Review Article

AKI in Adults with COVID-19 Infection: Mechanisms of Development and Role of Blood Filtration Devices in Treatment

Abstract

During the coronavirus disease 2019 (COVID-19) pandemic, acute kidney injury (AKI) was a common sequela of COVID-19 infection and predicted disease severity and mortality. Extracorporeal blood purification techniques involving blood filtration devices are an emerging treatment for AKI in the setting of severe COVID-19 infections. In this review, we discuss potential mechanisms for the development of AKI in COVID-19 patients as well as the various available blood filtration devices and the role they may play in managing the AKI in COVID-19 patients. A total of seven blood filters currently available were compared based on their potential in treating AKI in COVID-19 patients. Blood filtration devices show potential as an emerging treatment modality for COVID-19–induced AKI, but further clinical trials are necessary before their widespread adoption and usage.

Keywords: *AKI, COVID-19, critical illness, extracorporeal membrane purification*

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Introduction

As of September 2023, there were over 770 million cases of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with over 6.9 million deaths worldwide.[1] COVID-19 infections can cause symptoms ranging from asymptomatic illness to mild upper respiratory infection to respiratory failure and death. However, in addition to respiratory presentations, it is important to consider the effect SARS-CoV-2 has on other organs, namely, the renal system. Acute kidney injury (AKI) develops in up to 16% of all COVID-19 patients, with most cases occurring in adults.[1,2] Importantly, AKI appears to be a predictor of COVID-19 severity and mortality. As a measure of disease severity, AKI is found in 49.5% of COVID-19 patients with acute respiratory distress syndrome (ARDS).[1–3] As a measure of mortality, an AKI increases the odds of death in patients with COVID-19 (odds ratio [OR]: 15.27). Among COVID-19 patients with an AKI, 77% of patients experienced severe COVID-19 infection with a mortality rate of 52%.[4] Patients with severe COVID-19 without AKI had a mortality rate of approximately 11%.[4] This review summarizes the potential causes of AKI in adult COVID-19 patients and advancements in blood filtration treatments and protocols that may be useful in adults with COVID-19–induced AKI.

Pathophysiology of AKI in adult COVID-19 patients

The Spike (S) protein of SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptors on host cells. Membrane fusion is facilitated by transmembrane serine proteases (TMPRRs) and viral fusion peptides.[5] Besides lung epithelial tissue, the ACE2 receptor and TMPRRs are significantly expressed on podocytes and proximal convoluted tubule epithelial cells.[5] The ubiquitous nature of ACE2 receptors and TMPRRs in renal tissue is a potential explanation for the high frequency of AKI in adult patients with COVID-19. Furthermore, the presence of two risk alleles of the *APOL1* genotype may increase the risk of AKI after a second hit infection such as COVID-19.[6] In the hospital and intensive care unit (ICU) setting, there are numerous risk factors of AKI in COVID-19 patients, including the interactions between ARDS and AKI, rhabdomyolysis, hypercoagulability, and cardiomyopathy.[2]

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In a study of six postmortem examinations of kidneys in patients who died of COVID-19–induced ARDS, Diao *et al*.[7] showed the histopathologic findings of tubular necrosis, luminal brush border sloughing, vacuole degeneration, and leukocyte infiltration. Glomerulosclerosis was found in patients with comorbidities, which suggests that other conditions, such as hypertension and diabetic nephropathy could be involved in the pathogenesis of the development of COVID-19–related AKI. The complement system plays a potential role in the development of AKI in COVID-19 infection. Noris *et al*.[8] suggest that terminal complement system overactivation leads to an increase in endothelial dysfunction in COVID-19 patients. Due to the subsequent increased vascular permeability and inflammation, cytokine and chemokine levels sharply rise and lead to renal damage and dysfunction. Complement activation may also lead to hypercoagulability and the formation of microthrombi in renal blood vessels.[8] Considering the link between inflammation caused by COVID-19 infection and organ dysfunction, cytokine levels in the blood play a key role in predicting the severity of the disease course. The SARS-CoV-2 virus has been associated with a strong activation of the interleukin (IL)-1/IL-6 pathway in some patients. Patients with severe COVID-19 appear to have more significant elevations in IL-6 and C-reactive protein (CRP) levels than those with moderate COVID-19.[4,8] In particular, COVID-19 patients with elevated levels of IL-6 have been shown to have an increased occurrence of ARDS and mortality.[4] Also, the levels of IL-7, IL-8, IL-9, IL-10, fibroblast growth factor, granulocyte-colony stimulating factor, granulocyte-macrophage colony-stimulating factor, interferon-gamma, interferon-gamma inducible Protein 10kDa, monocyte chemoattractant protein-1, macrophage inflammatory protein-1 alpha, macrophage inflammatory protein-1 beta, and platelet-derived growth factor are elevated in COVID-19 infection.[9] The levels of cytokines in critically ill COVID-19 patients are predictors of the occurrence of cytokine storm syndrome and multi-organ dysfunction, leading to increasing renal function impairment.[9] Legrand *et al*.[10] suggest that patients with COVID-19 can exhibit humoral responses characterised by decreases in circulating memory B cells or increases in circulating plasmablasts. This may result in immunosenescence, the formation of SARS-CoV-2–sACE2 complexes, and the development of ACE2 autoantibodies that target the kidney, creating vasculitis-like lesions and organ damage. In addition, they found that the kidney damage seen in COVID-19 AKI is of a tubular origin, rather than glomerular origin. The high-risk *APOL1* allele was notable for the occurrence of collapsing glomerulopathy in COVID-19 AKI.

In patients with severe COVID-19 infection and concomitant ARDS, organ crosstalk may be a significant cause of AKI.[11] A severe lung injury caused by COVID-19 infection could cause an increase in inflammatory markers and cytokines that travel through the bloodstream and result in kidney damage and AKI.[12] In critically ill patients requiring mechanical ventilation, hypoxemia or an increase in positive end-expiratory pressure causing increased intrathoracic pressure could lead to a reduction in renal blood flow and cause renal ischemia.[12] In the hospital setting, it is also vital to consider iatrogenic causes such as the administration of nephrotoxic medications.[12,13]

A summary of the potential causes and mechanisms of AKI in adult COVID-19 patients can be found in Table 1. While the overall mechanism for COVID-19 renal damage is still unclear, likely, a combination of direct viral damage, cytokine-mediated damage, endothelial dysfunction, and systemic critical illnesses in COVID-19 patients leads to AKI.[14] Despite the multifactorial disease processes underlying AKI in patients with COVID-19, it is crucial to explore potential treatment modalities considering the importance that AKI has on COVID-19 disease severity and mortality.

Emerging treatment for COVID-19–induced AKI: Blood filtration devices

Extracorporeal blood purification techniques involving blood filtration devices are an emerging treatment for severe COVID-19 infections. A potential solution that filters out the harmful inflammatory markers and cytokines may reduce the incidence of AKI and improve patient mortality. In a systematic review of 47 studies and 33,427 patients, Raina *et al*.[2] found a pooled incidence of 30.30% in COVID-19 patients with AKI undergoing

Table 1: Potential causes of AKI in COVID-19 and their mechanisms of pathogenesis

Cause of AKI in COVID-19	Mechanism of pathogenesis
ACE2 and TMPRRS in renal tissue	Direct viral damage
Two risk alleles of the *APOL1* genotype	COVID-19 infection causes second hit
Comorbidities such as diabetes and hypertension	Exacerbation of AKI from previous glomerular injury
Host complement system overactivation	Increased endothelial dysfunction, inflammation, and hypercoagulability in renal tissue, cytokine storm
Humoral responses	ACE2 autoantibodies directed against kidney
Organ crosstalk	Increase in inflammation/ cytokines released from damage to other organs, such as the lungs, can lead to kidney injury.
Mechanical ventilation	Hypoxia/increased positive-end expiratory pressure leading to renal ischemia
Hospitalization	Nephrotoxic medications/ iatrogenic causes

ACE2=angiotensin-converting enzyme 2, AKI=acute kidney injury, COVID-19=coronavirus disease 2019

kidney replacement therapy (KRT). KRT effectively treats patients with severe COVID-19 by filtering harmful toxins and metabolites from the blood and stabilizing their clinical condition.[15] The addition of a specialised device that selectively filters the blood and removes targeted cytokines and endotoxins of COVID-19 patients with AKI may lead to further improvements in their recovery process. The consensus report of the 25th Acute Disease Quality Initiative Workgroup regarding COVID-19–associated AKI found that COVID-19 patients should be carefully considered for blood filtration by assessing clinical data such as respiratory and hemodynamic status and laboratory values such as kidney function and cytokine levels.[14] Nonetheless, the report concluded that the usage of blood filtration devices could lead to survival benefits and even prevent AKI.[14] The following blood filtration devices do not represent an exhaustive list of all devices currently on the market, but one that focuses on emerging technologies and their specific role in treating COVID-19–induced AKI [Table 2].

oXiris

The oXiris membrane set has been granted emergency use authorisation by the US Food and Drug Administration (USFDA) for use in adult COVID-19 patients in the ICU in need of blood filtration. It comprises three layers.[16] The AN69 membrane layer is negatively charged, allowing adsorption of cytokines and toxins while providing renal support by diffusion and convection. The polyethyleneimine layer is positively charged, allowing endotoxin adsorption. The third layer is heparin-coated, reducing thrombogenicity [Figure 1].

This reduction of cytokines and endotoxins in the filtered blood of COVID-19 patients may reduce end-organ damage, such as in ARDS or AKI.

Turani *et al*.[17] demonstrated the effectiveness of using the oXiris filter in 60 adult patients with septic shock, with 85% of the study patients having an AKI. With the usage of oXiris, they observed a decrease in cytokines, procalcitonin, and endotoxin levels and an improved Sequential Organ Failure Assessment (SOFA) score from 12.4 ± 2 to 9 ± 2 ($P < 0.001$). In the first use of the oXiris membrane in the USA, Padala *et al*.[18] found that the oXiris filter decreased the levels of IL-6, CRP, and erythrocyte sedimentation rate and improved clinical outcomes in critically ill patients with COVID-19. Villa *et al*.[19] evaluated 37 patients with COVID-19 and observed an IL-6 decrease during the first 72 h of initiating KRT with the oXiris filter, with the most significant decrease found in the first 24 h ($P = 0.001$). The reduction in serum IL-6 concentrations correlated with the improvement in organ function, as measured in a decrease of SOFA score (rho = 0.48, $P = 0.0003$). More specifically, in the setting of AKI, Zhang *et al*.[20] evaluated five COVID-19 patients with AKI on continuous renal replacement therapy using oXiris and found a decrease in cytokine levels and an improvement in organ function. A multicenter registry, oXirisNet, has been developed by the Global acute renal replacement therapy (ARRT) team to enroll roughly 270 patients in a

Table 2: Potential blood filtration device membranes and their properties and composition

Blood filtration device	Indication	Technique	Target of removal	Duration	Frequency	Anticoagulation	Blood flow
oXiris	Septic shock and severe sepsis	Hemodialysis/ hemofiltration/ hemodiafiltration	Endotoxins and cytokines	Up to 72 h	Variable	Citrate or heparin	150–250 ml/min
CytoSorb	AKI, severe sepsis, septic shock	Hemodialysis/ hemofiltration/ hemodiafiltration	Cytokines	Up to 72 h	1–3 days	Citrate or heparin	150–250 ml/min
Toraymyxin	Gram-negative sepsis/ endotoxemia	Hemodialysis/ hemofiltration/ hemodiafiltration	Endotoxins	2 h	1–3 days	Citrate or heparin	80–120 ml/min
Seraph 100	Septic shock, ARDS	Hemodialysis/ hemofiltration/ hemodiafiltration	Pathogens and cytokines	Up to 24 h	Variable	Citrate or heparin	100–350 ml/min
Spectra Optia/ Depuro D2000	Septic shock	Hemodialysis/ apheresis/therapeutic plasma exchange	Cytokines	Up to 4 h	Variable	Citrate or heparin	75–175 ml/min
HA330	AKI, septic shock	Continuous venovenous hemodiafiltration	Cytokines	4 h	Variable	Citrate or heparin	150 ml/min
MCO/HCO	AKI, increased myoglobin levels, hyperinflammation	Hemodialysis/ hemofiltration/ hemodiafiltration	Inflammatory markers including molecules with a MW of 20–50 kDa	Up to 72 h	Variable	Citrate or heparin	80–200 ml/min

AKI=acute kidney injury, ARDS=acute respiratory distress syndrome, HCO=High Cut-Off, MCO=Medium Cut-Off

clinical trial ending September 2023 to establish further protocols for critically ill patients in need of extracorporeal blood purification.[21] Basic treatment protocols have been established, but further trials are necessary to provide the most optimal outcomes [Figure 2].

In the setting of severe COVID-19 infection, Acute Kidney Injury Network (AKIN) class III, ARDS, and fluid overload, Raina *et al*.[22] published a case report in which the oXiris membrane was utilized, resulting in a total resolution of kidney function. Notably, in this instance, a protocol was developed for the priming of the filter. The oXiris filter was used for 72 h with a modification of the high flow continuous venovenous hemodiafiltration (HF-CVVHDF) protocol with a total effluent fluid of 50 ml/kg/h. One-third of the total effluent fluid was used as a prefilter, as recommended. One-third of the effluent fluid was provided postfilter and the remaining effluent fluid was utilised as dialysate. With continuous ICU monitoring, the patient showed significant improvement and eventual symptom resolution with this developed protocol.

The data suggests that early initiation of oXiris provides a larger reduction of cytokines and endotoxins and a more optimal outcome in COVID-19 patients with AKI.

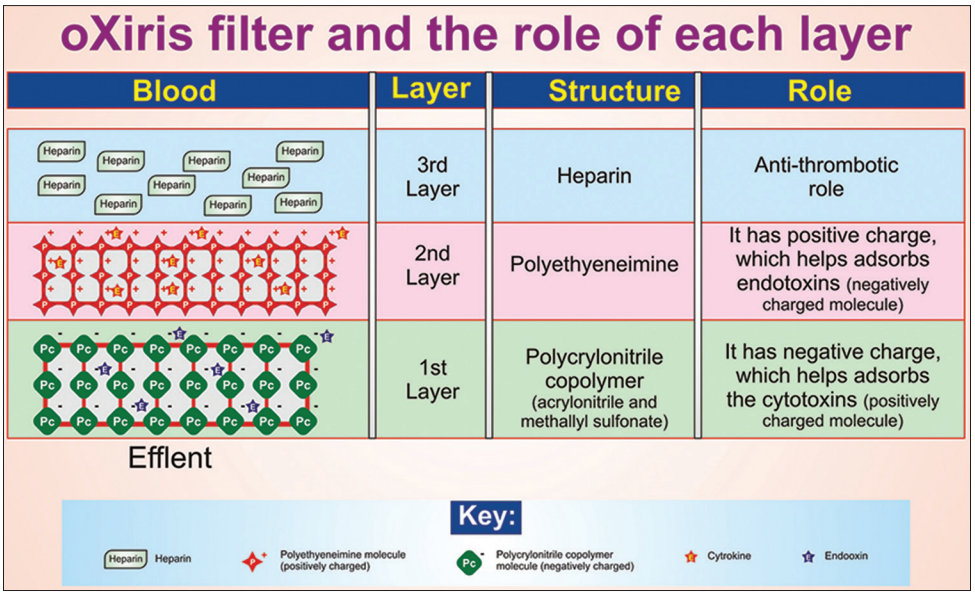

Figure 1: The composition and roles of each oXiris membrane layer

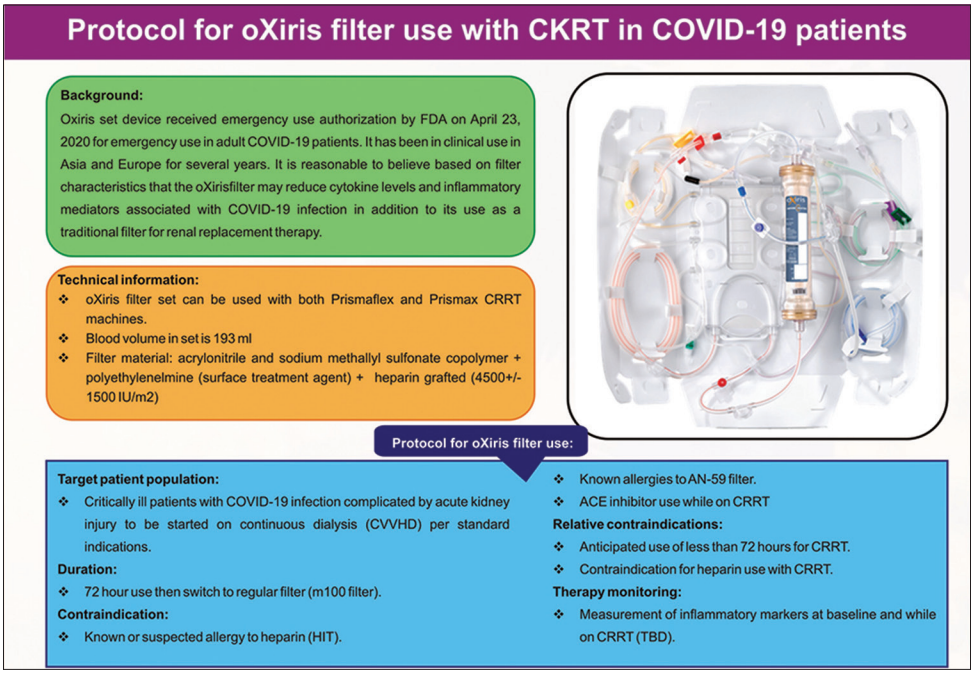

Figure 2: Protocol and target patient population for use of oXiris in patients with COVID-19. COVID-19 = coronavirus disease 2019

Earlier initiation of oXiris filtration also appears to predict improved outcomes.

CytoSorb membrane

The CytoSorb adsorber is a proprietary divinylbenzene polymer with an adsorption spectrum of small and mid-size hydrophobic molecules up to a size of approximately 60 kDa, allowing it to remove inflammatory markers and cytokines from the blood.[23]

A multicenter observational study by Song *et al*.[24] enrolled 52 patients and found that CytoSorb was associated with a potential therapeutic benefit and reduction in mortality among critically ill adult COVID-19 patients. Nassiri *et al*.[25] observed the efficacy of CytoSorb in 26 adults with severe COVID-19 and found improvements in vasopressor requirements, concentrations of procalcitonin, CRP, ferritin, and SOFA levels. However, there was no difference in the duration of stay in the ICU among survivors and nonsurvivors. In a case series, Alharthy *et al*.[26] investigated the use of CytoSorb cartridge with continuous kidney replacement therapy (CKRT) in 50 patients with life-threatening COVID-19, AKI, sepsis, ARDS, and cytokine release syndrome (CRS). They found that after one to three CKRT sessions with CytoSorb, survivors had decreased SOFA scores, lactate dehydrogenase (LDH), ferritin, D-dimers, CRP, and IL-6. PaO_2/FiO_2 ratios and lymphocyte counts were increased. In patients with stage 3 AKI, CytoSorb is recommended by the Italy Brescia Renal COVID Task Force and the Chinese Clinical Guidance for COVID-19.[27]

Toraymyxin

Toraymyxin, also known as Polymyxin B, is currently undergoing clinical trials in the USA for use in COVID-19 patients with septic shock. It is composed of polypropylene polystyrene fibres bound with Polymyxin B.[28] Unlike oXiris and CytoSorb, Toraymyxin is used to bind endotoxins rather than cytokines primarily. In a multicenter, multinational clinical trial registry (EUPHAS2) subgroup analysis, 12 patients with COVID-19 and septic shock were observed after Toraymyxin administration. SOFA scores for the patients improved, with a resultant decrease in endotoxin levels.[29] However, Dellinger *et al*.[30] found no reduction in 28-day mortality among patients with septic shock and high endotoxin levels who were treated with Toraymyxin. An additional concern for the clinician is a lack of built-in anticoagulation, requiring continuous evaluation for the prevention of circuit coagulation.[31] While there is a paucity of studies describing the renal outcomes in patients with COVID-19, there have been a few reports on the efficacy and safety of Toraymyxin in respiratory disease. Early case reports demonstrated a rise in PaO_2/FiO_2.[32,33] Ishiwari *et al*.[34] reported the first case of COVID-19–induced hyperferritinemia and severe respiratory failure successfully treated by Toraymyxin. The use of Toraymyxin in this patient halted progression to ARDS, thus preventing the need for mechanical ventilation. In a different case series, 12 COVID-19 patients with a PaO_2/FiO_2 ratio of 300 underwent 22 Toraymyxin sessions.[31] On day 14 after the first Toraymyxin treatment, disease severity decreased in 58.3% of the patients, with an increased PaO_2/FiO_2 ratio and decreased urine β2-microglobulin. After receiving Toraymyxin treatment, cytokine measurements showed a decline in IL-6 levels. However, coagulation-related events still occurred in 54.5% of the cases during the course of treatment, causing the need for reconfiguration of the circuit.

Seraph 100

Seraph 100 (ExThera Medical) is a microbind affinity sorbent hemoperfusion filter that contains ultrahigh-molecular-weight polyethylene beads with endpoint-attached heparin. Pathogens and inflammatory cytokines irreversibly bind to the immobilized heparin and are removed from the bloodstream.[35] This filter can be utilized alone for hemoperfusion or in series with hemodialysis and CKRT filters.[35]

In the first two patients in the USA treated with the Seraph 100 filter, it was found that its use improved hemodynamic stability in COVID-19 patients requiring mechanical ventilation and vasopressor support.[36] After reviewing these two cases, the FDA granted an emergency use authorization for Seraph 100 in the treatment of COVID-19. In a study conducted by Kielstein *et al*.,[37] it was demonstrated that treating critically ill COVID-19 patients with this filter decreased SARS-CoV-2 nucleocapsid protein in blood. Sandoval *et al*.[38] reported on the use of Seraph 100 in four hemodialysis patients with severe COVID-19. The patients were 81–87 years of age, had several comorbidities, severe pulmonary involvement, and criteria of bad prognosis. These patients were treated with two sessions of hemoperfusion with Seraph 100 over two consecutive days in parallel with standard hemodialysis. Among the four patients, three responded well with improvement in inflammatory marker levels. Mortality was observed in the other patient who was unable to complete treatment due to hemodynamic instability. A multicenter evaluation was conducted by Chitty *et al*.[39] to determine the efficacy and safety of Seraph 100 for the treatment of severe COVID-19. COVID-19 patients treated with Seraph 100 (n = 53) were compared with matched control patients (n = 53). It was found that use of Seraph 100 was associated with improved vasopressor-free survival (24.5 days [13–28] vs. 14.5 days [6–28], P = 0.022) and lower mortality (32.1% vs. 64.2%, P = 0.001).

The Registry of COVID-19 Patients Treated with the Seraph 100 Microbind Affinity Blood Filter (COSA) has been created to investigate the efficacy and safety of the Seraph 100 filter in these patients. The COSA registry study (NCT04361500) is enrolling patients from participating centers in Europe and Africa.[40] In an interim

analysis of the COSA registry,[41] 78 patients who received 102 treatments were included. The 30-day mortality rate among these patients was 46.2%. Mortality was associated with delayed initiation of Seraph 100 treatment after ICU admission (>60 h) and bacterial superinfection. The only adverse event noted was circuit clotting, which occurred in 8.8% of the sessions. There are two US registry trials underway to determine the efficacy and safety of the use of Seraph 100 filter in treating COVID-19 patients.[42,43]

Spectra Optia Apheresis system with the Depuro D2000 Adsorption Cartridge

Spectra Optia Apheresis System (Terumo BCT) with the Depuro D2000 Adsorption Cartridge (Marker Therapeutics, Houston, TX, USA) has been approved for the treatment of critically ill COVID-19 patients by the FDA Emergency Use Authorization (EUA).[44] The Depuro D2000 Adsorption Cartridge is composed of activated uncoated coconut shell charcoal and nonionic resins Amberlite XAD-7HP and Amberchrom GC300C.[32] While several reports of Spectra Optia Apheresis System being used for therapeutic plasma exchange (TPE) in COVID-19, only one report to date utilized the Depuro D2000 Adsorption Cartridge.[45-47] This report accounts the use of TPE with the D2000 adsorption cartridge in a 40-year-old-male patient with severe COVID-19 with respiratory failure complicated by reverse Takotsubo cardiomyopathy (RTCC).[45] Upon receiving daily TPE over 5 days with each session lasting 4 h, the patient's lactate levels, oxygenation, and left ventricle (LV) function normalized and he was weaned off vasopressors. There was a reduction in inflammatory cytokines, and reverse transcription polymerase chain reaction (RT-PCR) was negative on day 17. A US clinical trial (NCT04358003) to determine the safety and efficacy of Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge is underway.[48]

Other blood filters

The hemofilter HA330 is composed of polystyrene divinylbenzene copolymers and is effective in removing cytokines in blood in patients with shock and ARDS.[49] This is due to the pore size of HA330 ranging from 500 Da to 60 kDa. To date, its use in COVID-19 has only been evaluated in one single-center prospective cohort study including 29 patients. The findings demonstrated that early use of HA330 hemoperfusion along with standard therapy was associated with lower mortality and improvement in SOFA scores.[50] Further studies are required to determine the safety and efficacy of using HA330 filters in COVID-19 patients.

Medium Cut-Off (MCO) membranes and High Cut-Off (HCO) membranes are recent developments in KRT with a larger pore size radius of 5 and 10 nm, respectively. Thus, they allow for the successful removal of larger molecules by convection and diffusion. This includes middle molecular weight molecules such as cytokines (20–50 kDa).[51] Owing to the slightly smaller size of the MCO membrane pore size, it exhibits a more selective removal of solutes than HCO membranes. It has been demonstrated that the use of MCO leads to reduction in the plasma levels of serum cytokines, serum concentration of free light chains (FLC), transcription of proinflammatory cytokines, and inhibition of leukocyte chemotaxis.[52,53] Owing to these properties, MCO may prevent severe presentations of COVID-19 in patients with dialysis-dependent end-stage renal disease (ESRD).[54] Studies are required to demonstrate the role of these membranes in COVID-19 patients.

The role of TPE in COVID-19

Elevated levels of several inflammatory cytokines have been reported in critically ill patients with COVID-19.[55,56] TPE, or plasmapheresis, is a procedure where the patient's plasma is replaced by an iso-oncotic fluid, allowing for the elimination of inflammatory cytokines. Existing data suggest that TPE is an effective and safe treatment option for sepsis.[57–59] Owing to the similarity between severe COVID-19 and sepsis, it may be a valuable option in managing these patients.[60] Based on a literature review conducted by Beraud *et al*.,[60] TPE is typically initiated in the presence of septic shock, Multiple Organ Dysfunction Syndrome (MODS), and/or ARDS. Faqihi *et al*.[61] conducted a randomized controlled clinical trial of adult ICU patients with severe COVID-19. Upon comparing those receiving standard treatment (n = 43) to those receiving standard treatment plus TPE (n = 44), it was found that days on mechanical ventilation (15 [8–22] vs. 19 [7.7–30.3], P = 0.007) and ICU length of stay (19 [12–27] vs. 26 [11.5–31.5], P = 0.02) were lower in the TPE group versus controls. There was no statistically significant difference in mortality between the groups.[61] In a case–control series, Arulkumaran *et al*.[62] observed that TPE improved oxygenation, lowered the incidence of AKI, restored normal lymphocyte numbers, and decreased circulating inflammatory markers such as D-dimer and Von Willebrand factor antigen to ADAMTS13 (VWF Ag: ADAMTS13) ratio in patients with severe COVID-19. Gucyetmez *et al*. found that in patients with severe COVID-19 with D-dimer levels ≥2 mg/l, LDH, D-dimer, ferritin, IL-6, CRP, and procalcitonin levels were significantly decreased after three consecutive TPEs. Mortality rate was also significantly lower in the group receiving TPE compared to those not receiving TPE[63]. In a case–control series by Khamis *et al*.,[47] they evaluated the use of TPE in patients with severe COVID-19 with confirmed or imminent ARDS or severe pneumonia. They found that the TPE group had lower 28-day mortality, higher extubation rates, and improved laboratory and ventilatory parameters when compared to the control group. In another case–control study by Kamran *et al*.,[64] the use of TPE in COVID-19 patients with CRS was associated with increased 28-day survival (91.1% vs. 61.5%, P < 0.001). Length of stay

was significantly lower in the TPE-treated group (10 vs. 15 days, $P < 0.01$). They also found that earlier administration of TPE was associated with lower mortality. In a clinical trial by Fonseca-González *et al*.[65] patients with severe COVID-19 with CRS were divided into two groups. One group received TPE while the other received standard therapy. TPE reduced 60-day mortality (50% vs. 20%; OR: 0.25, 95% confidence interval [CI]: 0.071–0.880; $P = 0.029$). TPE also significantly decreased SOFA, National Early Warning Score 2 (NEWs-2), and proinflammatory mediators and increased the lymphocyte count.

Discussion

In an *in vitro* comparison of oXiris, Toramyxin, and CytoSorb, oXiris removed both cytokine and endotoxins more effectively (68% ± 4.4%) than Toraymyxin (83.4% ± 3.8%) and CytoSorb (6.3% ± 4.9%, $P < 0.05$).[65] While CytoSorb was able to effectively remove cytokines and Toramyxin was able to effectively remove endotoxins, the oXiris set was the only filter that was able to effectively remove both cytokines and endotoxins.[66] As the pandemic progresses and further improvements are made in treatment protocols, it is likely that outcomes with the use of blood filtration devices will improve. For example, on using the modified oXiris protocol alongside early initiation of extracorporeal blood purification, there is a possibility of an increased benefit in preventing and resolving AKI, leading to improved outcomes in adult patients with COVID-19.

Although there are many mechanisms that are theorized to cause AKI in COVID-19 patients, it is still difficult for clinicians to determine which patients are at risk. Factors such as gene expression, ACE2 receptor expression, and other comorbidities may be related to the severity of illness. However, cytokines and inflammatory markers appear to play a major role in AKI development in COVID-19 patients. A possible preventive measure is by using blood filtration devices. The mentioned filtration devices can reduce the amount of cytokines, inflammatory markers, and even viral particles in the blood, but more data is needed specifically in their role in preventing and treating AKI in patients with COVID-19. It is vital to be able to identify COVID-19 patients with a high risk of developing AKI and develop criteria to guide the early usage of these blood filtration devices for AKI prevention. At present, there is little evidence on the effectiveness of blood filtration devices for the prevention of COVID-19–induced AKI, although some case reports suggest that early usage of these devices can result in better outcomes. Registries are a promising method to collect real-world information about the feasibility and effects of blood filtration devices. They can collect information such as suggestions for drug adjustments and extracorporeal clearance changes and have a clinical calculator for body mass index or mechanical ventilation settings. In this way, clinicians have access to a clinical decision support tool and researchers can monitor outcomes and local practices. This will lead to further improvements in patient care, as medicine becomes more personalized.

More research is needed on developing membranes with properties that can affect some of the other potential causes of AKI in COVID-19 patients. For example, Wei *et al*.[67] published a study in which they developed a novel blood filter membrane compound, Cu-TAn@PMS, which scavenges reactive oxygen species in the blood and serves to decrease inflammation. It is composed of metal–phenolic nanozymes synthesized via metal ion–mediated oxidative coupling of polyphenols and constructed into a microsphere membrane. Further testing in human subjects is needed. Li *et al*.[68] used hydrogel microspheres made of polyethersulfone designed to bind intrinsic coagulation factors, calcium ions, and inflammatory histones to modulate dysregulated inflammation and thrombosis. They are investigating the use of anticoagulant hydrogel microspheres to reduce histones and inflammation in large animal models of sepsis. These unique membranes highlight that there are unexplored blood filter targets that can also treat AKI in COVID-19 patients.

Conclusion

AKI is a common sequela of COVID-19 infection. Although the mechanisms of injury are not yet fully understood, it is likely that it is a combination of viral proliferation and host immune system response that leads to AKI. Managing AKI in a COVID-19 infection can be complex but important, as AKI has a significant effect on COVID-19 disease severity and mortality. Emerging treatments such as blood filtration devices appear to be a promising solution. By filtering out cytokines as the CytoSorb membrane does, endotoxins as Toraymyxin does, or both cytokines and endotoxins as the oXiris set does, patients should have better outcomes. These blood filtration devices carry the risk of nonspecific removal of both proinflammatory and anti-inflammatory markers via convection, adsorption, and/or dispersion, in addition to risks inherent to extracorporeal therapy. As such, a multidisciplinary team should be considered in making treatment decisions for COVID-19 patients with AKI. More data is required regarding clinical indications for using a blood filtration device to provide the maximum benefit for the treatment of AKI in critically ill COVID-19 patients and to potentially prevent AKI in high-risk COVID-19 patients. Further research into extracorporeal blood purification and different blood filtration devices in COVID-19 patients with AKI involving large, multicenter trials is necessary. Using registries to collect real-world clinical data on the use of blood filtration devices is another possibility already being utilized that will lead to improvements in care and the development of better treatment protocols.

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Conflicts of interest

There are no conflicts of interest.

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