

# HIGHLIGHTS from the 38<sup>th</sup> Vicenza Course on AKI & CRRT

## Endotoxic Shock and COVID-19



Interesting findings and new data on endotoxemia, endotoxic shock, implications in COVID-19 disease, role of Polymyxin B hemoperfusion and new approaches in Septic-AKI, were presented during the 38th International Vicenza Course on AKI and CRRT organized by Prof. Ronco which took place virtually from November 2-6, 2020. Patients who are hospitalized for extended periods in ICU are more prone to superimposed infection. Gram-negative infections and/or direct mucosal gut translocation lead to the systemic circulation of endotoxin (endotoxemia) and presented data confirm a frequent presence of high endotoxin levels also in COVID-19 patients hospitalized in the ICU, with the involvement of gut-lung cross-talk contributing to dysregulated host response that may lead to multi-organ failure. Data presented clarify the rationale and timing of the use of Polymyxin B hemoperfusion in endotoxic shock patients including patients with pulmonary infection, such as COVID-19.

Together, the different scientific sessions provide concrete answers to the following questions:

- Q1 What is the evidence base for Polymyxin B hemoperfusion in septic shock?
- Q2 Is a biomarker for endotoxemia useful to support a targeted therapy?
- Q3 What is the importance of an observational study like EUPHAS-2 in addition to RCTs when trying to build the evidence base?
- Q4 Are specific patient populations who received PMX-HP in the EUPHAS-2 registry being studied?
- Q5 Based on data from EUPHAS-2 and clinical experience, is there a possible association between endotoxemia and septic shock severity?
- Q6 What could be a reference recommendation for implementing PMX-HP?
- Q7 In COVID-19 patients, what about superinfections and endotoxemia and what is the possible role for PMX-HP?
- Q8 What about septic-AKI and the role of a specific dialysis membrane?

### Endotoxic shock and the role of Polymyxin B hemoperfusion

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection (1) whereas septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.

The immune response plays an important role in the progression of sepsis and is initiated when pattern recognition receptors (PRRs) on the surface of host immune cells recognize pathogen-associated molecular patterns (PAMPs), like endotoxin and danger-associated molecular patterns

(DAMPs), released in response to inflammatory stress. Although “Cytokine Storm” has been described as a possible factor in septic shock and COVID-19, it is now more clear that inflammatory cytokine generation is a consequence of immune cell activation triggered by PAMPs and, in addition, mediator release vary over time and in relevance making it inaccurate to talk always about a “storm”. Instead, it is more relevant to consider co-infections and super-infections present in COVID-19, especially Gram-negative infections, as well as the presence of bacterial products, such as endotoxin. Another important factor is the immune-depression status developed that may make these patients more prone to super-infections.

Endotoxin is the most potent trigger of the septic cascade and the major component of the cell wall of Gram-negative bacteria. During the progress of sepsis, circulating endotoxin can increase up to 1,000-fold. The interest of endotoxin as a therapeutic target is therefore evident (2).

The polymyxin B immobilized hemoperfusion medical device, Toraymyxin<sup>®</sup>, combines the potent endotoxin neutralizing capabilities of polymyxin B with extracorporeal hemoperfusion. High affinity binding of endotoxin by polymyxin B may remove up to 90% of circulating endotoxin after two treatments (Device Adsorption Capacity, DAC = 64 µg or 640,000 EU).

In addition, although Polymyxin B hemoperfusion (PMX-HP) therapy was designed to adsorb endotoxin, other mechanisms of immunomodulation have been demonstrated during treatment. Some of these mechanisms are caused by elimination of endotoxin, while others result from the direct apheresis of activated immune cells, such as activated monocytes and neutrophils as well as inactivation of circulating apoptotic factors.

A number of clinical studies have shown that PMX-HP improves organ function and outcome in specific patient populations.

Dr. De Rosa showed her recent clinical experience from the San Bortolo Hospital, Vicenza ICU unit on un-responsive endotoxic shock patients treated with PMX-HP.

The so called “*golden hour of Polymyxin B Hemoperfusion*” approach depicted in a recent publication was applied, with the rationale that endotoxin neutralization by PMX-HP therapy might prevent or reduce the physiological (mainly hemodynamic) derangement typically observed during endotoxic shock.

Data presented refer to a group of patients (n = 20) with a median SAPS II value of 71.5 (52-77.5) points at baseline, following PMX-HP, who had a significant improvement in vasopressor requirement, mean arterial pressure (MAP), SOFA score and blood lactate levels with ICU and Hospital mortality of 30% and 35%, respectively. Furthermore there was a reduction of Endotoxin Activity levels over time. Notably, 40% of these patients had pulmonary acquired pneumonia as source of infection.

Specific data on five COVID-19 patients hospitalized in ICU were also presented. All with symptoms of endotoxic shock with mainly Endotoxin Activity levels > 0.6 and a median SAPS II score of 68 points. Following PMX-HP treatment there was an overall improvement in MAP, SOFA score, blood lactate levels and vasopressor requirement with an important mortality reduction, compared to predicted mortality. There was a reduction of Endotoxin Activity levels over time.

## Endotoxemia and COVID-19

### Is endotoxemia relevant in COVID-19?

Dr. Yamane from George Washington University, Washington DC described his clinical experience on the prevalence and relevance of endotoxemia in COVID-19 patients.

The study included n = 63 COVID-19 patients admitted to the ICU.

In all patients Endotoxin Activity (EA) level was measured. At baseline 9.5% of patients had low EA (< 0.4), 19% had intermediate EA (0.4-0.59) and 69.8% had high EA (> 0.6) levels. Despite the high proportion of patients with high EA only a small percentage of patients had confirmed bacterial infection.

High Endotoxin Activity level was associated with higher acute kidney injury and the consequent need for Renal Replacement Therapy (RRT).

Dr. Mallipattu from the Stony Brook University, New York talked about his experience with endotoxemia monitoring in

COVID-19 patients.

In his study of n = 32 COVID-19 patients admitted to the ICU who all had Endotoxin Activity measured at baseline, he found that high EA levels were present with an incidence of 44% and in addition was associated with a higher risk of AKI development, increased need for RRT and worse hospital outcome.

In conclusion, the answer to the initial question is:

**YES, endotoxemia can be relevant in COVID-19 patients.**

## EUPHAS 2 registry – a picture from the real clinical practice

EUPHAS 2 is an observational study (web-based registry) on the use of Polymyxin B hemoperfusion (PMX-HP) in septic patients (3). The registry was launched in 2010 and has tracked data from more than 600 patients treated with PMX-HP up to today.

Dr. Cutuli from University of Sacred Heart Hospital, Policlinico Gemelli, Rome, EUPHAS 2 registry Scientific Secretary and Data Manager, talked about the rationale of the use of PMX-HP and clinical experience in his unit presenting data from the EUPHAS-2 registry, specifically new promising data concerning an endotoxic shock population subset and data referring to a COVID-19 population.

First, data referring to Phase 1 of the EUPHAS 2 registry were presented, concerning n = 357 patients treated with PMX-HP, where significant improvement in Inotropic Score, Blood Lactates Levels and SOFA score was achieved over 72 hours from the baseline. In particular, an improvement in terms of survival benefit was identified in patients classified as Cardiovascular Responders.

Then, specifically, recent data arising from the Phase 2 of the Registry, particularly in a specific subset of patients with endotoxic shock (n=29) who all had their Endotoxin Activity levels monitored and treated with PMX-HP was shown.

SAPS II score at admission was 66 (52-78) with median Endotoxin Activity level was 0.75 (0.63-0.82) at baseline.

MAP increased significantly and Vasopressor Inotropic Score (VIS) decreased rapidly and significantly.

SOFA score, Lung Injury Score, RIFLE score all improved significantly. Endotoxin Activity levels showed a trend of reduction over time.

Furthermore, results on n = 12 critically ill patients with COVID-19 treated with PMX-HP were presented. These patients had a mean Endotoxin Activity level of 0.78 (0.70-0.92) at baseline. Data showed a trend of Endotoxin Activity (EA) reduction over time with a significant correlation at baseline between EA levels and SOFA score severity.

## Septic AKI – the role of the dialysis membrane

In the context of AKI and septic-AKI, a growing body of evidence indicates that complement activation system contributes to its pathogenesis (4). Short-term effects of complement activation include promoting inflammation and coagulation processes (5).

Prof. Cantaluppi and Prof. Castellano both presented results of research conducted in a recent collaborative research study aimed at exploring new pathogenic mechanisms in a swine model of LPS-induced AKI (6).

The results showed that CRRT with Polymethylmethacrylate (PMMA), in contrast to a Polysulfone (PS) based membrane, led to the recovery of renal function in animals with septic AKI. This resulted in a reduced requirement for catecholamines. Compared to PS, PMMA reduced infiltration of inflammatory cells in the renal parenchyma. CRRT with PMMA reduced acute renal fibrosis and glomerular thrombi. PMMA-CRRT reduced systemic complement activation, by reducing the activation of both the classical and alternative pathways. PMMA also decreased LBP serum levels in septic-AKI animals. In addition, PMMA decreased sCD40 serum levels. The researchers further studied how this effect was mediated and found that PMMA-CRRT reduced renal PTX3 deposits. A whole-genome gene expression profile of swine PBMCs showed that LPS activated circulating leukocytes, but in the PMMA group this effect was reduced.

The results explained above have implications also for COVID-19 patients with AKI development. It is now clear that severe COVID-19 is associated with a dysregulated host response to an infection, much like what happens in sepsis, with important involvement of the complement system.

## References

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The sessions are available on the Youtube channel [www.youtube.com/user/VicenzaNephroCourses](https://www.youtube.com/user/VicenzaNephroCourses)

# 38<sup>th</sup> Vicenza Course on AKI & CRRT ABSTRACTS AT A GLANCE

## The use of Polymyxin B Hemoperfusion for COVID-19 Patients with endotoxic shock

*S. De Rosa, M. De Cal, V. Danzi, G. Golino, G. Pierbellini, C. Ronco*

## Polymyxin B hemoperfusion therapy and extracorporeal CO<sub>2</sub> removal in a patient with COVID-19: a case report

*L. Monastra, A. Perrella, R. Garzia, F. Fraganza*

## Polymyxin B hemoperfusion in septic patients with acute myeloblastic and premyelocytic leukemia

*L. De Simone, K. Valentini, F. Maceri, S. Cidin, E. Benedetti, V. Del Pellegrino and A. M. Paladini*