

A Review of Extracorporeal Blood Purification Techniques for the Treatment of Critically Ill Coronavirus Disease 2019 Patients

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In late 2019, a novel betacoronavirus, later termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was discovered in patients with an unknown respiratory illness in Wuhan, China. SARS-CoV-2 and the disease caused by the novel coronavirus, coronavirus disease 2019 (COVID-19), spread rapidly and resulted in the World Health Organization declaring a pandemic in March 2020. In a minority of patients infected with SARS-CoV-2, severe illness develops characterized by a dysregulated immune response, acute respiratory distress syndrome, and multisystem organ failure. Despite the development of antiviral and multiple immunomodulatory therapies, outcomes of severe illness remain poor. In response, the Food and Drug Administration in the United States authorized the emergency use of several extracorporeal blood purification (EBP) devices for critically ill patients with COVID-19. Extracorporeal blood purification devices target various aspects of the host response to infection to reduce immune dysregulation. This review highlights the underlying technology, currently available literature on use in critically ill COVID-19 patients, and future studies involving four EBP platforms: 1) oXiris filter, 2) CytoSorb filter, 3) Seraph 100 Microbind blood affinity filter, and 4) the Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge. *ASAIO Journal* 2022; 68;1219–1227

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In late 2019, a novel betacoronavirus, later termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was discovered in patients with an unknown respiratory illness in Wuhan, China.¹ SARS-CoV-2, similar to other betacoronaviruses, can cause severe disease, leading to respiratory failure and death. However, in comparison with MERS-CoV and SARS-CoV-1, it has significant transmissibility in the asymptomatic phase of the illness. Given the enhanced transmission dynamics, SARS-CoV-2 and the disease caused by the novel coronavirus, coronavirus disease 2019 (COVID-19), have rapidly spread globally.² The World Health Organization (WHO) declared a pandemic on March 11, 2020.³ Since that time, there have been over 470 million cases and over 6 million deaths worldwide.⁴

Despite the implementation of several therapeutics, including monoclonal antibodies, remdesivir, and corticosteroids, there continues to be unacceptably high mortality in COVID-19, especially among those with severe illness.^{5–7} In response to the pandemic, the U.S. Food and Drug Administration (FDA) has utilized an emergency release authorization (EUA) process to grant conditional approval to therapeutics.⁸ One promising class of therapy approved under the EUA process is extracorporeal blood purification (EBP).

Extracorporeal blood purification therapies have been utilized previously as an adjunct in sepsis to control immune dysregulation.^{9,10} These technologies have targeted various aspects of infection, from clearing proinflammatory mediators driving the dysregulated host response to pathogen elimination.^{9,10} The pathophysiology of COVID-19, especially in severe disease, is marked by a hyperinflammatory response that results in multisystem organ failure and death.¹¹ Based on prior evidence of use in sepsis, proven safety record, and pathophysiology marked by severe immune dysregulation, the FDA approved four blood purification devices under EUA to treat COVID-19.⁸ This review was undertaken to assess the evidence available for the use of four FDA-approved EBP devices in the treatment of COVID-19: 1) oXiris filter (Baxter, Deerfield, IL), 2) CytoSorb filter (CytoSorbents, Monmouth Junction, NJ), 3) Seraph 100 Microbind blood affinity filter (ExThera Medical, Martinez, CA), and 4) the Spectra Optia Apheresis System (Terumo BCT, Lakewood, CO) with the Depuro D2000 Adsorption Cartridge (Table 1). There are other extracorporeal purification devices that have been utilized in the treatment of COVID-19; however, they are outside the scope of this review.

Pathophysiology of COVID-19

SARS-CoV-2 is an enveloped positive-sense, single-stranded respiratory virus that infects the respiratory epithelium.^{11,18}

Table 1. Comparison of Extracorporeal Blood Purification Technologies

Filter	Duration of Use	Intended Use	Advantages	Disadvantages
oXiris	24 hours; maximum 72 hours per filter ¹²	Standalone filter for SCUF, CVWH, CVWHD, CWHDF ¹²	Heparin bonded – potential to reduce rate of circuit clotting. ¹⁰ Single filter for CRRT and blood purification. ¹²	Limited experience – no previous randomized controlled trials. Limited for use with Baxter PrismaFlex and PrismaMax systems. ¹² Contraindicated with heparin allergy. ¹² No pathogen clearance. ¹⁰
CytoSorb	12 hours for first treatment, followed by 24 hours for subsequent treatments. Maximum 24 hours per filter ¹³	Hemoperfusion alone In conjunction with SLED, SCUF, CVWH, CVWHD, CWHDF, W ECMO ¹³	Concentration-dependent clearance of inflammatory factors. ¹⁴ Use as isolated hemoperfusion or in series with a variety of renal replacement therapy modalities. ¹³ Approved for use with venovenous ECMO. ¹⁴ Previous randomized controlled trial data. ¹⁴	No pathogen clearance or endotoxin removal. ¹⁴
Seraph 100 Microbind Blood Affinity Filter	Duration dependent on blood flow rate: ranging from 4 to 8 hours Maximum 24 hours per filter ¹⁶	Hemoperfusion alone In conjunction with HD, SLED, CVWH, CVWHD, CVWHD ¹⁶	Pathogen clearance in addition to cytokine clearance. ¹⁵ Use as isolated hemoperfusion or in series with a variety of renal replacement therapy modalities. ¹⁶	Limited experience – no previous randomized controlled trials. Contraindicated with heparin allergy. ¹⁶
Spectra Optia Apheresis and Depuro D2000 Adsorption Cartridge	4 hour treatment ¹⁷	In conjunction with therapeutic apheresis ¹⁷	Can utilize fresh frozen plasma as replacement fluid to correct coagulopathy. ¹⁷	Limited experience – no previous randomized controlled trials. Unable to use with concomitant monoclonal antibody treatment. ¹⁷

APACHE II, Acute Physiology and Chronic Health Evaluation II; CVWH, continuous venovenous hemofiltration; CVWHD, continuous venovenous hemodialysis; CWHDF, continuous venovenous hemodiafiltration; ECMO, extracorporeal membrane oxygenation; HD, hemodialysis; SCUF, slow continuous ultrafiltration; SLED, slow low efficiency dialysis; SOFA, Sequential Organ Failure Assessment.

In most patients, this results in mild-to-moderate respiratory symptoms, but in the minority, it results in a severe respiratory illness marked by the development of hypoxia, multifocal pulmonary infiltrates, and host immune dysregulation.¹¹ The initial step of infection is binding of the SARS-CoV-2 spike (S) protein to angiotensin-converting enzyme 2 (ACE2) receptor on respiratory epithelial cells.¹⁸ After internalization, the virus undergoes uncoating, translation of viral replication and transcription complexes, and, ultimately, viral replication and exocytosis.¹¹ The initial host response to viral infection includes innate immune system activation *via* the pathogen-associated molecular pattern (PAMP) and pattern recognition receptor (PRR) interaction.^{18,19} Viral antigen is also processed and presented by antigen-presenting cells (APCs), which subsequently mediate cell-mediated and humoral immunity.¹⁹ A final common pathway of immune activation in response to infection is proinflammatory cytokine production, potential mediators of end-organ damage in severe COVID-19 (Figure 1).^{20,21}

Rationale for the Use of Blood Purification Techniques

There is a strong rationale for blood-purification techniques that target different stages of the pathogenesis of COVID-19. One target of blood purification is direct pathogen removal to reduce direct viral cytotoxicity and prevent further downstream immune activation.^{9,10} Another is the PAMP-PRR interaction, prevention of the PAMP-PRR interaction reduces activation of leukocytes and proinflammatory pathways.¹⁰ Recent studies have shown increased bacterial endotoxin activity in severe COVID-19 from bacterial coinfection (e.g., bacteremia) or endogenous production from gut microbiota.²² Regardless of the source, considering the association with severe disease, bacterial endotoxin is a potential target for EBP devices. Finally, given the critical role of cytokines in the pathogenesis of end-organ damage in COVID-19, the removal of proinflammatory cytokines is a promising target of blood purification techniques.^{9,10} This last mechanism of action, amelioration of cytokine storm in COVID-19, was the central reasoning for the EUA of blood-purification devices by the FDA.⁸ In contrast to other immunomodulatory therapy, including corticosteroids and interleukin 6 (IL-6) inhibitors, blood-purification devices are able to remove preexisting proinflammatory mediators and pathogenic toxins. One major limitation of blood purification devices is their nonselective mechanism of action, in that, there is the removal of beneficial regulatory cytokines that suppress the immune system. However, given the imbalance of proinflammatory cytokines in COVID-19, most cytokines filtered will be proinflammatory, which may restore the balance between proinflammatory and regulatory cytokines.^{9,10} Despite the strong theoretical basis, a number of questions regarding clinical application of EBP devices remain unresolved despite previous experience in patients with sepsis, including the patient selection, timing of initiation, duration of therapy, and monitoring response to therapy.¹⁰

oXiris Filter

Technology and Intended Clinical Use

The oXiris filter is an EBP device that employs a unique coating to an AN69 hemodialysis filter to achieve cytokine

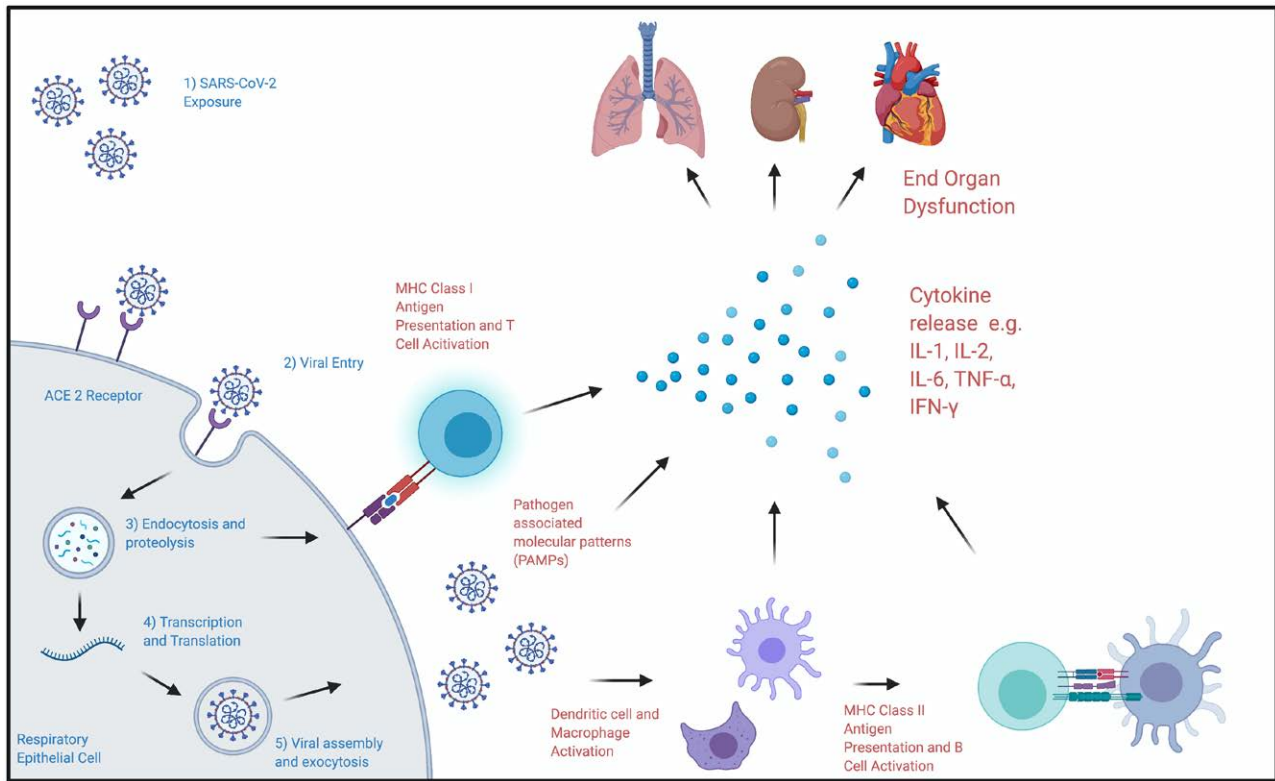


Figure 1. Lifecycle of SARS-CoV-2 and host immune response. SARS-CoV-2 enters the host through the respiratory epithelium. The virus is internalized by the respiratory epithelium *via* interaction with the ACE2 receptor. The virus is endocytosed which eventually results in release of viral RNA into the cell. The virus utilized host cell machinery to translate viral proteins including RNA-dependent RNA polymerase. The virus replicates and is released from the cell *via* exocytosis. During this process viral proteins are processed and presented by MHC Class I, which activates T-cell response. Viral proteins are also processed by antigen-presenting cells *via* MHC Class II and activate B-cell response. The innate immune system is activated by binding of pathogen-associated molecular patterns (PAMPs). The activation of both innate and adaptive immune response results in proinflammatory cytokine production, which can mediate end-organ dysfunction. ACE2, angiotensin-converting enzyme 2; MHC, major histocompatibility complex; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. Created with BioRender.com.

filtration and endotoxin removal, and has antithrombotic properties.¹⁰ The AN69 filter was first developed in 1969; it is a copolymer of acrylonitrile and sodium methallyl sulfonate, with cytokine adsorption properties due to negatively charged sulfonate groups. The AN69 filter interaction with blood results in bradykinin generation; this can result in an anaphylactoid reaction, especially in patients on ACE inhibitor therapy. To overcome this limitation, the AN69 surface treated (AN69ST) with polyethyleneimine (PEI) was developed. The PEI coating served to improve biocompatibility by preventing bradykinin generation and adsorbed heparin, allowing priming of the filter with heparin before use to improve thrombogenicity. The oXiris filter advances on the AN69ST by employing a linear grafting of PEI to enhance the binding of negatively charged endotoxin. In addition, the oXiris filter is pretreated with heparin, ensuring a high concentration ($4,500 \pm 1,500$ IU/m²) of bound heparin moieties and removing the need for heparin priming.¹⁰ Although there is a paucity of data utilizing oXiris in critically ill patients without circuit anticoagulation, and anticoagulation with either heparin or regional citrate is still routinely utilized. The filter has an effective surface area of 1,500 m². The oXiris filter is available for stand-alone use with continuous venovenous modalities *via* the PrismaFlex and PrismaMax systems (Baxter, Deerfield, IL). The recommended use is for 24 hour periods, with a maximum use of 72 hours.²³

Clinical Application of the Technology

A recent *in vitro* study compared the adsorption of inflammatory mediators and endotoxin between oXiris, Toraymyxin (Toray Industries, Tokyo, Japan), and CytoSorb filters.¹² Patient plasma was incubated with inflammatory mediators and endotoxin. The plasma was filtered in a closed-loop system to assess for clearance of the inflammatory mediators or endotoxin. The oXiris filter showed similar efficacy to Toraymyxin in terms of lipopolysaccharide (LPS) clearance and similar efficacy to CytoSorb in terms of inflammatory mediator clearance. Notably, the clearance of individual mediators did differ between the oXiris and CytoSorb filters, with relatively enhanced clearance of interferon-gamma by oXiris and IL-6, IL-10, and TNF- α by CytoSorb.

A case series of oXiris filter use in three critically ill patients with COVID-19 at Augusta Medical Center was published in June 2020.²⁴ In these three cases, continuous venovenous hemodiafiltration (CVVHDF) was utilized for 72 hours with the oXiris filter, with improved clinical outcomes and reduction in inflammatory markers in two of three patients. The patients varied in age, comorbidities, and time of initiation of oXiris filter, but all were critically ill with acute hypoxic respiratory failure and septic shock. In the patient with no clinical improvement, the oXiris filter was utilized 2 weeks into illness and after a

week of CVVHDF. There was no significant decline in inflammatory markers, and the patient subsequently suffered a cardiac arrest on his third day of treatment and died. The other two patients had a significant downtrend in inflammatory markers (C-reactive protein [CRP] and erythrocyte sedimentation rate) during treatment with improvement in clinical status.

A small observational study of oXiris filter use in five critically ill patients with COVID-19 at The People's Hospital of Zhengzhou University in Zhengzhou, China, was reported in July 2020.²⁵ A total of five patients with COVID-19 and Kidney Disease Improving Global Outcomes (KDIGO) stage 3 acute kidney injury (AKI) were enrolled in the study and treated with CVVHDF with oXiris filter. The average age of each patient was 70.2 ± 19.6 years old, time to initiation from ICU admission was 21.6 ± 19.2 hours, and the total treatment time with the oXiris filter was 172.8 ± 82.1 hours. There was a statistically significant reduction in IL-1 β , IL-6, IL-10, and CRP and a non-statistical downward trend in IL-4, IL-8, and procalcitonin after oXiris treatment. Markers of disease severity also decreased, with significant reductions in Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores. Due to the heparin moiety, reduced thrombogenicity has been theorized, but in this study, there was no significant decrease in D-dimer levels. Overall, the study showed improved hemodynamics, improved organ dysfunction, and reduction of several inflammatory markers. However, mortality overall remained high, and two of the five patients died.

A prospective single-center study at the Zan Mitrev Clinic in Northern Macedonia of 15 patients with COVID-19 pneumonia treated with oXiris filter was reported in August 2020.²⁶ The study enrolled patients with moderate-to-severe COVID-19 pneumonia with or without renal failure. The patients were treated with an oXiris filter 4–12 hours after presentation, and repeat treatment was performed for worsening inflammatory markers. In addition, the study utilized a protocol including systemic anticoagulation with heparin, early antibiotics with azithromycin, and daily dexamethasone. The authors noted decreases in inflammatory markers, including CRP, IL-6, and IL-8, that correlated temporarily with oXiris treatments. These data are difficult to interpret given the heterogeneous patient population and multiple interventions, including corticosteroids.

The largest study to date is an observational prospective pilot study of 37 patients with COVID-19 treated with oXiris filter. The patients were obtained from the oXirisNet registry.²⁷ The study included patients from four Italian hospitals, all required ICU care for respiratory support, and the majority of patients had AKI with an indication for renal replacement therapy (RRT), although 30% had no indication for RRT. The median time from ICU admission to treatment was 3.6 days. The patients were treated with oXiris for a median length of 37 hours. The study showed a statistically significant decline in IL-6 levels at 24, 48, and 72 hours from initiation of oXiris treatment, whereas SOFA score statistically decreased from baseline at 48 and 72 hours. The decrease in SOFA score was largely driven by decreased vasopressor requirement and improved oxygenation by P/F ratio. The study also showed a statistically significant difference between expected mortalities based on APACHE IV score, with a mean mortality difference of 8.3% (predicted $64.7\% \pm 16.2$; actual 56.4%). Of note,

patients were not treated with corticosteroids, but around 40% of patients received immunomodulatory therapy with tocilizumab. There was little signal of harm, with the only reported adverse event related to extracorporeal purification treatment being a single-line infection that required line replacement. Although promising, this study is limited by its observational design and small sample size.

While there are multiple trials ongoing with the oXiris filter, predominantly in septic shock and AKI, only a few trials are ongoing evaluating the oXiris filter in COVID-19. There is a single-center open-label single-arm study at the Zan Mitrev Clinic in Northern Macedonia with a target enrollment of 35 patients (NCT04478539).²⁸ The primary outcomes in this study are change in proinflammatory cytokines, inflammatory markers, coagulation markers, and duration of ICU stay. There is a multicenter trial comparing continuous RRT (CRRT) with AN69 vs. oXiris in COVID-19 patients with AKI lead by the Salvador Zubirán National Institute of Health Sciences and Nutrition in Mexico City (NCT04597034).²⁹ The primary outcome is change in vasopressor requirement, with key secondary outcomes of change in inflammatory markers, adverse outcomes, and length of ICU stay. Additionally, Baxter recently announced a grant from the German Federal Ministry of Education and Research (BMBF) specifically to advance EBP technology.

CytoSorb Filter

Technology and Intended Clinical Use

CytoSorb (CytoSorbents) is a whole blood filter composed of a highly porous polymer of adsorbent beads.³⁰ These beads are comprised of biocompatible polystyrene crosslinked with divinylbenzene and polyvinylpyrrolidone that adsorb a variety of inflammatory factors through size exclusion (<55 kD) and hydrophobic interactions. The filter provides a surface area of roughly 45,000 m² for adsorption. Adsorption is non-selective and concentration-dependent so that substances at higher concentrations are adsorbed at higher rates. In addition to cytokines, the CytoSorb filter removes a variety of lower molecular-weight substances, including albumin-bound substances and pathogenic toxins; however, it does not effectively remove endotoxin. The CytoSorb filter can be used for hemoperfusion or in series with hemodialysis, CRRT, and venovenous extracorporeal membrane oxygenation (VV ECMO) circuits. The maximum filter lifespan is 24 hours, with a total recommended duration of therapy of 72 hours.¹⁴

Clinical Application of the Technology

The first case reported in the literature of CytoSorb in a critically ill patient with COVID-19 was reported in July 2020 by Rizvi *et al.*¹³ The patient was a 51 year old male with COVID-19 ARDS requiring mechanical ventilation and KDIGO stage 3 AKI requiring initiation of CRRT. The CytoSorb filter was utilized with CRRT starting on hospital day 11. The patient received hemoperfusion with CytoSorb during a 12 day period, with interruption on hospital day 15 due to hemodynamic instability. The patient had initial improvement upon treatment with CytoSorb filter in CRP but then had clinical worsening with development of shock and uprending inflammatory markers. The patient also received IL-6 inhibitor tocilizumab

during therapy on hospital days 18 and 19, before clinical improvement and a second downtrend in inflammatory markers. Overall, from the case presented, CytoSorb may have contributed to early improvement in inflammatory markers, but despite treatment, the patient clinically worsened with shock and respiratory failure. The patient ultimately survived, but it is unclear if the hemoperfusion treatment with CytoSorb was beneficial in the presented case. There were no adverse events reported with the use of hemoperfusion.

Melegari *et al.*³¹ reported a case of successful use of CytoSorb hemoperfusion in severe COVID-19 at Ospedaliero-Universitaria di Modena in Modena, Italy, in July 2020. The patient was a 71 year old male with severe COVID-19 with respiratory failure requiring mechanical ventilation and severe AKI requiring RRT. The patient was started on CRRT combined with hemoperfusion with CytoSorb 2 days after admission to the ICU. The patient was treated for a total of five hemoperfusion treatments with CytoSorb in conjunction with CRRT. At the same time, the patient received a loading dose of methylprednisolone 1 mg/kg followed by 0.5 mg/kg daily for a 7 day total course. The patient had improvements in IL-6 levels and oxygenation and ultimately survived. Overall, the patient tolerated the treatment well without complication and had improvement in clinical status with CytoSorb therapy.

Another case was reported by Berlot *et al.*,³² also at Ospedaliero-Universitaria di Modena in Modena, Italy. They describe a case of combined use of IL-6 inhibition and hemoperfusion with CytoSorb in severe COVID-19. The patient was a 40 year old male who was admitted to the ICU for COVID-19 ARDS. The patient had no renal dysfunction. The patient had baseline-elevated CRP and IL-6 levels and was treated with two doses of tocilizumab and isolated hemoperfusion with CytoSorb for three 24 hour treatments. The patient had improvement in CRP, IL-6, and oxygenation corresponding to IL-6 blockade and hemoperfusion treatments.

Reider *et al.*³³ published preliminary results of the use of hemoperfusion therapy with CytoSorb in critically ill patients with COVID-19 requiring VV ECMO support at Freidberg Medical Center in Germany. They reported a comparison of eight patients, with half assigned to receive 72 hours of hemoperfusion with CytoSorb. They showed improved IL-6 levels in the hemoperfusion group. However, a larger follow-up study of 34 patients by the same group failed to show any difference in primary outcome of reduction of IL-6 level by 72 hours after initiation of hemoperfusion with Cytosorb.³⁴ The study also showed a statistically significant decrease in 30 day survival in the hemoperfusion arm, with 18% (3/17) survival in the hemoperfusion arm and 76% (13/17) in the untreated group surviving ($p = 0.0016$). The patients had similar baseline characteristics, in terms of disease severity, inflammatory markers, comorbidities, and time from admission to ECMO initiation. The causes of mortality were reported as respiratory failure, pulmonary hemorrhage, septic shock, multiorgan failure, and intracranial hemorrhage. While the study was underpowered for mortality and the reason for such a large difference is unclear, the authors posited it may be due to clearance of protective factors or alteration in the coagulation cascade. The group initially planned for a follow-up study CYCOV II (NCT04385771), but due to signal of excess mortality with hemoperfusion, the study was suspended.³⁵

The largest study to date is a retrospective single-center study of 50 critically ill patients with COVID-19 in Saudi Arabia reported by Alharty *et al.*³⁶ They enrolled 50 patients with COVID-19 admitted to their ICU with AKI requiring CRRT therapy to receive concomitant hemoperfusion with CytoSorb. The patients received standardized protocolized care, including ARDS net ventilation strategy, prone positioning, antiviral therapy with ribavirin and interferon beta-1b, empiric antibiotics, hydrocortisone (200 mg daily), and prophylactic anticoagulation. CytoSorb treatment was initiated within 24 hours of developing ARDS, developing an APACHE II score >20, or development of severe sepsis or septic shock. The Cytosorb was utilized with CVVHD and was continued until clinical criteria of improvement were achieved (normalization of oxygenation and resolution of shock). Overall mortality was 30% in the study. The survivors underwent an average of 2 ± 1 24-hour hemoperfusion treatments, whereas nonsurvivors underwent an average of 6 ± 2 treatments. The survivors had improvement in organ dysfunction (SOFA), inflammatory markers (IL-6 and CRP), and oxygenation, whereas nonsurvivors did not have improvement. There were no reported serious adverse events of therapy with CytoSorb therapy.

The current literature utilizing the CytoSorb filter consists predominantly of case reports and small retrospective single-center studies. However, there are several studies on the horizon. There is another trial in Germany (NCT04344080) with planned completion in 2021.³⁷ It is a randomized, open-label study of CytoSorb versus standard care in critically ill patients with COVID-19. Planned enrollment is 24 patients, and the primary outcome is the stabilization of hemodynamics within 24 hours of treatment initiation. A trial in Belgium (NCT04518969) plans to enroll 24 critically ill patients with COVID-19 to evaluate CytoSorb against standard of care, with a primary outcome of the percentage of proinflammatory cytokine clearance.³⁸ Finally, a large registry study out of Aurora, CO (NCT04391920), of 500 critically ill patients with COVID-19 planned to finish in August 2022.³⁹ These studies should help clarify the role of CytoSorb as a potential therapy in severe COVID-19.

Seraph 100 Microbind Affinity Blood Filter

Technology and Intended Clinical Use

The Seraph 100 Microbind Affinity Blood Filter (Seraph 100) (ExThera Medical) is an extracorporeal hemoperfusion device composed of ultrahigh molecular weight polyethylene beads bound with heparin.⁴⁰ The negatively charged heparin moieties, like endogenous heparin sulfate located in cell surface glycocalyx, act to bind pathogens and proinflammatory cytokines. The heparin is bound to the beads and results in limited systemic absorption. *In vitro* data show the ability to clear pathogens, including resistant bacteria methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and carbapenem-resistant *Enterobacteriaceae* (CRE) and viruses, including SARS-CoV-2.^{15,40} The Seraph 100 filter can be used alone for hemoperfusion or in series with hemodialysis and CRRT filters. The recommended treatment duration varies depending on the blood flow rate (BFR), ranging from 4 hours with a BFR 400 ml/

min to 8–24 hours with a BFR of 200 ml/min. The maximum recommended duration of treatment with a single filter is 24 hours.⁴¹

Clinical Application of the Technology

The first reported cases of use of the Seraph 100 filter in COVID-19 was reported by Olson *et al.*¹⁵ in July 2020. The first patient was a 67 year old male with COVID-19 ARDS, complicated by septic shock, requiring mechanical ventilation. The patient developed worsening circulatory shock on hospital day 3 despite treatment with hydroxychloroquine, empiric antibiotics, and tocilizumab. He was treated with hemoperfusion with the Seraph 100 filter for 24 hours with rapid improvement in vasopressor requirements. He developed recurrent shock and repeat treatment with the Seraph 100 filter again resulted in marked improvement in hemodynamics, and vasopressors were weaned. Ultimately, the patient was transferred for refractory hypoxemia for consideration of ECMO therapy. The second case was a 57 year old male with COVID-19 ARDS requiring mechanical ventilation and septic shock. The patient had refractory shock despite treatment with hydroxychloroquine, empiric antibiotics, and oral BTK inhibitor acalabrutinib. The patient was treated with two hemoperfusion treatments with the Seraph 100 filter. The patient had rapid improvement in hemodynamics with both treatments. The patient ultimately survived. In both cases, the patients had prompt improvement in circulatory dysfunction and improvement in inflammatory markers CRP and IL-6.

Another case report of Seraph use in a critically ill patient with COVID-19 was reported by a group in Hannover, Germany.¹⁶ They describe the case of a 53 year old male with respiratory failure requiring mechanical ventilation and septic shock requiring multiple vasopressors treated with a single treatment of hemoperfusion with the Seraph 100 filter. The patient was admitted after 7 days of symptoms. He had progressively worsening respiratory status and, on day 3 of hospitalization, was intubated. He received hydroxychloroquine and empiric antibiotics. On hospital day 4, he underwent hemoperfusion treatment with the Seraph 100 filter; the treatment was complicated by worsening agitation requiring an increase in sedation and filter clotting, resulting in early termination of the treatment after 70 minutes. Despite the short treatment, the patient had improvement in hemodynamics, respiratory status, CRP, and D-dimer level.

Sandoval *et al.*⁴² reported the use of the Seraph 100 filter in four patients with end stage renal disease on hemodialysis and severe COVID-19 in Spain. The four patients were all elderly multimorbid patients, ages ranging from 81 to 87. The patients were treated with two sessions of hemoperfusion with the Seraph 100 filter. Mortality was observed in one of four patients, who was only able to tolerate partial treatments with the Seraph 100 filter due to hemodynamic instability. The other patients all had improved inflammatory markers (ferritin and IL-6) and clinical status after completing two hemoperfusion treatments.

Schmidt *et al.*⁴³ reported interim analysis from the COVID-19 patients treated with the Seraph 100 Microbind Affinity Blood Filter (COSA) registry. The COSA registry study (NCT04361500) is enrolling patients with COVID-19 treated

with hemoperfusion therapy with the Seraph 100 filter at participating centers in Europe and Africa.⁴⁴ Up until October 2021, the outcomes of 78 critically ill COVID patients treated with the Seraph 100 filter were reported. The primary end point was 30 day mortality, and secondary endpoints were adverse events, circuit clotting rates, and time to ICU discharge. The 78 patients received a total of 102 treatments, treatment duration was median of 5 hours (4–13.42), and the majority 56.9% of treatments were performed with concomitant hemodialysis. The 30 day mortality rate of 46.2% in patients receiving hemoperfusion with the Seraph 100 filter. Mortality was associated with delay in therapy from ICU admission greater than 60 hours and bacterial superinfection. Circuit clotting was seen in only 8.8% of treatments. No other adverse events were reported. These data are limited by lack of a control group, but the low rates of adverse events are reassuring.

There are a number of upcoming trials involving the Seraph 100 filter in COVID-19. There is a U.S. registry trial (NCT04413955) in addition to the COSA European registry trial (NCT04361500) discussed above, with a planned enrollment of 100 patients treated with Seraph 100 filter.^{44,45} The main outcome of the U.S. registry trial is adverse events within 24 hours of device use, with additional outcomes including hemodynamic support requirements, ventilatory requirements, and markers of inflammation. The PURIFY-OBS trial (NCT04606498) is a currently enrolling multicenter U.S.-based observational study with retrospective and prospective arms, which plans to compare patients treated with the Seraph 100 filter to historical matched controls.⁴⁶ The primary outcome is the length of time utilizing vasoactive medications, and other secondary outcomes include duration of mechanical ventilation, RRT, ICU care, hospitalization, and 28 day mortality. A preliminary report of the retrospective arm of the PURIFY-OBS trial was reported in April 2021, with final publication still pending currently.⁴⁷ These studies will provide important insights into the role of the Seraph 100 filter in the treatment of critically ill COVID-19 patients.

Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge

Technology and Intended Clinical Use

The Spectra Optia Apheresis System (Terumo BCT) is a platform that allows for therapeutic apheresis *via* centrifugation. The FDA EUA specifically approved the Spectra Optia Apheresis System for therapeutic apheresis in combination with a hemoperfusion filter, the Depuro D2000 adsorption cartridge (Marker Therapeutics, Houston, TX), for the treatment of critically ill COVID-19 patients.⁴⁸ The Depuro D2000 adsorption cartridge is a hemoperfusion device composed of activated uncoated coconut shell charcoal and nonionic resins Amberlite XAD-7HP and Amberchrom GC300C. This filter has been shown to act *via* a variety of mechanisms to adsorb various proinflammatory cytokines, including IL-6, IL-8, IL-10, and TNF- α . The filter is located downstream in the apheresis circuit after the plasma is separated, allowing for cytokine removal from the plasma. The treated plasma can then be returned to the patient. The D2000 cartridge can be used for 4 hours per treatment.⁴⁹

Clinical Application of the Technology

To our knowledge, there is only one report published utilizing the Spectra Optia Apheresis System with the Depuro D2000 adsorption cartridge.¹⁷ There are, however, several reports in the literature that describe the use of the Spectra Optia Apheresis System for therapeutic plasma exchange (TPE) in COVID-19, but without the D2000 adsorption cartridge.^{50,51}

Faqihi *et al.*¹⁷ describe the use of TPE with the D2000 adsorption cartridge in a patient with severe COVID-19 complicated by reverse Takotsubo cardiomyopathy (RTCC). The patient was a 40 year old male who was admitted with severe COVID-19 with respiratory failure requiring mechanical ventilation. He subsequently developed cardiogenic shock and was found to have RTCC. The patient was started on TPE with the Spectra Optia Apheresis System with the Depuro D2000 Adsorption Cartridge the day after admission to the ICU. The patient was treated with a dose of 1.5 plasma volume for the first dose and then one plasma volume for subsequent doses. He was treated for a total of five treatments. Albumin was utilized as a replacement fluid. He had improvement in left ventricular function on day 2 of treatment and was weaned off vasopressors by day 3 of treatment. His respiratory status improved, and he was extubated on ICU day 7. He ultimately was discharged home in good condition.

There are several planned trials to evaluate TPE with plasma adsorption further. Faqihi *et al.*⁵² reported plans for a pilot randomized controlled multicenter trial in Saudi Arabia, comparing TPE with plasma adsorption to usual care in critically ill COVID-19 patients. They plan to enroll a total of 120 patients. The main outcome is 28 day mortality and safety of TPE. Additionally, a large U.S. multicenter single-arm clinical trial (NCT04358003) of TPE with plasma adsorption in critically ill patients with COVID-19 is currently enrolling patients.⁵³ They plan to enroll a total of 2,000 participants. The primary outcome is 28 day all-cause mortality, and the main secondary outcome is the change in SOFA score.

Emerging Blood Purification Platforms

There are several other novel and promising extracorporeal therapies that are currently being developed. The hemoperfusion devices reviewed above predominantly act by either cytokine or pathogen removal; another target to modulate the immune response in COVID-19 is activated inflammatory cells. Selective cytopheretic device (SCD) (SeaStar Medical, Denver, CO) is a membrane that binds activated neutrophils and monocytes.¹⁰ The device is placed postfilter in the CRRT circuit and requires citrate anticoagulation to maintain a low calcium concentration to facilitate leukocyte binding to the filter. The device has been studied in sepsis with mixed results in regard to mortality.¹⁰ Yessayan *et al.*⁵⁴ published a case report of the use of SCD in several critically ill patients with COVID-19 and elevated IL-6 levels. The patients in the study had improvement in oxygenation and reduction in IL-6 concentration and ultimately survived. There is a multicenter, single-arm pilot study currently recruiting critically ill patients with COVID-19 to treatment with SCD (NCT04395911).⁵⁵

Another emerging technology is the GARNET device (Boa Biomedical, Cambridge, MA); it is an EBP device that utilized a genetically engineered mannose-binding lectin

(MBL), a component of the innate immune system, to adsorb pathogens and pathogenic toxins. The MBL is fused to an Fc antibody fragment and specifically engineered to retain the ability to opsonize pathogens but lack complement and coagulation activating domains. The GARNET device is unique in its ability to target both pathogens and pathogenic toxins *via* binding of PAMPs.⁵⁶ The technology has been successful in animal studies, and a human study in hemodialysis patients with bloodstream is planned, but not yet recruiting (NCT04658017).^{10,57}

Conclusions

Overall, this review highlights the current evidence supporting the use of EBP techniques in the treatment of severe COVID-19. Although EBP is not a new technology, its use in the treatment of patients with COVID-19 is an emerging application. The current body of evidence suffers from several limitations, including small study size, heterogeneous patient populations, lack of randomized controlled trials, and the reliance on surrogate end points. Additionally, these studies were conducted at varying time points in the pandemic and included a variety of different anti-inflammatory therapies that were utilized in combination with hemoperfusion. However, this review highlights that there are several promising technologies that target hyperinflammation, a key aspect of the pathogenesis of severe COVID-19 infection. For now, EBP as an adjunct to the treatment of critically ill patients with COVID-19 is an unproven technology that requires further study before widespread adoption. There is a need for large prospective trials with well-defined enrollment criteria and rigorous treatment protocols to evaluate the potential benefits of EBP in treatment of COVID-19.

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