Perspective

Déjà-vu from the nineties: is there a perspective for anti-endotoxin strategies to improve the outcome of multiple trauma patients?

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Abstract: A recent cohort study of Charbonney *et al*. indicates that multiple trauma patients develop endotoxemia also in the absence of Gram-negative infection. This is most probably due to an increase of gut permeability. Non-survivors as well as patients with cardiovascular dysfunction and multiple organ failure (MOF) show significantly higher endotoxin levels at 24 h after injury compared to survivors and patients without MOF. These results are like a déjà-vu from the nineties of the last century, where several studies reported endotoxemia during the initial 24 h after multiple trauma with development of MOF and death at endotoxin levels >10 and >12 pg/mL, respectively. Of interest, other multiple trauma patient studies in the nineties have shown endogenous anti-endotoxin antibody production in survivors and reduced antibody production in non-survivors, which died from MOF. Although all these studies have pointed towards a mechanistic role of endotoxin in the fatal outcome after multiple injuries, clinical anti-endotoxin studies are still lacking. Thus, the future perspective must be prospective randomized multicenter trials, which have to elucidate the capability of anti-endotoxin treatment strategies to improve outcome in multiple trauma patients.

Keywords: Multiple trauma; endotoxemia; multiple organ failure (MOF); anti-endotoxin treatment; anti-endotoxin antibody

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The treatment of multiple trauma patients remains still a major challenge in medical health care. Worldwide, multiple traumas are a leading cause of death (1). While in the nineties of the last century traumatic brain injury accounted for 58.4% of causes of death, the distribution of causes of death has changed today, showing a reduction of traumatic brain injury-related mortality but an increase of deaths due to multiple organ failure (MOF) and sepsis (2). Of interest, MOF after multiple traumas developed to the main mechanism leading to sepsis and death despite the major progress of intensive care management achieved during the last two decades (3). Analysis of 31,154 patients from the Trauma Register DGU showed that 21% to 30% of the MOF patients but only 4% of the non-MOF patients develop sepsis, and 43.1% of the MOF patients but only 7.5% of the non-MOF patients die during the first 30 days after trauma (3). Thus, the lethality of multiple trauma patients has to be considered as still high. This requires a more intense search to elucidate the mechanisms and to develop novel therapeutic strategies, which may finally improve the overall patient outcome.

Lipopolysaccharide (LPS) is a bacterial endotoxin, originating from the outer membrane of gram-negative bacteria (4). LPS is a potent trigger of the innate immunity, inducing a massive activation of PMN leukocytes and macrophages, which results in an overwhelming pro-inflammatory cytokine response (5,6). Of interest, endotoxin has also been suggested as the trigger of a complex cascade of inflammation in the development of MOF and death after multiple traumas (7).

In a recent issue of *Critical Care Medicine* Charbonney

et al. (8) present a single-center cohort study on 48 severely injured patients. They have analyzed endotoxin levels over a 5-day period after multiple trauma, and assessed risk factors and prognostic implications. The analyses revealed that 75% of the multiple trauma patients develop endotoxemia, also in the absence of Gram-negative infection. Of interest, the authors indicate that at admission in 96% of the patients the endotoxin levels were found within normal limits. During the following days the endotoxin levels slowly but significantly increased, demonstrating peak levels at days 3 and 5. According to these results, the authors state that their study is "the first to detect increasing levels of endotoxemia following multiple traumas" and draw the main conclusion "that delayed endotoxemia in multiple trauma patients is common and associated with adverse clinical outcome" (8). However, a more detailed view on the data of the study of Charbonney *et al*. (8) gives additional information, which we feel is even of greater importance compared to the finding of the development of "delayed endotoxemia". In fact, the data of the study indicate that the endotoxin response during the early 24-h period after multiple traumas seem to be of utmost importance. Patients with shock at admission had significantly higher day 1 endotoxin activity (EA) levels. In addition, an EA of ≥0.4 EA units at the early time point day 1 after admission was associated with some more respiratory complications, a significantly higher cardiovascular dysfunction and a significantly increased Multiple Organ Dysfunction Score. Finally, non-survivors had also a significantly higher EA level on day 1 compared to survivors (8). Thus, the delayed increase of endotoxin levels after multiple traumas with peaks at day 3 and 5 may not be of particular importance for the final outcome, because most of these patients survived. In contrast, we feel that the early increase of endotoxin levels within the first 24 h, observed in some of the patients, is of more importance, because this was associated with development of MOF and death.

These results are like a déjà-vu from the nineties of the last century. In 1996, Pfeiffer *et al*. (7) reported on a series of 32 patients with severe polytraumatic injury. In these patients endotoxin levels were measured hourly over the first 24 h after admission. Thirty of the 32 patients showed episodes of endotoxemia, however, the authors realized that not the fact of endotoxemia episodes during this early period after trauma but the height of endotoxin concentration during these episodes predicts the development of later MOF and death. If the endotoxin peak concentration during the first 24 h after admission was >10 pg/mL, the positive predictive value concerning development of MOF was 100%. If the endotoxin peak concentration during the first 24 h after admission was >12 pg/mL, the positive predictive value for death was 100% (7). Thus, the main message of the 1996 report of Pfeiffer *et al*. (7) was that increased endotoxin levels during the first 24 h after multiple traumas are associated with the development of MOF and death. This is quite similar compared to that shown by Charbonney *et al*. (8) in their recent 2016 report in *Critical Care Medicine*.

The relevance of the delayed increasing endotoxin levels during the first 5 days after multiple traumas, observed by Charbonney *et al*. (8), remains to be determined. In fact, most other studies which have analyzed serum concentrations of endotoxin in multiple trauma patients revealed a rapid elevation during the first few hours after trauma, and a subsequent decline over the following days (9,10).

The source of the circulating endotoxin after multiple traumas remains a matter of discussion. Charbonney *et al*. (8) indicate the limitation of their study that they did not assess markers of gut permeability to more directly support their hypothesis that the gastrointestinal tract was the source of circulating endotoxin. Their hypothesis is based on the fact that many patients in their study presented with circulating endotoxin, although a Gram-negative infection could be excluded. Indeed, others have previously shown that multiple trauma induces an increase of gut permeability which correlates with the severity of injury of the trauma patients (11).

Thus, the findings of the study of Charbonney *et al*. (8) may not be particularly new, but mainly confirm the findings from several studies of the nineties of the last century. Nonetheless, we feel that the study has a high relevance, because it returns to mind endotoxin in multiple trauma patients. Not only that endotoxin may be an interesting marker for monitoring and predicting the outcome after multiple traumas, but also that endotoxin may represent an interesting target for therapy.

In sepsis, neutralization, absorption or binding of endotoxin was suggested as an attractive strategy to improve patient outcome. In a first study in the early nineties the use of the HA-1A monoclonal antibody showed promising results in gram-negative sepsis patients (12). However, although suggested by the authors of the study, the antibody therapy did not make its way into clinical routine. This might be due to the fact that further clinical trials which studied anti-endotoxin strategies did not show reproducible

survival benefits (13). This is most probably due to the complex etiology and pathophysiology of sepsis.

We hypothesize that the etiology of endotoxemia after multiple trauma is less complex compared to sepsis, and, thus, may be more suitable for an anti-endotoxin treatment. Our view is supported by the fact that multiple injuries, which are associated with endotoxemia, cause specific increases in anti-endotoxin antibodies from the IgM-class (14). This endogenous response may guarantee that most of the multiple trauma patients survive despite endotoxemia. In fact, it has been demonstrated that if patients with severe trauma show an only low production of anti-endotoxin antibodies, they have a significantly higher risk of death due to MOF (6). Accordingly, we speculate that in those patients the application of anti-endotoxin antibodies or other anti-endotoxin treatment strategies, such as LPS absorption or binding, should exert beneficial results, reducing the development of MOF and improving the survival rate.

In conclusion, the study of Charbonney *et al*. (8) and previous studies from the nineties of the last century indicate that multiple trauma increases the intestinal permeability which results in endotoxemia. Endotoxemia induces MOF and post-trauma death. Surprisingly, there is no clinical study reported, which has counteracted endotoxemia after multiple trauma. Charbonney *et al*. (8) indicate in their report that a trial of extracorporeal endotoxin removal in septic patients with elevated EA levels is currently in progress. Indeed, we propose that there is a must for future clinical trials. These, however, should not primarily be performed in septic patients, but in multiple trauma patients. The trials should be designed as prospective, randomized multi-center trials with an adequate number of patients. In particular, they should include an endotoxin monitoring as well as an anti-endotoxin treatment strategy. Those studies may be capable of revealing whether in non-infected multiple trauma patients the development of MOF and death due to increased endotoxin levels can be reduced by anti-endotoxin treatment strategies.

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Footnote

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