

WHITE PAPER

The Role and Benefit of Extracorporeal Blood Purification in Critically Ill COVID-19 Patients

Summary of Current Information from Fresenius Medical Care (EMEA Region[†])

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ABSTRACT

- The ongoing COVID-19 pandemic results in a high number of critically ill patients developing multiple organ failure with need for extracorporeal organ support.
- With respect to AKI and need for renal support, the proportion of critically ill COVID-19 patients needing renal support has been reported at about 23% in a large European case series;¹ as a consequence a rise in need for renal support is to be expected in parallel with the rise in number of critically ill COVID-19 patients.
- Renal support for AKI should follow established standard practices. Use of citrate anticoagulation can generally continue while monitoring for sufficient citrate metabolism. CRRT and certain SLEDD devices seem preferable from a volume control as well as an infection protective point of view. However, as need arises, other forms of renal support should be used also.^{2,3}
- COVID-19 patients have been described being hypercoagulable and citrate anticoagulation alone might be insufficient to prevent clotting in the extracorporeal circuit. Adding systemic anticoagulation or switching to another anticoagulation mode (e.g. unfractionated heparin) would be options for clinicians to consider.³⁻⁵
- With respect to elimination of SARS-CoV-2 virus from the blood stream as well as tackling cytokine storm, variations in CRRT as well as various adsorbers (manufactured by 3rd parties) are under evaluation on their effect on COVID-19 patients with so far insufficient data for definitive conclusions.

This document is intended as an aid in supporting supplementary training and education of physicians and nurses as well as any instructions for use of any products (medical devices, medicinal products etc.). It is intended only as a scientific medical support and is not intended to replace the judgement or experience of the attending physicians and nurses. The treatment as well as the decisions concerning specific patient treatments are within the sole responsibility of the prescribing physicians and nurses. Hence, this document does not replace a personal training and a careful review of the relevant user guides and summary of product characteristics. Also note that the hygienic guidelines applicable in each country, hospital or other facility are to be complied with at all times.



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INTRODUCTION

The ongoing COVID-19 pandemic results in a high number of critically ill patients developing multiple organ failure and being treated in intensive care units, including makeshift intensive care units. Despite mechanical ventilation being the mostly needed organ support, questions have arisen on need for extracorporeal organ support including renal replacement therapy.

INCIDENCE OF AKI IN COVID-19

In the context of severe COVID-19 infection multiple organ failure is observed with a predominance of lung failure. Initial reports on frequency of AKI and of renal support stated single digit percentage frequencies for renal support being required.⁶⁻¹⁰ However, more recent, large data series report higher frequencies. The ICNARC (Intensive Care National Audit and Research Centre) has reported COVID-19 data based on 200+ ICUs in the UK, including a renal support incidence of 23.1% of COVID-19 patients admitted to ICUs (1163 out of 5139 patients), which appears to somewhat exceed the 17.9% incidence rate reported for other viral pneumonia in the years 2017-2019 (see Tab 7 in¹). Dreher et al.¹¹ reported the experience with the first 50 COVID-19 patients hospitalized at the university hospital in Aachen (Germany), with approx. half of these (24 pts.) requiring mechanical ventilation on the ICU while the remaining patients were treated on an isolation ward. 11 of the 24 ICU patients required renal support (46%). This rate relates to a tertiary care center and might therefore be above average seeing that it includes severely ill patients referred from surrounding hospitals.

Despite some heterogeneity in the reported data, we believe still that the percentage of patients with severe AKI needing for renal support is roughly at otherwise established levels also in COVID-19 patients and that the 23.1% from the large ICNARC data set may be an appropriate estimate.¹ With the surge in number of critically ill patients during a COVID-19 outbreak however, absolute number of COVID-19 patients needing renal support likely will rise.

TREATMENT OF SEVERE AKI IN COVID-19

Generally, the locally established indications and standards of care for treating AKI should be continued, as any substantial change goes along with a risk of mistakes as well as likely with training needs occupying staff time.²

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Therefore, it seems appropriate to continue with the established best practices and local procedures. Demand for treating AKI may require using all locally available therapeutic options, including CRRT, intermittent HD and SLEDD/PIRRT options, while considering the therapeutic needs of the patients.³ Devices depending on access to reverse osmosis-water supply might be bound to specific locations, which may pose difficulties with transportability of mechanically ventilated patients.

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CRRT or semi-continuous renal support treatment methods like SLEDD appear preferable over intermittent dialysis techniques based on better volume control due to continuous treatment. Also, CRRT devices as well as certain SLEDD treatment devices (e.g. GENIUS) can be prepared outside the patient room and brought ready to therapy initiation into the patient room, limiting time close to the patient and associated infection risk as well as the need to wear personal protective equipment.² There is various guidance in the literature on generally optimizing CRRT, e.g.¹²

Peritoneal dialysis has been discussed as an option for supporting COVID-19 patients with AKI. However, it requires inserting a PD catheter (ICU staff typically inserts CVCs, while rarely PD catheters) and experience of ICU staff with PD may often be limited. Further, with frequent use of prone-positioning of mechanically ventilated COVID-19 patients, there might be interference with performing PD.¹³ For increasing capacity for renal support, PD is typically added in a last step.^{3,14}

THERAPY DETAILS

With respect to convective vs. diffusive CRRT options, there are no clinical data supporting differences in hard outcome parameters with diffusive and convective CRRT modalities while there is a signal towards better patency with CVVHD.^{15,16} In line with this, Claudio Ronco suggests the use of CVVHD in COVID-19 patients needing renal support to limit filtration fraction and thereby reduce the risk of clotting.¹⁷ Thus, we currently continue advocating Ci-Ca CVVHD with the filter options Fresenius Medical Care provides. Alternatives with other anticoagulation methods, e.g., heparin anticoagulation, encompass also CVVHDF with also targeting a low filtration fraction.

Despite hypoxemia being a frequent issue with COVID-19, we currently believe that citrate can be used in general if mechanical ventilation (or in some cases possibly also ECMO) allows for appropriate oxygen supply.^{3,4} This is in-line with the recommendation to use citrate anticoagulation with CRRT by the Brescia Renal Covid Task Force, a locally established document made available on the ERA-EDTA webpage.¹⁸ However, with some of the drugs applied in COVID-19 patients being potentially hepato-toxic and multi-organ failure possibly associated with limited citrate metabolism, monitoring for sufficient citrate metabolism is required,¹⁸ including time course of systemic ionized calcium and total-to-ionized-calcium ratio. Cases of impaired citrate metabolism when using Ci-Ca CVVHD in COVID-19 patients have been reported to Fresenius Medical Care, with the consequence of switching to another anticoagulation mode. This emphasizes the need to monitor for signs of insufficient citrate metabolism.

With respect to anticoagulation of note, severely ill COVID-19 patients are reported to develop a hypercoagulable state and disseminated intravascular coagulation (DIC) as evidenced by high levels of D-dimers.⁷ Zhou et al. report high D-dimers (> 1µg/ml) as risk factor for mortality.⁹ Tang et al. report less mortality being associated with systemic anticoagulation in COVID-19 patients with elevated D-dimers (above 3µg/ml) or an elevated SIC score (+ 4 points; reflecting elevated INR, low platelets and elevated SOFA score).¹⁹ The same group subsequently compared COVID-19 patients with severe pneumonia patients of other etiology. Different to the situation with other etiologies, COVID-19 patients with elevated D-dimers had a better survival with systemic anticoagulation.²⁰ As part of the overall treatment thus, signs of intravascular coagulation well might trigger the need of appropriate systemic anticoagulation. The combination of (low dose) systemic anticoagulation and citrate anticoagulation for the extracorporeal circuit is considered feasible and can be considered if systemic anticoagulation is desired in addition to anticoagulation of the extracorporeal circuit. Further, when systemic anticoagulation is applied at a sufficient level this might be sufficient to cover anticoagulation needs of the extracorporeal circuit and treating without citrate anticoagulation is an option.

Of note, another hypercoagulable state, i.e. heparin induced thrombocytopenia type II has been linked with premature clotting during citrate anticoagulation which needs to be taken into consideration. In such cases adding an appropriate systemic anticoagulation was beneficial, with using, e.g., danaparoid²¹ and argatroban.²² Clinicians considering proceeding analogously in case of a hypercoagulable state with COVID-19 appears plausible to us.

Besides clotting (usually associated with pressure increases in the extracorporeal circuit) this hypercoagulable state might also promote membrane clogging (associated with reduced diffusive performance of the membrane, resulting in one or more of the following with Ci-Ca treatments: hypercalcemia / reduction of calcium substitution needs, metabolic alkalosis, hypernatremia, less than expected lowering of creatinine levels). We consider it possible that a hypercoagulable state of a COVID-19 patient contributes also to the likelihood of membrane clogging and, therefore, the same statement as with clotting risk applies also in this scenario.

ROLE OF CYTOKINES / CYTOKINE STORM WITH COVID-19

High IL-6 had been observed in non-survivors of COVID-19 (e.g.⁹) which makes IL-6 a potential target in attempts to treat COVID-19, with both IL-6 serum concentration and IL-6 receptors being thinkable targets. Mehta P. et al. have raised the point that some (not all) COVID-19 patients may have a cytokine storm with potential detrimental consequences. Drugs targeting the cytokine response are considered with COVID-19, e.g. tocilizumab (blocks the IL-6 receptor) is tested in a clinical study.²³ With respect to extracorporeal blood purification therapies, various CRRT modifications (such as high-volume haemofiltration) and also adsorbers can be considered (see, e.g., a review on options by Karkar and Ronco¹²).

With respect to cytokine removal, some differences in performance between CRRT set-ups have been shown in septic patients. For example, the EMiC2 filter showed a significantly higher IL-6 clearance versus the AV1000S filter (both used in Ci-Ca CVVHD).²⁴ However, the absolute cytokine clearance with CRRT set-ups generally is limited and cytokines often have short half-lives which correspond to high internal generation and clearance rates. This led to concerns with

expectations on direct clinical impact of cytokine removal with CRRT techniques.²⁵ Bottom-line filter choice and other details of a renal support prescription should follow largely standard processes, considering patient conditions (e.g. degree of systemic inflammation and clotting activation) and intended performance profile.

With respect to adsorbers, we are aware that several 3rd party products are discussed for use in COVID-19 patients, among others addressing cytokine storm. Evidence for this is limited as of now, with some initial, promising data reported in webinars, press releases etc. Of note, cytokine removal strategies via adsorbers in an extracorporeal circuit have to be judged in relation to pharmaceutical interventions like tocilizumab.¹⁸

STRATEGIES FOR MINIMIZING MEDICAL STAFF INTERACTIONS WITH THE CRRT DEVICE

This aims at limiting infection risks and can include several measures as listed below. Further orientation might be derived from literature describing application of renal replacement therapy in other contagious diseases, e.g. Ebola,^{26,27} while recognizing differences between diseases, e.g. Ebola and COVID-19 apparently differ in case fatality rate. Also, strategies will differ depending on whether isolation areas are limited to single patient rooms or larger areas (including hallways) of an ICU.

Potential measures:

- Setting up the devices outside the potentially contaminated area (e.g. machine prior to therapy as well as bags preparation during the therapy)
- Separating locations for dismantling and set-up of the systems as well as other standard hygiene measures
- Fully use the scale capacities to reduce number of bag changes
- Consider changing different bag types together at one point in time to avoid unnecessary contacts
- Use citrate anticoagulation where and as locally established; long filter patency with citrate should help in reducing manual interactions with the CRRT device;²⁶ however, adequate monitoring and vigilance for sufficient citrate metabolism is required (see above)
- As generally stated, Ci-Ca CVVHD or Ci-Ca EMiC2 (Ci-Ca CVVHD using the EMiC2 filter) can be used, if already established at that center. The comparatively low blood flow as designed with the Ci-Ca protocol might limit frequency of pressure alarms related to the vascular access and thereby support the goal of minimizing interactions with the catheter in the patient.

CONCLUSIONS

In the ongoing COVID-19 pandemic, we see also a high rate of AKI requiring renal support therapy. In regions with an outbreak of COVID-19 this can lead to high demand for renal support. Renal support itself should largely be applied as established for AKI. When continuing with an established citrate anticoagulation protocol, the usual monitoring including for citrate metabolism is required. A hypercoagulable state of COVID-19 patients might trigger the need for systemic anticoagulation at the discretion of the treating physician, which might cover the needs to anticoagulate the extracorporeal circuit also. With respect to extracorporeal blood purification options directly addressing the cytokine storm described with COVID-19, further data have to be awaited prior to definitive conclusions on its clinical relevance.

Meet Our Experts



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Fatih Kircelli leads the medical information and education team throughout Fresenius Medical Care's Europe/Middle East/Africa region. His team provides medical expertise to all related departments on the company's product portfolio and therapies. Over his eight years with Fresenius Medical Care, he has served as a country medical director as well as marketing and renal pharma business unit director for Turkey. He is a nephrologist with over 60 publications in peer-reviewed journals. He received his associate professor degree in nephrology in 2012.



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Dr. Robert Pohlmeier is trained as a physician and in addition has a diploma in electrical engineering. He provided medical oversight and managed the implementation of the Ci-Ca regional citrate anticoagulation project and has worked with Fresenius Medical Care for more than 20 years in different scientific functions and with a focus on treatment of acute kidney injury in critically ill patients.

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