Commentary

Endotoxemia in critically ill patients: why a reliable test could be beneficial

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Abstract

The detection of endotoxemia may provide a clue to the cause of sepsis or may indicate translocation of endotoxin from the gastrointestinal tract. A reliable endotoxin activity assay (EAA) offers the potential to determine Gram-negative infections in critically ill patients. In addition, a reliable EAA may indicate the adequacy of gastrointestinal tract perfusion, as well as potentially help to predict morbidity and mortality. A recent study by Marshall and colleagues, published in the present issue of *Critical Care*, evaluated the use of a whole blood EAA in a medical–surgical intensive care unit and found that 58% of the patients had positive endotoxin assays. However, only 13.5% of the population had a documented Gram-negative infection. This discrepancy and the observation that translocation and other causes of endotoxemia may not reflect true Gram-negative infection might severely limit the clinical utility of this EAA. Further study may better define the potential role of this technique in the diagnostic evaluation of the critically ill patient.

Keywords endotoxemia, Gram-negative infection, prognosis, sepsis, translocation

In the present issue of *Critical Care*, John Marshall and colleagues report on a clinical trial designed to evaluate the use of an EAA in patients admitted to a medical–surgical intensive care unit [1]. Endotoxin plays a central role in sepsis [2,3]. The current 'gold standard' for the determination of endotoxemia is the limulus amebocyte lysate (LAL) assay, which requires specific expertise to perform and which is notorious for wide variability in results [4,5]. Would the EAA evaluated by Marshall and colleagues be more reliable? And what are the benefits of a reliable test to detect endotoxemia in critically ill patients?

Potential benefits of reliable endotoxin detection

Endotoxin, a lipopolysaccharide component of the cell wall of Gram-negative organisms, is a central component in the initiation and/or propagation of the septic cascade [2,3]. When endotoxin is administered to experimental animals or to human volunteers, a physiological and clinical picture resembling sepsis is produced [6,7].

There are several potential benefits of a reliable, reproducible, reasonably rapid endotoxin assay in the management of critically ill patients. The detection of circulating endotoxin in the blood of patients may signal the presence of a Gram-negative infection. This result could theoretically trigger the administration of antibiotic therapy directed against the Gram-negative bacteria. Also, endotoxemia can result from translocation of Gram-negative organisms and/or endotoxin from the terminal ileum and cecum in the setting of gastrointestinal tract mucosal barrier dysfunction that has been observed during hypoperfusion of the gastrointestinal tract [8]. In this setting, the detection of endotoxemia may signal the necessity for improved resuscitation and restoration of splanchnic perfusion. Third, some investigators have speculated that the level of endotoxin in the circulation may have prognostic ability for critically ill patients [9–12]. Finally, it has been suggested that the presence of endotoxemia may identify a population of patients who could benefit from the administration of antibodies against endotoxin [13].

EAA = endotoxin activity assay; LAL = limulus amebocyte lysate.

Targeted administration of anti-endotoxin therapy

Endotoxemia has been the target of previous clinical trials evaluating the potential benefit of binding and/or neutralizing endotoxin in an attempt to improve the clinical outcome of patients with a presumed Gram-negative infection [13–15]. Unfortunately, these efforts have so far failed [13]. While this failure may reflect the inadequacy of the neutralizing agents, some have questioned whether the lack of efficacy reflected the variability in endotoxin levels or the actual presence of endotoxemia in the study population. These observations prompted speculation that a reliable, rapid endotoxin assay might identify a population of patients with circulating endotoxemia who could theoretically benefit from the administration of an anti-endotoxin treatment strategy. The current 'gold standard' for the determination of endotoxemia is the LAL assay, which requires specific expertise to perform and is notorious for a wide variability in results [4,5].

Effective antibiotic therapy of Gram-negative infections

John Marshall and colleagues showed an association between endotoxemia and Gram-negative infections in patients admitted to a medical–surgical intensive care unit [1]. They evaluated the use of an EAA and compared it with the 'gold standard' LAL assay in standardized whole blood samples, demonstrating a good correlation. Fifty-eight percent of the 74 patients studied had endotoxin levels >50 pg/ml. Proven infection was present in 26% of the patients on admission to the intensive care unit, while only 13.5% of the patients had culture-proven Gram-negative infections. These patients with documented Gram-negative infection had a significantly elevated mean EAA compared with the mean level in patients without a documented Gram-negative infection. There was an association between elevated EAA and Gram-negative infection, sepsis, and an elevated white blood cell count [1].

If endotoxemia could be reliably detected, it may serve as an indicator of a Gram-negative infection and may direct the clinician to administer effective antibiotic therapy directed against Gram–negative organisms. In an age of increasing resistance among the microorganisms encountered in the intensive care unit, it would be advantageous to only administer broad-spectrum antibiotics directed against Gram-negative bacteria to those patients who actually have a Gram-negative infection. Depending on the sensitivity of the test and the negative predictive value, there may be a potential to withhold Gram-negative antibiotic therapy in those patients who did not manifest a positive EAA.

Predicting outcome

There may also be a potential to use an EAA alone or in combination with other markers to prognosticate the outcome of patients with sepsis or the systemic inflammatory response syndrome. In Marshall and colleagues' small study, there was no statistically significant association between admission EAA and shock, mortality, APACHE II level, and length of stay [1]. Casey and colleagues, however, have previously demonstrated a greater risk of mortality among critically ill patients with a high lipopolysaccharide–cytokine score, in contrast to the lower mortality observed in those patients who had a lower lipopolysaccharide–cytokine score [9]. These observations are of interest and certainly merit further investigation.

Conclusions

The study by Marshall and colleagues was relatively small, with less than 30% of the study population having a documented infection. Less than one-half of these documented infections was caused by Gram-negative bacteria. Endotoxemia was found five times as often as documented Gram-negative infection. This demands further explanation. It may represent contamination of the assay technique, translocation from the gastrointestinal tract, or some other phenomenon. Such a large discrepancy indicates that the EAA tested by Marshall and colleagues may not be as valuable in detecting or directing antibiotic therapy as the rapid *streptococcal* test that is used by many pediatricians in the evaluation of children with sore throats. An EAA that could reliably differentiate between the presence and absence of Gram-negative infection would allow early initiation of empiric antibiotic therapy directed at the probable causative organisms. The reliable documentation of circulating endotoxemia could also help to determine whether there is a need for anti-endotoxin therapy or for improved splanchnic circulation. Further study is required before we can accept either of these conclusions.

Marshall and colleagues have presented us with a new test to detect endotoxin in the circulating blood. What we now need is a better definition of what endotoxemia signifies and how it can beneficially guide us to provide better care for our critically ill patients.

Competing interests

None declared.

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