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Apheresis and COVID-19 in intensive care unit (ICU)

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is a contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first known case was identified in Wuhan, China, in December 2019. The disease has since spread worldwide, and on March 2020 the World Health Organization (WHO) declared it as pandemic, causing a public health crisis. Symptoms of COVID-19 are variable, ranging from mild symptoms like fever, cough, and fatigue to severe illness. Elderly patients and those with comorbidities like cardiovascular disease, diabetes, chronic respiratory disease, or cancer are more likely to develop severe forms of the disease. Asymptomatic infections have been well documented. Accumulating evidence suggests that the severity of COVID-19 is due to high levels of circulating inflammatory mediators including cytokines and chemokines leading to cytokine storm syndrome (CSS). Patients are admitted in ICU with severe respiratory failure, but can also develop acute renal failure and multi organ failure. Advances in science and technology have permitted the development of more sophisticated therapies such as extracorporeal organ support (ECOS) therapies that includes renal replacement therapies (RRTs), venoarterial (VA) or veno-venous (VV) extracorporeal membrane Oxygenation (ECMO), extracorporeal CO2 removal (ECCO2R), liver support systems, hemoperfusion, and various blood purification devices, for the treatment of ARDS and septic shock.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first known case was identified in Wuhan, China, in December 2019. The disease has since spread worldwide, and on March 2020 the World Health Organization (WHO) declared it as pandemic, causing a public health crisis. SARS-CoV-2 is a zoonotic virus, genetically clustered within Betacoronavirus subgenus Sarbecovirus. Its genome structure, transmission mode, and pathogenesis is similar to Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS) [1].

A continual problem is that viruses naturally mutate as they attempt to survive. At the time of writing there are almost 459 million global cases of COVID-19. Around 392 million people had recovered from the disease, while there had been around six million deaths, making it one of the deadliest viruses in history. Indeed, the disease mortality rate is 1 %, which is close to influenza pandemic in 1918 (2 %). On the other hand, it is much harder to control than SARS and MERS [2].

Symptoms of COVID-19 are variable, ranging from mild symptoms like fever, cough, and fatigue to severe illness. Elderly patients and those with comorbidities like cardiovascular disease, diabetes, chronic respiratory disease, or cancer are more likely to develop severe forms of the disease. Asymptomatic infections have been well documented. One review performed prior to the introduction of COVID-19 vaccination estimated that 33 % of people with SARS-CoV-2 infection never develop symptoms [3]. Most people infected will experience mild to moderate respiratory illness and recover without requiring special treatment. However, almost 14 % of patients develop a severe disease that requires hospitalization and oxygen support and 5 % require admission to an intensive care unit (ICU) [4]. Among critically ill patients, 67 % present with additional organ dysfunction syndrome and their mortality rate is 49 % [5].

Patients with poor prognosis usually die from complications of acute respiratory distress syndrome (ARDS), multiorgan failure (MOF) and blood clots [6]. Accumulating evidence suggests that the severity of COVID-19 is due to high levels of circulating inflammatory mediators including cytokines and chemokines leading to cytokine storm syndrome (CSS). It can cause complications including ARDS, shock, acute heart damage, and acute renal failure [7]. It has been demonstrated that ICU patients have higher levels of cytokines [8].

For the first two years of the pandemic, no specific and effective

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treatment was available. Since December 2020, several COVID-19 vaccines have been approved and are being used in various countries, improving the course of the pandemic. Also, treatments aiming at reduction of viral load with novel antiviral drugs and attenuation of the inflammation with monoclonal antibodies have been developed. For non hospitalized patients with mild to moderate disease who are at high risk of progressing to severe disease, the European Medicines Agency's (EMA) have approved the oral antiviral Paxlovid (ritonavir- boosted nirmatrelvir) and the molnupiravir and the immunodulator therapy baricitinib. Dexamethasone and remdesivir are used in patients who need hospitalization and supplemental oxygen, while the monoclonal antibody- based therapy tocilizumab that inhibits the Interleukin-6 (IL-6) receptor is recommended in rapidly progressive cases.

Patients are admitted in ICU with severe respiratory failure, but can also develop acute renal failure and multi organ failure. Advances in science and technology have permitted the development of more sophisticated therapies such as extracorporeal organ support (ECOS) therapies that includes renal replacement therapies (RRTs), venoarterial (VA) or veno-venous (VV) extracorporeal membrane Oxygenation (ECMO), extracorporeal CO2 removal (ECCO2R), liver support systems, hemoperfusion, and various blood purification devices, for the treatment of ARDS and septic shock [9]. During Covid-19 pandemic, extracorporeal blood purification (EBP) methods using different types of membranes, are proposed as promising adjuvant therapy, for elimination of toxins and inflammatory mediators in an effort to restore immune balance [9]. In this review we will focus on the potential role of the EBP therapies in suppressing the excessive inflammation in those Covid-19 patients who are at high risk for organ dysfunction.

2. Cytokine storm syndrome (CSS)

Cytokine storm syndrome is a condition of uncontrolled systemic hyper-inflammation caused by increased cytokine levels, leading to multi-organ failure and even death. The concept of cytokine storm was initially recognized in acute graft-versus-host disease in the process of hematopoietic stem cell transplantation [10]. Also, may occur in various diseases, such as malignancy, rheumatologic disease, and sepsis [10]. Upon outbreak of the pandemic there was the clinical suspicion that the rapid clinical deterioration and high mortality in severe Covid-19 could be related to cytokine storm. CSS is characterized by an excessive inflammation, immune dysregulation, hypercoaguable state and endothelial dysfunction with high levels of CRP, ferritin and D-dimers [11].

Several studies demonstrated that blood levels for various cytokines, such as IL-1b, IFN-γ, IFN-γ-induced protein 10 (IP10), and monocyte chemoattractant protein 1 (MCP1), were elevated in Covid-19 patients [11]. Of note, among the elevated inflammatory proteins, IL-6 is significantly elevated in Covid-19 patients and is highly correlated with poor outcome [10]. IL-6 has also been correlated with need for mechanical ventilation and thrombotic condition [12]. In addition, patients admitted to ICU had higher cytokine levels than those non requiring ICU treatment [8]. Other studies demonstrated the presence of inflammatory infiltrates in various tissues of Covid-19 patients, both from bioptic and autoptic samples [11]. In fact, even though in most cases, disease is self-limiting with flu-like symptoms, in predisposed subjects the infection of airway epithelial cells can cause a rich inflammatory cell infiltrate, consisting of neutrophils, macrophages, CD8 + and CD4 + T lymphocytes with massive release of cytokines leading to bilateral pneumonia, ARDS, and multi-organ damage [11].

Several pathogenetic mechanism have been proposed in order to explain the development of cytokine storm during SARS-CoV-2 infection. The innate immune system may not be able to efficiently clear the infected cells and, on the contrary, could favor the replication of the virus. It has been demonstrated that infected cells show an impaired capacity to produce interferons, which are signaling proteins released from host cells in order to strengthen their anti-viral defense. Simultaneously, they produce high levels of neutrophil- and macrophage-recruiting chemokines [13]. In addition, an another pathogenetic mechanism associated with severe disease and death is the production of autoantibodies against several immuno-modulatory proteins and, in particular, the presence of anti-type I interferon antibodies [14].

Also, the renin-angiotensin-aldosterone system (RAAS), has been implicated in the pathogenesis of COVID-19. In fact, the main receptor used by SARS-CoV-2 to enter in human cells is angiotensin-converting enzyme 2 (ACE 2), which is a transmembrane glycoprotein with enzymatic activity and integral part of RAAS. It is known that the local RAAS can mediate pro-inflammatory, prothrombotic, and profibrotic effects, through activation of the angiotensin II receptor type 1 (AT1 receptor) by angiotensin II. However, ACE2 counterbalances angiotensin II activity through conversion of angiotensin II to angiotensin 1–7. It is believed that SARS-CoV-2 virus, after binding and subsequent endocytosis of the ACE2-virus complex causes downregulation of ACE2 molecule in the host cell membrane, resulting in an uncontrolled activity of AngII (continuous stimulation of AT1R), due to loss of ACE2 regulatory activity on RASS. Based on the above data, it has been hypothesized that the loss of anti-inflammatory, antithrombotic, and anti-fibrotic effects mediated by ACE2, may contribute to the onset of the cytokine storm and the thrombotic state of the disease [11].

3. Apheresis techniques

Several treatments have been used in order to moderate the cytokine storm generated by SARS Covid-19 virus, however no specific treatment recommendation has been developed until now. Recently, several treatments based on blocking cytokines signaling pathways, such as interleukin (IL)- 1 and IL-6 or Janus kinase (JAK) pathway have been used with promising results [10]. Nevertheless, it is rather complicated to target multiple cytokines via pharmaceutical agents. Given the uncontrolled immune response resulting in continuous activation of immune cells, removing cytokines from bloodstream could be a promising treatment.

Several studies have demonstrated that the traditional continuous renal replacement therapy (CRRT) even in high doses, seem not to be able to remove efficiently inflammatory mediators produced in sepsis and to improve patient outcome [15]. The main reason could be the fact that traditional blood purification technologies are based on mechanisms of convention and diffusion and thus the removal of high molecular substances, such as cytokines, becomes non effective [16]. Even though, traditionally EBP methods have been recommended as adjuvant therapy for a serious overdose from toxins such as salicylates, lithium, ethylene glycol and methanol [17], they were also used for treatment of severe disorders refractory to conventional therapies, such as fulminant liver failure, collagen diseases, and transplant rejection [18].

Over the last years, more sophisticated devices have been developed focused on the optimization of adsorption materials and anticoagulation techniques, in order to improve the removal of endotoxins and inflammatory mediators, such as cytokines/chemokines and coagulation factors [16]. Although bacterial sepsis is not a common feature of Covid- 19 infection, critically ill patients may also benefit from extracorporeal blood purification (EBP) therapies due to severe cytokine storm syndrome (CSS). Moreover, there are cases that Covid-19 patients have superimposed sepsis. In fact, the mechanism of organ damage seems to be quite similar to the immune dysregulation and the cytokine release syndrome observed in septic patients [9]. As mentioned before, CSS could lead to multiorgan dysfunction. Further organ damage may be induced by intravascular coagulation or micro- and macrovascular thrombosis [9].

During pandemic, several single-center reports and case series, have focused on the potential reset of immune homeostasis in Covid-19 patient with CSS, through EBP methods and many of them revealed a potential profit [9]. There are many extracorporeal blood purification techniques but in this review we will focus on the methods with a potential profit for covid-19 patients including: a) Therapeutic plasma

exchange (TPE), b) Haemoperfusion techniques, c) CRRT with surface-modified AN69 (Oxiris) or polymethylmethacrylate membranes (PMMA) that can remove molecules by adsorption and d) CRRT with medium cut-off or high cut-off membranes that remove molecules by diffusion or convection [19].

4. Therapeutic plasma exchange (TPE)

Therapeutic plasma exchange (TPE) is a non-selective blood purification method that removes plasma from the blood cells and replace it with fresh frozen plasma or and/or albumin and crystalloid solution, using two techniques centrifugation or filtration. With centrifugation technique, blood is spun and blood components are separated into layers based on their different densities. Its major advantage is that there is no limit on the size of the molecules being removed. With filtration plasmapheresis, whole blood passes through a filter to separate the plasma components from the cellular element of blood. It uses highly permeable membrane with pore sizes between 0.2 and 0.6 μm for large-molecular-weight molecules (greater than 500 kDa).

However, this method could be ineffective for the removal of certain molecules larger than existing available filters, as for example von Willebrand factor multimers that can measure up to 20,000 kDa [20]. In clinical practice, TPE is commonly used by nephrologists and intensivists, in order to remove harmful molecules, such as injurious autoantibodies, clotting factors, immune complexes and cytokines from the plasma [21]. TPE is indicated as first line therapy for thrombotic thrombocytopenic purpura (TTP), Guillain-Barre, Goodpasture's syndrome, antineutrophil cytoplasmic antibody (ANCA)-associated rapidly progressive glomerulonephritis and antibody-mediated renal transplant rejection [21].

The application of TPE in patients with sepsis has been studied previously with the hypothesis that the removal of toxic cytokines could modulate the adverse immune response to infection. Busud et al. in a prospective randomized trial proposed that plasmapheresis could be a safe and beneficial method, correlated with lower mortality in patients with gram negative sepsis [22]. However, a subsequent meta-analysis assessing the effect of the method on survival in patients with sepsis or septic shock did not found any survival benefit, detecting bias and criticizing the small sample of size of the previous study [23]. In addition, plasmapheresis technique has been used as rescue therapy during the 2009 H1N1 influenza A outbreak in three pediatric patients with severe ARDS and hemodynamic instability, with fully recovery from their illness [24].

Similarly, since the outbreak of Covid-19 pandemic, there have been reports suggesting that TPE might be a rescue therapy in a severe COVID-19 patient with ARDS and cytokine storm [25–27], demonstrating improved cytokines and coagulation markers levels immediately after TPE procedure. Also clinical studies examined the clinical effect of TPE on critically ill Covid-19 patients. The first reported retrospective study was conducted on invasively ventilated patients and hemodynamically unstable receiving >2 vasopressors, which showed the greatest mortality benefit in patients treated with TPE (47.8 %) compared with patients receiving standard therapy (81.3 %) [28].

In comparison, Kamran et al., analyzed retrospectively a larger sample size −280 hospitalized patient- who developed CSS at various stages of illness (moderate, severe and critical cases), and showed that patients treated with TPE had superior 28-day survival rate 91 % vs. 62 %; $p < 0.01$) and reduced median duration of hospitalization (10 days vs. 15 days; $p < 0.01$). Also an earlier use of the method had a significant benefit on survival [29].

Another retrospective study suggested application of the method among patients with high D-dimer (≧ 2 mg/L) levels, as TPE group had a significantly lower mortality rate. Also, D-dimer, ferritin, IL-6, C- reactive protein (CRP), and procalcitonin levels were significantly decreased after three consecutive TPE sessions [30]. Dealing with same clinical question Faqihi and colleagues designed a randomized controlled trial (RCT), enrolling 43 patients treated with standard therapy and TPE and 44 with standard therapy, showed that the duration of mechanical ventilation (15 days vs 19 days, $p < 0.01$) and ICU stay (19 days vs 26 days, $p = 0.02$) was significantly reduced in TPE group. However, the 35-day mortality rate was not significantly different in the two group of patients [31].

More sophisticated technique such as Coupled plasma filtration and adsorption (CPFA) was developed for the management of sepsis in 1990 s. The circuit consists of a plasma filter and a CRRT dialysis hemofilter connected in series. Initially the plasma of the patient passes through the plasma filter which is a hydrophobic polymer resin adsorbent cartridge with a high affinity for inflammatory cytokines (such as IL-1, TNF-a, IL-6, and IL-10) and endotoxins. Then, the filtered plasma is returned to the patient through a dialysis hemofilter with further solute and fluid removal [32]. Although CPFA is a promising method there are not enough data in treating Covid-19 patients. Ciftci et al., in a case report used CPFA method in two patients with Covid-19 and improvement was observed in the clinical status and cytokine levels [33]. Similarly, in a retrospective study of 20 patients CPFA was demonstrated to be a well-tolerated and safe method with beneficial effects on oxygenation and sofa score through removal of pro-inflammatory mediators [34].

Another adjunctive potential extracorporeal therapy is lectin affinity plasmapheresis. It was used in the past for the treatment of other viruses like MERS and Embola. Blood runs into a plasma filter, and the filtered plasma containing viral copies passes through a matrix of lectins. Enveloped viruses like coronovirus have a high affinity with lectins. Some viral copies are captured and the viremia is reduced. Some experts have proposed this therapy as a promising therapy for Covid-19 disease [7], however until now there are not available data on bibliography.

5. Hemoperfusion methods

Hemoperfusion is an extracorporeal blood purification therapy that was firstly used for uremic toxin removal in dogs in 1940 [35]. Over the years its use was expanded in several clinical applications. The mechanism of action is the elimination of circulating inflammatory mediators and endotoxins through attachment to an absorptive membrane. The sorbent system is made up of a biocompatible fixed bed, or cartridge, which contains the adsorbent particles. There are two major types of adsorbent materials, including the activated charcoal and the resins. Charcoal has greater affinity for water-soluble molecules, whereas resins have higher affinity to lipid-soluble molecules [35].

Even though its initial use was the elimination of toxin and drugs, the improvement of biocompability and absorptive capacity of the hemoperfusion methods, allowed its widespread use in ICU in the context of septic shock. Based on the above data, many hospitals in various countries have investigated the potential benefit of hemoperfusion methods as adjuvant therapy for critically ill Covid-19 patients, including Cytosorb, Polymyxin B Hemoadsorption and H330/H380 cartridges hemoperfusion [35].

6. Cytosorb

The Cytosorb is a non-selective extracorporeal purification therapy based on hemoabsorption, that through nanotechnology, can modulate immune response. It is a highly porous biocompatible polymer that can bind and remove from the blood a broad spectrum of hydrophobic substances with molecular weight of up to 55 kDa, like cytokines and other inflammatory mediators. It was originally designed for conditions with increased cytokines plasma concentration such as septic shock or other noninfectious hyperinflammatory conditions such as trauma, burns, and pancreatitis, but it also seems to be highly efficient with myoglobin and bilirubin removal without affecting larger beneficial substances like albumin, coagulator factors and immunoglobulins [36]. Also, the removal ability of the method is due to the fact that is concentration – dependent, where high plasma concentrations of substances

are cleared more efficiently than those with lower levels. As far as technical part is concerned, it is easy to install either as stand- alone hemoprefusion mode, or via intergration with a CRRT circuit or an ECMO [36].

CytoSorb was originally approved in the European Union (EU) in 2011, and since then, it has been safely used in >130.000 treatments worldwide, mainly for management of systemic hyperinflammation, refractory shock and cardiac surgery [36]. Also, reported cases with Hemophagocytic Lymphohistiocytosis (HLH) has been successfully treated with this method [37]. CytoSorb has been demonstrated to be a safe method that reduces plasma cytokine levels and vasopressor requirements in patients with sepsis or septic shock and normal kidney function as a stand-alone hemoperfusion therapy. Similar results have been demonstrated with CytoSorb as an adjuvant blood purification therapy in septic patients receiving dialysis and/or ECMO [32].

In pandemic Covid-19 era, Cytosorb was included in the guidelines treatment of several national medical societies. Firstly, Italian Society of Nephrology recommended CytoSorb use in combination with continuous renal replacement therapy (CRRT) in COVID19 patients with acute kidney injury (AKI) stage 3 [38]. On April 2020, the United States Food and Drug Administration (FDA) authorized the Emergency Use of CytoSorb in "critically ill COVID-19 patients with confirmed or imminent respiratory failure" [39]. The experts suggest that Cytosorb treatment should be used as adjuvant therapy when medical treatment is not sufficient, in unstable patients.

Therapy should not be delayed for more than 24 h after the diagnosis of a life-threatening Covid-19 [40]. The maximum time treatment per device is 24 h, and a new device should be used until clinical improvement on pulmonary and hemodynamic status is achieved. It is proposed that the clinical assessment should be made after 72 h of use, in order to decide whether to continue the therapy. Flow rate through the device is recommended to be between 150 mL/min and 700 mL/min. It is important to take into consideration that hydrophobic drugs may be removed by the device. Unfortunately date on removal of antiviral medication is scarce. Tocilizumab is not expected to be removed due to its large molecular weight (148 kDa) [39].

Even though there are no large randomized clinical trials (RCT), Cytosorb method was widely used worldwide in treating critically ill Covid-19 patients. There is a common finding among published data that is a safe and well tolerated method with a relative benefit as an adjunctive therapy [36]. Indications for starting Cytosorb therapy was most frequently severe ARDS and/or hemodynamic instability. Alharthy et al., retrospectively analyzed 50 COVID-19 patients with acute renal failure (AKI) treated with CRRT and Cytosorb and found significant reduction in vasopressor needs, Sequential Organ Failure Assessment (SOFA) score, lactate, IL-6, and ferritin levels, and an improvement in the PaO2/FiO2 ratio [40].

Similarly, results from clinical studies with a small number of Covid-19 patients treated with hemoperfusion using Cytosorb combined with vv-ECMO [41] or tosulizumab [42], showed a significant reduction in IL-6 in patients treated with Cytosorb. An interesting case series of nine non- intubated patients, where five of whom received Cytosorb treatment, demonstrated a better clinical course when hemoperfusion therapy was used. Even though the sample was limited the researchers suggested CytoSorb hemoperfusion as a potential adjuvant treatment in the early course of the disease [43]. On the contrary, other studies failed to show a better survival in patients treated with the method [44], or demonstrated even higher mortality when Cytosorb was combined with ECMO therapy [45,46], probably randomized trials with large number of patients could help to clarify whether this method improves the outcomes of these severe patients.

7. Polymyxin B Hemoperfusion (PMX-HP)

Polymyxine B Hemoperfusion (PMX-HP) is an absorbent method that uses polystyrene fibers with immobilized Polymyxin B. Polymyxin B is a polycationic antibiotic which binds the lipid A portion of the endotoxin and neutralizes its toxicity [32]. It selectively absorbs endotoxin, even when up to 95 % of the endotoxin in the body is lipid-bound [47]. It was developed in Japan in 1990 s and approved for use in Europe in 2002. Several randomized trials (RCTs) studied the efficacy of PMX-HP on survival of patients with septic shock, with the survival benefit to remain unclear. The Early Use of PMX-HP in Abdominal Septic Shock (EUPHAS) trial was the first RCT to examine the effects of the method on mortality. Use of PMX-HP demonstrated increase of arterial blood pressure, reduction of SOFA score and a lower mortality compared with conventional therapy, although the number of enrolled patients (64 pts) was relative small [48].

Unfortunately, two subsequent studies contradicted the above promising results. The ABDOMIX multicenter RCT with 243 enrolled patients after emergency surgery for peritonitis [49] and the EUPHRATES multicenter RCT of 450 patients with septic shock [50] failed to demonstrate survival benefit when using PMX-HP. Nevertheless, post hoc analysis of EUPHRATES trial excluded patients with septic shock and extreme endotoxin activity assay (EAA $\geq$ 0.9) and found that PMX-HP could be beneficial in septic shock patients with EAA $\geq$ 0.6–0.89 concerning mean arterial pressure, ventilator-free days and mortality [51]. Moreover, PMX-HP use was shown to be beneficial during the respiratory viral pandemic influenza (especially H1N1 and H5N1 subtypes) [52].

Based on the above data, in the COVID-19 pandemic, the method was used empirically. Health Canada's Interim Order has recently approved the use of kind of PMX-HP the Spectral's Toraymyxin (PMX) hemoperfusion cartridge to treat COVID-19, particularly in cases with severe ARDS and hemodynamic instability [35], however the data are limited in case reports or in single center trials. In Italy, PMX-HP treatment in twelve critically ill Covid-19 patients with septic shock due to secondary bacterial infection was accompanied with a reduced level of EAA, clinical improvement and stabilization of hemodynamic status, proposing that endotoxin adsorption could be salvage therapy in this group of Covid-19 patients [53]. Similar results had a case series from Japan with two patients with severe Covid-19 pneumonia [54].

In an interesting case report of a Covid-19 patient with ARDS and septic shock from gram negative infection, PMX-HP therapy was combined with continuous low flow extracorporeal CO2 removal therapy (ECCO2R) with favorable outcome, indicating a management with combined therapies in Covid-19 patients with multi-organ failure [55]. Other studies also revealed that PMX-DHP could decrease levels of IL-6 and other inflammatory chemokines [56].

8. Hemoperfusion HA330/ HA380

The HA type hemoperfusion cartridges HA330 and HA380 are widely used in China, for the removal of inflammatory mediators aimed at treating septic shock. H330 & HA380 are similar product with different surface capacity. The cartridges contain highly biocompatible sorbents and neutro-macroporous resin made of styrene-divinylbenzene copolymer. The pore size of adsorbing beads ranged from 500D to 60kD, giving them the ability to absorb various medium-sized factors, including most inflammatory cytokines (IL-1, IL-6, IL-8, and TNF-a) in addition to complements, free hemoglobin, and endotoxin [32,47]. HA 280 cartridge is another type of hemoperfusion able to absorb various inflammatory mediators used especially for autoimmune disease therapy [47].

Depending the device, these hemoperfusion cartridges can be used as stand-alone hemoperfusion therapy, or in combination with other EBP methods such as CRRT and ECMO, depending on patients' clinical condition. A series of published studies have demonstrated that use of HA 330 treatment reduced levels of pro-inflammatory cytokines in severe septic shock and acute lung injury and improved patients' hemodynamics, reduced the length of stay in ICU, and ICU mortality [35]. Data from single center reports of beneficial effects of the method on

covid-19 patients exist, but solid evidence is lacking. Soleimani et al. in retrospective study of 48 patients, 24 of whom received hemoperfusion with HA330 and HA 280 filters, improved respiratory distress and reduced CRP levels, but did not have any benefit on mortality [57]. In a case report a patient with clinical presentation of CSS due to Covid-19 infection underwent hemoperfusion with an HA380 cartridge, leading to increased level of SpO2, improvement of the patient's clinical condition and decrease IL-1, IL-6, IL-8, and TNF-α levels [58].

Asgharpour et al. reported an improvement in 60 % of patients with COVID-19 after hemoperfusion with cartridges (HA-280 and HA-230) combined with continuous vevo-venous hemofiltration (CVVHF) demonstrating decrease in IL-6 and CRP and increase in sO2 levels [59]. Also, a case series of six patients received three sessions of hemoperfusion HA380 showing improvement of clinical condition of 5 out of 6 patients with extubation and increase of PO2 and O2 saturation [60]. A single center prospective study in 29 patients had also respective results, with improved severity of organ failure (sofa score, X – ray), a benefit on mortality rate, even though the sample was small [61].

On the contrary, Shvadar et al. although demonstrated improvement on inflammatory and respiratory parameters after daily therapy with HA 380 for 3 consecutive days, failed to show a clear effect on prognosis [62]. In an interesting cross- sectional study Abbassi et al., tried to define the optimal time for hemoperfusion initiation based on severity of pulmonary disease. Hemoperfusion with HA280 cartridge was applied in 37 patients divided in 3 groups depending on the necessity of mechanical ventilation (MV) (no need for MV, before and after MV). The mortality rate was significantly lower in patients with no need for MV, whereas the duration of MV was lower when hemoperfusion initiated before MV. Applying hemoperfusion before the intubation, might reduce the need for MV. However, no impact on the duration of hospital and ICU stay was found. [63].

9. Oxiris and polymethyl methacrylate (PMMA) membranes

Oxiris (USA,Baxter) is hemofilration technique that consists of a medium cut-off (35–40 kDa) polyacrylonitrile (AN69) membrane coated with a positively charged polyethyleneimine (PEI) surface and a heparin graft (4500 iu per m^2) in order to reduce thrombogenicity. This allows membrane to absorb negatively charged endotoxin and cytokines, providing in parallel renal support through removal of fluids and toxins by diffusion and convection [32]. In vitro measurement of 27 inflammatory proteins compared Cytosorb with PMX-HA and Oxiris filters. The study showed that Oxiris removed both cytokines and endotoxin, similarly to endotoxin removal of PMX-HP and cytokine removal of CytoSorb [64]. However, there are not RCTs to support this finding. In septic shock patients this method could reduce SOFA score [65,66], improve hemodynamic state and reduce IL-6, IL-10, procalcitonin levels and endotoxin activity [66], though without survival benefit. The US Food and Drug Administration (FDA) gave emergency approval to the Oxiris membrane filter for the treatment of critically ill Covid-19 patients.

Data exist from case series and case reports. Premuzic et al. used the Oxiris filter in 15 covid-19 patients as a blood purification method or for renal support in patients suffering from AKI, demonstrating significant reduction of IL-6 and SOFA score and improvement of clinical and imaging (chest x-ray severity score) respiratory status [67]. Similarly, reduced of increased cytokines levels, hemodynamic stabilization and improvement of SOFA and APACHE scores was observed in five covid-19 patients after therapy with CVVHDF using Oxiris filter [68]. In addition, an observational study of 44 patients, therapy with Oxiris filter showed a reduction of the overexpressed inflammatory mediators but without a clear benefit on mortality rate [69]. On the contrary, Kang et al., proposed that CRRT with Oxiris filter when used in critically ill Covid-19 patients without AKI, may not attenuate the cytokine storm and should be used with caution in this group of patients [70].

Polymethyl methacrylate (PMMA) is a hemofilter with hollow fiber membrane which have an adsorption property for proteins including β2-microglobulin, interleukin-6, and albumin, and it can remove high molecular weight proteins not removed efficiently by classic hemodialysis or hemodiafiltration. Hemodialysis therapy using a PMMA dialyzer shows anti-inflammatory effects and improves anemia in hemodialysis patients [71]. Clinical experience with PPMA hemofilter in Covid-19 critically ill patients is limited compared to other devices. In a case report a Covid-19 patient with AKI was treated with CRRT through PMMA absorbing membrane demonstrated a beneficial outcome [72].

9.1. Pentrasorb CRP apheresis and adsorptive granulocyte and monocyte apheresis (GMA)

PentraSorb is a selective adsorption device that received certification of use in Europe in 2014. It is a resin filled with agarose beads, which are coated with phosphocholine in order to adsorb C-Reactive Protein (CRP) and almost no other proteins. It can lower CRP levels drastically in few hours. Clinical experience remains limited to a few clinical trials in patients with high CRP levels due to myocardial infraction [73]. It has been demonstrated that lowering CRP in myocardial infarction reduces systemic inflammation and cardiac tissue damage [73].

Studies on using Pentrasorb in patients with systematic inflammatory diseases such as acute pancreatitis, stroke, Chrohn's disease are currently ongoing [74]. In Covid-19 patients, the method was used in limited case reports, based on the hypothesis that activation of the macrophages and complement mediated by CRP could be responsible of pulmonary fibrosis and acute respiratory failure in Covid-19 [75]. Ringel et al., applied Pentrasorb on 4 continuous days in a non- intubated patient with high CRP levels showing improvement of patient's clinical condition without need of intubation [75]. In an another case report in patient with severe respiratory failure, the application of the method did not have a good outcome [76].

Adsorptive granulocyte and monocyte apheresis (GMA) is an extracorporeal circulation therapy designed for selective absorption of elevated and activated myeloid lineage cells, inducing immunomodulartory effects with decrease of inflammatory cytokines. It has been shown efficacy in inflammatory bowel disease and psoriatic arthritis [77]. In Covid-19 it has been used in one case report in a patient having comorbidity ulcerative colitis. Apart from the control of the colitis there was an unexpected improvement of the pulmonary symptoms and the septic shock [78]. Even though these methods seem to have a good safety profile, there are not enough data in order to propose them as a relevant therapeutic option for Covid-19 patients.

9.2. Acute kidney injury in critically ill Covid-19 patients

Acute kidney injury (AKI) is a severe complication in hospitalized Covid-19 patients. The incidence in ICU is estimated at 20–40 %. Among COVID-19 patients who develop AKI, about 1.5–9 % of them required CRRT [79]. In ICU, severe AKI occurs usually in the context of Multi Organ Failure. The pathophysiology of AKI in Covid-19 is poorly understood and seems to be multifactorial due to pre-renal and intrinsic renal causes. A direct renal damage could be mediated by the virus through the interaction with the ACE2 receptor which is expressed in tubular epithelial cells and podocytes. Another mechanism could be due to cytokine storm and immune dysregulation. Endothelial injury, diffuse proximal tubular injury and micro-vascular occlusion had been found in post mortem findings in Covid-19 patients [80].

A pre-renal etiology has been proposed due to aggressive diuretic therapy that is frequently used in these patients for homeostasis regulation. In addition, mechanical ventilation could affect renal function by reducing renal perfusion and glomerular filtration through increase in intrathoracic pressure, reduction of venous return (preload) and Cardiac Output [81]. Ottolina et al., found that patients who developed AKI were treated with higher PEEP levels than those who did not [81].

Like AKI in general population, in Covid-19 patients the management requires general and supportive measures and initiation of renal

replacement therapy (RRT) when considered necessary based on the KIDGO (Kidney Disease Improving Global Outcomes) guidelines, for example severe electrolyte imbalance and metabolic acidosis, uremia, uremic pericarditis, and hypervolemia. In particular, mechanically ventilated patients due to ARDS, may benefit from early initiation of RRT because volume overload in these patients could reduce the efficacy of ventilatory support [79]. In critically ill patients is generally preferred continuous RRT (CRRT) due to hemodynamically instability. Due to the hypercoagulable state of the disease the experts propose use of continuous venovenous hemodialysis (CVVHD) and continuous venovenous hemodiafiltration (CVVHDF) instead of continuous venovenous hemofiltration (CVVHF) because they have lower risk of circuit clotting and decreased filtration factor (FF) [9,82].

The CRRT dosing follows the recommendation of the KDIGO guidelines as in non Covid-19 patients with AKI with a minimum dose of 20–25 mL/kg/h. In severe sepsis a high volume hemofiltration with clearance dose > 35 mL/kg/h has been used in order to help remove inflammatory mediators, even though there are still conflicting views regarding the optimum dose [79]. The use of high cut-off (HCO) filters possessing pores with size > 60 kDa have a great permeability and could remove molecules with high molecular weight such as cytokines and other inflammatory parameters. The anticoagulation therapy that is proposed is regional citrate anticoagulation. It seems that is more efficacious than other anticoagulants because prolongs the extracorporeal circuit lifespan and reduces the risk of bleeding [9,82].

Nalesso et al. developed a protocol in seven Covid-19 patients with AKI using CVVHD with an HCO filter with regional citrate anticoagulation (RCA). Compared with the standard CVVH modality the writers proposed that this protocol have the advantages of minor effluent volume, fewer bag interventions and a lower FF with a higher filter lifespan [83]. The facility of use combined with safety and effectiveness is very important in particular in this Covid-19 patients where therapeutic practices such as prone position or ECMO therapy could be used in combination in order to treat ARDS.

10. Extracorporeal organ support (ECOS) in Covid-19 patients

Covid-19 infection, as mentioned before, can lead to Multi Organ Failure in the severe phase of the disease. Significant advances in biotechnology and science allows the development of new treatment strategies that include multi organ support. ECOS uses specific extracorporeal circuits and devices that support even partially except of kidneys, also heart, lungs and liver. Two or more methods can be combined in order to treat Multi Organ Failure in critically ill Covid-19 patients. Even though heart and liver damage are not common in these patients, there are available left ventricular assist devices in case of refractory heart failure or hemoperfusion devices for liver dysfunction and hyperbilirubinemia [7,82].

In Covid-19 disease the target organ is lungs. If lung protective ventilation and prone position are not effective in severe ARDS, extracorporeal membrane oxygenation (ECMO), could be used. ECMO devices exist in various forms according to the configuration of the circuit and components, such as veno-venous ECMO (VV-ECMO) and veno-arterial ECMO (VA-ECMO). It is an invasive technique that oxygenates the blood and removes CO2, while giving the lung the possibility to rest through lung protective ventilation. When ECMO therapy is applied combined with a CRRT method, it is preferable that venous access should be different in the two extracorporeal supportive methods, in order to minimize the clot formation in the circuit. However, some times the connection of the CRRT to ECMO, might be the only choice due to lack of vascular access [82].

The existing data concerning a beneficial role in Covid-19 patients are ambiguous. Initial data from China at the begging of the pandemic showed high mortality in patients treated with ECMO. Data from Extracorporeal Life Support Organization (ELSO) Registry and from a meta- analysis demonstrated that the mortality rate for patients who received ECMO support was lower around 39 % [84]. It seems that mortality is improving over time, probably due to stricter inclusion criteria for starting therapy with ECMO, thus favoring survival. The results were consistent with experience from randomized trials in non Covid-19 patients.

Furthermore, extracorporeal CO2 removal (ECCO2) is another option that can be performed in less severe cases to limit further Ventilator Induced Lung Injury (VILI). ECCO2R is a device with a polymethylpentene, hollow fiber, gas-exchanger membrane, certified to be used in conjunction with CRRT platforms for combined renal and respiratory support. In ICU low-flow ECCO2R (blood flow <500 mL/min) using CRRT platforms is a safe and easy to apply method that could be carried out any time of the day and might be an option for Covid-19 patients with hypercapnia [82].

11. Conclusion

COVID-19 is a new pandemic disease with high morbidity and mortality. In severe cases, it complicated with an excessive release of cytokines and patients die with ARDS and MOF. It has been demonstrated that high circulating cytokine levels and in particular IL-6 are responsible for the majority of symptoms in severe and critical patients. Therefore, based on the pathophysiological rational, the removal of the inflammatory proteins theoretically could prevent the organ damage. Mainly during the beginning of the pandemic where target therapy and vaccines were not existed, several centers adopted different extracorporeal blood purifications therapies as adjuvant therapy for the critically ill Covid-19 patients, demonstrating some beneficial effects and reduced progression of the disease.

However, the results were not always favorable and were based on case reports or clinical trials with limited sample of patients. The precise indication for extracorporeal blood purification methods in Covid-19 patients remains to be determined. Each case should be individualized according to the severity of the disease, the available treatment options and personnel training. Further research with randomized prospective clinical trials are needed in order to show the efficacy of these approaches.

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