Commentary

A targeted extracorporeal therapy for endotoxemia: the time has come

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Abstract

Endotoxemia, whether primary (due to Gram-negative infection) or secondary (due to epithelial barrier dysfunction), appears to be extremely common in the critically ill and injured. High levels of endotoxin activity are associated with worse clinical outcomes. In Japan, polymyxin B hemoperfusion has been available to treat endotoxemia for more than ten years. Multiple small trials, often limited by methodological quality, show that polymyxin B hemoperfusion may have favorable effects on survival and hemodynamics. Further study of this therapy would seem justified.

Cruz and colleagues [1] report a meta-analysis examining a novel treatment of sepsis and septic shock predicated on the removal of endotoxin from the bloodstream. The term endotoxin came from the 19th century discovery that portions of various Gram-negative bacteria could cause toxicity. Over the next 50 years, studies revealed that the effects of endotoxin were due to lipopolysaccharide found in the bacteria's outer membrane. Endotoxin need not be derived from pathogenic strains of bacteria; indeed, commensal microbial flora of the gut is an excellent source [2]. However, endotoxin is recognized as a key trigger of sepsis and septic shock [3].

Although our gut contains large quantities of endotoxin, endotoxin is scarcely detectable in the blood of healthy humans [4]. However, in sepsis, endotoxin levels in the blood can increase as much as 1,000-fold, even when there is no Gram-negative infection identified [5], perhaps occurring secondary to increased permeability of the gastrointestinal tract and subsequent translocation of bacteria or bacterial products (that is, endotoxin) [6]. Whatever the source, endotoxemia is associated with increased organ dysfunction and risk of death in critically ill patients [7]. Furthermore, blood levels of endotoxin have been reported to vary over time [8] in patients, suggesting subsequent waves of exposure either from infection or from intestinal translocation.

In the past, endotoxin was measured in the blood using a limulus assay where an aqueous extract of blood cells (amebocytes) from the horseshoe crab (*Limulus polyphemus*) is combined with a pyrochrome yielding a chromogenic readout. However, this assay detects only circulating endotoxin and most endotoxin is rapidly taken up by cells. Recently, the US Food and Drug Administration approved a method of assay for endotoxin activity in whole blood using a chemiluminescent detection system (Spectral Diagnostics, Toronto, Canada). The assay involves incubating whole blood with an anti-lipopolysaccharide antibody and then stimulating it with opsonized zymosan. The resulting respiratory burst activity of the subjects own white blood cells is then detected as light release from a lumiphor, which is used to quantify the amount of endotoxin activity [9]. Studies using this assay have shown that increased endotoxin activity is common in critically ill patients [7].

However, despite new methods of detecting endotoxin, treatment is quite limited. Bacterial infection is treated with antibiotics but there is no effective method of restoring gut barrier function. Furthermore, many antibiotics result in endotoxin release as bacterial are killed [10]. Anti-endotoxin therapies have been disappointing. Although an earlier trial suggested benefit from an anti-endotoxin antibody (HA-1A) when *post hoc* analysis was limited to subjects with Gram-negative infection [11], a subsequent trial failed to show a benefit in this population [12]. A second drug (E5) also failed to demonstrate benefit in patients with confirmed Gram-negative sepsis [13]. However, the activity of these antibody therapies in endotoxemia has been questioned.

Polymyxin B is an antibiotic that has high affinity for endotoxin, although it is associated with neurotoxicity and nephrotoxicity, precluding its systemic use. However, polymyxin B has been bound and immobilized to polystyrene fibers and

when used for hemoperfusion can effectively bind endotoxin both *in vitro* and *in vivo* [14]. This therapy has been available in Japan for more than a decade and thousands of patients have been treated. Unfortunately, despite widespread use in Japan, no large randomized trials have established efficacy of polymyxin B hemoperfusion. Several small studies have been conducted, however, and most have studied similar patients.

Cruz and colleagues [1] identified a total of 28 publications, including 9 randomized controlled trials, of polymyxin B hemoperfusion for treatment of sepsis and septic shock [1]. Their results reveal significant heterogeneity among trials ($p < 0.001$). However, these differences became non-significant when the analysis was adjusted for baseline blood pressure. Polymyxin B hemoperfusion was associated with a significantly lower mortality compared to conventional therapy (relative risk 0.53, 95% confidence interval 0.43 to 0.65). Secondary endpoints such as mean arterial pressure increase, vasopressor decrease, and mean partial pressure of oxygen in arterial blood/forced inspiratory pressure of oxygen ratio increase were also highly significant. However, the trials assessed were limited by methodological quality. Nevertheless, polymyxin B hemoperfusion appears to have favorable effects on survival and hemodynamics and the authors argue for the need for further rigorous study of this therapy.

Indeed, given the poor overall outcomes associated with endotoxemia, polymyxin B hemoperfusion would seem to be a welcome intervention, particularly now that better methods for detection of endotoxemia have become available. Thus, the time is right for an adequately powered trial of this promising therapy.

Competing interests

JAK has consulted for several companies interested in blood purification and endotoxin removal.

References

1. Cruz DN, Perazella MA, Bellomo R, de Cal M, Polanco N, Corradi V, Lentini P, Nalesso F, Ueno T, Ranieri VM, Ronco C: **Effectiveness of polymyxin B-immobilized fiber column in sepsis: a systematic review.** *Crit Care* 2007, **11:**R47.
2. Alexander C, Rietschel ET: **Bacterial lipopolysaccharides and innate immunity.** *J Endotoxin Res* 2001, **7:**1571-1574.
3. Opal SM: **The clinical relevance of endotoxin in human sepsis: a critical analysis.** *J Endotoxin Res* 2002, **8:**473-476.
4. Klein DJ, Derzko A, Seely A, Foster D, Marshall J: **Marker or mediator? Changes in endotoxin activity as a predictor of adverse outcomes in critical illness.** *Crit Care* 2005, **9(Suppl 1):**161.
5. Opal SM, Scannon PJ, Vincent JL, White M, Carroll SF, Palardy JE, Parejo NA, Pribble JP, Lemke JH: **Relationship between plasma levels of lipopolysaccharide (LPS) and LPS-binding protein in patients with severe sepsis and septic shock.** *J Infect Dis* 1999, **180:**1584-1589.
6. Fink MP, Delude RL: **Epithelial barrier dysfunction: a unifying theme to explain the pathogenesis of multiple organ dysfunction at the cellular level.** *Crit Care Clin* 2005, **21:**177-196.
7. Marshall JC, Foster D, Vincent JL, Cook DJ, Cohen J, Dellinger RP, Opal S, Abraham E, Brett SJ, Smith T, Mehta S, Derzko A, Romaschin A: **Diagnostic and prognostic implications of endotoxemia in critical illness: results of the MEDIC study.** *J Infect Dis* 2004, **190:**527-534.
8. Singh S, Evans TW: **Organ dysfunction during sepsis.** *Intensive Care Med* 2006, **32:**349-360.
9. Romaschin AD, Walker PM: **Endotoxin activity in whole blood by neutrophil chemiluminescenceVa novel analytical paradigm.** *Clin Chem* 2000, **46:**1504-1506.
10. ALKharfy KM, Kellum JA, Matzke G: **Unintended immunomodulation: Part II. Effects of pharmacological agents on cytokine activity.** *Shock* 2000, **13:**346-360.
11. Ziegler EJ, Fisher CJ Jr, Sprung CL, Straube RC, Sadoff JC, Foulke GE, Wortel CH, Fink MP, Dellinger RP, Teng NN, *et al.*: **Treatment of gram-negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin. A randomized, double-blind, placebocontrolled trial. The HA-1A Sepsis Study Group.** *N Engl J Med* 1991, **324:**429-436.
12. McCloskey RV, Straube RC, Sanders C, Smith SM, Smith CR: **Treatment of septic shock with human monoclonal antibody HA-1A. A randomized, double-blind, placebo-controlled trial. CHESS Trial Study Group.** *Ann Intern Med* 1994, **121:**1-5.
13. Angus DC, Birmingham MC, Balk RA, Scannon PJ, Collins D, Kruse JA, Graham DR, Dedhia HV, Homann S, MacIntyre N: **E5 murine monoclonal antiendotoxin antibody in gram-negative sepsis: a randomized controlled trial. E5 Study Investigators.** *JAMA* 2000, **283:**1723-1730.
14. Shoji H: **Extracorporeal endotoxin removal for the treatment of sepsis: endotoxin adsorption cartridge (Toraymyxin).** *Therapeutic Apheresis Dialysis* 2003, **7:**108-114.