Editorial

Endotoxin hemadsorption in septic shock

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The mid-20th century heralded an era of broad spectrum antibiotics that provided us with the false notion that we could treat resistant strains of organisms. We, however, continue to see an increase in both morbidity and mortality due to sepsis despite adherence to the latest surviving sepsis guidelines, which stress on early resuscitation of shock, timely administration of broad spectrum antibiotics and organ function support. With the increasing incidence of nosocomial infections, multidrug resistant organisms, inappropriate use of antibiotics and with only a limited availability of newer drugs, we need to focus on other innovative therapies such as discussed in the current article by Shum *et al*.[1] on extracorporeal removal of endotoxins.

Sepsis and its sequelae remain one of the leading causes of death worldwide. The prognosis depends not only on the pathogen and its virulence but more of an interaction between the pathogen (endotoxins/lipopolysaccharides [LPS]) and the host factors. This interaction evokes both pro and anti-inflammatory responses caused by the interplay between cytokines, procoagulants and fibrinolysis that contribute to a mixed antagonist response syndrome. In health, however, the innate immune system has the ability to sense and not respond to normal physiologic indigenous flora.[2,3]

Clinical studies have shown that elevated levels of circulating LPS are associated with severe illness, organ dysfunction and mortality. There have been attempts to target endotoxin and cytokine activity with hope to interrupt the cellular cascade and thereby prevent clinical worsening. Many such strategies to minimize or prevent the action of endotoxins have been described but required more extensive studies; one such being extracorporeal hemoperfusion to bind and neutralize LPS from whole blood. Among the endotoxin hemadsorption devices, available are: (i) Polystyrene fiber cartridge with immobilized polymyxin-B (PMX-B) (Toraymyxin®)[4] (ii) hemadsorber of macroporous beads immobilized with human serum albumin (Matisse®)[5] and (iii) polyethylene matrix with tailormade synthetic peptides with an affinity for endotoxins (Alteco®).[6,7] The cytokine removal devices are cytokine hemadsorber and polymethylmethacrylate membrane hemofilter (continuous hemodiafiltration).[6]

Interestingly in 2003, Nakamura *et al*.[8] published the largest study to date on PMX-B, an open labeled controlled study enrolling 314 patients with severe sepsis of which 206 met the criteria. The study showed a significant reduction in mortality and in endotoxin levels as well. It was estimated that by 2010, over 80,000 patients had received treatment with PMX hemadsorption filter in Japan with encouraging results. The company marketing this is Toray, Japan and is popularly known as Toraymyxin.

In this issue, Shum *et al*. have presented their study on the therapeutic effects of a LPS hemadsorption device (Alteco LPS Adsorber®) on patients with intra-abdominal Gram-negative septic shock. This randomized clinical trial (RCT) had 15 patients (7 in therapy and 8 in the control group). As per the Sequential Organ Failure Assessment (SOFA) score, the control group showed more obvious improvement but was not

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statistically significant. Whereas the PaO_2/FiO_2 ratio showed improvement in the therapy group, once again not statistically significant.

Both groups were similar with respect to decrease in vasopressor support, ICU stay, hospital length of stay and mortality. The study had to be terminated early as the interim analysis did not reveal any statistically significant findings between the two groups.

The inherent weakness of the study is in its numbers. The small sample size decreases the validity of its results. Further, it is a nonblinded, single center study that only includes patients with abdominal sepsis. It did not mention the time of sepsis at therapy-induction and was terminated early due to lack of positive/significant outcomes. There was no quantitative endotoxin assay to determine the level of endotoxemia and thus the effect of the filter.

The authors have accepted the limitation of their study, but the negative results have, inadvertently, raised our doubts regarding the results of other small studies which may have over-estimated the true magnitude of a clinical effect. These previous studies by Ala-Kokko *et al*.[6] and Kulabukhov *et al*.[9] with this filter were equally small, and done on patients with septic shock and endotoxemia, showed improved survival with no significant side-effects.

The larger studies, EUPHAS (n = 64)[4] and EUPHAS2 (n = 306)[10] have been with the PMX filter. They have shown an improvement in Mean arterial pressure (MAP), decrease in inotropes, SOFA scores and a decrease in 28 days mortality. The patients with intra-abdominal sepsis in both the EUPHAS and EUPHAS2 studies were similar in terms of time-to-enrolment, severity of the illness, 28 days mortality and in-hospital mortality, with a significant reduction of the SOFA score after 72 h of treatment. Those with nonabdominal sepsis, separately studied in the EUPHAS2, did not show a significant response in both the SOFA score and mortality, but further studies were recommended. However, the major criticism of the trial has been a lack of blinding, with a potential risk of introducing a bias.

The Euphrates trial,[11] a blinded RCT, the largest on-going multicentric trial, aims to overcome the limitations of the previous trials by including septic shock patients with endotoxemia, measuring the endotoxin levels and doing a longer term follow-up.

Hemoperfusion/hemadsorption may reduce endotoxin levels and consequently modulate the cascading events in sepsis thereby improving hemodynamic parameters, oxygenation, organ dysfunction and short term survival. Resuscitation, source control and appropriate antibiotics remain the mainstay of conventional treatment; but this cannot reverse the effects of the bacterial toxins already released into blood or of the endogenous mediators produced by the host in response to bacteria. We, therefore, need to target endotoxemia and conduct larger preferably blinded multicentric studies like the Euphrates trial.

Among the present series of studies available, some of the unanswered questions remain the efficacy of this therapy in patients without intra-abdominal sepsis and the comparison between the currently available therapies. There is also little doubt that the future of diagnosis and therapy lies in our better understanding of the pathogenesis of sepsis and the host immune response to elevated levels of cytokines and bacterial endotoxins. Accepting the fact that endotoxemia rather than sepsis is the specific therapeutic target, the challenge then remains as to which patients with endotoxemia will benefit from these therapies.

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