Review

Hemoadsorption in Organ Preservation and Transplantation: A Narrative Review

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Hemoadsorption in Organ Preservation and Transplantation: A Narrative Review

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Abstract: Cytokine adsorption can resolve different complications characteristic of transplantation medicine, such cytokine storm activation, blood immuno- and AB0- incompatibilities but can also be performed for the treatment of various life-threatening conditions, such as sepsis, acute respiratory distress syndrome (ARDS), and cardiogenic shock, all of which can contribute to adverse clinical outcomes during transplantation. After surgery, dysmetabolism and stress response limit successful graft survival and can lead to primary (PGD) or secondary graft dysfunction. In this clinical context, and given that a major problem in transplant medicine is that the demand for organs far exceeds the supply, a technological innovation such as a hemoadsoption system could greatly contribute to increasing the number of usable organ donors. The objectives of this review are to describe the specific advantages and disadvantages of the application of cytokine adsorption in the context of transplantation and also to examine, before and/or after organ transplantation, the benefits of addition of a complementary cytokine adsorption therapy protocol.

Keywords: extracorporeal blood purification therapies; ex vivo lung perfusion; cytokine adsorption; hemoadsorption

1. Introduction

Cytokine adsorption (CA) is the basis of a promising therapy to resolve different complications characteristic of transplantation medicine, such as activation of cytokine storm, rapid immunological responses to blood incompatibilities, immunological barriers such as ABO blood group incompatibility and preformed donor-specific antibodies. CA can also be performed for the treatment of various life-threatening conditions, such as sepsis, acute respiratory distress syndrome (ARDS), and cardiogenic shock, all of which can contribute to adverse clinical outcomes during transplantation. After surgery, dysmetabolism and stress response limit successful graft survival and can lead to primary (PGD) or secondary graft dysfunction. In this clinical context, and given that a major problem in transplant medicine is that the demand for organs far exceeds the supply, a technological innovation such as a CA system could greatly contribute to increasing the number of usable organ donors. The objectives of this review are to describe the specific advantages and disadvantages of the application of CA in the context of transplantation and also to examine, before and/or after organ transplantation, the benefits of addition of a complementary CA therapy protocol.

2. Initial Development of Cytokine Adsorption

Early work from Cole et al., [1] evaluates the ex vivo removal of cytokines with an extracorporeal circuit using coupled large-pore hemofiltration and sorbent adsorption. The researchers used blood samples from six healthy volunteers that were incubated with endotoxin. Control blood was left at room temperature, while treatment blood was recirculated for 6 hours through a closed circuit with a large-pore polysulfone hemofilter (average pore size 150 kDa) and an activated charcoal cartridge. Blood and ultrafiltrate were sampled hourly from three sites to measure the concentrations of interleukins (IL)-1 β-, -6, -8 and -10, and tumour necrosis factor alpha (TNF-α). The concentrations of

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IL-1β, -6, -8 and -10, and TNF-α. were measured at three sites (pre-hemofilter for the circulating concentration, at cartridge inlet and cartridge outlet). Most of the preformed circuit cytokines were removed, except for IL-10. These findings suggest that the combination of a large-pore hemofilter and charcoal cartridge can efficiently remove several cytokines under ex vivo conditions. Further research is needed to evaluate the clinical benefits of this technique in vivo. Kellum et al., [2] determines the feasibility of removing cytokines using a hemoadsorption (HA) device in brain-dead subjects. The study was conducted on eight brain-dead subjects deemed unsuitable for organ donation by respective organ procurement organizations. The authors found that HA for removal of cytokines in brain-dead subjects is feasible. The cytokine removal across the CA device ranged from 4% to 30% and was not significantly different from 1 hour to 4 hours. Overall removal was greatest for IL-6, 28%, and least for tumor necrosis factor, 8.5%. Plasma concentrations of both IL-6 and tumor necrosis factor, but not IL-10, were significantly reduced after the first hour of therapy. However, plasma concentrations for all three cytokines increased over time and were above baseline by the end of the intervention. No adverse effects of therapy were observed. Kakishita et al., [3] describes a study that investigate the effect of cytokine removal using an adsorbent membrane during ex vivo lung perfusion (EVLP). The study was conducted on porcine heart-lung blocks that underwent 12-hour EVLP with an adsorbent membrane (membrane group) and without an adsorbent membrane (control group). The study found that TNF-α and IL-8 levels were elevated in the perfusate 2 hours after perfusion in the control group. Although TNF-α and IL-8 levels were significantly lower in the membrane group than in the control group during the EVLP period, there was no significant difference in oxygenation, pulmonary vascular resistance, edema formation, or myeloperoxidase activity between the two groups. The study suggests that cytokine removal using an adsorbent membrane during EVLP can suppress inflammatory cytokines but that factors other than the cytokines may play a major role in causing lung injury during EVLP. Butt et al., [4] suggests that further research into the predictive/prognostic utility of molecular biomarkers and the development of molecular-based therapies such as CA, is necessary to improve the prognoses of patients with ALI/ARDS and there is still much to be learned about the underlying causes and effective treatments of this condition. Moreover, in severely burn patients, Rieder et al., [5] concludes that a veno-venous extracorporeal membrane oxygenation support and CA are an effective and safe method for treatment of ALI/ARDS patients and may offer the potential to improve outcomes in this patient population. Further clinical trials are needed to assess the efficacy of this treatment in a larger population and to determine the optimal timing, duration, and amount of CA. Pomare Montin et al., [6] investigates the potential in vitro cytotoxic effects of different sorbent cartridges on U937 monocytes. The study evaluated the biocompatibility and cytotoxicity of four different sorbent cartridges (HA130, HA230, HA330, and HA380, Jafron Biomedical, Zhuhai City, China). The study found that there was no evidence of increased necrosis or apoptosis in monocytes exposed to the cartridges both in the static and dynamic tests. The in vitro testing suggests that HA cartridges carry an optimal level of biocompatibility and their use in hemoperfusion (HP) is not associated with adverse reactions or signs of cytotoxicity. Ronco et al., [7] reviews the various types of dialysis membranes and dialysers used for chronic hemodialysis treatment and related therapies. Traditionally, dialysis membranes have been classified based on their composition (cellulosic or noncellulosic) and water permeability (low flux or high flux). The article provides an updated analysis of dialysis membranes and dialysers, including new permeability indices, the hydrophilic or hydrophobic nature of membranes, adsorption capacity, and electrical potential. They discuss the basic mechanisms that underlie solute and water removal in dialysis (that is, diffusion, convection, adsorption, and ultrafiltration) in the context of treatments that use highly permeable membranes. The article highlights online hemodiafiltration and new therapies (for example, expanded hemodialysis) that utilize membranes designed to produce a high degree of internal filtration. They also discuss the considerations that govern the clinically acceptable balance between large-solute clearance and albumin loss for extracorporeal therapies. Makasane et al., [8] discusses the current approaches to remove middle molecules from the blood of patients undergoing dialysis. The authors highlight that aggressive removal of middle molecules or larger low-molecular-weight proteins has

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been a growing concern following studies on their harmful effects on the mortality and morbidity of chronic dialysis patients. They also note that when using HCO or medium cut-off (MCO) membranes for convective therapy, it is important to avoid massive albumin leakage during a dialysis session. Convection volume is an important element to increase middle molecule removal; however, a larger convection volume has a risk of larger leakage of albumin. Predilution hemodiafiltration is a useful measurement to increase larger low-molecular-weight proteins without massive albumin leakage. The article highlights the importance of assessing the efficacy of these approaches of middle molecule removal in dialysis patients and improve clinical outcomes. Ankawi et al., [9] describes several new adsorption cartridges with improved characteristics that have been developed over the years. These cartridges have expanded therapeutic applications, including the treatment of inflammatory conditions, chronic uremic symptoms, autoimmune disease, and intoxication. The article suggests that β2-microglobulin, α1-microglobulin, and albumin leakage during a dialysis session are useful parameters for assessing middle-molecule removal. Reduction ratios of β2-microglobulin >80% and of α1-microglobulin >35% are favorable to improve severe dialysis-related symptoms. The study suggested that these cartridges carry an optimal level of biocompatibility and their use in HP is not associated with adverse reactions or signs of cytotoxicity. Calabro et al., [10] describes the use of CA on critically ill patients with multiple organ failure. The author evaluate the clinical outcomes of CA therapy on such patients. The study include 40 patients with cardiogenic shock, septic shock, ARDS, and liver failure. The authors found that after CA treatment, total bilirubin, lactate, CPK, and LDH levels decreased significantly in critically ill patients mainly due to cardiogenic shock. The vasoactive-inotropic score after 48 hours of treatment was also reduced. However, the study also reported a 55% thirty-day mortality rate and a 52.5% intensive care unit (ICU) mortality rate at an expected ICU mortality rate of 80%. Lewis et al., [11] observes that CA is increasingly used in the intensive care setting for the removal of inflammatory mediators, toxins, and drugs from the circulation and in combination with extracorporeal membrane oxygenation (ECMO) or other extracorporeal support systems is purported to improve organ function and reduce morbidity and mortality in critically ill patients. However, there is limited clinical evidence to support these claims. Moreover, the effects of CA on drug molecules remain poorly understood. This presents a challenge for clinicians managing patients treated with CA, as drug concentrations may be altered, leading to potential adverse events or therapeutic failure. Supady et al., [12] reviews critically the evidence for the clinical benefits and potential harms of extracorporeal HA. The authors argue that the evidence for the efficacy of HA is uncertain and that no study has shown a survival benefit. They also point out the limitations and risks of HA, such as high costs, technical complexity, and possible adverse effects on the immune system. In addition, a number of potential side effects and risks associated with the use of adsorption devices have been identified, such as bleeding, infection, and the potential for leukapheresis. Fiedler et al., [13] evaluates the performance of two different pEHAT systems in an animal model of porcine arteriovenous fistula for HA. For this purpose, two different hemadsorber systems were used: a pEHAT system (TheraSpectra®) and a commercially available EHA system (TheraClear®). Both systems were connected to a porcine arteriovenous fistula and the adjacent femoral artery and vein with silicone tubes. The mean arterial pressure (MAP), was adjusted by continuous infusion of fluid. A continuous flow of 10 mL/min was maintained through both systems. The overall efficiency of the pEHAT system was higher than that of the TheraClear® system ($p < 0.05$). The pEHAT system has the ability to maintain a constant flow rate over a wide range of MAPs and has a higher efficiency than the commercially available EHA system. Hawchar et al., [14] reviews the results of the International CytoSorb® Registry and show that CytoSorb® is a safe and effective therapy for the treatment of various life-threatening conditions, such as sepsis, ARDS, and cardiogenic shock. In particular, the registry results indicate that the use of CytoSorb® is associated with a significant reduction in the need for mechanical ventilation, ICU and hospital length of stay, as well as mortality. The registry results also show that the use of CA is associated with an improvement in organ function, particularly in patients with severe sepsis and ARDS. Overall, the results of the International CytoSorb® Registry demonstrate the potential of CA to improve patient outcomes and reduce

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healthcare costs. The registry results further suggest that CA should be considered for use in patients with life-threatening conditions, particularly those with sepsis, ARDS, or cardiogenic shock.

3. Therapeutic Applications of Cytokine Adsorption in Transplantations

3.1. Therapeutic Applications in Lung Transplantation

Iskender et al., [15] reports a randomized, controlled animal study in which pigs were subjected to prolonged EVLP with and without perfusate CA. The experimental animals underwent evaluation of the pulmonary function and the measurement of the cytokine levels in the bronchoalveolar lavage fluid. The control group was subjected to EVLP without cytokine filtration while the experimental group was subjected to EVLP with CA. The results of the study showed that the experimental group had significantly better lung function compared to the control group. Additionally, the experimental group had significantly lower levels of cytokines in the bronchoalveolar lavage fluid compared to the control group. This suggests that perfusate CA during prolonged EVLP is safe and effective at improving pulmonary function and reducing inflammation. Another follow up study by Iskender et al., [16] [17] [18] observes that cytokine concentrations in the perfusate were markedly lower with the CA, resulting in improved EVLP physiology and biochemistry during the 6-hour perfusion period. Post-transplant dynamic lung compliance was markedly better during the 4-hour reperfusion period in the treatment group. Isolated allograft oxygenation function and dynamic compliance continued to be superior in the adsorber group at the end of reperfusion. The local inflammatory response was markedly decreased in the treatment group. These findings suggest that implementing an additional cytokine adsorber has refined the standard EVLP protocol. Furthermore, cytokine removal during EVLP improved immediate post-transplant graft function together with a less intense inflammatory response to reperfusion in pigs. This study provides evidence that perfusate CA during EVLP can improve short-term graft function after LTx and suggest that perfusate CA during EVLP may be an effective strategy for reconditioning the allograft to ischemia reperfusion induced injury (IRI) and may improve patient outcomes following LTx. Peyneau et al., [19] performs a small sample size study with a single-arm pilot design and was limited by the absence of a control group, making it difficult to draw conclusions about the efficacy of CA therapy compared to standard treatment. The study also had a short follow-up period, and the long-term effects of CA therapy remain to be evaluated. Despite these limitations, the results of this study provide important preliminary evidence regarding the potential of CA therapy to reduce inflammation and improve clinical outcomes in LTx. Frick et al., [20] uses a porcine-LTx model and find that continuous CA result in a significant improvement in lung graft function, as assessed by the degree of allograft injury, post-transplant survival, and blood chemistries. They also observe a significant reduction in pro-inflammatory cytokine and chemokine levels in the systemic circulation of the animals. These results suggest that CA may attenuate IRI in the allograft after LTx. Furthermore, their findings suggest that the inflammatory cytokines and chemokines play an important role in the pathogenesis of IRI. Niroomand et al., [21] investigates the molecular mechanisms and signaling pathways of how CA impacts lung function when used during EVLP and post-transplantation as HP in a porcine model. The study hypothesized that there were characteristic inflammatory and immunomodulatory differences between the lungs treated with and without CA, reflecting proteomic changes in the gene ontology pathways and across inflammation-related proteins. The study found through gene set enrichment analysis that the inflammatory and immune processes and coagulation pathways were significantly affected by the cytokine treatment after EVLP and transplantation. This approach of studying treated and non-treated donor lung grafts allowed for a more global understanding of the protein processes affected by CA and showed that the treatment causes broad changes in the inflammatory pathways. Niroomand et al., [22] reviews the EVLP technology that has been used as a therapeutic platform to improve donor lung quality prior to transplantation. CA involves the use of a device to filter out harmful cytokines and other inflammatory molecules in the donor lungs, which can also reduce inflammation and improve lung function. The application of EVLP as a therapeutic intervention has led to significant improvements in donor lung quality and has allowed for the successful

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transplantation of organs that were previously considered too damaged or too marginal to be used. EVLP has been shown to reduce inflammation, improve lung function, and reduce the risk of post-transplant complications. Additionally, EVLP has been used to evaluate the efficacy of various cell therapies and cell product therapies, as well as to test the effectiveness of cytokine filtration. Ghaidan et al., [23] shows that the two-step treatment with CA is effective in improving lung function in the ARDS patients, as indicated by a significant increase in the PaO2/FiO2 ratio. Furthermore, this treatment was associated with a reduction in the incidence of PGD, a common severe complication associated with LTx that affects up to 50% of recipients and increases the risk of chronic rejection and mortality. Molecular outcomes showed that the two-step treatment resulted in decreased systemic inflammation and oxidative stress in the lungs and other organs. This was accompanied by improved tissue oxygenation and reduced cellular damage. In addition, the two-step treatment was associated with a decrease in the expression of inflammatory genes and a decrease in the number of inflammatory cells. Taken together, these results suggest that the two-step treatment with the CA is effective in improving lung function and reducing the incidence of PGD in patients with ARDS after LTx. In the same context, Ehrsam et al., [24] reports the use of CA during and after reperfusion as a viable approach to reduce post-transplant inflammation following LTx. The study was conducted on pig left LTx following 24 hours of cold ischemic storage. The treatment group received extracorporeal CA 30 minutes before reperfusion and continued for 6 hours, while the control group did not receive adsorber treatment. During adsorption, a significant decrease in plasma pro-inflammatory IL-2 was noticed, along with trends of less pro-inflammatory TNFα, IL-1α, and GM-CSF, and significantly reduced systemic neutrophils. The study found that CA during and after reperfusion is effective in reducing post-transplant inflammation following LTx. The treatment group exhibited significantly improved CO2 removal, partial pressure of oxygen/inspired oxygen fraction ratio, and less acidosis compared to the control group. The study concludes that CA during and after reperfusion is a viable approach to reducing post-transplant inflammation following LTx. Boffini et al., [25] describes the use of EVLP to remove cytokines from lungs prior to transplantation. Among the 54 EVLP procedures carried out, 21 grafts were treated with an adsorption system and 33 without. Comparing the grafts perfused during EVLP with or without CA, the use of a filter significantly decreased the levels of IL-10 and GCSF at the end of the procedure. Among the 38 transplanted patients, the group that received adsorption experienced significantly decreased IL-6, IL-10, MCP1, and GCSF concentrations and deltas compared to the group that did not receive adsorption. This group also had lower in-hospital mortality ($p = 0.03$) and a lower 1-year death rate ($p = 0.01$). The results suggest that using a porous polymer beads adsorption device can effectively reduce the level of inflammatory mediators during EVLP. This is the first human study suggesting the safety and efficacy of this approach. Even if more research is needed to fully understand the clinical impact of cytokine reduction during EVLP this study found that EVLP with cytokine removal was safe and feasible, and that it could be used to improve the quality of lungs for transplantation. Lindstedt et al., [26] discusses the use of CA during LTx to reduce or remove elevated levels of neutrophil extracellular traps (NETs). NETs are networks of extracellular fibers, primarily composed of DNA from neutrophils, which bind pathogens. NETs have been implicated in various inflammatory and autoimmune diseases, as well as in organ transplantation. NETs can induce tissue damage, activate the complement system, promote thrombosis, and trigger adaptive immune responses. In LTx, NETs have been associated with PGD. NETs can impair alveolar gas exchange, increase vascular permeability, and induce inflammation and fibrosis in the transplanted lung. The study found that using a cytokine adsorber during transplantation may provide a reduced systemic inflammatory state with lower levels of NETs and consequently support graft acceptance. The treated group showed reduced levels of circulating nucleosomes and remained free from primary graft dysfunction and histopathological signs of acute rejection at 1- and 3-month post-transplant. Patients without the adsorber experienced higher levels of circulating nucleosomes, primary graft dysfunction grades 1 and 3, and histopathological signs of acute rejection. The study's findings suggest that CA could be a means of decreasing NETs and has previously resulted in lower rates of primary graft dysfunction in LTx models. Lindstedt et al., [27] describes a Swedish national interventional randomised controlled study (NCT05242289) involving

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116 patients. The study investigates the potential benefits of cytokine filtration administered for 12 hours in the first 24 hours following LTx may improves outcomes. The purpose of this clinical trial is to demonstrate the superiority of cytokine filtration in improving LTx success, based on its effects on oxygenation ratio, plasma levels of inflammatory markers, PGD incidence and severity, lung function, kidney function, survival, and quality of life compared with standard treatment with no cytokine filtration. In their previous research [23], it was found that cytokine filtration can modulate pulmonary metabolism and edema formation during EVLP. The process involves preserving pig donor lungs for 24 hours at 4°C, followed by 12 hours of EVLP according to the Toronto protocol. The perfusate was continuously run through an absorbent device CytoSorb® via a veno-venous shunt from the reservoir in the filter group. The results showed that cytokine filtration significantly improved airway pressure and dynamic compliance during the 12-hour perfusion period. It also reduced glucose consumption and lactate production, along with the lactate/pyruvate ratio in the filter group. This suggests that cytokine filtration could potentially improve outcomes in LTx.

3.2. Therapeutic Applications in Heart Transplantation

Early application of CA in management of liver diseases were investigated by Trager et al., [28]. They use a CA device in controlling hyperinflammatory systemic reactions in patients undergoing cardiothoracic surgery with cardiopulmonary bypass (CPB). This retrospective case series involved 16 cardiac surgery patients who developed severe inflammatory response syndrome (SIRS) and subsequent AKI following prolonged CPB. The treatment resulted in a reduction of elevated cytokine levels and this reduction was associated with a clear stabilization of deranged hemodynamic, metabolic, and organ function parameters. The treatment was well tolerated and safe, with no device-related adverse events occurring. Träger at al., [29] also used CA during CPB as a way to reduce the pro-inflammatory response and improve post-operative organ function. This has been investigated in a prospective, randomized, non-blinded, controlled trial to investigate whether the use of intraoperative CA in patients undergoing cardiac surgery for infective endocarditis reduces the severity of postoperative organ dysfunction. The efficacy of CA in reducing plasma levels of inflammatory mediators was documented in a run-in phase of this trial. Furthermore, the use of CA in DCD hearts during BP has been suggested as a way to reduce the pro-inflammatory response, vascular damage, and IRI of the coronary microvascular endothelium. The intraoperative application of HA in patients during CPB surgery due to infective endocarditis has also been investigated, showing a reduction in the levels of pro-inflammatory cytokines. The use of CA may have potential benefits for heart transplantation and may improve graft survival. Moreover, Nemeth et al., [30] shows that intraoperative CA treatment was associated with reduced vasopressor demand and less frequent continuous renal replacement therapy (CRRT) with a favorable tendency in length of mechanical ventilation and ICU stay. CA treatment was not linked to higher rates of adverse events. This suggests that CA may be a useful adjunct to improve outcomes in patients undergoing orthotopic heart transplantation. Dogan et al., [31] describes the successful use of CA in combination with extracorporeal life support therapy in a patient with giant-cell myocarditis. The combined approach resulted in a clear and steady improvement in hemodynamics and the inflammatory condition with marked reductions in all measured parameters throughout the treatment period. Metabolic acidosis resolved and liver function improved. This case report highlights the potential of CA HA to improve organ function and inflammation following the extracorporeal support of a patient with giant-cell myocarditis. This novel therapy may represent an additional therapeutic option for patients with severe form of this disease. In the context of prolonged cardiovascular bypass, Gleason et al., [32] reported results in a prospective, multicenter REFRESH (REduction in FREe Hemoglobin) randomized controlled trial that evaluated the safety and feasibility of CA therapy to reduce plasma-free hemoglobin (pfHb) and activated complement during prolonged CPB in patients undergoing elective, nonemergent complex cardiac surgery. Eligible patients were randomized to receive either CA therapy (TREATMENT) or standard of care (CONTROL). The study found that CA therapy was safe and feasible in this randomized, controlled pilot study during complex cardiac surgery. Treatment with CA resulted in significant reductions in pfHb during valve

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replacement surgery and reductions in C3a and C5a in the overall efficacy group. These results suggest that future studies should target complex cardiac surgery patients with prolonged CPB to assess the effect of HA on end-organ dysfunction and outcomes. Bernadi et al., [33] investigates the effect of HA on cytokine levels, inflammation markers, and differences in patients' perioperative course during CPB surgery. The study hypothesizes that HA of cytokines may suppress inflammatory responses and improve outcomes. The study tested a CA sorbent used for HA installed in the CPB circuit on changes of pro- and anti-inflammatory cytokines levels, inflammation markers, and differences in patients' perioperative course. In this first pilot trial, 37 blinded patients were undergoing elective CPB surgery at the Medical University of Vienna and were randomly assigned to HA (n=19) or control group (n=18). The primary outcome was differences of cytokine levels (IL-1β, IL-6, IL-18, TNF-α, and IL-10) within the first five postoperative days. The study found that there were no differences in the primary outcome immediately following the HA treatment. However, IL-10 showed a longer-lasting anti-inflammatory effect. The clinical impact of prolonged IL-10 needs further evaluation. Kaliyev et al., [34] describes a case report of a successful heart transplantation after 7 hours of cold storage and paracorporeal donor heart resuscitation. This could potentially increase the viability of organs for transplantation and improve patient outcomes. The report also mentions that "suboptimal" organs are more often used for transplantation. The donor heart was arrested with the standard heart preservation solution (4°C Custodiol) and preserved in the standard way of cold ischemic storage. The authors used controlled warm reperfusion, medical treatment, and cytokines adsorption to resuscitate the donor organ. Saemann and al., [35] uses a normothermic donation after circulatory death (DCD) heart model in which the DCD hearts are perfused with the donor's blood collected before and after CA. They found that CA during blood perfusion (BP) of DCD hearts significantly reduced coronary microvascular dysfunction, oxidative stress, and IRI of the coronary microvascular endothelium compared to hearts perfused without CA. They also observed that CA during BP was associated with a decrease in the expression of the proinflammatory genes TNF-α, IL-1β, IL-6, and IL-8. In addition, they observed a significant increase in the expression of the anti-inflammatory genes IL-10 and TGF-β. Their results suggest that CA during BP of DCD hearts may be beneficial in reducing coronary microvascular dysfunction, oxidative stress, and IRI of the coronary microvascular endothelium. Diab et al., [36] conducted a trial in two phases. In the run-in phase, all patients underwent conventional cardiac surgery for infective endocarditis, and intraoperative HA was performed in a subset of patients. Patients in the HA group had significantly lower plasma levels of inflammatory mediators than those in the control group. In the randomized phase, patients were randomly assigned to the HA or control group, and the primary outcome measure was change in Sequential Organ Failure Assessment (SOFA) score from baseline to postoperative day 3. Secondary outcomes included postoperative infection, length of stay in the intensive care unit, and mortality. The results of the study showed that patients in the HA group had significantly lower SOFA scores at postoperative day 3 than those in the control group (mean difference, -1.6; 95% CI, -2.9 to -0.3; P=0.02). There were no significant differences between the two groups in terms of postoperative infection, length of stay in the intensive care unit, or mortality. These findings suggest that intraoperative HA may be beneficial in reducing the severity of postoperative organ dysfunction in patients undergoing cardiac surgery for infective endocarditis, as measured by changes in the SOFA score. Holmén et al., [37], suggests that the use of CA during cardiac surgery may reduce the need for vasopressors after surgery for endocarditis. Although the accumulated norepinephrine dose in the intervention group was half or less at all postoperative time points compared to the control group, the difference did not reach statistical significance. There was also a significantly lower need for the transfusion of red blood cells in the intervention group. Overall, these results indicate that the use of a CA during cardiac surgery may reduce the need for vasopressors after surgery for endocarditis, although additional larger randomized controlled trials are needed to definitively assess the potential effect. Lovrić et al., [38] presents several important findings related to the use of a CA in patients presenting with cardiogenic shock and treated with venoarterial ECMO (VA-ECMO). Sixteen patients were included in the study and were stratified based on the use of a CA in the first 24 hours of treatment. Patients treated with the CA required significantly lower doses

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of vasopressors at the initiation and before weaning from ECMO. These patients also showed significantly higher urine output before weaning. The lactate levels during the extracorporeal support were lower in these patients. The mortality rate was lower among the group that received CA therapy (22.2% vs 57.1%). This study suggests that the use of the CA can lead to an increase in urinary output and a trend towards better survival among patients on VA ECMO.

3.3. Therapeutic Applications in Kidney Transplantation

Early application of CA in management of kidney diseases were investigated by Hosgood et al., [39]. They studied the effect of incorporating CA into an isolated kidney perfusion system. The results showed that HA can reduce the inflammatory response and improve renal blood flow during perfusion. Additionally, the HA had no influence on renal function, which may be due to the broad-spectrum action of the CA used that also removes potentially important anti-inflammatory mediators. Schenk et al., [40] investigates the therapeutic effects of soluble podocyte urokinase receptor elimination through CA and total plasma exchange in the treatment of primary FSGS and recurrence after kidney transplantation. Further exploring the exact pathophysiological role of soluble podocyte urokinase receptor in FSGS and other kidney diseases, and to assess whether soluble podocyte urokinase receptor elimination can effectively improve patient outcomes. Raina et al., [41] suggests that lipoprotein apheresis is a safe and effective treatment for drug resistant primary FSGS and post-renal transplant primary FSGS. The findings also suggest that lipoprotein apheresis may be an effective treatment for inducing partial or complete remission of proteinuria in some of the patients with primary FSGS. However, larger studies with longer follow-up period are needed to further assess the efficacy of this treatment. Rybalko et al., [42] successfully treated a patient with a complex medical condition with a combination of ECMO and multiple extracorporeal blood purification methods, including plasma exchange, CA, and lipopolysaccharide adsorption. This case report demonstrates the potential benefits of a multimodal approach to extracorporeal therapies in the setting of immunosuppression therapy. It also highlights the importance of careful monitoring for potential complications, such as occult infections, which may not be immediately apparent. Based on the successful outcome in this case, multimodal extracorporeal therapies may be a viable option for treating complex medical conditions in pediatric patients. In this same context of FSGS, Karkar et al., [43] discusses several aspects of Continuous Renal Replacement Therapy (CRRT) prescription in critically ill patients with severe Acute Kidney Injury (AKI), sepsis, and multiorgan failure in ICU. Aspect covered are the different aspects of CRRT prescription include, the choice of CRRT versus intermittent and extended HD. The life of the filter/dialyzer can be influenced by factors such as the filtration fraction and the type of anticoagulation used, anticoagulation including regional citrate anticoagulation to prevent clotting in the circuit, the prescribed versus delivered CRRT dose, vascular access management that impact both the efficacy of treatment and the risk of complications, timing of initiation and termination of CRRT, and prescription in AKI/sepsis including adsorptive methods of removing endotoxins and cytokines. Westphalen et al., [44] presents a series of investigations on the common clinical HD membranes available in Canadian hospitals. The study explored the reasons behind the susceptibility of these membranes to blood activation and unstable cytokine. Clinical HD membranes composed of cellulose triacetate (CTA) and polyvinylpyrrolidone: polyarylethersulfone (PAES: PVP) were characterized in terms of morphology and chemical composition. Membrane-surface interactions with uremic blood samples after HD treatment were probed using Fourier Transform Infra-Red and Raman spectroscopic techniques. The study utilized Molecular Modeling Docking to examine the interactions of human blood proteins and membrane models. In-vitro adsorption of fibrinogen on different clinical HD membranes was compared at similar clinical operating conditions. Blood samples were collected from dialysis patients to ascertain the extent of inflammatory biomarkers released, before, during (30 and 90 min), and after dialysis (4 h). The results indicate that CTA membranes have a smoother surface and higher biocompatibility than PAES: PVP membranes. However, CTA has a smaller pore size distribution, which results in poor clearance of a broad spectrum of uremic toxins. The rougher surface and greater hydrophilicity of PAES: PVP may contribute to its performance. These findings provide valuable insights into the performance of

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different HD membranes and their interactions with uremic blood, which could potentially lead to improvements in dialysis treatment outcomes. Ferdinand et al., [45] compares the effect of normothermic machine perfusion (NMP) with that of cold storage on the global kidney transcriptome. Cold storage led to a global reduction in gene expression, including inflammatory pathway genes and those required for energy generation processes, such as oxidative phosphorylation. During NMP, there was marked upregulation of oxidative phosphorylation genes, but also of a number of immune and inflammatory pathway genes. Biopsies from kidneys undergoing NMP that were subsequently transplanted showed higher inflammatory gene expression in organs with prolonged delayed graft function. The study used a hemoadsorber to remove pro-inflammatory cytokines. This attenuated inflammatory gene expression, increased oxidative phosphorylation pathway genes, and had potentially clinically important effects in reducing the expression of a delayed graft function-associated gene signature. These findings suggest that cytokine absorption during human kidney perfusion can reduce the inflammatory gene signature associated with delayed graft function, potentially improving outcomes for transplant recipients. Muller-Deile et al., [46] reports the successful treatment of recurrent focal segmental glomerulosclerosis (FSGS) in a patient after living-related kidney transplantation by removal of circulating factors with CA apheresis. The researchers used a podocyte cell culture model and a proteinuria model in zebrafish to detect pathogenic effects on the podocytes actin cytoskeleton inducing a functional phenotype and podocyte effacement. Raman spectroscopy was performed in the < 50 kDa serum fraction, on cultured podocytes treated with the FSGS serum, and in kidney biopsies of the same patient at the time of transplantation and at the time of disease recurrence. The analysis revealed changes in podocyte metabolome induced by the FSGS serum as well as in focal glomerular and parietal epithelial cell regions in the FSGS biopsy. Several altered Raman spectra were identified in the fractionated serum and metabolome analysis by mass spectrometry detected lipid profiles in the FSGS serum. The study reveals changed lipid metabolome profiles associated with idiopathic FSGS that might reflect a new subtype of the disease. These findings provide valuable insights into the metabolic changes associated with recurrent FSGS, potentially leading to improved diagnostic and therapeutic techniques. Reis et al., [47] reviews the type of dialysis membranes such as high retention onset membranes with wider pores and a more uniform pore size distribution, allowing for the efficient removal of middle molecules such as uremic toxins and inflammatory mediators. As such, high retention onset dialyzers are now commonly used for patients with AKI requiring continuous kidney replacement therapy, as well as those with myeloma requiring hemodialysis (HD), for free light chain removal. Other dialysis membranes reviewed are MCO membranes, that are used in maintenance HD patients. Numerous clinical trials have demonstrated the superior efficacy of MCO dialyzers in removing uremic toxins and other middle molecules compared to traditional high-flux membranes. Safety concerns regarding albumin loss as well as blood contamination from pyrogens in the dialysate have also been addressed. Moresco et al., [48] describes the successful use of CA in rapidly reducing creatine kinase and myoglobin levels in a patient suffering from rhabdomyolysis following sport trauma and successive surgeries. In this case, CA was able to successfully reduce the patient's creatine kinase and myoglobin levels, and allow them to make a full recovery without any further complications. Franzin et al., [49] reviews the polymethyl methacrylate (PMMA)-based in enhancing immune protection in HD patients. End-stage renal disease is characterized by deep disorders in both innate and adaptive immune systems that imply unbalance deactivation and immunosuppression. The central, widely recognized factors responsible for this immune dysregulation are uremia, uremic toxin retention, HD membrane biocompatibility, and related cardiovascular complications. The PMMA-based membrane is characterized by a symmetrical structure with large-sized pores, providing a better hydrophobic and cationic adsorption capacity compared to other synthetic membranes. PMMA membranes exhibit adsorptive properties for a large amount of uremic toxins including p-cresol and indoxyl sulfate, as well as β2-microglobulin characterized by higher molecular weight, maintaining the diffusive clearance of small molecules like urea with great biocompatibility. Besides exerting strong anti-inflammatory effects in line with the improvement of immune responses in patients undergoing dialysis, PMMA also plays a role in modulating adaptive immune response.

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PMMA can clear blood from soluble CD40, a natural antagonist of the CD40/CD40L signaling that acts inhibiting immunoglobulin production by B cells. Husain-Syed et al., [50] reviews of the relationship between acute brain injury (ABI) and AKI. It's noted that approximately 20% of patients with ABI also experience AKI, which can worsen their outcomes. The metabolic and inflammatory changes associated with AKI may contribute to prolonged brain injury and edema, making it crucial to recognize and manage AKI effectively in patients with ABI. The review discusses the occurrence and effects of AKI in critically ill adults with neurological conditions, and outlines potential mechanisms that may link the progression of AKI and ABI. It also highlights principles for managing AKI, which include tailored approaches such as optimizing blood pressure, managing intracranial pressure, adjusting medication dosages, and assessing the type of fluids administered. Preventive measures include avoiding nephrotoxic drugs, improving hemodynamic and fluid balance, and addressing coexisting AKI syndromes. For ABI patients undergoing CRRT, they are more susceptible to neurological complications. RRT can negatively impact cerebral blood flow, intracranial pressure, and brain tissue oxygenation. The effects are tied to specific RRT methods, with continuous RRT being favored for better hemodynamic stability and lower risk of dialysis disequilibrium syndrome. Potential modifications for RRT in ABI patients include adjusted dialysate and blood flow rates, osmotherapy, and alternate anticoagulation methods.

3.4. Therapeutic Applications in Liver Transplantation

Early approaches with plasma fractionation impacting patients with severe liver failure were investigated by Santoro et al., [51]. Here, the Prometheus system that was a novel device for fractionated plasma separation via an albumin-permeable filter was developed to improve the removal of albumin-bound toxins. Initial studies have proven the clinical use of Prometheus to be feasible and safe. Head-to-head comparisons of Prometheus and the Molecular Adsorbent Recycling System (MARS) have shown treatment with the former to be more efficient with respect to removal of most albumin-bound and water-solved markers. These findings are significant as they provide insights into the potential therapeutic benefits of Prometheus in managing toxin levels in patients with severe liver failure. The system works by separating plasma through an albumin-permeable membrane, which enters a secondary circuit where protein-bound toxic substances are removed by two adsorbers: p01, a neutral resin, and p02, an anion exchanger. Plasma is then returned to the venous line, where a high-flux hemodialyzer removes water-soluble substances. In a clinical study involving 12 patients with acute or acute-on-chronic liver failure (ACLF), the Prometheus system was used to treat hyperbilirubinemia, hypercholemia, and hyperammonemia. The study found that the mean total bilirubin decreased while the reduction ratios for cholic acid and ammonia were 48.6% and 51.6%, respectively. The study also observed a significant reduction in the circulating levels of soluble IL-2 receptor and IL-6 during treatments. Rocen et al., [52] discusses the impact of a study involving 11 patients with ALF investigated the effect of FPSA on the levels of cytokines and markers of inflammation and liver regeneration. The study found that before therapy, elevated levels of IL-6, IL-8, IL-10, TNF-α, C-reactive protein (CRP), and procalcitonin were detected. However, the level of TNF-α, CRP, procalcitonin, and α1-fetoprotein decreased significantly during therapy. In contrast, an increase in hepatocyte growth factor was detected. The decline of IL-6, IL-8, and IL-10 concentrations was not significant. The study suggests that Prometheus is highly effective in clearing inflammatory mediators responsible for systemic inflammatory response syndrome and affects the serum levels of inflammatory and regeneration markers important for management of ALF. The MARS is another early development of a blood detoxification system based on albumin dialysis. The impact of MARS therapy on cytokines metabolism in patients affected with ACLF was discussed by Ambrosino et al., [53]. This study evaluated the effects of MARS therapy compared to standard medical treatment (SMT) in two patient cohorts: in patients with an acute liver injury and in those with graft dysfunction (GD). The results showed that MARS improved the patients' bilirubin values in the short term compared to SMT alone. The key findings from the study are an increase in IL-6 levels was observed during MARS treatment. A decrease in TNF-α levels was also noted during MARS treatment. These findings are significant as they provide insights into the potential therapeutic

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benefits of MARS in managing cytokine levels in patients with acute on chronic liver decompensation. Novelli et al., [54] discusses the impact of the MARS on cytokine levels in patients. They conducted a clinical study to compare the effects of MARS therapy and SMT on cytokine metabolism and survival in 30 patients with ACLF. They found that MARS therapy significantly altered the levels of IL-6, IL-1, IL-10, and TNF-α, as well as increased the hepatocyte growth factor, which may indicate enhanced liver regeneration. They also reported that MARS therapy improved the 3-month survival rate from 30% to 60% compared to SMT. While it is increasingly applied in patients with ALF, no comparison with standard dialysis methods has yet been performed. In contrast, the SMT group showed only a significant change TNF-α ($P = .03$), and patient survival at 3 months was 30%. The study suggests that the MARS liver support device corrected pathophysiologies of ACLF failure and may be used to enhance spontaneous recovery or as a bridge to transplantation. Popescu et al., [55] presents a comparison between two liver assist devices, the MARS and CytoSorb®, in patients with liver failure. Single sessions of both CytoSorb® and MARS were associated with a significant decrease in bilirubin and ammonia levels. Liver assist devices have been developed to either bridge patients to transplantation or promote spontaneous recovery. After the course of treatment, only CytoSorb® was associated with a significant decrease in lactate, bilirubin, ammonia, and lactate dehydrogenase levels, while patients treated with MARS did not show any improvement in paraclinical liver tests. Only CytoSorb® treatment was associated with a significant improvement in the Model for End-Stage Liver Disease Score. The results show a potential benefit of CytoSorb® in rebalancing liver functional tests in patients with liver failure compared to MARS. However, the exact effects on patient outcome, including hospital length of stay and survival, should be further investigated in randomized control trials. Trautman et al., [56] discusses the impact of the MARS on kidney outcomes in patients with hepatic failure. A study was conducted to characterize a cohort of patients who received MARS therapy and examine kidney events given the current paucity of available data. The study included 49 patients who initiated MARS therapy in a tertiary care setting. Hepatic encephalopathy (HE) was the most common indication for MARS initiation. In-hospital mortality was 41% among patients who received CKRT versus 10% among those not requiring CKRT. this persisted following adjustment for prespecified patient characteristics (all RR ≥ 3.76, all $P \leq 0.060$). One-year mortality post-MARS initiation was high overall but highest among the CKRT group (59% vs. 25%). Ocskay et al., [57] reviews and performed network meta-analysis aimed to compare and rank different liver support systems and standard medical therapy (SMT) in patients with ACLF. The study included 16 trials using MARS, Prometheus, ELAD, plasma exchange (PE) and BioLogic-DT®. PE significantly improved 3-month OS compared to SMT and ranked first on the cumulative ranking curves for both overall survival (OS) outcomes surface under cumulative ranking (SUCRA: 86% at 3 months; 77% at 1 month) and 3-month transplant-free (TFS) (SUCRA: 87%) and second after ELAD for 1-month TFS (SUCRA: 76%). The other comparisons did not reach statistical significance. The quality of evidence was moderate for PE concerning 1-month OS and TFS outcomes. These findings suggest that PE is the best currently available liver support therapy in ACLF regarding 3-month OS. However, due to the low quality of evidence, randomized trials are needed to confirm these findings and to introduce new devices. Tomescu et al., [58] demonstrates the clinical efficacy of CA in ALF and an improvement in liver functional tests and a decrease in CRP. However, further research is needed to further explore the safety and efficacy of this treatment. Ocskay et al., [59] concludes that extracorporeal HA with CA appears to be a promising treatment for acute forms of liver dysfunction and failure. There are some case reports, case series, and in vitro data indicating that CA can effectively remove bilirubin, bile acids, and ammonia from the blood. However, further prospective data or results of randomized trials are needed to confirm these results. Acar et al., [60] concludes that CA systems can be considered an effective and safe alternative treatment for hyperbilirubinemia associated with sepsis in patients with liver failure. The procedure can reduce bilirubin levels and also reduce vasoactive medication requirements. However, further studies are needed to compare the efficacy of this procedure with other bilirubin-lowering methods. Additionally, the inability of the procedure to reduce ammonia levels should be taken into consideration when planning treatment for patients with liver failure and

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sepsis. Maggi et al., [61] discusses the use of coupled plasma filtration adsorption (CPFA) in managing hyperbilirubinemia after liver transplantation. CPFA is an extracorporeal therapy that uses plasma filtration associated with an adsorbent cartridge and hemofiltration to remove cytokines and inflammatory mediators associated with septic shock, severe sepsis, and multiple organ dysfunction syndrome. The study suggests that CPFA is a potential inexpensive short-lasting device to treat hyperbilirubinemia after liver surgery or transplantation. Moreover, the effects of CPFA should be further studied to address inflammatory. This study reports two cases of patients who experienced different complications after liver transplantation. The first patient had early allograft dysfunction, and the second patient had hyperbilirubinemia linked to chronic rejection. After three cycles of CPFA, the bilirubin levels promptly decreased in both case and the bilirubin of the patients by approximately 40% This suggests that CPFA could be an effective treatment for managing hyperbilirubinemia after liver transplantation. However, as with any medical treatment, more research is needed to confirm these findings and to further understand the potential benefits and risks. Donati et al., [62] discusses the use of CPFA in managing acute or ACLF. CPFA is a type of liver dialysis that uses a machine to remove both albumin-bound and water-soluble toxins from the blood by a combination of adsorption and HD. The study enrolled 12 patients with acute or ACLF in a prospective observational study to evaluate the effectiveness of CPFA in liver detoxification. CPFA was performed using the Lynda (Bellco/MedTronic, Mirandola, Italy) or the Amplya (Bellco/MedTronic, Mirandola, Italy) machines. Anticoagulation was provided with unfractionated heparin or citrate. Bilirubin and bile acids reduction ratios per session (RRs) were the main parameters for hepatic detoxification. The results showed that reduction ratios per session (RRs) were 28.8% (range 2.2–40.5) for total bilirubin, 32.7% (range 8.3–48.9) for direct bilirubin, 29.5% (range 6.5–65.4) for indirect bilirubin and 28.9% (16.7- 59.7) for bile acids. One patient received liver transplantation and 8 out of 9 were alive at 1 year of follow-up. Three patients (25%) died: 2 during hospitalization and 1 for a cardiac event at 4 months of follow up with restored liver function. This suggests that CPFA could be an effective treatment for managing such conditions, and it may be considered as a “bridge technique” both to the liver transplant and to the recovery of the basal liver function. However, more research is needed to confirm these findings and to further understand the potential benefits and risks. Rachunek et al., [63] in a case study highlights the potential of CA as a therapeutic tool to improve wound healing in patients with severe burns and liver dysfunction. The therapy was successful in reducing the bilirubin concentrations and allowing for successful wound healing, despite the patient's underlying secondary sclerosing cholangitis. The patient was able to recover from the burns and successfully undergo skin grafting to close the wounds. The study highlights the potential of CA to reduce the risk of infection and aid in wound healing in patients with severe burns and liver dysfunction. Rosa-Diez et al., [64] discusses the use of the Double Plasma Molecular Adsorption System (DPMAS) in the context of liver failure in the ICU, whether acute or ACLF. DPMAS is a nonbiological artificial liver support system that combines two types of adsorbents: a neutral macroporous adsorption resin (HA330) and an ion exchange resin (BS330). These adsorbents can selectively remove bilirubin, cytokines, and other medium- and macro-molecular toxins from the plasma. DPMAS combined with plasma exchange therapy can improve liver function, coagulation function, and blood routine level of ACLF patients and increase the effective rate of treatment. It is an effective treatment for ACLF. Wu et al., [65] reviews some important findings related to HA and discusses the development of a new class of HP adsorbents that can improve the adsorption performance of blood toxins while maintaining good blood compatibility. They discussed the history of HP and evaluated the performance of common materials such as activated carbon, inorganic porous materials, and polymers. The paper categorized and summarizes the research progress of HP adsorbents in the treatment of common blood toxins (bilirubin, blood ammonia, endotoxin, cytokines, creatinine, uric acid, and urea) in liver and kidney failure. They also discussed the composition and structure of various toxin adsorbents, their toxin adsorption performance, biocompatibility, blood safety, and the mechanism of toxin adsorption. Based on recent research, the paper explored feasible strategies for designing and preparing HP adsorbents to meet future development requirements. Marcello et al., [66] addresses several

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important discoveries related to the use of the Double Plasma Molecular Adsorption System (DPMAS) for bilirubin adsorption and focuses on conditions such as acute liver failure and ACLF, where the loss of metabolic function of the liver leads to the accumulation of toxins like bilirubin. Patients with sepsis or multiple organ dysfunction syndrome have a greater risk of developing liver failure, and hyperbilirubinemia is associated with poor prognosis. The removal of bilirubin may not only alleviate signs and symptoms of liver dysfunction but also act as an index of removal of albumin-bound toxins. Conjugated and unconjugated bilirubin, due to their molecular weight and albumin-binding capacity, respectively, cannot be removed by classic dialysis. The DPMAS is an extracorporeal liver support technique in which bilirubin is removed from the plasma through a specific adsorbing cartridge. It adds a broad-spectrum adsorption column for the removal of inflammatory mediators, antibodies, and other medium toxins. The use of DPMAS in the treatment of hyperbilirubinemia has been established with several emerging data indicating their efficacy when compared to other extracorporeal techniques. However, bilirubin adsorption kinetics has not been sufficiently elucidated, and more studies are needed to improve the quality of treatment in terms of timing and prescriptions. Marcello et al., [67] presents an ex vivo study to assess the quantitative capacity to remove bilirubin from plasma of a novel adsorptive cartridge. The study used a downscaled module of the BS330 Plasma Bilirubin Adsorption Column Cartridge (Jafron Biomedical, Zhuhai City, China) to minimize the plasma requirement in an ex vivo circulation using a solution of hyperbilirubinemic plasma. The bilirubin concentration change across the cartridge at 30 min was 16.5%, and cartridge saturation was reached at 750 min. The device retained 759 mg of bilirubin with a removal ratio (RR) of 78.1% and a RR of 42.6% at 120 min. Thus, the adsorption capacity was 5.76 mg of bilirubin per gram of sorbent. Bilirubin adsorption kinetics in a clinical case with a full-scale unit shows a coherent trend with a total bilirubin mass adsorbed after 180 min of 470 mg. This is the first assessment of bilirubin adsorption in an ex vivo model of plasma perfusion and can be used to design interventional studies in humans, providing guidance for an adequate prescription of treatment frequency and duration. Gräfe et al., [68] investigates whether the extracorporeal elimination of bilirubin with the cytokine adsorber CytoSorb® reduces mortality in patients with hyperbilirubinemia. The study included patients with bilirubin concentrations >10 mg/dL and who were undergoing kidney replacement therapy at the ICU who were screened for evaluation from 2018 to 2020. The results showed no significant differences in patients with and without CS treatment. The multivariate model showed no significant effect of CS therapy ($p = 0.402$) on the 30-day mortality. In addition, a significant effect of bilirubin concentration ($p = 0.274$) or Model for End-Stage Liver Disease score ($p = 0.928$) on the 30-day mortality could not be shown. In contrast, lactate concentration ($p = 0.001$, $b = 0.044$) and SAPS II ($p = 0.025$, $b = 0.008$) had a significant impact on 30-day mortality. The conclusion of the study was that the use of CS in patients with hyperbilirubinemia did not result in a significant reduction in 30-day mortality. The authors suggest that randomized and controlled studies with mortality as the primary outcome measure are needed in the future to justify their use. Hui et al., [69] find that extracorporeal blood purification (EBP) with HA is an effective and safe modality for bilirubin removal among children aged 1 month to 18 years old who received EBP for hyperbilirubinemia in the pediatric intensive care unit of Hong Kong Children's Hospital from 3/2019 to 7/2022. The overall bilirubin removal ratio by HA was 44.6 (14.5%). Higher HA effective dose and a higher pre-HA bilirubin level were both associated with better bilirubin removal. No major EBP-specific complication was encountered. The liver enzymes showed improvement in all children. No patients required liver transplantation. There was no EBP-related mortality, but the overall pediatric intensive care unit mortality of the cohort was 50%. Future studies should investigate the impact of bilirubin removal on clinical outcomes and explore the factors responsible for better removal efficacy. Frimmel et al., [70] discusses the combined use of single-pass albumin dialysis (SPAD) with CA in a patient suffering from ALF and probable hemophagocytic lymphohistiocytosis (HLH) with SIRS who was listed for liver transplantation. The study found that the IL-6 concentration before treatment was 81,059 pg/mL (normal range < 7.00 pg/mL). After 12 hours of treatment, it had fallen to 17,177 pg/mL. The norepinephrine dosage could be reduced to 0.25 mg/kg/minute, and clinically, no further deterioration of the patient was observed. The treatment was safe and well-tolerated, without any

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adverse events. This suggests that the combined use of SPAD with CA could be an effective treatment for managing such conditions. Ghinolfi et al., [71] describes a new ex-situ machine perfusion device that uses a model of donors after circulatory death liver grafts procured from slaughterhouse pigs. The device allowed stable perfusion in both hypothermic (n = 6) and normothermic (n = 8) conditions, and no technical failure was observed. During perfusion, perfusate and bile samples were collected to assess liver metabolism and viability and had an integrated CA device that efficiently removed inflammatory cytokines, which are molecules that can cause inflammation and organ damage. Li et al., [72] discusses the use of endotoxin and CA-CRRT in managing septic shock after liver transplantation. The study reports a case of a 35-year-old man with a 20-year history of hepatitis B who developed septic shock after liver transplantation. The patient was immediately treated with endotoxin and CA-CRRT (oXiris® hemofilter) along with tigecycline, caspofungin, and ganciclovir as anti-infectives. After 48 hours on CRRT, the patient's blood pressure gradually stabilized, the CLIF Consortium Acute-on-Chronic Liver Failure score decreased from 63 to 43, and procalcitonin, endotoxin, and the inflammatory factors IL-6 and IL-10 also decreased gradually. The patient's liver and kidney functions were completely restored. This suggests that oXiris® CRRT combined with antibacterial therapy could be an effective treatment for septic shock after liver transplantation.

3.5. Therapeutic Applications in Lymphome and Allogeneic Transplantation

Stahl et al., [73] uses extracorporeal CA for cytokine release syndrome (CRS). The CRS rising form potential life-threatening complications of CD-19 Chimeric antigen receptor-T is usually treated with IL-6 blockade and steroids but here, multiple soluble inflammatory factors were reduced by more than 50% following the procedure. However, markers of endothelial injury increased steadily, indicating the need for further research into the efficacy of the procedure. Raedemacher et al., [74] provides in a case study evidence for the potential efficacy of CA as a supportive treatment for lymphoma-associated hemophagocytic lymphohistiocytosis (HLH) in patients undergoing allogeneic stem cell transplantation. The patient in this case was able to achieve hematopoietic engraftment and disease-free discharge due to the combination of CA and stem cell transplantation.

4. Therapeutic Applications of Cytokine Adsorption in Complication after Organ Transplantations

4.1. Therapeutic Plasmapheresis

Tomescu et al., [75] makes use of a combination of HA and continuous venovenous hemofiltration (CVVH) that has the potential to be an effective therapy for SIRS associated with emergency re-transplantation. Hemoadsorption is a technique that removes cytokines, toxins, and other mediators of inflammation from the patient's bloodstream. It works by passing the patient's blood through a column containing a special adsorbing material. This material binds the cytokines, toxins, and mediators, preventing them from circulating in the bloodstream. CVVH is an extracorporeal technique that works by removing fluid and toxins from the patient's bloodstream. It works by passing the patient's blood through a filter that removes excess fluid and toxins, allowing them to be safely removed from the body. The combination of HA and CVVH allowed for the rapid and efficient removal of pro- and anti-inflammatory cytokines from the patient's bloodstream. This allowed for the normalization of cardiac output and systemic vascular resistance, and improved liver function. The combination of these two techniques may prove to be an effective and safe therapy for SIRS associated with emergency re-transplantation. Nakanishi et al., [76] reviews therapeutic plasmapheresis has become an important treatment for a variety of diseases that cannot be cured by conventional drug therapy. This is due to its ability to remove pathogenic antigens or substances in the plasma fraction, and to supplement essential factors such as albumin and coagulation factors. Plasma separators and/or fractionators are essential for the therapy. Plasma exchange is the most commonly used modality and it is used for conditions such as thrombotic microangiopathy and acute hepatic failure. Double-filtration plasmapheresis is used for the removal of macromolecules, such as immunoglobulins, while avoiding the use of substitution fluids. This is used for conditions such as

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hyperviscosity syndrome and AB0-incompatible kidney transplantation. Plasma adsorption is used to specifically remove pathogenic agents such as low-density lipoprotein or autoantibodies in the IgG fractions by the adsorption column and does not require substitution fluids. This is used for a wide variety of neurological diseases, including chronic inflammatory demyelinating polyneuropathy. The use of therapeutic plasmapheresis is constantly evolving and improving in order to increase the efficacy and specificity of removal of the target substance. As this technology advances, new modalities and treatments are being developed to address a variety of conditions and diseases. Salvadori et al., [77] reviews the role of therapeutic apheresis in kidney transplantation. There are several therapeutic apheresis procedures available, including plasmapheresis, erythrocytapheresis, leukapheresis, plateletpheresis, therapeutic plasma exchange, cytapheresis (including red cell exchange), and extracorporeal photopheresis. Therapeutic apheresis can be classified into two main categories: plasma exchange and selective apheresis. PE involves the removal of plasma from the patient and its replacement with a suitable fluid, such as albumin solution, fresh frozen plasma, or a combination of both. Selective apheresis involves the removal of specific blood components or substances, such as red blood cells, platelets, leukocytes, immunoglobulins, lipoproteins, or cytokines, using different techniques, such as centrifugation, filtration, adsorption, or immunoadsorption. Therapeutic apheresis is recognized for increasing the donor pool by treating HLA-sensitized patients and making AB0-incompatible kidney transplantation possible. Its use in patients with donor-specific antibodies has a beneficial effect on graft survival. In the setting of kidney transplantation, immunological barriers such as AB0 blood group incompatibility and preformed donor-specific antibodies can complicate the outcome of deceased- or living-donor transplantation. Postoperatively, additional problems such as antibody-mediated rejection and a recurrence of primary FSGS can limit therapeutic success and decrease graft survival. The review aims to describe the available techniques of therapeutic apheresis with their specific advantages and disadvantages. It also examines the evidence supporting the application of therapeutic apheresis as an adjunctive therapeutic option to immunosuppressive agents in protocols before and after kidney transplantation. Further studies are needed to establish the effectiveness of apheresis in kidney diseases. Wallet et al., [78] discusses the case of a 79-year-old patient treated for an aggressive diffuse large B-cell lymphoma refractory to several lines of therapy. The patient was treated with a T-cell-engaging bispecific antibody linking CD3 T cells to CD20 malignant B cells. Unfortunately, a few hours after infusion, the patient developed a grade-2 CRS that rapidly deteriorated to grade 4 and needed ICU admission. Infection was ruled out by blood and bronchoalveolar lavage culture for both bacteria and fungi, and viral PCR analysis of bronchoalveolar lavage, peripheral blood, and bone marrow aspirate. The patient received three injections of tocilizumab 8 mg/kg over a 24-h period and 10 mg dexamethasone 4 times a day. Tocilizumab is a monoclonal antibody that targets the IL-6 receptor and may compete with IL-6, leading to a paradoxical rise in blood level. It has been previously reported that tocilizumab may result in a transient increase in IL-6 level, rising concerns about transient worsening especially for neurotoxicity. The authors hypothesize that CytoSorb® lowered cytokine levels thus helping us to quickly control the shock, allowing other therapies (corticosteroids) to control CRS which is responsive for cytokines secretion. Despite these treatments, the CRS did not improve, leading to the use of extracorporeal CA as a rescue therapy. One major concern regarding CA, particularly in septic patients, is the potential adsorption of anti-microbial treatment. However, in the case presented herein the plasma concentration of antimicrobial agents during the 48 h of CytoSorb® epuration were all within the expected range.

4.2. Sepsis Complications

Septic shock can be caused by a variety of mechanisms, including the direct effects of bacterial toxins such as endotoxin. Annually, approximately 5–7 million patients worldwide develop sepsis with very high endotoxin activity in the blood, and more than half die. The term endotoxic septic shock has been used for these patients, but it is important to emphasize that endotoxin may be a factor in all forms of septic shock, including non-bacterial etiologies like COVID-19, since translocation of bacterial products is a common feature of septic shock. A pattern of organ failure

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including hepatic dysfunction, AKI, and various forms of endothelial dysfunction ranging from disseminated intravascular coagulation to thrombotic microangiopathy characterize endotoxic septic shock. However, while characteristic, the clinical phenotype is not unique to patients with high endotoxin, and the diagnosis relies on the measurement of endotoxin activity in addition to clinical assessment. Therapies for endotoxic septic shock are limited with immune modulating therapies under investigation and extracorporeal blood purification still controversial in many parts of the world [79]. Early applications of CA in management of sepsis were proposed by Tetta et al., [80]. They used continuous plasma filtration with sorbent adsorption for the removal of cytokines. The study showed that plasma filtration rather than ultrafiltration significantly increased the clearance of all cytokines, particularly TNF-α. The synthetic Amberlite-type of resin, but not natural uncoated charcoal, could extensively absorb almost 100% of plasma filtered IL-Ra, IL-1β and IL-8, but only 40% of TNF-α. Two protein bands of approximately 400,000 D and 200,000 D were eluted only from Amberchrome resins and immunoprecipitated by anti-human alpha2-macroglobulin and anti-human C3c antibodies, respectively. These studies suggest an efficient removal of cytokines in continuous plasma filtration with sorbent adsorption. The binding of alpha2-macroglobulin, a carrier of cytokines in plasma, might be an additional mechanism in the removal of cytokines from plasma. Song et al., [81], in an experimental approach with rats found that the adsorption rate of the cytokines onto the polymer beads was concentration-dependent and increased with increasing temperature. The highest adsorption rate was observed at 40°C, followed by 37°C and then 30°C. In addition, the kinetics of adsorption of the cytokines onto the beads was found to be independent of calcium concentration. These results suggest that the adsorbent polymer is an effective and efficient adsorbent for various inflammatory cytokines and that temperature and calcium do not appear to significantly affect the adsorption rate. In an early hemofiltration approaches, Rimmele et al., [82] discusses the use of a new hemofiltration membrane with enhanced adsorption properties due to a special surface treatment, allowing the adsorption of endotoxins. The study compared this membrane to a standard hemofiltration membrane both in vitro and in 20 sepsis-induced pigs, randomized in two groups. One group was hemofiltered with the treated membrane and the other with the standard hemofiltration membrane during 6-h high volume hemofiltration sessions. At the end of the experiment, mean crystalloids requirements, colloids requirements, lactic acidosis, and pulmonary arterial hypertension were less pronounced when high volume hemofiltration was performed with the treated membrane. In addition, mean ± SD endotoxins levels were lower in the treated membrane group after 1 hour of high volume hemofiltration (1.91 ± 1.19 versus 11.07 ± 10.64 EU/ml, P = 0.035). Cytokines levels were not different between groups except for IL-1β, which was slightly lower in the treated membrane group. The conclusion of the study was that the use of a membrane with enhanced adsorption properties during a 6-h high volume hemofiltration session in septic pigs improves hemodynamics compared to a standard hemofiltration membrane. These results are probably due to an efficient endotoxins and cytokines adsorption. Panagiotou et al., [83] discusses the role of extracorporeal therapies, such as Sequential Extracorporeal Therapy in treating sepsis. This involves targeting circulating molecules for removal at various stages. The sequence of events and the use of different techniques at different points for specific targets are discussed. Over the years, multiple extracorporeal techniques have evolved, with the intent of influencing the circulating levels of inflammatory mediators like cytokines and chemokines, the complement system, as well as factors of the coagulation system. These include high-volume hemofiltration, use of high cutoff membranes, and systems based on adsorption, such as coupled plasma filtration adsorption and the polymyxin-B column. Hemoperfusion with CytoSorb® is able to efficiently remove cytokines and other medium-sized molecules involved in CRS, thus playing a synergistic effect with CRRT. The paper also discusses the potential role of blood purification in treating sepsis. This approach is proposed as an adjuvant therapy for sepsis, aiming at controlling the associated dysregulation of the immune system. In early experiment with a CA system, Lees et al., [84] discusses the successful use of extracorporeal support and the CA therapy in treating a patient with severe acute respiratory failure, septic, and cardiogenic shock. The case report describes the successful treatment of a 33-year-old patient who developed acute cardiovascular collapse and ARDS secondary to superinfection of Panton-Valentine

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leukocidin-positive Staphylococcus aureus and H1N1 pneumonia using extracorporeal membrane oxygenation and CA therapy. The patient underwent successful combination therapy for severe sepsis-related cardiomyopathy and respiratory failure using ECMO and CA therapy. This case demonstrates the novel and successful use of ECMO and cytokine removal in severe PVL-S aureus sepsis with ARDS and cardiomyopathy. It adds to the evidence showing CA as a compelling adjuvant therapy in severe sepsis. This case is the first report to our knowledge of the successful use of extracorporeal support and the CA therapy in combination to treat a patient with severe acute respiratory failure, septic, and cardiogenic shock due to PVL-S. aureus superinfection with H1N1. Schädler et al., [85] suggests that HA therapy is not associated with improved outcomes in septic patients with respiratory failure. Their treatment was found to remove IL-6 from the patient's blood, but this did not lead to a reduction in plasma IL-6 levels or improved outcomes. The study did find a higher rate of mortality in the treatment group, but this was not statistically significant after adjustment for morbidity and baseline imbalances. Zuccari et al., [86] suggests that HA with CA may be a promising adjunctive therapy for sepsis in critically ill adult patients. Their findings indicate that it may be able to reduce plasma levels of IL-8 and improve microvascular perfusion, despite no significant variation in macro-hemodynamic parameters. The improvements in microcirculation may lead to an overall improvement in outcome in septic patients. Further research is needed to confirm these findings and to determine the optimal use of this technology in clinical practice. De Rosa et al., [87] discusses several important aspects of extracorporeal blood purification therapies for managing sepsis and sepsis-associated AKI. Polymyxin B hemadsorption (PMX-HA) has been tested in several experimental and clinical studies for endotoxic shock. The results have shown that PMX-HA can effectively reduce endotoxin and cytokine levels in plasma, improve hemodynamics and oxygenation parameters, and decrease mortality rates in endotoxic animals and patients. However, the optimal timing, frequency, and duration of PMX-HA are still unclear, and the long-term effects of PMX-HA on organ function and quality of life are not well established. The clinical indication for PMX-HA is widely debated in the literature. Some experts suggest that PMX-HA should be initiated as early as possible in patients with suspected or confirmed Gram-negative sepsis who have signs of organ dysfunction or refractory shock. Others propose that PMX-HA should be reserved for patients with confirmed endotoxemia who have high levels of Endotoxin Activity Assay (EAA), a rapid test that measures the biological activity of endotoxins in whole blood. The EAA can be used to monitor the response to PMX-HA and to guide its duration and frequency. Ronco et al., [88] reviews the use of extracorporeal therapies for sepsis and septic shock has the potential to improve outcomes. However, further research is needed to evaluate the safety, efficacy, and cost-effectiveness of these treatments. In particular, the optimal timing of treatment, the selection of patients who are most likely to benefit from extracorporeal therapies, and the development of new devices that are able to target specific molecules are needed. Furthermore, randomized controlled trials should be conducted to determine whether extracorporeal therapies are superior to conventional treatments. Ricci et al., [89] reviews HP as a process that has been studied and applied in the treatment of various medical conditions, such as sepsis, liver failure, and kidney failure. Recent randomized controlled trials have shown that HP may be beneficial in the treatment of septic shock and multi-organ failure. In these trials, HP was found to reduce the levels of proinflammatory cytokines in the blood and improve clinical outcomes. In addition, the use of HP was found to be safe and well tolerated by patients. Despite the promising results of these trials, more research is needed to further evaluate the efficacy and safety of HP in the treatment of septic shock and multi-organ failure. Future studies should focus on the potential benefits of using it in combination with other treatments, such as antibiotics, to further improve the prognosis of patients with sepsis and multi-organ failure. Furthermore, more research is needed to elucidate the mechanisms of action of HP and to identify other potential indications for its use. Forin et al., [90] analyzes a single center, retrospective, observational web-based database (extracted from the EUPHAS2 registry) of critically ill patients admitted to the ICU between January 2016 and May 2021 who were affected by endotoxic shock. From January 2016 to May 2021, 61 patients were treated with PMX-HA out of 531 patients diagnosed with septic shock and of these, fifty patients (82%) developed AKI during their ICU stay. The most common source of infection was secondary

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peritonitis (36%), followed by community-acquired pneumonia (29%). Fifty-five (90%) out of 61 patients received a second PMX-HA treatment, with a statistically significant difference between the two groups (78% of the Pre-F vs. 100% of the Post-F group, p = 0.005). In both groups, between T0 and T120, the EAA decreased, while the SOFA score, MAP, and Vasoactive Inotropic Score improved with no statistically significant difference. Furthermore, when performing a propensity score matching analysis to compare mortality between the two groups, statistically significant lower ICU and 90-day mortalities were observed in the Post-F group [p = 0.016]. Although in this experienced center data registry, PMX-HA was associated with organ function recovery, hemodynamic improvement, and current EAA level reduction in critically ill patients with endotoxic shock. Following propensity score-matched analysis, ICU mortality and 90-day mortalities were lower in the diagnostic-therapeutic flowchart group when considering two temporal groups based on strict patient selection criteria and timing to achieve PMX-HA. In a pilot study that Friesecke et al., [91] conducted a study on 17 patients with refractory septic shock. Hemodynamic measurements and laboratory tests were performed before and after each HP session. The results showed that CA HP significantly decreased levels of pro-inflammatory cytokines and improved hemodynamic parameters such as MAP and cardiac index. Moreover, the study revealed a decrease in markers of oxidative stress, suggesting that the technique may have beneficial effects on the metabolic aspects of septic shock. Overall, the results of this pilot study suggest CA is a promising approach for the treatment of refractory septic shock. Kogelmann et al., [92] evaluates the impact of a new HA device, CytoSorb®, used as adjunctive therapy on hemodynamics and clinically relevant outcome parameters in 26 critically ill patients with septic shock who needed CRRT. Treatment of these patients with septic shock was associated with hemodynamic stabilization and a reduction in blood lactate levels. Actual mortality in the overall patient population was lower than mortality predicted by Acute Physiology and Chronic Health Evaluation II (APACHE II). The effects seem to be more pronounced in patients in whom therapy started within 24 hours of sepsis diagnosis. A delay in the start of therapy was associated with a poor response to therapy in terms of reduction of catecholamine demand and survival. Treatment using the CytoSorb® device was safe and well-tolerated with no device-related adverse events during or after the treatment sessions. Hemoadsorption using CytoSorb® resulted in rapid hemodynamic stabilization and increased survival, particularly in patients in whom therapy was started early. Kogelmann et al., [93] shows that their septic shock dynamic scoring system (DSS) can be used to identify patients with a high risk of death and in our cohort with a DSS score >4.4 that was associated with a mortality rate of >30%, indicating a clear cut-off for the initiation of adjunctive CA therapy. Furthermore, a delay of more than 12 h between the onset of septic shock and the start of CA therapy was associated with a worse outcome, in terms of mortality and length of stay. This suggests that the earlier a patient is treated, the better the outcome. These findings support the use of the DSS as a tool to identify patients with refractory septic shock who might benefit from adjunctive CA treatment. The results of this analysis are in line with the results of recent studies, which suggest that the early initiation of adjunctive CA therapy might be beneficial for patients with septic shock. De Rosa et al., [94] describes the successful management of a 49-year-old man who presented in the emergency department with a 5-day history of cough, fever, and dysuria and was admitted to the intensive care unit due to septic shock. An endotoxic shock was suspected and the patient was initially treated with PMX-HA alternate with high-volume hemofiltration sessions, which resulted in a marked decrease in the serum endotoxin level. However, due to the progression of circulatory insufficiency, veno-arterial extracorporeal membrane oxygenation (VA-ECMO) was initiated for circulation assistance on day 3 from admission. CA was incorporated into the VA-ECMO circuit for 48 h without a considerable improvement. Subsequently, a 72-h continuous veno-venous HD session was started in which a high cutoff filter was used. Tachycardia and myocardial dysfunction improved, and VA-ECMO was withdrawn on the tenth day. Nutrition management and rehabilitation were then performed, and the patient was discharged from our hospital on day 113. This case highlights the importance of sequential extracorporeal therapy when concomitant with circulatory assistance in severe cases of septic shock. David et al., [95] tests the effects of CA on a 32-year-old female patient with septic shock and accompanying AKI.

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The study analyzed the endothelial phenotype in vitro before and after extracorporeal cytokine removal and found that there were severe alterations in cell-cell contact and the cytoskeletal architecture as well as profound functional permeability changes. However, the endothelial barrier was protected from these adverse effects when challenged with septic shock serum that was collected after extracorporeal cytokine removal. This suggests that beneficial observations of extracorporeal cytokine removal in septic shock patients might be promoted via protection of vascular barrier function. In a 70-year-old male patient who presented with severe sepsis due to S. aureus bacteremia, complicated by ARDS, septic shock, and multiorgan failure. Bruenger et al., [96]. describes the successful management of patient that had been admitted to the intensive care unit and was initially stabilized using conventional supportive care, including antibiotics, fluids and vasopressors. However, his condition deteriorated and he developed severe hypotension, increased lactate levels, and metabolic acidosis. The team started left ventricular assist device support, ECMO, CVVH, and CA. The patient responded well to the combined therapy, with improved organ perfusion, normalization of lactate levels, and resolution of metabolic acidosis. The patient was weaned off ECMO and left ventricular assist device support. He was subsequently discharged from the hospital in good condition. This case report demonstrates that the combined use of left ventricular assist device, ECMO, CVVH, and CA is a viable option for management of severe sepsis in critically ill patients. The combination of devices provided effective organ support and improved the patient's clinical outcome. The combination of devices could be a reasonable approach for management of sepsis in patients with multiple organ dysfunction, especially when conventional supportive care is not sufficient. Linden et al., [97] performs CA HA as a therapy for patients with refractory septic shock to improve hemodynamic stability and reduce the need for vasopressors. A patient with septic shock and multi-organ failure who was treated with CA HA for five consecutive days. Following the treatment, the patient experienced a significant reduction in the need for vasopressors and a marked improvement in the clinical status. Their results suggest that CA HA may be a viable and effective therapeutic option in the management of refractory septic shock. Netti et al., [98] investigates the therapeutic efficacy of LPS removal in decreasing albuminuria through the reduction of CD80 expression, a co-stimulatory molecule, in podocytes, which are specialized cells that form the filtration barrier in the kidney. CD80 expression in podocytes can cause proteinuria, or the leakage of protein into the urine, which is a sign of kidney damage and a risk factor for CKD. To elucidate the possible relationship between LPS-induced renal damage, proteinuria, and CD80 expression in Gram sepsis, a swine model of LPS-induced AKI was set up. The treatment with CPFA significantly reduced serum cytokines, CRP, procalcitonin, and endotoxin levels in patients with Gram-negative sepsis-induced AKI. CPFA treatment also significantly lowered proteinuria and albuminuria levels, along with CD80 urinary excretion. The study suggests that selective removal of LPS reduces albuminuria and CD80 expression both in the experimental and clinical settings and propose a possible role of this therapeutic approach in preventing the increased risk of progressive chronic kidney disease (CKD) in patients with septic AKI. Li et al., [72] discusses the use of endotoxin and CA-CRRT in managing septic shock after liver transplantation. The study reports a case of a 35-year-old man with a 20-year history of hepatitis B who developed septic shock after liver transplantation. The patient was immediately treated with endotoxin and CA CRRT (oXiris hemofilter) along with tigecycline, caspofungin, and ganciclovir as anti-infectives. After 48 hours on CRRT, the patient's blood pressure gradually stabilized, the Consortium Acute-on-Chronic Liver Failure score decreased from 63 to 43, and procalcitonin, endotoxin, and the inflammatory factors IL-6 and IL-10 also decreased gradually. The patient's liver and kidney functions were completely restored. This suggests that oXiris CRRT combined with antibacterial therapy could be an effective treatment for septic shock after liver transplantation. Ankawi et al., [99] reviews the role of various extracorporeal techniques in treating sepsis, since diffferent extracorporeal techniques have been studied in recent years in the hope of maximizing the effect of CRRT in modulating the exaggerated host inflammatory response, including the use of high volume hemofiltration, high cut-off (HCO) membranes, adsorption alone, and CPFA. These strategies are not widely utilized in practice, depending on resources and local expertise. Monard et al., [100] reviews several important aspects of extracorporeal

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blood purification therapies for managing sepsis and sepsis-associated AKI. They describe the use of the oXiris® membrane that has a unique 4-in-1 device that combines cytokine and endotoxin removal properties, renal replacement function, and antithrombogenic properties. oXiris® treatment in septic patients enables optimization of hemodynamic status, clears inflammatory mediators such as TNF-α, IL-6, IL-8, and interferon-γ, and ultimately improves prognosis. This membrane has attracted attention due to its ability to remove both endotoxins and cytokines, which are mediators released by microorganisms and injured cells involved in the pathogenic mechanisms of organ dysfunction, including sepsis-associated AKI. Ricci et al., [89] reviews the use of CA as a process in which blood is circulated through a device containing a biomaterial in order to remove molecules from the flowing blood. The process involves binding of molecules, such as endotoxins and proinflammatory cytokines, to the biomaterial surface. The biomaterial can be in the form of a resin or a membrane, and is tailored to bind the specific molecules in order to remove them from circulation. This process has been studied and applied in the treatment of various medical conditions, such as sepsis, liver failure, and kidney failure. Recent randomized controlled trials have shown that HP may be beneficial in the treatment of septic shock and multi-organ failure. In these trials, HP was found to reduce the levels of proinflammatory cytokines in the blood and improve clinical outcomes. In addition, the use of HP was found to be safe and well tolerated by patients. Despite the promising results of these trials, more research is needed to further evaluate the efficacy and safety of HP in the treatment of septic shock and multi-organ failure. Future studies should focus on the potential benefits of using it in combination with other treatments, such as antibiotics, to further improve the prognosis of patients with sepsis and multi-organ failure. Ankawi et al., [101] reviews the use of polysulfone adsorption column with an adsorption capacity of up to 6,000 g/L. It has been demonstrated to be an effective technique in the removal of endotoxins, cytokines, myeloperoxidase, and other pro-inflammatory mediators. It has been used in clinical studies for the treatment of sepsis and septic shock, as well as for other acute inflammatory conditions, such as AKI, ARDS, and post-CPB syndrome. The most common method of use is CVVH with CA. The potential advantages of using CA for the treatment of acute inflammatory conditions include the removal of high concentrations of mediators in a short period of time. This can potentially lead to a faster resolution of symptoms and improved outcome. Additionally, the use of this adsorption column has been shown to be safe and well tolerated, with no reports of adverse reactions. The evidence supporting the use of CA for the treatment of acute inflammatory conditions is still limited, and further studies are required to confirm its efficacy. Additionally, further studies are needed to explore the potential of this technique for other clinical applications. Nevertheless, CA has demonstrated potential efficacy and safety in the treatment of acute inflammatory conditions, and should be considered as a potential therapeutic option. Ruegg et al., [102] demonstrates the potential of CA to improve hemodynamics and metabolism in refractory septic shock. The study analyze septic shock patients who received CytoSorb® in addition to CCRT. This group was compared to a matched control group. The baseline comparability between the two groups was high, with differences mainly in higher initial SOFA scores and requirements of norepinephrine equivalents in the CytoSorb® group. The requirement for catecholamines decreased to 0.26 microg/kg/min within 24 hours after the initiation of CytoSorb® therapy, while it remained fairly constant in the control group. The in-hospital mortality was significantly lower in the CytoSorb® group (35.7% vs. 61.9%). Within the CytoSorb® group, high lactate levels and low thrombocyte counts prior to initiation were identified as risk factors for mortality. A cut-off value of 7.5 mmol/L lactate predicted mortality with high specificity (88.9%). High lactate levels may indicate absent benefits when confronted with septic shock patients considered eligible for CytoSorb® therapy. These findings suggest that HA with CytoSorb® could potentially reduce catecholamine requirements and in-hospital mortality in septic shock patients. Mariano et al., [103] evaluates the efficacy and safety of CPFA in severe burn patients with septic shock and AKI needing CRRT. The study was conducted between January 2001 and December 2017, and it included 39 severe burn patients who were treated with CPFA (CPFA group) and 87 patients who were treated with RRT but not CPFA (control group). The study found that the observed mortality rate was 51.3% in the CPFA group and 77.1% in the control group (p 0.004). The SOFA score

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on the first day of CPFA resulted significant in the multivariate analysis logistic model. The study also collected data regarding CPFA safety (hemorrhagic episodes, catheter associated-complications, hypersensitivity reactions) and efficiency (number and duration of CPFA sessions, plasma treated amount, plasma processed dose). Reis et al., [104] emphasizes the need for a new classification of solutes of interest in chronic kidney disease and HD. It highlights that the retention of solutes is already detected in the early stages of the disease when patients are pauci-symptomatic or asymptomatic. The role of therapies to retard the loss of kidney function in patients with chronic kidney disease (e.g., modulators of the renin-angiotensin-aldosterone system, sodium-glucose cotransporter inhibitors) in reducing uremic toxins is poorly understood. In the past 2 decades, blood purification strategies with enhanced convective properties, such as high-volume online hemodiafiltration and expanded HD, have considerably amplified the ability to mechanically extract middle molecules (molecular weight >0.5 kDa) from the blood compartment. However, the role of therapies to retard the loss of kidney function in patients with chronic kidney disease in reducing uremic toxins is still poorly understood. De Rosa et al., [105] reviews several important aspects of Sepsis-Associated AKI (SA-AKI), a life-threatening condition leading to high morbidity and mortality in critically ill patients. Over the past decades, several extracorporeal blood purification therapies have been developed for both sepsis and sepsis-associated AKI management. Despite the widespread use of these therapies, it is still unclear when to start this kind of treatment and how to define its efficacy. Several questions on SA-AKI and extracorporeal blood purification therapy still remain unresolved, including the indications and timing of CRRT in patients with septic vs. non-septic AKI, the optimal dialysis dose for CRRT modalities in SA-AKI patients, and the rationale for using these therapies in septic patients without AKI. Dubler et al., [106] assesses the outcome relevance of adequately treated putative invasive pulmonary aspergillosis (pIPA) in a cohort of critically ill patients with and without solid organ transplantation. The study included data from 121 surgical critically ill patients with pIPA (n = 30) or non-pIPA (n = 91). the adequately treated putative invasive pulmonary aspergillosis (pIPA) did not increase the risk of death or an unfavorable outcome. Instead, a higher SOFA score and evidence of bacteraemia were identified as risk factors for mortality and unfavorable outcomes. Adequately treated pIPA did not increase the risk of death or an unfavorable outcome in this mixed cohort of critically ill patients with or without solid organ transplantation, whereas higher disease severity and bacteraemia negatively affected the outcome..

4.3. Covid Complications

Villa et al., [107] suggests that EBP with a heparin-coated hemodiafilter featuring CA properties may be a safe and effective treatment for critically ill patients with COVID-19. The study showed that EBP was associated with significant reduction in serum IL-6 levels, attenuation of systemic inflammation, improvement in multiorgan dysfunction, and a reduction in expected ICU mortality rate. While there were some technical complications and adverse events, overall treatment was safe and effective. This study highlights the potential benefits of EBP with a heparin-coated hemodiafilter featuring CA properties and provides promising evidence that this therapy may be beneficial in the treatment of COVID-19. Ronco et al., [108] used a MCO dialyzers for HD that has been proposed as a possible strategy to reduce the risk of COVID-19 infection among dialysis patients. The MCO dialyzers are designed to remove large uremic toxins, such as β-2-microglobulin and indoxyl sulfate, which are known to cause chronic inflammation and immunosuppression in dialysis patients. The removal of these toxins with MCO dialyzers may be beneficial to COVID-19 patients as it may reduce the systemic inflammation and immunosuppression induced by the virus. In addition, MCO dialyzers have been shown to reduce the risk of infection in dialysis patients. Furthermore, the removal of toxins with MCO dialyzers may reduce the severity of infection, resulting in lower mortality rates. Lastly, MCO dialyzers may reduce the risk of kidney damage or AKI progression due to direct cytopathic effects of the virus on renal tissue. It is also important to consider the cost-effectiveness of this strategy and to evaluate the safety of the MCO dialyzers in long-term use. Ronco et al., [109] suggests that the mechanism of kidney involvement in COVID-19 is still not fully understood but in severe cases is most likely caused by a combination of direct viral infection and an

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inflammatory response. The SARS-CoV-2 virus, has also been detected in the urine of some patients. In addition, microvascular thrombosis, complement activation, and CRS could be important factors in the development of AKI. As the disease progresses, there is evidence of interstitial inflammation, tubular dysfunction, and glomerular and vascular damage. Furthermore, direct and indirect evidence suggests that a variety of drugs used to treat COVID-19 may directly or indirectly contribute to renal toxicity. In patients who are critically ill, there can be an increased risk of AKI and sepsis-induced AKI, which can be exacerbated by the presence of underlying chronic kidney disease. In such cases, extracorporeal support with various blood purification strategies, such as HD, hemofiltration, and plasmapheresis, can be used to remove inflammatory mediators, cytokines, and other toxins. These strategies are also beneficial in reducing fluid overload and controlling electrolyte and acid-base imbalances. Additionally, extracorporeal therapies may help to protect and improve kidney function, reduce mortality, and improve the prognosis of patients with severe COVID-19. Raina et al., [110] reviews the use of blood filters in the treatment of kidney failure, either as a part of dialysis or as an adjunct to kidney transplantation. During the COVID-19 pandemic, the use of blood filters has been evaluated as a potential treatment for severe cases of the virus in children. The use of these filters has been suggested to reduce the levels of cytokines and other inflammatory mediators that can lead to a CRS, which can be a major cause of organ failure in pediatric patients. Cytokine removal has been studied with the use of CA, HA330, and HCO/MCO filters, while endotoxin removal has been studied with the use of Toraymyxin and CPFA filters. The oXiris® filter has been studied for both cytokine and endotoxin removal, while the PMMA filter has been studied for the nonspecific removal of proteins. All of these filters have the potential to reduce the effects of a CRS in pediatric patients with COVID-19. The efficacy of blood filters in the treatment of pediatric COVID-19 patients has yet to be fully evaluated, as there are still many unknowns about the virus and its effects on the body. However, the use of these filters could help reduce the levels of cytokines and other inflammatory mediators, which could reduce the severity of the disease and the risk of organ failure. In addition, the use of these filters could reduce the need for other treatments, such as steroids and immune-modulating drugs, which may have their own adverse effects. Nadim et al., [111] suggests that when diagnosing COVID-19 AKI, clinicians should consider the presence of proteinuria and/or haematuria and the presence of acute or worsening renal impairment (defined as a >25% decrease in estimated glomerular filtration rate (eGFR) from baseline or a decrease to <60 ml/min/1.73 m2) and/or an increase in serum creatinine (SCr) in the absence of a pre-existing chronic kidney disease (CKD). An alternative method for assessing renal impairment is to calculate the urinary sodium/creatinine ratio; a ratio of <1 suggests a pre-renal cause for AKI, while a ratio of >1 suggests an intrinsic renal cause. Additionally, clinicians should consider other causes of AKI, such as sepsis, drug toxicity and volume overload, as well as other causes of AKI in the setting of COVID-19, such as thrombotic microangiopathy and contrast-induced nephropathy. In order to do the management of COVID-19 AKI, clinicians should ensure that the patient is optimally hydrated and that any underlying causes of AKI are addressed. If RRT is required, clinicians should ensure that the patient is adequately monitored and that they receive the appropriate level of supportive care while receiving CRRT. Additionally, clinicians should ensure that the patient is monitored for the development of dialysis-associated complications, such as hypotension, infection, and electrolyte disturbances. Clinicians should also monitor for the development of thrombotic microangiopathy and take appropriate steps to address it if it is present. Iannacone et al., [112] suggests that potential immunomodulatory therapies in COVID-19 to reduce the exaggerated cytokine release in response to viral infection, otherwise known as CRS. Pharmacological approaches, such as glucocorticoids and other immunosuppressants, can be used to inhibit inflammation and reduce the risk of developing ARDS and multiple organ failure. Non-pharmacological approaches, such as diet, exercise, and stress management, can also be used to reduce inflammation and improve the body's immune response. Both of these approaches have the potential to improve clinical outcomes and prognosis in COVID-19 patients. It is important that further research is conducted to understand the effectiveness of these therapies in COVID-19 patients in order to develop more effective treatments. Ronco et al., [109] explores the still not fully understood mechanism of kidney involvement in COVID-19. In severe

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cases, there is evidence of AKI, which is most likely caused by a combination of direct viral infection and an inflammatory response. The primary infection of the kidney is believed to be caused by the SARS-CoV-2 virus, which has been detected in the urine of some patients. In addition, microvascular thrombosis, complement activation, and CRS could be important factors in the development of AKI. As the disease progresses, there is evidence of interstitial inflammation, tubular dysfunction, and glomerular and vascular damage. Furthermore, direct and indirect evidence suggests that a variety of drugs used to treat COVID-19 may directly or indirectly contribute to renal toxicity. In patients who are critically ill, there can be an increased risk of AKI and sepsis-induced AKI, which can be exacerbated by the presence of underlying chronic kidney disease. In such cases, extracorporeal support with various blood purification strategies, such as HD, hemofiltration, and plasmapheresis, can be used to remove inflammatory mediators, cytokines, and other toxins. These strategies are also beneficial in reducing fluid overload and controlling electrolyte and acid-base imbalances. Additionally, extracorporeal therapies may help to protect and improve kidney function, reduce mortality, and improve the prognosis of patients with severe COVID-19. Esmaeili Vardanjani et al., [113] suggests that CA and CRRT is an effective and safe method for treating patients with ARDS caused by COVID-19. It can reduce the need for intubation, reduce respiratory distress and dependence on oxygen, prevent other complications, and reduce mortality and hospital length of stay. CA/CRRT should be considered as a first-line therapy for patients with ARDS caused by COVID-19, especially in the early stages. Paisey et al., [114] advocates that the use of adjunctive HA as an adjunctive therapy can significantly reduce inflammation in severe COVID-19 patients. Additionally, further studies should explore how HA can be used in combination with other treatments for COVID-19, such as antivirals and immunomodulators, to further optimize patient outcomes. Rizo-Topete et al., [115] suggests that as the number of patients with COVID-19 increases, it is essential that the critical care nephrology team is available to evaluate the patients' kidney function and provide timely advice on the initiation and management of CRRT and ECOS. In order to facilitate early involvement of critical care nephrology in critical care teams, the institutions should create protocols and/or pathways to identify and rapidly refer patients to nephrologists who are part of the multidisciplinary team. Additionally, it is important to ensure that critical care nephrology are adequately trained to provide timely and appropriate advice on the management of renal failure in patients with COVID-19. The early involvement of critical care nephrology in critical care teams is essential to ensure that patients with COVID-19 receive optimal care. This can help prevent complications from renal failure and reduce mortality. Furthermore, early involvement of CCN in the management of patients with COVID-19 can provide valuable insights into the mechanisms of renal injury in this population, which can help inform the development of better treatment strategies. Yalın et al., [116] proposes the use of MCO membranes in HD for COVID-19 patients may be beneficial for reducing cytokine levels and potentially preventing CRS. This study suggests that MCO membranes can be used to reduce the risk of CRS in COVID-19 patients undergoing HD. Further research is needed to better understand the impact of MCO membranes on the outcomes of COVID-19 patients. Murt et al., [117] suggest that MCO membranes may be effective in reducing inflammation in COVID-19 HD patients. Further studies are needed to confirm this finding and further investigate the potential protective effects of MCO membranes on COVID-19 patient outcomes. Raina et al., [110] reports that during the COVID-19 pandemic, the use of blood filters has been evaluated as a potential treatment for severe cases of the virus in children. Blood filters are used in the treatment of kidney failure, either as a part of dialysis or as an adjunct to kidney transplantation and the use of these filters has been suggested to reduce the levels of cytokines and other inflammatory mediators that can lead to a CRS, which can be a major cause of organ failure in pediatric patients. Cytokine removal has been studied with the use of CA, HA330, and HCO/MCO filters, while endotoxin removal has been studied with the use of Toraymyxin and CPFA filters. The oXiris® filter has been studied for both cytokine and endotoxin removal, while the PMMA filter has been studied for the nonspecific removal of proteins. All of these filters have the potential to reduce the effects of a CRS in pediatric patients with COVID-19. The efficacy of blood filters in the treatment of pediatric COVID-19 patients has yet to be fully evaluated, as there are still many unknowns about

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the virus and its effects on the body. However, the use of these filters could help reduce the levels of cytokines and other inflammatory mediators, which could reduce the severity of the disease and the risk of organ failure. In addition, the use of these filters could reduce the need for other treatments, such as steroids and immune-modulating drugs, which may have their own adverse effects. Jarczak et al., [118] describes the results of a prospective, single-center, randomized, controlled, open-label clinical trial that was conducted from April to June 2020. Patients aged 18 years or older admitted to the ICU with a diagnosis of COVID-19 infection were eligible for inclusion. Patients were included if they had proven hypercytokinemia (IL-6 > 100 pg/mL and/or IL-10 > 30 pg/mL). Patients were randomized to either conventional treatment (CT) or CT combined with HA (CT+H). Randomization was performed by computer-generated random numbers and stratified by the severity of the disease (severe vs. critical). All patients received standard ICU care, including maintenance of fluid balance, sedation, analgesia, and mechanical ventilation if necessary. Patients in the CT+H group also received HA with CA. The device was connected to the extracorporeal circuit of a hemofiltration/HD machine and HA was performed for 10–12 h with a flow rate of 300–400 mL/min and a transmembrane pressure of 350–400 mmHg. The HA procedure was repeated once daily for a maximum of 5 days. The primary outcome measure was the change in the SOFA score from baseline to 24 h after treatment. Secondary outcome measures included changes in hemodynamic parameters, laboratory values, and cytokine levels. All outcome measures were assessed at baseline, 24 h, and 48 h after treatment. Rampino et al., [119] suggests that CA cartridge-based HP may have a potential therapeutic role in the early course of COVID-19 pneumonia. This is further supported by the observed differences in clinical outcomes between the treated and control groups. The limited sample size and observational study design, however, preclude a sound statement about the potential effectiveness of this therapy. A randomized clinical trial is ongoing and will provide more insight into the potential benefits of CA-based HP for the treatment of COVID-19 pneumonia. Pieri et al., [120] evaluates the safety and efficacy of CA treatment in critically ill patients with SARS-CoV-2 syndrome. They included patients admitted to the intensive care unit with a diagnosis of SARS-CoV-2 syndrome and an APACHE score of ≥ 25. Patients were treated with a single session of CA therapy for a period of 4 hours and followed for 30 days. The primary outcome measure was 30-day mortality. Secondary endpoints included organ dysfunction, cytokine levels, and safety. They studied a total of 30 consecutive patients (median age 62 years, range 28–87 years) with SARS-CoV-2 syndrome admitted to the intensive care unit of our institution. Of these, 15 patients (50%) were male and 15 (50%) were female. The primary outcome measure, 30-day mortality, was achieved in 13 (43%) of the 30 patients. The 30-day mortality rate was significantly lower in the CA-treated group compared with the control group (15% vs. 50%, $p = 0.019$). Twenty-four patients (80%) showed improvement in organ function during the course of treatment, with 17 (57%) achieving complete resolution of their organ dysfunction. Cytokine levels, measured before and after the 4-hour session of CA therapy, showed significant reductions in levels of IL-6 and TNF-α. No serious adverse events were observed during or after the treatment. Overall, their results demonstrate that CA treatment is safe and effective in critically ill patients with SARS-CoV-2 syndrome. The treatment was associated with significantly lower 30-day mortality rates, improved organ dysfunction, and reduced levels of inflammatory cytokines. These findings suggest that CA therapy may be a promising therapeutic option in the treatment of SARS-CoV-2 syndrome. Further studies are needed to confirm these results and explore the full potential of this therapy. Stockmann et al., Supady et al., [121] concludes that CA is an effective therapy for the treatment of CRS associated with COVID-19. It has been used in clinical practice in the EU for other conditions in which a CRS occurs, such as sepsis, and an observational study has just been completed on COVID-19 patients. The technology is also being tested in a phase IIb clinical trial in critically ill COVID-19 patients with vasoplegic shock resistant to vasopressor therapy. The primary endpoint is the time to resolution of vasoplegic shock, which is a clinically relevant endpoint in critical care studies. The use of CA may improve outcomes in these patients. Premuzic et al., [122] investigates the impact of sequential extracorporeal treatments with oXiris® or CytoSorb® plus Seraph-100® on the clinical and laboratory parameters of critically ill COVID-19 patients with bacterial superinfection. A significant reduction in SOFA score 3 days after treatment

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was observed in patients undergoing sequential BP compared to those undergoing "standard BP". The differences between the observed and expected mortality rate based on APACHE IV was greater in the sequential BP group than the "standard BP" group. Patients treated with sequential BP had a longer survival than those treated with "standard BP". The study concluded that the sequential approach may enhance the positive effect of BP on organ dysfunction among critically ill patients with COVID-19 and bacterial superinfection.

4.4. Poisoning Complications and Removal of Pharmaceuticals

Bouchard et al., [123] reviews the literature and the EXTRIP workgroup conclude that extracorporeal treatments could be beneficial in some cases of β-adrenergic antagonist poisoning. For propranolol, the workgroup recommends against the use of extracorporeal treatments. For atenolol and sotalol, extracorporeal treatments is suggested in patients with impaired kidney function with refractory bradycardia and hypotension for atenolol or sotalol poisoning, and recurrent torsade de pointes for sotalol. Other β-adrenergic antagonists were assessed as dialyzable, but clinical data were too limited to develop recommendations. It is important to note that the findings of this systematic review should be interpreted with caution due to the low quality of evidence and the limited number of studies included. Hawchar et al., [124] reviews the literature and indicates that CA is effective in reducing norepinephrine requirements in critically ill patients. The pooled effect size at 24 h was large and characterized by high heterogeneity. Further research is needed to determine the full extent of the potential of this therapy. Giuntoli et al., [125] presents a patient case of a 27-year-old female with no known significant medical history was brought to the emergency department after voluntary quetiapine (Seroquel®) intake. The patient reported that she had taken 10 tablets of quetiapine, each containing 25 mg of quetiapine fumarate. Given the patient's mental status and the presence of a prolonged QTc interval, she was intubated and admitted to the Intensive Care Unit. To accelerate quetiapine elimination, they decided to employ CA HP, in combination with CRRT. After the CA HP procedure, the patient was extubated the following day and recovered uneventfully. The combination of HP and CRRT resulted in a rapid reduction of the quetiapine plasma concentration, allowing the patient's mental status and ECG parameters to improve. This approach could be useful in the management of large quetiapine overdoses, especially in cases where the traditional supportive measures are not effective. Dalmastri et al., [126] presents a case report with the successful treatment of an 82-year-old Caucasian man with AKI who was on chronic anticoagulation with Apixaban therapy. Apixaban is a non-vitamin K antagonist oral anticoagulant that inhibits factor Xa, a key enzyme in the coagulation cascade and has emerged as an effective alternative to conventional vitamin K antagonists (VKAs) in the treatment of several thromboembolic disorders. However, in case of overdose or in patients requiring emergency surgery, there is a high bleeding rate and severe adverse side effects due to the absence of an antidote. There is promising data from in vitro and clinical studies that certain antithrombotic agents, such as Rivaroxaban and Ticagrelor, have been successfully removed by the extracorporeal HA therapy CA. Here, the patient required emergency nephrostomy placement while on chronic anticoagulation with Apixaban therapy. Combined treatment with CRRT and CA was associated with the rapid and effective removal of Apixaban allowing for prompt and urgent surgery while simultaneously ensuring the low risk of bleeding as well as an uneventful post-operative course. Godi et al., [127] determines the adsorption capacity of the HA380 cartridge towards the antibiotic Vancomycin. In vitro circulation confirmed the affinity of the HA380 beads material in binding Vancomycin molecules. The kinetics of Vancomycin adsorption showed a rapid decay of the concentration in the first part of the experiments, after which a plateau was observed. A total of 4500 mg of the 5000 mg were adsorbed by the end of the experiment (Removal Ratio = 94%), of which 90% was adsorbed in the first 40 minutes (Removal Ratio = 87%); after this period, the curve became flat and the adsorption phenomenon negligible. In an experiment with 10,000 mg, after 60 minutes of rapid adsorption (Removal Ratio = 55%), the curve reached a plateau converging to a Removal Ratio higher than 60%. The sorbent beads were able to bind 6100 mg out of 10,000 mg injected. This amount saturated the mini-module binding sites. These findings suggest that the HA380 cartridge has a significant capacity to adsorb Vancomycin, which could have

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implications for its use in clinical settings. Scandroglio et al., [128] suggets that CA treatments did not significantly decrease the dose requirements of vancomycin (antistaphylococcal antibiotic) or bivalirudin (an anticoagulant) in the critically ill patients studied. The study concluded that CA is a safe and effective extracorporeal treatment for critically ill patients and does not significantly affect the dose requirements of vancomycin or bivalirudin. Both medications have been shown to be effective in preventing clot formation and in improving outcomes in patients undergoing cardiovascular procedures. However, the combination of these two medications has not been studied in a clinical setting. In addition, the potential synergistic effects of combining these two medications have not yet been explored. Therefore, further research is needed to evaluate the efficacy and safety of combining vancomycin and bivalirudin for prevention of clotting during CPB surgery and other medical procedures. Lorenzin et al., [129] conducts a study to determine the amount of vancomycin adsorbed by a sorbent cartridge (HA380, Jafron Biomedical, Zhuhai City, China). Vancomycin is a glycopeptide antibiotic that is commonly used to treat infections caused by Gram-positive bacteria. However, its use is often associated with adverse side effects such as nephrotoxicity, ototoxicity, and the development of antibiotic-resistant strains. The experiments were carried out using incremental concentrations of vancomycin in the test solution (500 and 1,000 mL) in a recirculation circuit until sorbent saturation was observed. A maximum of 10 g of vancomycin was injected, and mini-modules containing 25 g of dry resin were utilized. The results showed that a maximum amount of 244 mg/g of sorbent was adsorbed, reaching saturation between 60 and 80 min from the beginning of the experiments. The kinetics of adsorption appears to be governed by a Langmuir-like isotherm with maximal removal speed in the early minutes and a plateau after 60 min. De Cal et al., [130] discusses the use of an absorbent cartridge in extracorporeal therapy for sepsis treatment. The study aimed to evaluate the effect of an absorbent cartridge (HA380, Jafron Biomedical, Zhuhai City, China) on the removal of bacteria and vancomycin by HP and its interaction with antibiotic therapy. The study was conducted in vitro and found that the absorbent cartridge was effective in reducing bacterial concentration in blood samples. Adjusting the achieved results with the experimental mini-module to a full-scale cartridge, a total of 25 g of antibiotic can be removed. However, further studies are needed to evaluate the clinical efficacy of this approach. Koster et al., [131] uses of a CA absorption column effectively for extracorporeal removal of argatroban, a thrombin inhibitor to manage heparin-induced thrombocytopenia during a heart transplantation. This strategy allows rapid reduction of argatroban concentrations and helps to achieve satisfactory hemostasis.

5. Conclusions

The literature examining the use of hemoadsoption in transplantation procedures is growing and promising but the evidences to support its application during or after transplantation are at this stage only at their infancy. In this context, the accumulating evidences of the parameters that play a role in hemoadsorption applied during transplantation procedures are essential components for improving the quality of clinical outcome. Therefore, carefully designed and monitored clinical trials is crucial to obtain consistent results.

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Abbreviations

acute respiratory distress syndrome	ARDS

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acute kidney injury	AKI
acute liver failure	ALF
acute lung injury	ALI
acute-on-chronic liver failure	ACLF
acute physiology and chronic health evaluation	APACHE
blood perfusion	BP
cytokine adsorption	CA
cytokine release syndrome	CRS
cardiopulmonary bypass	CPB
cellulose triacetate	CTA
continuous renal replacement therapies	CRRT
continuous venovenous hemofiltration	CVVH
coupled plasma filtration and adsorption	CPFA
C-reactive protein	CRP
donation after circulatory death	DCD
Endotoxin Activity Assay	EAA
extracorporeal membrane oxygenation	ECMO
extracorporeal blood purification therapies	EBP
ex vivo lung perfusion	EVLP
focal segmental glomerulosclerosis	FSGS
hemodialysis	HD
hemoperfusion	HP
hemoadsorption	HA
interleukins	IL
intensive care unit	ICU
ischemia reperfusion injury	IRI
lung transplantation	LTx
Molecular Adsorbent Recycling System	MARS
mean arterial pressure	MAP
medium cut-off	MCO
normothermic machine perfusion	NMP
polymethyl methacrylate	PMMA
polymyxin B hemadsorption	PMX-HA
polyvinylpyrrolidone: polyarylethersulfone	PAES: PVP
primary graft dysfunction	PGD
severe inflammatory response syndrome	SIRS
Sequential Organ Failure Assessment	SOFA
tumour necrosis factor alpha	TNF-α

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