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For safe and adequate blood purification therapy in severe COVID-19 — what we have learned so far

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Abstract: Acute kidney injury (AKI) is defined as an increase in serum creatinine within 48 h or 1 week, or a decrease in urine output within 6-24 h. Continuous renal replacement therapy (CRRT) plays an important role in patients with severe AKI. In addition to direct cytotoxicity caused by the severe acute respiratory syndrome coronavirus 2, patients with coronavirus disease (COVID-19) experience endothelial cell damage, increased thrombogenic inflammation, and impaired immune responses. It has been reported that the more severe the case, the greater overproduction of cytokines and the more advanced the multiorgan failure. The kidney is widely recognized as one of the primary target organs; and COVID-19 positive AKI has been reported to have a greater rate of subsequent decline in renal function than COVID-19 negative AKI. Blood purification therapy has been used to prevent or alleviate organ damage in patients with moderate-to-severe COVID-19. Cytokine regulation is one of the primary therapeutic goals for these patients. Even with the widespread use of vaccines and antibody therapy, a certain percentage of patients develop moderate-to-severe diseases.

***Keywords*:** blood purification, cytokines, acute kidney injury, Japan

Introduction

Acute kidney injury (AKI) is defined as an increase in serum creatinine within 48 h or 1 week, or a decrease in urine output within 6-24 h. At present, despite many opportunities to consider renal dysfunction as a part of multi-organ failure in the intensive care unit (ICU), drugs for AKI with clear clinical evidence have not reached clinical application. Acute hemodialysis, especially continuous renal replacement therapy (CRRT), plays an important role in severe AKI.

The spike protein (S protein) in the envelope of the new severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) binds to a receptor on the cell membrane (ACE2 receptor). It enters the cell through the transmembrane protease serine 2 (TMPRSS2). In addition to direct cell damage caused by the virus, endothelial cell damage, promotion of thrombotic inflammation, and impaired immune response are known to occur. In new coronavirus infections (coronavirus disease 2019; COVID-19), cytokine overproduction occurs, especially in severe cases, leading to progressive multi-organ failure. The kidney is widely recognized as the primary target organ (Figure 1) (*1*). Overseas, it has been reported that among COVID-19 cases, the incidence of AKI occurs in a range of 0.5-29% (*2*).

In general, AKI in a certain percentage of patients progresses to chronic kidney disease, and COVID-19-positive AKI has been reported to have a greater rate of subsequent decline in renal function than COVID-19-negative AKI (*3*). The initial symptoms of COVID-19 are similar to those of influenza, such as fever, cough, malaise, and dyspnea. The median time to hospitalization is 7 days. Diarrhea and taste and smell disorders may occur in some cases, although they are not inevitable. According to data from COVIREGI-JP, the Japanese registry for COVID-19 patients, 60% of hospitalized patients did not require oxygen administration, while 30% did, 9% required a ventilator or extracorporeal membrane oxygenation (ECMO), and 7.5% died. Predicting which patients will become critically ill is crucial for utilizing limited medical resources. We have reported that non-invasive urinary liver type fatty acid-binding protein (L-FABP) at the time of admission can be used to predict the severity of the disease (*4*).

Blood purification therapy is used to prevent or alleviate organ damage in patients with moderate-to-severe COVID-19. The goal is to remove circulating mediators, such as cytokines and damage-associated molecular patterns, including blood perfusion and plasma exchange for cytokine removal. However, when the disease progresses to multiple organ failure, blood purification is used to treat AKI and endotoxemia caused by various infections. The goal of therapy is to prevent

progression of organ failure, and renal replacement therapy (RRT), endotoxin adsorption, and plasma exchange are used to continue to remove cytokines (Figure 2) (*1*). This review aimed to investigate safe and adequate blood purification therapies for severe COVID-19.

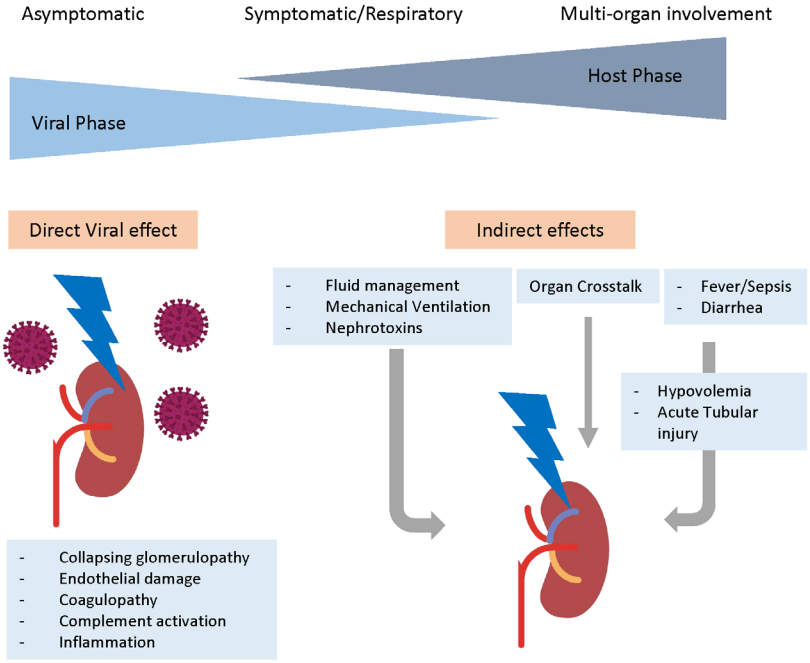

Figure 1. COVID-19 and acute kidney injury*. The effects of COVID-19 on the kidneys have been suggested to be direct viral damage and indirect effects. *Modified from *Ref. 1.*

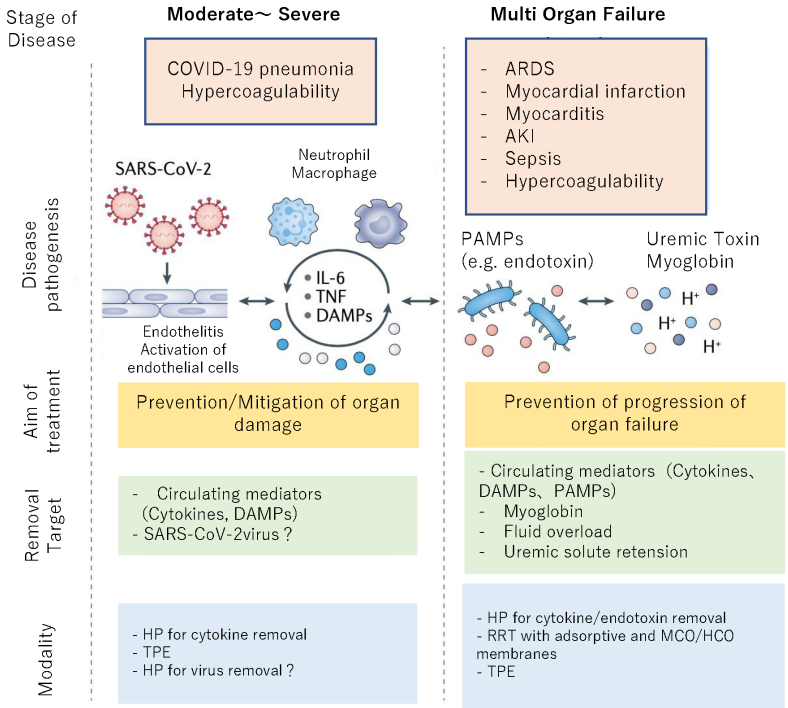

Figure 2. Blood purification therapy according to COVID-19 pathology*. Extracorporeal blood purification (EBP) has been proposed as a potential adjunctive therapy for critically ill patients with COVID-19 EBP may improve the condition by removing circulating immunomodulators. *Modified from *Ref. 1.* AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; DAMPs, damage-associated molecular patterns; HCO, high cut-off; HP, hemoperfusion; MCO, medium cut-off; PAMPs, PAMPs, pathogen-associated molecular patterns; RRT, renal replacement therapy; TPE, therapeutic plasma exchange.

CRRT

The benefits of early introduction of RRT include adjustment of positive water balance, electrolyte and acid-base balance, and elimination of inflammatory mediators. Meanwhile, the combination of vascular access insertion, anticoagulant use, and limited medical resources must be considered. The AKIKI study (*5*), published in 2016, is a French multicenter randomized controlled trial (RCT) that compared an early group of invasively treated patients with stage 3 AKI who started RRT within 6 h of study inclusion with a waitlist group that started RRT when an absolute indication for RRT emerged or when oliguria persisted for at least 72 h (51% of the waitlist group received RRT). No significant difference was observed in 60-day mortality between the early group and the waitlist group (48.5% *vs.* 49.7%; $p = 0.79$), while catheter-related infections and hypophosphatemia were significantly higher in the early group. The 2018 IDEAL-ICU study (*6*) was another French multicenter RCT. No significant difference in mortality at 90 days was observed (57.7% *vs.* 53.8%). In 2020, the STARRT-AKI study (*7*), the largest multicenter RCT ever conducted, was published in Canada. No significant difference in 90-day mortality (43.9% *vs.* 43.7%; $p = 0.92$) was identified, and RRT dependence was higher in the early start group. Based on the above, postponing RRT in patients with stage 3 AKI until it is indicated under close supervision is acceptable (*8*). The 2016 Japanese guidelines for the treatment of AKI, which were published before the results of STARRT-AKI were issued, stated that "there is little evidence that early initiation of blood purification improves prognosis, and the timing of initiation should be determined based on a wide range of clinical symptoms and conditions (strength of recommendation; no grade)".

The 25th Work Group (WG) of the Acute Disease Quality Initiative (ADQI) stated that there is no evidence that AKI due to COVID-19 should be managed differently from AKI due to other causes (*i.e.*, it should be managed in the same way as before) (*1*). The following are the proposals for WG (Table 1). First, the use of ultrasound for vascular access insertion and RRT administration should remain based on the KDIGO AKI guidelines (level of evidence: 1A). Second, the timing of RRT initiation, site of vascular access, and modality of acute RRT should be based on patient needs, the expertise of the institution, and availability of staff and equipment (NOT GRADED). Last, because COVID-19 often causes a hypercoagulable state, we suggest the use of continuous venous-venous hemodialysis or continuous venous-venous hemodiafiltration to reduce the filtration rate and reduce the risk of circuit coagulation when CRRT is performed (level of evidence: 2C).

In our hospital, when CRRT is performed, the first choice for a hemofilter is a membrane that can be expected to adsorb cytokines, such as polymethyl methacrylate membrane. When CRRT was first introduced in our institution in the first wave of severe COVID-19 cases, the problem was disposal of RRT effluents. In our study, the genomic material of SARS-CoV-2 was detected in the effluent (*9*). Considering the pore size of the hemofilter (7-10 nm) and the size of SARS-CoV-2 (approximately 100 nm), the virus appearing in total length in the CRRT effluent is unlikely. However, from the perspective of infection prevention for ICU staff and the psychological stress of treatment, drainage fluid is first solidified with a coagulant and then disposed of as regular infectious waste. Additionally, 24-hourly circuit replacement is advocated for CRRT due to concerns of circuit coagulation (*10*), and the circuit is changed every 24 h at most (Figure 3).

Table 1. Recommendations on RRT for COVID-19 patients*

Items	RRT Method	Responding to the growing demand for RRT
Introduction	Consider RRT when solutes and fluid retention are greater than renal function. (Consider a wide range of factors that can be corrected with RRT, not just BUN and sCre.)	If the response to conservative treatment such as bicarbonate administration and K adsorbents is poor, RRT should be considered.
Modalities	Choose prolonged RRT (*e.g.*, CRRT, SLED) if circulatory instability is present; consider treatments that reduce the risk of circuit coagulation, such as CVVHD and CVVHDF.	The modality of RRT can be influenced by the supply of machines and consumables on the medical side and the availability of trained staff. Consider short-duration IHD or CRRT if possible. Consider PIRRT with equipment. If equipment is not available, PD is an option.
Dialysis Prescription	For CRRT, a filtration rate of 20-25 mL/kg/hr is recommended. Target is 25-30 mL/kg/hr. Three times per week for IHD. For prolonged dialysis, prescribe with consideration for circuit coagulation.	In the case of PIRRT using short IHD or CRRT equipment, the water removal and filtration flow rate settings are adjusted to achieve the treatment goal.
Vascular Access	The right internal jugular vein is the first choice. Prone position, obesity, and hypercoagulability can affect access performance.	Create a system that can insert PD catheters for emergency evacuation.

*Modified from *Ref. 1.*

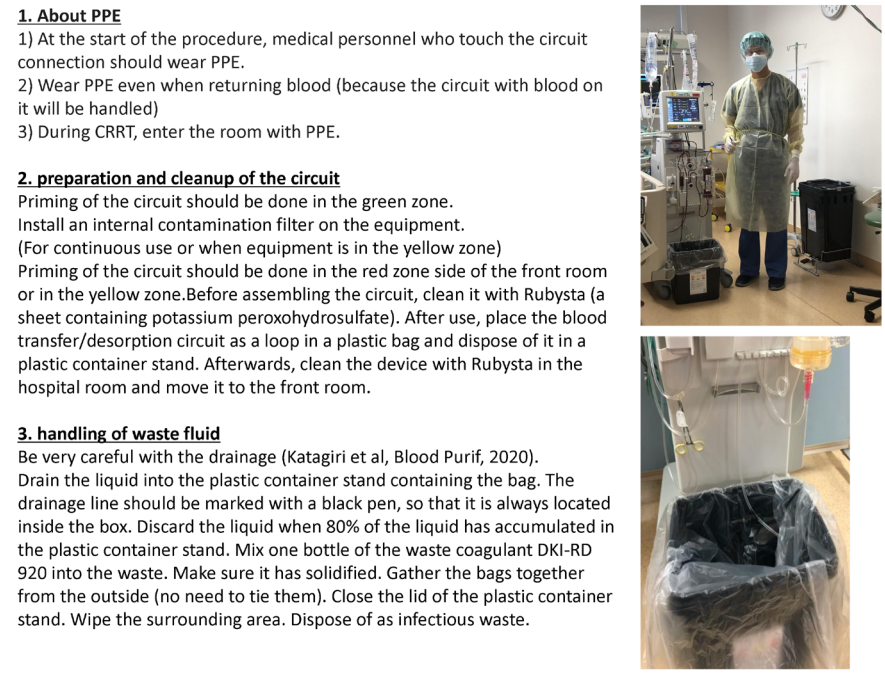

Figure 3. How to perform CRRT for COVID-19 in our hospital. In the beginning, we gathered information by hand and went through a trial and error process to ensure safe CRRT implementation.

PMX-DHP

Polymyxin B-immobilized fiber column direct hemoperfusion (PMX-DHP) therapy is a medical device that uses the polypeptide antibiotic polymyxin B to bind to lipid A, the active center of the endotoxin. In 2018, the EUPHRATES study (*11*) was published, which revealed that PMX-DHP was influential in treating sepsis (n = 450) with a high endotoxin activity assay of ≥ 0.6. The study compared PMX-DHP administered twice for 2 h within 24 h with sham treatment. The results indicated that the 28-day mortality rate was 37.7% in the PMX group and 34.5% in the sham group, which was not significantly different. Based on these results, the 2020 Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock also state that, "it is weakly recommended that PMX-DHP not be used in patients with septic shock (Grade 2B)".

PMX has been suggested to be effective not only as a sepsis treatment device, but also for respiratory diseases. In addition to endotoxin removal, PMX may be involved in the removal of mediators such as inflammatory cytokines causing a cytokine storm and adsorption of cellular components such as activated leukocytes that directly damage lung tissue. In 2014, as an advanced medical treatment B, the efficacy of PMX was studied in patients with acute exacerbation of idiopathic pulmonary fibrosis when it was added to the treatment. In our first case of PMX for COVID-19 (*12*), oxygen demand increased, the P/F ratio decreased to approximately 150 on the fifth day of hospitalization, and the central department requested PMX-DHP for 3 h over 2 days. Immediately after PMX-DHP administration, the patient demonstrated rapid fever resolution, and worsening of the respiratory condition was alleviated. Subsequently, we reported our experience with PMX-DHP in 12 patients during the so-called first wave (*13*), including those who required oxygenation at the time of PMX (n = 5), those who were on ventilators (n = 5), and those who had already received ECMO (n = 2) (Table 2). Since this was a single-center, backward-looking observational study, we cannot definitively state the efficacy of the treatment. Nevertheless, it may be helpful to consider it in patients with a P/F ratio < 300 or moderate disease II or higher requiring oxygenation, but before progressing to severe disease requiring ventilatory management or ECMO. In approximately half of the sessions, we experienced an increase in inlet pressure and short circuit coagulation within 15-30 min of the start of the procedure, which may be due to the presence of thrombosis in severe COVID-19 (circuit problems have decreased since then, probably due to the spread of anticoagulant therapy). Currently, we are continuing a multicenter prospective specific clinical study, and case reports suggesting that efficacy of PMX-DHP for COVID-19 continues to occur in Japan, Italy, and Thailand (*14-17*).

Plasma exchange therapy

Plasma exchange plays a role in acute hemodialysis by *i*) removing pathogenic substances from plasma (which are relatively large and cannot be removed by hemodialysis) and *ii*) efficiently replenishing plasma

Table 2. Results of PMX-DHP for COVID-19 patients at our hospital*

Variables	*n* = 12
Age	66.5 (36-83)
Sex	Male 9 (75.0 %), Female 3 (25.0 %)
Number of days since onset	6.5 (3-16)
BMI	25.4 (19.2-31.9)
Smoking	5 (41.7 %)
Hypertension	5 (41.7 %)
Diabetes	3 (25.0 %)
Oxygen administered at the start of PMX (no ventilator)	5 (41.7 %)
Ventilator at the start of PMX (no ECMO)	5 (41.7 %)
ECMO already in place at the start of PMX	2 (16.6 %)
Number of PMX attempts	One (2, 16.7 %), Two (10, 83.3 %)
Day 15 Severity	
improvement	7 (58.3 %)
constant	1 (8.3 %)
worsening	4 (33.3%)
P/F ratio	
Day 1	153.9 (69.0-327.1)
Day 4	214.1 (122.3-438.1)
Day 8	271.3 (172.8-464.8)
Inlet pressure rise	7/22 (31.8 %)
Circuit coagulation	5/22 (22.7 %)
Patient death	3 (25.0 %)

*Modified from *Ref. 13.*

proteins. Depending on the removal goal, simple plasma exchange (TPE), double filtration plasma exchange (DFPP), plasma adsorption, or even selective plasma exchange (SePE) can be used. Fresh frozen plasma (FFP) and albumin are options for replacement fluid, and the advantages and disadvantages of each need to be properly understood. Fibrin and factor 13 have a large molecular weight of 300 kDa and are removed by DFPP. Fibrinogen has a long half-life, and attention should be paid to appearance of bleeding tendencies. FFP replacement should be considered if fibrinogen levels are < 100-150 mg/dL prior to treatment.

Reports on the efficacy of TPE for COVID-19 continue to come from various regions (*18,19*), and only one RCT has been identified (*20*). This RCT compared the standard of care plus TPE (*n* = 43) with the standard of care (*n* = 44). The standard of care included ribavirin, dexamethasone, and anticoagulation; and the TPE used a centrifugation method rather than the membrane separation method. The results suggested that the number of days on ventilator and ICU stay as well as the SOFA score was lower in the TPE group than in the sham group. However, the mortality rate at day 35 was not significant in the TPE group. However, the usefulness of plasma exchange remains debatable (*21*).

Other blood purification therapies

LIXEL™ is covered by insurance for use in three hemodialysis sessions per week for the treatment of dialysis amyloidosis. LIXEL exerts its therapeutic effect by selectively adsorbing β2-microglobulin, the causative agent of dialysis amyloidosis, through hydrophobic interactions and molecular sieving effects, and has been reported to adsorb cytokines because of its structure (*22*). At our institution, maintenance hemodialysis patients with a history of dialysis for more than ten years who were admitted with moderate grade II COVID-19 were treated with LIXEL during dialysis (*23*). In Japan, Adacolam™, a blood cell removal purifier used during granulocyte monocyte ablation (GMA) therapy in ulcerative colitis, Crohn's disease, cystic psoriasis, and psoriatic arthritis, has been suggested as effective against COVID-19 (*24*). The main action of GMA is to adsorb and remove activated myeloid cells, although it is also expected to reduce inflammatory cytokines (*25*). oXiris™ is another biocompatible hemodialytic filter coated with heparin, which is used in RRT, is also known to adsorb and remove cytokines and endotoxins, and has antithrombotic properties. The adsorbent CytoSorb (CytoSorbents Corp, NJ, USA) is composed of porous polymer beads and adsorbs hydrophobic molecules of 5-55 kDa such as cytokines, myoglobin, and bilirubin (*26,27*). The adsorbent can be integrated into external circulation circuits such as ECMO and CRRT. The US Food and Drug Administration issued an emergency use authorization for the treatment of COVID-19 in 2020. Although its efficacy has been reported in some case reports, an RCT has reported that not only was there no effect on IL-6 reduction, but also 30-day mortality was significantly higher in the Cytosorb treatment group of critically ill patients randomized to ECMO (*28*). The increase in IL-6 in COVID-19 was slower than that in sepsis and ARDS, while the increase in D-dimer was more marked (*29*), suggesting that simply controlling IL-6 alone may not improve prognosis.

Conclusion

Blood purification therapy is complementary to drug therapy. Even with the widespread use of vaccines and antibody therapy (*30*), it is expected that a certain percentage of patients will develop moderate-to-severe diseases due to breakthrough infections. It is hoped that clinical studies will continue to accumulate evidence to investigate safe and adequate blood purification therapies for COVID-19.

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