

Multiple-Organ Extracorporeal Support Therapies in Critically Ill Patients

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Abstract

The critically ill patient is capable of presenting a multiple organ dysfunction syndrome (MODS) caused by different diseases, which can be infectious (sepsis, septic shock) as well as non-infectious (pancreatitis, large surgeries, traumatic injuries, burn patients and brain injuries), this syndrome is characterized by global hemodynamic and organ perfusion alterations accompanied by an uncontrolled and marked inflammatory response unresponsive to pharmacological treatment due to which extracorporeal organ support can be a viable option. Acute renal lesion can occur in up to 60% of patients receiving intensive care, and close to 10% - 20% require renal replacement therapy (RRT) globally this can be provided as peritoneal dialysis (PD) or intermittent hemodialysis (IHD), continuous renal replacement therapy (CRRT), hybrid therapies known as sustained slow efficiency dialysis (SLED), which combines the benefits IHD and CRRT, slow continuous ultrafiltration (SCUF). Extracorporeal membrane oxygenation (ECMO) and extracorporeal elimination of CO₂, have been used more frequently lately, these are temporal artificial support used for respiratory and/or cardiac insufficiency that is refractory to conventional treatment. Acute liver failure in adults has a mortality rate close to 50% furthermore one-third of patients hospitalized for cirrhosis are likely to progress to acute liver failure which will drastically increase its mortality. Based on concepts of albumin dialysis, one of its most known is the following: Molecular Adsorbent Recirculating System (MARS), Fractionated Plasma Separation and Absorption—FPSA (Prometheus[®]) and also, hemoperfusion with different cartridges used in different extracorporeal therapies, used in liver failure, rhabdomyolysis, cytokine release syndrome and more in the context of the pandemic covid19. The objective of this review is to know the different extracorporeal therapies and the therapeutic utility in critical patients.

Keywords

MODS (Multiple Organ Dysfunction Syndrome), RRT (Renal Replacement Therapy), CRRT (Continuous Renal Replacement Therapy), SLED (Slow Efficiency Dialysis ECMO (Extracorporeal Membrane Oxygenation), ECCO2 (Extracorporeal Elimination of Carbon Dioxide), ARDS (Acute Respiratory Distress Syndrome), AKI (Acute Kidney Injury)

1. Introduction

Critically ill patients are known to be at risk of developing organ dysfunction during their stay within the intensive care unit, when this dysfunction compromises three or more organs this mortality can reach up to 90% [1]. Multiple organ dysfunction syndrome (MODS) can be classified as primary or secondary.

Primary MODS: the result of well-defined aggression wherein the organ dysfunction presents in an early stage and can be attributed directly to the aggression itself (e.g. kidney injury due to rhabdomyolysis).

Secondary MODS: organ dysfunction that is not a direct response to aggression itself, but a consequence of a host-regulated response (e.g. acute respiratory distress syndrome presenting in a patient with pancreatitis) [2].

Early deterioration of an organ's function is often followed by dysfunction or damage to other organs resulting in negative interactions with different systems [3] an example of this is the cardiorenal syndrome, hepatorenal syndrome, alterations within the cardiopulmonary circulation, which become a vicious cycle with deleterious consequences.

The different therapies available for multiple organ dysfunction syndrome include oxygenation and ventilatory support (invasive mechanical ventilation and non-invasive [MV], veno-venous (VV) extracorporeal membrane oxygenation [ECMO].

And extracorporeal carbon dioxide elimination [ECCO2], mechanical circulatory support (intra-aortic balloon pump, veno-arterial (VA) ECMO, percutaneous and surgical ventricular assist devices (PVAD) and total artificial heart), renal replacement therapy (RRT) and extracorporeal liver support (molecular adsorbent recirculating system, plasmapheresis and hemoperfusion [4].

MODS: defined as the acute and potentially reversible dysfunction of two or more organ systems that are triggered by multiple clinically diverse factors [5].

Presenting as a hypo-metabolic and immunosuppressed state with clinical and biochemical evidence of a reduced function of various organ systems of the body which develops after an injury or acute illness [6].

The mechanism of injury or infection implies a complex interaction of different interdependent factors, such as genetic factors and this generates differences of the gene expression and its proteome this could explain the individual differences seen in the likelihood of presenting MODS and its severity, also the im-

portance of patients' comorbidities making them more susceptible to organ deterioration [7].

Macrocirculatory changes resulting in systemic vasoplegia due to nitric oxide synthase induction secondary to inflammation and reduced delivery of oxygen (DO₂) to different tissues, microcirculatory changes producing microvascular thrombi, reduced red blood cell deformity, an increase in blood viscosity, endothelial and glycocalyx dysfunction [8].

The dysregulation of pro-inflammatory factors triggers a systemic inflammatory response mediated by multiple cytokines (for example, IL6, TNF alpha, IFN gamma), the coagulation cascade is activated by the tissue factor, endotoxins, cytokines and bacterial antigens, neuroendocrine factors which produce immunosuppression mediates the response to stress through the involvement of supra-renal hormones, a hypothyroid state due to the production of inverse T3 which is inert [9], mitochondrial dysfunction which could be mediated by humoral factors that contribute to cellular dysoxia and organ dysfunction, this organ dysfunctions plays a fundamental role in the underlying process of MODS [10].

Due to the complex and diverse nature of the physiopathology of this syndrome it is common for patients to develop negative interactions between the different organs the combined dysfunction of the kidney and liver is common and is described within the different types of hepatorenal syndromes [11].

Cardiac dysfunction resulting in cardiorenal syndrome, alterations of the cardiopulmonary circulation, acute respiratory distress syndrome, the intestine and kidney can also present reciprocal negative interactions and due to primary alterations within the host's intestinal microbiota and a disturbance of the intestinal barrier's function which leads to systemic inflammation [12].

2. Extracorporeal Therapies

The most frequent cause of severe acute kidney injury in the ICU is sepsis which oftentimes requires RRT in the form of intermittent hemodialysis (IHD), peritoneal dialysis (PD) and extended hemodialysis (sustained low efficiency dialysis: SLED) or CRRT (continuous renal replacement therapy) [13]. The objectives of renal substitution therapy (RST) are the elimination of solutes and water, and the correction of electrolyte abnormalities and the normalization of acid-base alterations in some observational studies involving septic patients being treated with RST can present a rapid and significant improvement of their hemodynamic state, with a reduced need for vasopressor support few hours after the implementation of an extracorporeal circulation [14].

Regarding the continuous modalities of renal replacement therapy (CRRT), these include continuous veno-venous hemofiltration (CVVH), continuous veno-venous hemodiafiltration (CVVHDF), hybrid therapy (HT) which a recently discovered modality of acute renal replacement therapy SLED (daily sustained low efficiency dialysis), prolonged intermittent hemodialysis [15] which combines the benefits of intermittent hemodialysis pertaining to solute removal and the hemodynamic stability related to CRRT (**Figure 1**).

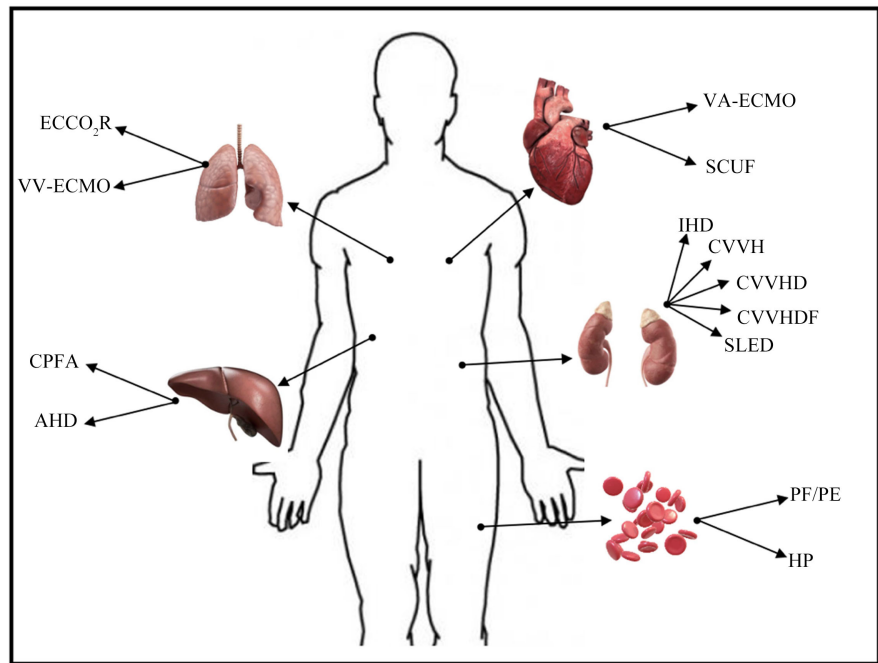


Figure 1. Schematic representation of extracorporeal therapy methods. ECCO₂R, extracorporeal extraction of CO₂; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; SCUF, slow continuous ultra-filtration; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration; SLED, sustained low efficiency dialysis; IHD, intermittent hemodialysis; PF, plasmapheresis; PE, plasma exchange; HP, hemoperfusion; AHD, albumin hemodialysis; CPFA, coupled plasma filtration adsorption; VVECMO, veno-venous extracorporeal membrane oxygenation.

The KDIGO (Kidney Disease Improving Global Outcomes) guidelines for acute kidney injury (AKI) recommend the use of CRRT for patients presenting with hemodynamic instability or intracranial hypertension this is based on clinical factors specific to the patient [16] these advantages from the CRRT have not been demonstrated in randomized clinical trials.

A recent meta-analysis did not encounter any significant difference in the renal recovery and in-hospital mortality during ICU admission between patients presenting with AKI receiving CRRT and those receiving SLED, furthermore those patients with AKI receiving CRRT had a higher mortality rate during ICU admission, compared to those who received IHD. All three modalities have their own advantages and disadvantages. This highlights the need for a well-designed more rigorous clinical trial with large cohorts to explore the differences related to renal recovery, in-hospital mortality and ICU mortality rate comparing the different types of RST [17].

3. Hemoperfusion

Sepsis is one of the main causes of morbidity and mortality within the intensive care units worldwide, this is due to organ dysfunction [18]. This implies an early activation of pro- and anti-inflammatory pathways, through a dual mechanism

which induces cytokine-mediated cellular damage and a state of gravely deteriorated immunity (immuno-paralysis) [19]. Mediators of pro-inflammatory actions, such as tumoral necrosis factor alpha (TNF- α) interleukin-1, interleukin-6 and anti-inflammatory cytokines such as interleukin-10, interleukin-4. Both responses can take place at the same time and not in a sequential manner as was previously thought [20].

These pro-inflammatory cytokines are the main factors responsible of the activation of leucocytes, oxidative stress, glycocalyx and endothelial dysfunction as well as alteration of the activation pathway of nitric oxide, which results in a reduced deformability of the red blood cell and an alteration of the hemorrheology, loss of microvascular tone, microcirculatory shunting, tissue edema and a shortage of oxygen extraction [21] [22].

Due to the presence of these different sepsis phenotypes and the massive release of cytokines. Various extracorporeal blood purification therapies have been proposed as a strategy to improve the results of septic patients, weakening the systemic expression of pro-inflammatory factors and anti-inflammatory mediators and restoring the homeostasis of the immune system [23] hemoadsorption places sorbents in direct contact with the blood and the extracorporeal circuit, the solutes are attracted by the sorbents through a series of hydrophobic interactions and ionic attractions, it is important that this elimination is non-specific for a wide spectrum of inflammatory mediators [24], there are different cartridges available on the market currently, the technology (CytoSorbents Corporation Monmouth Junction, NJ, USA) is based on cartridges containing copolymer pearls of biocompatible polystyrene-divinylbenzene capable of eliminating various cytokines *in vitro* as well as *in vivo* [25]. This preclinical data in a sepsis mouse model is encouraging, as it shows a reduction in circulating cytokines, an increase in arterial pressure and improved short-term survivability rates with hemadsorption Cytosorb [26] however these studies are observational, with limitations, this preliminary data justifies more investigation to clarify the mechanisms of this effect in a larger environment [27].

4. Plasmapheresis

Plasmapheresis is an extracorporeal filtration technique in which the plasma is separated from its remaining blood components and is exchanged for a replacement liquid, generally fresh frozen plasma (FFP) or albumin, according to the disease, the general of state of coagulation and the immune system [28] [29] the basic premise of therapeutic apheresis is centered around eliminating or reducing the levels of certain pathological substances within the plasma, which could be auto-antibodies, immune complexes, cryoglobulins, light myeloma chains, endotoxins, lipoproteins containing cholesterol or other substances [30].

The diseases known to cause MODS, in which an overwhelming systemic immune response is triggered by the release of pro-inflammatory cytokines and damage associated molecular patterns (DAMP) as can be seen in the case of

acute liver failure, where acute necrosis and at times a massive release of the hepatocytes [31] [32] the extracorporeal elimination of circulating excess pro-inflammatory molecules could be a therapeutic option.

It has been used with success in patients with severe sepsis, MODS and fulminant SARS-CoV infection, however its benefits in severe ARDS are not clear [33].

The use of plasmapheresis with a variety of adsorption cartridges has been a subject of various cohort studies and clinical trials, it is supposed that its benefit comes from its reduction of inflammatory cytokines, and the cytokine release syndrome (CRS) [34] [35] [36] (See **Table 1**).

Small observational studies have shown that plasmapheresis when used with adsorption cartridges is associated with a discrete improvement in the biomarkers related to cytokine release syndrome (CRS), ARDS, septic shock and MODS related to fulminant COVID-19, it also appears to be of low risk despite the severity of these patients. More randomized clinical trials of larger scale are required to confirm the findings of these observational studies [37] [38].

5. Liver Dialysis with Albumin/Continuous Adsorptive Plasmafiltration

The estimated frequency of liver failure, either as an isolated case of acute liver failure or as an acute worsening of a chronic form of liver failure across all age groups in the United States is approximately of 17 cases per 100.000 inhabitants annually, with a mortality of 50% [39].

Within this context and due to the shortage of organs available for transplant, different efforts have been made to find therapeutic alternatives for these patients awaiting a new organ (bridge to transplant therapy) or for patients not in need of a transplant but with a possibility of recovery.

Two systems are used, the Molecular Adsorbent Recirculating System (MARS), the single pass albumin dialysis system (SPAD) and a fractionated plasma separation and adsorption system—FPSA (Prometheus). These systems are based on the concept of albumin dialysis and, therefore, are capable of eliminating albumin-linked toxins which accumulate in the context of liver failure.

Table 1. Cytokine release syndrome criteria (one or more of the following criteria).

CRP > 100 mg/l or more than 50 mg/l that has doubled in the last 48 hours

Lymphocyte recount < 0.6×10^9

Interleukin-6 (IL-6) > 3 its normal limit

Ferritin > 300 µg/L

DHL > 250 U/L

D dimer > 1 µg/L.

CRP: C-reactive Protein; DHL: deshydrogenasa lactic.

The difference between these two systems (MARS) and the fractionated plasma separation and adsorption system: FPSA (Prometheus) is that MARS utilizes a solution of exogenous albumin and the available Prometheus system allows for the patient's own albumin to enter the first circuit using the AlbuFlow[®] (Molecular cut-off of 250 kDa), this albumin is reactivated and returns to the circulation using a neutral resin adsorbent (Prometh[®] 01) and an anion exchange column (Prometh[®] 02), afterwards, the blood enters a second circuit where it is treated through conventional high-flow hemodialysis prior to returning to the patient [40].

There are no precise recommendations on the most effective moment to start these systems of artificial liver support, meanwhile and in absence of alternative options to support this vital organ, it is difficult to criticize the cautionary use of these safe artificial liver devices, as a "rescue" therapy for patient suffering from acute liver failure [41].

6. Venous-Venous Ecmo (VV) – Venous-Arterial (VA)

Extracorporeal membrane oxygenation is designed to provide a temporal extracorporeal respiratory support through the use of artificial oxygenation membranes in the case of pulmonary failure not responsive to conventional treatment, with clear indications according to current guidelines (ELSO) [42].

In patients with respiratory insufficiency, the common approach is through a VVECMO bypass, in contrast to VA-ECMO it is a temporal mechanical circulatory support it is most frequently used in patients with refractory cardiogenic shock and cardiac arrest [43].

Although septic shock in adults has generally been described as a vasoplegic shock or distributive with high cardiac output [44], a possible complication of septic shock is sepsis-induced cardiomyopathy, this condition is often characterized by a reversible left ventricular dilation accompanied by a reduced left ventricular function [45] which results in a sepsis-induced cardiogenic shock, theoretically the use of VA-ECMO could be considered, however it is a controversial treatment strategy for septic shock. In-hospital mortality rates reported for patients with sepsis-induced cardiogenic shock receiving VA-ECMO were quite inconsistent making it difficult to conclude its safety and benefits [46].

Myocardial infarction is the most common cause of cardiogenic shock, accounting for 80% of total cases [47]. The most severe cases can be treated with mechanical circulatory support as a bridge to recovery of cardiac function or bridge to cardiac transplant, among these is VA-ECMO [48].

Although non-randomized clinical trials suggest advantages in the survival rates of patients with cardiogenic shock receiving early VA-ECMO. Nevertheless 39% of the cases developed complications due to an increased left ventricular afterload which could affect the recovery rate of the myocardium, severe pulmonary edema [49].

A recent meta-analysis included 3997 patients, among them 1696 (42%) received VA-ECMA combined with a concomitant strategy for left ventricular un-

loading, such as intra-aortic balloon pump or other ventricular devices and found a reduction in mortality [50]. Reperfusion and early implantation of circulatory support strategies are essential in improving the overall results in cardiogenic shock.

7. Extracorporeal Carbon Dioxide Removal (ECCO2)

These devices remove CO₂ from the venous blood, through a membrane which is similar to those of ECMO devices, its fundamental difference is based on the usage of much lower blood flows and therefore arterial or venous cannulas of smaller sizes [51] its main utility is for patients with severe ARDS that develop important hypercapnia from a protective ventilation strategy [52].

Hypercapnia generates pulmonary vasoconstriction which in turn will develop into pulmonary hypertension that contributes to the appearance of cor pulmonale in patients with ARDS and increase its mortality [53].

In comparison with VV-ECMO, where a lower number of complications has been associated with the newer systems due to a lower degree of invasiveness and due to technological advances. also the need for lower blood flow rates of 0.4 to 0.1 L/min required for the elimination of CO₂ which can be achieved with cannulas of sizes between 14 and 18 Fr [54].

Table 2. Available extracorporeal support devices and strategies.

TYPE OF THERAPY	MECHANISM	OBJECTIVE
HEMOPERFUSION	The passage of the blood through a column containing adsorbent particles (activated charcoal or resin).	Strategy to improve the evolution of septic patients, reducing the systemic expression of pro-inflammatory factors and anti-inflammatory mediators and restoring the balance of the immune system.
PLASMAPHERESIS	Separation of the blood components and exchanged for a replacement fluid, usually fresh frozen plasma (FFP) or albumin, depending on the disease, the general state of coagulation and the immune system.	The basic premise of therapeutic apheresis focuses on eliminating or reducing the levels of certain pathological substances in the plasma, which can be autoantibodies, immune complexes, cryoglobulins, light myeloma chains, endotoxins, cholesterol-containing lipoproteins or other substances.
LIVER DIALYSIS WITH ALBUMIN /CONTINUOUS ADSORPTIVE PLASMAFILTRATION	Eliminate albumin-bound toxins that accumulate in the context of liver failure. Actually exist the molecular recirculation adsorbent system (MARS), the one-step albumin dialysis system (SPAD) and a fractionated plasma separation and adsorption system - FPSA (Prometheus).	There are no precise indications on the opportune use. In the absence of alternative options to support this vital organ, it is difficult to restrict the cautious use of these safe artificial liver devices, as "salvage therapy" for patients suffering from acute liver failure. There are no precise indications on the opportune use.
VENO-VEINUS ECMO (VV) – VENO-ARTERIAL (VA)	Extracorporeal membrane oxygenation provide temporary extracorporeal respiratory support through the use of artificial oxygenation membranes in the case of pulmonary insufficiency that does not respond to treatment.	Improve cardiovascular and respiratory function with the extracorporeal oxygenation. In patients with respiratory insufficiency the VV-ECMO bypass is the most used. The use of VA-ECMO is frequently used in patients with refractory cardiogenic shock and cardiac arrest.
CARBON DIOXIDE REMOVAL (ECCO2)	Extract CO ₂ from venous blood, through a membrane similar to those of ECMO devices, its difference is based on the use of much lower blood flows and therefore smaller arterial or venous cannulas.	The utility is for patients with severe ARDS who had an important hypercapnia from a protective ventilation strategy.

ECMO: extracorporeal membrane oxygenation; ARDS: acute respiratory distress syndrome.

It has become a therapeutic option that's situated between conventional ventilatory support and total respiratory support (ECMO), it's a therapeutic option that must be considered in patients with severe ARDS, however more future clinical trials are needed to prove its effectiveness and safety.

8. Conclusions

Multiple organ dysfunction syndrome is very common among critically ill patients with an elevated mortality rate and its annual incidence is close to 51%, this incidence has been rising during the last ten years, no specific treatment exists [5].

Advances within the area of multiple-organ extracorporeal therapy have not been able to change the mortality rate in a significant way [55] new machines with improved technologies are needed to avoid negative interactions between the different organs, as well as more studies looking to establish an ideal moment for these interventions, to find out if early implementation has an impact in the recovery of organs and to optimize the use of resources and improving results.

The Prevention It is the best treatment for multiple organ dysfunction syndrome. Fast and optimal volume at resuscitation, adequate protection myocardial in cardiac operations, proper nutrition detection and adequate treatment of low spending cardiac arrest, appropriate use of antibiotics (Table 2).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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