**Academic Perspectives**

**Hemoperfusion in Organ Support: Clinical Evidence Sharing**

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**Rationale for hemoperfusion in Sepsis, COVID-19 and organ support: The case of HA380 sorbent device**

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1. **Sepsis Cascade**

   Well known that sepsis cascade begins with original infection and further leads to cascade of immune response. The final common process is the disruption of the immune system, result in organ damage.

   Thus, septic patients may have different therapeutic targets in different disease period. In the beginning, source control and endotoxin removal would be the targets. Although drugs may help, there are no specific drugs. When immune dysregulation occurs, immune modulation and cytokine removal are the most important aspects. Finally, to provide organ support to patients with organ failure will be necessary.
In the beginning, there is pro-inflammatory response with the activation of specific cytokines such as TNF-α, IL-6, IL-8. In this case, the system starts to respond with a very high level of inflammation. At the same time, this might be counterbalanced with severe anti-inflammatory response, which might help to overcome the inflammatory response. Pro-inflammatory response and anti-inflammatory response are two sides of the same coin, represent the innate immune response and adaptive immune response.

Under the circumstances, patients might die due to intractable inflammation-induced organ injury or due to persistent immunosuppression and recurrent infections. Therefore, sequential extracorporeal therapy has been proposed to remove endotoxin in the infection stage, to remove excessive cytokines in the immune dysregulation stage, and to provide organ support in the organ damage stage.

2. Peak Concentration Hypothesis & Cytokinetic Model in Sepsis

The Peak Concentration Hypothesis explains the reason for applying ECOS to patients with sepsis. As patients have high levels of pro-inflammatory and anti-inflammatory, the application of ECOS (e.g. CRRT and hemoperfusion) could lower the peaks of cytokines. Therefore, patients are likely to recover hemostasis for a better condition to face the infection.

The Cytokinetic Model proposed that reducing the cytokine level could relieve organ infiltration and tissue injury. On the other hand, the redirection of immunocompetent cells will improve bacterial clearance.
3. Organ Crosstalk can be prevented or supported by specific therapies

Organ crosstalk, which is the interaction of different organ that can be prevented or supported by specific therapies to modify the level intensity and complexity.

Sequential extracorporeal therapy in sepsis is a novel approach to the septic patient with multiorgan damage to provide the critical patient with the most suitable therapy moment by moment. It is based on expert multidisciplinary team, able to perform appropriate and dynamic patient prescription based on close monitoring of the patient’s clinical condition at bedside.

4. The rationale of hemoperfusion therapy for patient with pneumonia

The mechanism of pneumonia is similar to Sepsis. The viral infection caused pneumonia can be aggravated by the application of ECMO or mechanical ventilation, which might lead to pro-inflammatory and responding anti-inflammatory responses. Finally, lead to endothelial dysfunction and organ failure.

Applying the ECOS system to block the level of cytokine and to lower the level of immune hemostasis, which can protect endothelial and provide organ support. These can be achieved by using the HA380 sorbent device in conjunction with the CRRT filter both before and after the dialyzer.
5. Therapeutic methods to manage severe COVID-19 patients

The COVID-19 can be controlled by ECOS by providing different extracorporeal therapies such as CRRT, hemoperfusion (HP), ultrafiltration and etc, to help to control organ crosstalk and cytokine release syndrome, and to support important organs.

6. The ADQI consensus

The latest publication in Nature Review Nephrology described the treatment aims of the different stages of disease and recommended extracorporeal blood purification treatment as a solution.
**Hemoperfusion in Sepsis and Liver Disease**

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1. **Critical care rationale for ECLS devices**
   - To treat hepatic encephalopathy, cerebral edema, intracranial HT
   - To restore/maintain hemodynamics
   - To prevent end-organ damage (MODS)
   - To be bridging therapy (e.g. organ transplant and spontaneous recovery)

2. **Goals of extracorporeal liver support systems**
   - To expedite recovery from acute decompensation in ACLF
   - To avoid premature and unnecessary treatment in ALF patients with the potential for liver regeneration and spontaneous recovery
   - To serve as a bridge to liver transplantation in ALF, ACLF, and decompensated cirrhosis
3. Analysis of randomized control trials in extracorporeal liver support (ECLS)

In the studies of applying MARS and Prometheus in patients with ALF and ACLF, results indicated little benefit in survival. On the other hand, the study conducted by Prof. Larsen showed that a high volume of plasma exchange has advantages on hospital mortality.

4. Case sharing: using HA330 hemoperfusion in patient with Sepsis

An 86-year-old male diagnosis with pneumonia with ARDS on day 1 of admission and later develop into septic shock on day 2. Provided HA330 HP to the patient for two sessions. Improvements were shown immediately after the hemoperfusion treatments, with lower dose vasopressor was needed.
Hemoperfusion in Sepsis and COVID-19

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1. Leptospirosis introduction

Leptospirosis is a bacterial disease that results in exposure of mucous membranes to the urine of infected animals, usually rats in urban cities. The most severe complication is Weil’s disease while patients would suffer from jaundice, renal failure, and pulmonary hemorrhage. Leptospirosis presenting with renal failure is often accompanied by pulmonary hemorrhage and carries high mortality despite standard therapy. In a review of 194 patients suffering from Leptospirosis, 25% of patients died and are mostly due to pulmonary hemorrhage, sepsis, or multiple organ failure. Significant predictors of mortality of leptospirosis are low platelet count, prolonged prothrombin time, and parenchymal infiltrates on chest X-ray.

2. The role of hemoperfusion in sepsis management of leptospirosis

According to the inflammatory mechanisms in sepsis, the cytokines storm plays an important part in the disease progress. Both the occurrence and management of cytokine storms are closely related to the immune response behavior. While the pro-inflammatory arm reaches the peak (Phase B in the Picture), it would be likely to gain the maximal benefits from extracorporeal therapy. For severe leptospirosis patients, ECMO is conducted for pulmonary hemorrhage, while HA330 hemoperfusion plus RRT is conducted for sepsis in the treatment protocol.
The experience shows that hemoperfusion therapy for patients with severe leptospirosis with renal failure and pulmonary hemorrhage is a useful method to support the management of AKI in critically ill patients. The results turned out:

1) 30% mortality among patients with pulmonary hemorrhage and dialysis–dependent AKI.
2) The SOFA scores significantly decreased by the 3rd HP
3) Procalcitonin significantly decreased by the 3rd HP
4) Inotropes were tapered off by the 1st HP

By improving the organ function, stabilizing the hemodynamic and controlling the inflammatory status, HA330 hemoperfusion cartridge is useful to prevent complications in these patients with multi-organ failure.

3. HA330 hemoperfusion therapy in COVID-19

Indications for Hemoperfusion for HA 330 are:
- Severe or critical COVID
- CXR - multilobar or diffuse infiltrates plus any one of the following such as increasing Ferritin, increasing LDH, lymphopenia, High D- Dimer, Increasing HsCRP, etc.

HA330 hemoperfusion is based on 4 cartridges therapy while on Day 1 there are 2 cartridges every 12 hours apart and on Day 2& 3 each day 1 HA330 cartridge. Patients are commonly seen on hemodialysis with hemoperfusion because it is a kidney department with ESRD patients. Duration for hemoperfusion is 3 hours. The blood flow rate is 250 ml/min and low dose heparin is used for anticoagulation. For non-ESRD and PD patients, the central line was inserted for the therapy. Outcomes of five patients showed that HsCRP, ferritin, and LDH decreased and lymphocytes increased after the 4 cartridges hemoperfusion therapy. CXR improvements were observed in both single hemoperfusion and hemoperfusion combined with tocilizumab cases.

Conclusively, HP may be an effective therapy in lowering inflammation in severe pneumonia due to COVID-19. Moreover, early HP, before invasive ventilation, might be more effective.