Editorial

Polymyxin B hemoperfusion in septic shock: nothing overmuch (Meden Agan)!

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Sir William Osler [1849–1919], the father of modern medicine, supported that "Except on few occasions, the patient appears to die from the body's response to infection rather than from it". Today more than hundred years later, the concept is the same if we consider the new Sepsis-3 definition. Sepsis is defined as a life-threatening organ dysfunction induced by a maladapted response of the host to an infectious insult (1). As the infective insult occurs, pathogen molecular pathways are triggered causing host immune molecular signals, which in turn provoke an uncontrolled inflammatory cascade. Endotoxins are large molecules consisting of lipopolysaccharides (LPS) of O-antigen with outer and inner cores, found in the outer membrane of Gram-negative bacteria or rods (GNR). LPS is capable of eliciting strong immune responses in the host, triggers the sepsis cascade by inducing a systemic inflammatory-hormonal response (2), and increases the risk of multiple organ failure and death. Last decades the concept of targeted interventions to decrease the circulating mediators of sepsis to intercept the dysregulated host response grew enthusiasm, and endotoxin was a reliable target to consider for therapy. Treatment interventions at various steps of the endotoxin pathway, including the heat shock protein-72 and -90 "danger signal" induction (3), have been tested experimentally in human *in vivo* and *in vitro* studies (4,5) without convincing results (6,7). Attempts to remove endotoxin with monoclonal antibodies failed, so extracorporeal removal by hemoperfusion was introduced using polymyxin B cartridges, where endotoxin can be bound and neutralized (8). However, the clinical efficacy of polymyxin B hemoperfusion (PMX-HP) in sepsis remains controversial, and there are no recommendations in the recently released guidelines (Surviving Sepsis Campaign 2016) related to endotoxin removal techniques (1). Moreover, coupled plasma filtration adsorption or high volume hemofiltration for removing endotoxin or selective vasoactive mediators have also been inconclusive (9).

In the recently published article entitled "*Potential survival benefit of polymyxin B hemoperfusion in patients with septic shock*: *a propensity-matched cohort study*" (10) on the *Critical Care*, Nakamura, colleagues and Japan Septic Disseminated Intravascular Coagulation (JSEPTIC DIC) study group investigated whether PMX-HP affects the septic shock morbidity and mortality. The authors performed retrospective analyses by propensity-score matching of the JSEPTIC DIC study database on patients treated during a 3-year period. They aimed to evaluate the PMX-HP usefulness for different septic shock types, and various infections caused not only by GNRs but also by non-GNRs and various other pathogens. Septic shock adult patients from 42 Japanese intensive care units (ICUs) were classified into PMX-HP-intervention and control non-PMX-HP-treatment groups. The endpoints included: (I) hospital all-cause mortality; (II) mortality in the ICU; (III) ICU-free days (ICUFDs) during the first 28 ICU-days. Of the 522 patients who had received PMX-HP, the propensity

scores enrolled 262 septic shock patients in the PMX-HP study group and 262 patients in the non-PMX-HP septic shock control group. The proportion of all-cause hospital mortality rates were decreased in the PMX-HP treated group (32.8%) compared to the non-PMX-HP control group (41.2%, P<0.05); more ICUFDs were recorded in the PMX-HP (18 days) compared to the non-PMX-HP group (14 days) in the ICU first 28 days (P<0.05); ICU mortality did not differ between the two groups.

In unmatched for illness-severity patients with definite or possible abdominal septic shock, although PMX-HP and non-PMX-HP postoperative groups did not differ regarding mortality (11), this 28-day mortality was lower than in previous studies (12). Supporting the work of Nakamura *et al.*, previous studies have reported that PMX-HP reduces the sepsis-related mortality (12) or the septic shock-related 28-day mortality in patients on continuous renal replacement treatment (RRT) for acute kidney injury (13).

Although PMX-HP has been initially introduced to treat GNR-related septic shock by binding and neutralizing endotoxin, Nakamura *et al.* study suggest that PMX-HP may also benefit Gram-positive cocci (GPC) or other kinds of septic shock, by probably adsorbing endogenous cannabinoids and improving immunoparalysis. In septic shock, cannabinoids are activated and interact with vascular cannabinoid receptors, causing hypotension and cytotoxicity or leading to immunoparalysis (14). The efficiently absorbed cannabinoid by PMX-HP (15) reverses the repressed in sepsis and septic shock human leukocyte antigen (HLA)-DR (16). PMX-HP might also attenuate pro-apoptotic plasma activity on septic renal tubular cells (17). Beneficial effects concerning GPC infection have scarcely been reported while the PMX-HP treatment strategy for severe toxic shock syndrome in children has also been proposed (18).

As the study of Nakamura *et al.* was not initially designed to evaluate PMX-HP treatment effect, significant variables are missing, such as number and duration of PMX sessions, time of administration, and possible adverse events (10). PMX-HP has been used as rescue therapy in patients unresponsive to a goal-directed protocol or with catecholamine-resistant septic shock. After completing two sessions of PMX-HP, patients' catecholamine support was decreased by 76% and lactate levels by 50%, shock reversed rapidly and organ system dysfunction improved (19). However, the optimum frequency, length, or the most efficient PMX-HP intervention time in septic shock patients remains unknown. Previous studies reported improvement in patient hemodynamics and oxygenation after use of PMX cartridges in abdominal sepsis (12), yet this evidence was not exhaustively examined but derived from a shortening of ICU stay. Moreover, monitoring of endotoxin levels by endotoxin activity assays would probably facilitate to determine either the reduction of the "endotoxin burden" which is associated with the outcome or the low levels, which are not always high in sepsis and therefore strategies for its removal may not be efficient. However, more biomolecules should be assessed in various infection types caused by GPC or fungi (20).

Despite encouraging results of different pharmacological approaches directed against endotoxin in animal models, controlled clinical studies have shown controversial results in patients with septic shock, mainly of abdominal origin. Most of the series of studies were performed in Japan, where PMX-HP is widely used in patients presented with GNR-related severe sepsis or with septic shock (21). A recent large randomized controlled trial (RCT) (ABDOMIX group) did not demonstrate any benefit of PMX-HP in organ failure or mortality in patients with peritonitis- induced septic shock (22). Another European RCT, the "Early use of polymyxin B hemoperfusion in abdominal septic shock" (EUPHAS) trial (12), reported the opposite, namely improved hemodynamics and pulmonary oxygenation, reversal of organ dysfunction, and reduction of 28-day of mortality. Similar results were demonstrated in the retrospective EUPHAS 2 registry, a study designed to reproduce the prospective data of EUPHAS project (23). Results from EUPHAS 2 supported the clinical utility of PMX-HP in treating patients with sepsis or septic shock, confirmed outcome improvement by using this technique of extracorporeal endotoxin purification and did not record any PMX-HP associated adverse events (23). Currently, another placebo-controlled multi-centered blinded trial is ongoing in the USA, the "Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized controlled trial of Adults Treated for Endotoxemia and Septic Shock" (EUPHRATES). Preliminary results of the study showed a significant reduction in mortality (P=0.046) in a subgroup of septic shock patients who were highly endotoxemic (24). On top of that, recent systematic reviews by Chang *et al.* (25) and Terayama *et al.* (26) demonstrated that PMX-HP treatment might reduce mortality in critically ill patients with severe sepsis or septic shock in specific disease severity subgroups. The evidence mentioned above leads to the conclusion that PMX-HP treatment may have a definite clinical benefit in a particular target population group, but this postulates further investigation.

Despite these encouraging results, most of the studies of PMX-HP treatment for severe sepsis and septic shock suffer from serious methodological flaws. Most studies are not randomized, are of limited sample size, include heterogeneous populations of patients, do not measure endotoxin circulating levels, and are not providing inflammatory indices or any other biomolecules (12). Moreover, the appropriate number of sessions, the duration, and the timely initiation of PMX-HP administration are not clearly documented and need to be defined. Focus not only in the short term but also in long term outcomes would better clarify the implications before the widespread use of this high-cost treatment.

In conclusion, there is accumulated evidence today to suggest a possible role for PMX-HP as a rescue therapy in the management of septic shock by improving hemodynamics, organ function, and survival. Careful identification of the candidate patients is of most importance for the success of this blood purification technique, as it seems that highly endotoxemic septic shock patients may benefit from PMX-HP treatment. Recently, Nakamura *et al.* suggested that PMX-HP improves outcome by reducing all-cause hospital mortality and the length of ICU stay in patients with a variety of infections causing septic shock types induced by not only GNR but also GPC and other microorganisms (10). Smart randomized studies in distinct homogenous populations of septic patients using strict criteria, including endotoxin measurements, are urgently needed to confirm or refute these results. Because, as Chilon of Sparta, 1 of the 7 sages of ancient Greece said, "nothing (in) excess", meaning we should find the golden mean in everything and avoid extremities.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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