of Sepsis Organ Failure Assessment (SOFA) score [14]. Age, sex, type of admission (ie, medical, elective surgery, emergency surgery),