



Additive treatment considerations in COVID-19—The clinician's perspective on extracorporeal adjunctive purification techniques

Abstract

The aim of this document was to inform the scientific community of sparse preliminary results regarding advanced supportive therapies and technology-driven systems in addition to highlighting the benefits and possibilities of performing concise research during challenging times. Advanced organ support for lung and heart offers the possibility to buy the time needed for recovery. However, remaining a bridging strategy, extracorporeal life support cannot act as the ultimate treatment for the underlying COVID-19 disease. Appropriate patient selection criteria addressed by experts and scientific organizations, such as Extracorporeal Life Support Organization and World Health Organization, may provide significant help in the difficult decision-making and to reduce mortality in patients with profound respiratory and/or cardiac failure due to COVID-19. Severe, systemic cytokine-mediated inflammation associated with the SARS-CoV-2 has also been described. Effects of crosstalk between coagulation and inflammatory pathways appear to significantly affect disease progression and lead to poor outcomes. Multiple therapeutic strategies, including antibody therapies (such as Tocilizumab, Sarilumab, Siltuximab), therapeutic plasma exchange (TPE), and blood purification techniques for direct removal of cytokines, including filtration, dialysis (diffusion), and adsorption are available. Further, we believe, that research should be facilitated and promoted, particularly under the guidance of recognized scientific societies or expert-based multicenter investigation, with rapid communication of critical and relevant information to enhance better appraisal of patient profiles, complications, and treatment modalities.

1 | INTRODUCTION

Within the past twenty years, diverse viruses, including corona and influenza, have spread worldwide and caused

significant mortality and global economic catastrophe. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus is very contagious, and infection with this virus has resulted in a significant number of deaths.¹ The number of patients suffering from SARS-CoV-2-related infectious diseases has now passed six million cases with more than 370 000 deaths globally, according to available data.¹ Coronavirus disease 2019 (COVID-19) presents unique clinical and logistical challenges to governments, healthcare practitioners, and healthcare systems. Because of the spread of COVID-19, hospital administrators and policymakers had to face a substantial increase in critical care bed capacity with a focus not just on infrastructure and supplies but also on staff management, including personal protection equipment.² Isolation, quarantine, social distancing, and community containment play a pivotal role in public health measures aimed at slowing the spread of this virus.³ Testing methods for detecting the presence of virus itself (reverse-transcriptase polymerase chain reaction and isothermal nucleic acid amplification), followed by quarantine of those who tested positive, and tracing of those with whom the SARS-CoV-2-positive people had contact can result in provable reduction in the spread of the virus in the population.⁴⁻⁶ The impact of viral load and exposure time on symptom severity, which might explain the mortality rate of young healthy individuals, still remains uncertain. Due to the novelty of the virus to date, no clinical data for a specific antiviral therapy or a workable vaccination against the virus are available. At present, therapy focuses on supportive treatment, especially in intensive care for very severe cases.^{2,7-13} Advanced organ support for lung and heart offers the possibility to buy the time needed for recovery.¹⁴⁻¹⁶ Although the amount of newly published information is enormous, much of this information contains uncertain or dangerous misinterpretations of the virus and treatments.^{17,18} Prospective randomized controlled trials and observational studies based on large cohorts are lacking due to the limitations caused by the global pandemic. The aim of this document was to inform the scientific community of sparse preliminary results regarding advanced supportive therapies and technology-driven systems in addition to



highlighting the benefits and possibilities of performing concise research during challenging times.

2 | HEALTHCARE AND PATIENT MANAGEMENT

Overall, the final denominator for calculating the COVID-19 mortality rate may not be available or may be unknown for now.¹⁹ Public health measures, clinical management, and care of COVID-19 patients and the guideline of admission to hospital for patients with confirmed COVID-19 varied across countries.^{8,10,11,13,20-25} Healthcare systems in any country also had to face an overwhelming demand for hospital and intensive care unit (ICU) beds.^{8,9,23,26} In case of resource overload, inadequate care of patients with mild symptoms resulted in the development of more severe illness or even death. However, the performance of the healthcare system in each country depended on the strategy that the governments chose to address the outbreak and when the lockdown aimed at flattening the curve was enforced. Also, coordination of capacities and resource availability (hospital and ICU beds, ventilators, extracorporeal life support devices) in national or even international interactive platforms enabled, in some circumstances, adequate help to be provided in addition to the best chance of survival for severely ill patients with good prognosis.^{27,28}

So far, no proven therapy and no vaccination for COVID-19 exist. Unproven therapies have been or are being administered off-label or on a compassionate use basis. Widespread and desperate adoption of mostly different types of pharmacological interventions with little or no supportive evidence based on case series, non-randomized, retrospective cohorts without reasonable benefits was released quite early. However, several agents, such as remdesivir, lopinavir, ritonavir, hydroxychloroquine, tocilizumab, and favipiravir, that were previously used against SARS-CoV and MERS-CoV have been used empirically without definitive recommendation for use.²⁹⁻³² The first and the only placebo-controlled, double-blinded, multi-center RCT of remdesivir was stopped early due to poor recruitment after including 237 patients.³³ Wang et al observed no effect of remdesivir on any endpoint, including viral load and a very small reduction in the time to clinical improvement (21 vs. 23 days).³³

Non-invasive ventilation, high-flow nasal cannula, and corticosteroids serve as the primary supportive approaches before invasive mechanical ventilation (IMV) and prone positioning are considered in more severe cases.^{2,7,10,12} First, observations showed that patients intubated on mechanical ventilation had long ICU courses and ventilator-induced lung injury may have occurred during this period.^{7,12} A lower threshold than normal to initiate IMV created two conflicting issues: iatrogenic harm and depletion of finite resources, ICU

beds, and ventilators. The early clinical experience with this emerging pathogen has indicated that approximately 15%-30% of hospitalized patients develop respiratory failure, and 12% require mechanical ventilation with 3% needing extracorporeal life support (ECLS).¹³

Advanced organ support, such as ECLS, presents complex patient-device interactions in circumstances of already profound inflammatory, cardio-circulatory, and coagulative abnormalities. Remaining a bridging strategy to buy the time to recovery, ECLS cannot act as the ultimate treatment of the underlying COVID-19 disease.¹⁴⁻¹⁶ The use of ECLS has been described with controversial mortality rate of up to 100%.³⁴⁻³⁶ However, appropriate patient selection criteria addressed by experts and scientific organizations, such as the Extracorporeal Life Support Organization (ELSO, Ann Arbor, MI, USA), may provide significant help in the difficult decision-making.¹⁵ Also, the World Health Organization (WHO, Geneva, Switzerland) guidance document includes a statement to consider referring patients with refractory hypoxemia despite lung-protective ventilation in settings with access to experts in ECLS support.¹ Geographical differences in ECLS case counts are evident, and are likely due to the regional extent and impact of the outbreak and the previously established capacity for ECLS.^{26,28,37-39} The vast majority of ECLS are veno-venous, but the severe cardio-circulatory effects of COVID-19 have given rise to a relative increase in the use of veno-arterial ECLS in almost 5% of the cases.³⁷⁻³⁹ The goal of ECLS use during a pandemic is to reduce mortality in patients with profound respiratory and/or cardiac failure. Weekly reports of an Euro-ELSO survey on ECLS provision in adult COVID-19 patients in Europe have been released online since March 21, 2020 on the Euro-ELSO website.³⁹ Total counts of COVID-19-confirmed patients and counts of COVID-19 suspected but not confirmed by testing cases on ECLS in the ELSO Registry are displayed as real-time data stream on the ELSO website.^{37,38}

3 | UNDERSTANDING COVID-19 AS A SYSTEMIC DISEASE

The first reports from China described mainly respiratory and inflammatory symptoms of COVID-19.^{21-23,40-43} The type of respiratory involvement also showed almost normal lung compliance and considerable disease heterogeneity and severity among affected patients, leading some to hypothesize different disease phenotypes.⁷ A common observation was the “silent hypoxemia” phenotype of COVID-19, an individual who does not otherwise show signs of respiratory failure.⁷ Also, more and more lines of evidence have appeared indicating that patients have a new kind of hypercoagulability.⁴⁴ Early histopathological data showed that pulmonary microvascular thrombosis may play a role in progressive



respiratory failure.^{45,46} Furthermore, involvement of the cardiovascular system^{41,47,48} ranges from myocarditis, cardiac tamponade, and acute pulmonary embolism to cardio-circulatory collapse, often representing the ultimate cause of death. Beyond cardiopulmonary involvement, other organ systems have been severely affected and have shown severe dysfunctions. These dysfunctions included profound immunological impairment, sometimes leading to secondary immunosuppression as demonstrated by lymphocytopenia in more than 80% of the patients.^{22,41,49} Furthermore, coagulopathy may occur, ranging from a pro-thrombotic to anticoagulated state due to antiphospholipid antibodies with thrombocytopenia. Severe, systemic cytokine-mediated inflammation associated with this virus has been described.^{42,43,45,46,49} Effects of crosstalk between coagulation and inflammatory pathways appear to significantly affect disease progression and lead to poor outcomes.^{45,46} Due to these presentations, COVID-19 should be defined and understood as a systemic disease.

4 | IMMUNE RESPONSE, CYTOKINE STORM, AND ADDITIVE TREATMENT CONSIDERATIONS

In severe cases, the pronounced release of vasoactive mediators (cytokine storm) was repeatedly observed.^{42,43} Ruan et al and Zhou et al have identified a high interleukin 6 (IL-6) level as a potential predictor of a fatal outcome of COVID-19 disease as an increase in IL-6 levels results in pronounced vasodilatation and membrane leakage, which ultimately leads to refractory vasoplegia and multiple organ failure.^{21,23,45} Finally, a sepsis-like syndrome occurred frequently that could have resulted from the virus itself or to a superimposed bacterial infection. Multiple therapeutic strategies, including antibody therapies (such as Tocilizumab, Sarilumab, Siltuximab), therapeutic plasma exchange (TPE), and even direct removal of cytokines, might also mitigate the “cytokine storm”.⁵⁰⁻⁵³ In general, three main blood purification techniques are available: filtration, dialysis (diffusion), and adsorption.

The use of convalescent plasma was recommended as an empirical treatment during outbreaks of the Ebola virus in 2014, Middle East respiratory syndrome coronavirus in 2015, and other viral infections, such as SARS-CoV, H5N1 avian influenza, and H1N1 influenza. Previous findings have raised the hypothesis in which the use of convalescent plasma transfusion could be beneficial in patients infected with SARS-CoV-2.⁵⁴⁻⁵⁶ Shen et al presented the results from treatment of five critically ill COVID-19 patients on IMV with convalescent plasma.⁵⁷ This limited case series precludes a definitive statement about the potential effectiveness of this treatment, but following plasma transfusion, viral loads also decreased and became negative within 12 days after transfusion with

a concurrent increase in SARS-CoV-2-specific ELISA and neutralizing antibody titers.^{54,57}

TPE can cause a reduction in cytokine levels as a result of separation and removal of plasma from blood and replacement of the removed plasma with fresh frozen plasma.⁵⁸ Keith et al retrospectively reviewed COVID-19 patients receiving adjunct TPE performing propensity match to patients who received standard of care without TPE.⁵⁹ A subgroup analysis showed the greatest mortality benefit with TPE in a subgroup of patients with pneumonia as the primary source of infection (47.8% mortality vs. 81.3% mortality; $P = .05$). The authors' practice has changed based on the experience of earlier TPE use in the clinical course of septic shock rather than as “rescue therapy”.⁵⁹

The use of blood purification to improve clinical outcomes is not a novel concept.^{50,52-54,60} In fact, extracorporeal filtration techniques, such as coupled plasma filtration adsorption, have shown promise as a potential adjuvant therapy in sepsis and septic shock.^{54,58} The rationale for the use of hemo-adsorption, double filtration plasmapheresis (DFPP) and plasma exchange (TPE) is the reduction in circulating pro-inflammatory and anti-inflammatory cytokines (IL-8, -1ra, -1 α , -10, and -6) and other circulating mediators, thus avoiding severe complications and facilitating an improvement of patient outcomes.^{52,53} The potential effects of blood purification therapy in reducing cytokine storm as a late complication of two critically ill COVID-19 patients were reported by the group from Beijing, China.⁵⁷ Furthermore, as the corona viruses are larger than 100 nm, all secondary filtration membranes may work toward the reduction in virus load. However, targeting the overactive cytokine response with anti-cytokine therapies or immunomodulators should be balanced with maintaining an adequate inflammatory response for pathogen clearance.^{45,49}

The United States Food and Drug Administration (US FDA, Silver Spring, MD, USA) approved an Investigational Device Exemption (IDE) for a therapeutic hemoperfusion device that removes circulating endotoxin from the bloodstream (PMX, Spectral Medical, Toronto, Canada). The IDE approval has provided the opportunity for the use of PMX in COVID-19 patients suffering from septic shock and is a supplement to the company's current Tigris trial, which is an FDA-approved clinical trial in the USA for studying the use of PMX for septic shock. Direct hemoperfusion using a polymyxin B endotoxin-adsorbing column (PMX-DHP) is a modality developed in Japan and marketed as Toraymyxin (Toray Industries, Tokyo, Japan). PMX-DHP is a polycationic antibiotic column containing multiple polymyxin B-immobilized fibers, which have been shown to neutralize bacterial endotoxins. A major concern related to polymyxin B hemoperfusion, however, is the risk of cartridge clotting, which can cause premature interruption of the treatment and acute blood loss in patients who are already critically ill. As opposed to Emergency Use

Authorization (EUA), Spectral's IDE supplement approved by the FDA recognizes that there are sufficient safety and effectiveness data to allow clinicians to use PMX to treat patients who are similar to patients in the Tigris trial and are also COVID-19 positive. Spectral will provide these therapeutic cartridges free of charge.

There are a multitude of adsorption hemofilters currently being investigated, including, but not limited to, polymethylmethacrylate (PMMA) membranes, AN69 surface-treated (ST, Baxter, Meyzieu, France) membranes, and modified ST membranes (oXiris Baxter, Meyzieu, France). The oXiris membrane is intended to adsorb both endotoxin and cytokines, and it has been shown to adsorb more of both when compared with the AN69 membrane.

Spectra Optia Apheresis System (Terumo BCT Inc, Lakewood, CO, USA) combined with Marker Therapeutics' D2000 Adsorption Cartridge (Marker Therapeutics Inc, Houston, TX, USA) device has been authorized by the FDA for emergency use to treat adult patients who have been admitted to the intensive care unit (ICU) with confirmed or imminent respiratory failure and with confirmed COVID-19 in order to reduce pro-inflammatory cytokine levels.

CytoSorb (CytoSorbents Corporation, Monmouth Junction, NJ, USA) is a recently developed, commercially available hemo-adsorption device that utilizes extracorporeal blood purification to reduce serum level of both pro-inflammatory and anti-inflammatory cytokines. CytoSorb is being used to treat COVID-19 patients, and with the recent FDA Emergency Use Authorization of CytoSorb adsorber in the USA may be integrated into a bypass circuit in the ECMO or CRRT and changed every 24 hours. Specifically, CytoSorb has been reported to work most effectively when treatment is initiated within 24 hours of a sepsis diagnosis. The CytoSorb hemo-adsorption technique is unique in that its efficacy is concentration dependent. High concentrations of cytokines in the blood will be removed more quickly in comparison to blood with lower cytokine levels. These results indicate that CytoSorb in combination with ECLS is apparently an effective therapy to prevent escalation of sepsis with rapid weaning off high-dose catecholamine infusions and quick reduction in procalcitonin (PCT) and C-reactive protein (CRP) levels. The use of CytoSorb with ECLS was associated with a shorter mean duration on ECMO of 8.2 days (range: 2-23 days) versus 26.5 days (range: 13-30 days) in the control, a rapid reversal of septic shock within 48 hours, and a marked decrease in lactate dehydrogenase and inflammatory markers. The optimal timing for immunomodulatory therapy and impact on ECLS-related inflammation still needs to be investigated further (Figure 1).

To validate the safety and efficacy of this emerging technology, diverse registries have been created.

The International CytoSorb Registry has been established to collect and analyze treatment data from all over the world

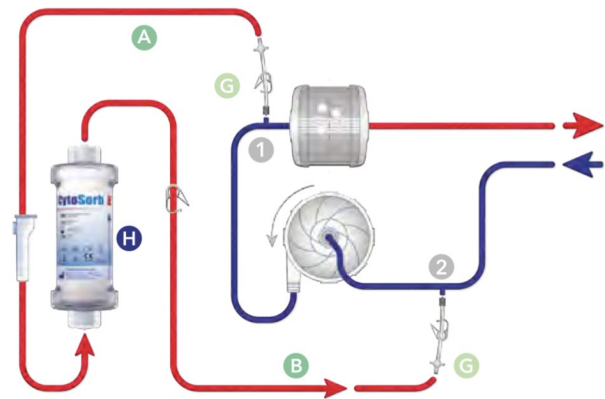


FIGURE 1 Integration of CytoSorb adsorber bypass in extracorporeal life support (ECLS) circuit. The recommended blood flow rate should be between 150 and 700 mL/min, with a minimum rate of at least 100 mL/min. The blood flow through CytoSorb can be monitored with the aid of an ultrasound Doppler probe (on line A or B) if necessary (courtesy of CytoSorbents Europe GmbH, Berlin Germany). A, bypassing line from ECLS circuit to CytoSorb adsorber; B, bypassing line from CytoSorb adsorber to ECLS circuit; G, connector on CytoSorb bypass to ECLS circuit; 1, connector before ECLS oxygenator membrane; 2, connector upstream of the ECLS pump; H, CytoSorb adsorber [Color figure can be viewed at wileyonlinelibrary.com]

and is being independently managed by the Center of Clinical Studies at the University of Jena, Germany. Its goal is to track patient mortality (primary endpoint) and secondary outcomes such as hospital length of stay and intensive care unit length of stay, vasopressor use, renal replacement therapy, and end-organ function.

COVID-19 treatment by Seraph Apheresis (COSA) Registry is now online after a positive Institutional Review Board (IRB) vote from the Hannover Medical School Review Board.

E-ISFA has joined the German Center for Infection Research and the ESCMID Emerging Infections Task Force and a number of other renowned institutions such as the Robert-Koch Institute in their activity regarding the LEOSS (Lean European Open Survey on SRAS-CoV-s Infected Patients) registry. LEOSS is an open, international, and anonymous registry covering all aspects of COVID-19 infections from diagnosis, laboratory measurements, and medical treatments to final outcomes. LEOSS also covers apheresis treatments, such as TPE, CytoSorb, and DFPP. Weekly statistics from the registry data will provide data according to the disease stage in which the treatment was started, the treated plasma volumes for TPE, the number of treatments per number of days, and the physician's judgment of TPE effectiveness.

Last but not least, the new study Cytokine Adsorption in Severe COVID-19 Pneumonia Requiring Extracorporeal Membrane Oxygenation (CYCOV) should be mentioned. The study aims to investigate the influence of extracorporeal cytokine adsorption on humoral inflammation parameters and patient survival under controlled conditions in patients

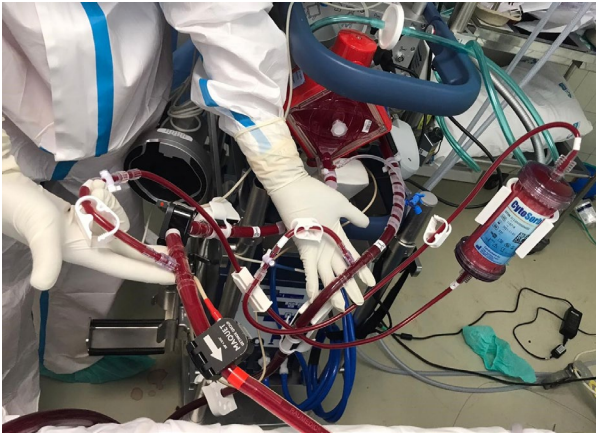


FIGURE 2 Clinical application of CytoSorb adsorber and extracorporeal life support (courtesy of CytoSorbents Europe GmbH, Berlin, Germany) [Color figure can be viewed at wileyonlinelibrary.com]

with severe COVID-19 disease requiring extracorporeal membrane oxygenation. The primary goal is to investigate the efficacy of treatment with a CytoSorb adsorber in patients with severe COVID-19 disease requiring veno-venous ECLS. The primary endpoint is the reduction in plasma IL-6 levels 72 hours after initiation of ECLS support (Figure 2).

5 | CLINICIAN'S PERSPECTIVE

In the scenario of a severe pandemic, resources that are limited for advanced organ support, such as ECLS or blood purification techniques, may be de-prioritized to redirect care toward numerous patients with a higher likelihood of survival.⁶¹ Due to the intensive hospital resource utilization, substantial staff training, and multidisciplinary needs associated with starting an ECLS program, ELSO recommends against starting new ECLS centers for the sole purpose of treating patients with COVID-19.¹⁵ A list of experienced ECLS centers is provided on the ELSO website.^{37,38}

Treatment under uncertainty and surge conditions, the understandable urge to use untested interventions, staffing and equipment shortages, risk of healthcare worker infection, and research staff deployment to provide clinical care are also significant barriers against research implementation during a pandemic. Under such conditions, no one really has much time to wait for evidence. Clinical trials have been initiated but the awaited outcome results will not help current patients.⁶² Registries may at least provide a rapid response as to why the clinical course is so heterogeneous but the critical point remains as to which procedures in COVID-19 patients should be initiated.^{37,39} The Thoracic Society-led International Task Force recommends that data be collected from COVID-19 patients who have received or are receiving one or more of the interventions suggested in Interim

Guidance on Management Pending Empirical Evidence. The data should be assessed periodically so that patients who received the intervention can be compared to those who did not. Such data will provide interim guidance until superseded by randomized trial results when they become available.


Epidemiological management, including tests detecting antibodies produced in response to infection in individuals exposed to the virus, clinical interventions, and scientific research, needs to be a coordinated. Further research should be facilitated and promoted, particularly under the guidance of recognized scientific societies or expert-based multicenter investigation, with rapid communication of critical and relevant information to enhance better appraisal of patient profiles, complications, and treatment modalities.^{16,62}

With any antiviral treatments, timely administration before complications develop will be crucial. Randomized controlled trials of the most promising treatments are a leading priority, and, hopefully, the road to an effective treatment and a vaccine will not be too long in development. Interestingly, the development of a successful vaccine at the end of the movie *Contagion* (2011), one of the infectious disease outbreak and pandemic films, also provides a bit of hope.⁶³

CONFLICT OF INTEREST

Roberto Lorusso is a consultant for Medtronic and LivaNova and medical advisory board member for EUROSETS (all honoraria to the university for research funding).

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