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Review Article

Blood Purification in the Management of Cardiorenal Organ Failure in Critical Patients with COVID-19 in ICU: A Review

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Abstract

Background: COVID-19 dissemination began at the end of 2019 and resulted in an ever-increasing number of cases and deaths worldwide. Due to the lack of effective antiviral drugs, severely and critically ill patients need full active supportive treatment, including extracorporeal organ support therapies for multiple organ support. However, evidence of specific treatments, such as blood purification, for cardiorenal organ failure with COVID-19 is still lacking.

Summary: This review reports the current understanding and principles for blood purification management of patients with COVID-19 based on recent experience, latest publications, and expert reports, to encourage safe, accurate, and effective performance. Recommendations on modality selection, indication and timing, infection prevention and control management, selection of equipment and filter, and technical and clinical monitoring are discussed. The fundamental practice of blood purification management in these settings is described for vascular access, mode and dosage, anticoagulation strategy, fluid management, drug adjustment, and weaning time of blood purification.

Key Messages: The recommendations on the clinical practice of blood purification in all aspects, including modality, indication and timing, infection prevention and control management, and selection of equipment and filters based on the latest publications.

Keywords: *SARS-CoV-2; COVID-19; Blood Purification; CRRT; Extracorporeal Therapies; Extracorporeal Organ Support; AKI; Cytokine Storm; Recommendation*

Introduction

The World Health Organization declared COVID-19 a pandemic, COVID-19 patients admitted to the ICU display a range of symptoms and organ dysfunction of varying degrees of severity. The majority have pneumonia with single-organ failure, while others suffer from a significant derangement of the immune system. Cytokine release syndrome (CRS), also known as cytokine storm, is induced by the virus itself or by a superimposed septic syndrome as a result of viral infection [1] and is considered an important pathophysiological basis for severe COVID-19 disease [2-4]. Critically ill patients usually have elevated plasma concentrations of TNF-α, IL-2, IL-6, and IL-10 [5], which are regarded as the leading cause of acute respiratory distress syndrome (ARDS) and multi-organ dysfunction syndrome (MODS) [2]. Besides cytokine damage and direct viral colonization of the kidney [6], angiotensin-converting enzyme 2 (ACE2) may represent a factor involved in the increased risk of acute kidney injury (AKI) in severe COVID-19 patients [7,8]. Moreover, acute heart failure, respiratory acidosis, impaired gas exchange, systemic congestion, and respiratory support/replacement therapies for pulmonary disorders also result in renal dysfunction [9], Depending on these variable factors, the incidence of AKI has been reported to range from 2.3% to 23% of all hospitalizations and from 20 to 50% of all ICU admissions [10-12].

In the absence of targeted and effective pharmacological treatments for the viral and organ dysfunction syndromes associated with COVID-19, extracorporeal organ support (ECOS) appears to be a plausible therapeutic strategy. Since it is impossible to anticipate the extent of the epidemic and the consequent number of patients who require intensive care management, intensive care clinicians must be prepared to provide specific ECOS to a large number of patients [13], which will contribute to replacing or supporting the function of the heart, lungs, kidneys, and liver during the severe phase of the syndrome [1]. Acute heart failure, which occurs in at least 10% of patients hospitalized and 25% to 35% or more of critically ill patients with COVID-19 [14], may cause or aggravate AKI, while AKI could also cause or aggravate acute heart failure; thus, they need to be treated in time. Renal replacement therapy (RRT) is an important therapeutic approach for severe COVID-19 that combines kidney support and cytokine removal, and has been successfully applied in the treatment of severe acute respiratory syndrome (SARS), Middle East respiratory syndrome coronavirus (MERS), and sepsis [15]. In China, blood purification techniques have been adopted for the management of critically ill COVID-19 patients, supported by local guidelines [16]. The purpose of this study was to provide guidance on the appropriate use of blood purification therapies in COVID-19 by reviewing existing expert consensus/recommendations and guidelines.

Modality of blood purification

Critically ill COVID-19 patients with AKI and/or multiorgan failure (MOF) require specific blood purification modalities to achieve hemodynamic stability, recover organ function, and avoid deleterious consequences by controlling solute and fluid levels and reducing circulating cytokines. Blood purification techniques, such as continuous renal replacement therapy (CRRT) with special membranes, plasma exchange, hemoadsorption/hemoperfusion, and different forms of apheresis, can remove inflammatory factors and/or endotoxins to prevent the development of a cytokine storm, thereby reducing the potential damage from the inflammatory response. These techniques have been included in the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia released by the National Health Commission and National Administration of Traditional Chinese Medicine for managing severe COVID-19 cases [16].

Indication and timing

Renal indications

AKI is the classical CRRT indication, also in patients with COVID-19, and should be considered when the patient has AKI stage 2 or higher based on the Kidney Disease: Improving Global Outcomes (KDIGO) definition [17], or fulfils one of the criteria indicated by Ronco and Bellomo [18]: 1) nonobstructive oliguria (urine output < 200 mL/12h) or anuria; 2) severe acidemia (pH < 7.1) because of metabolic acidosis; 3) azotemia (blood urea nitrogen [BUN] >30 mmol/L); 4) hyperkalemia (potassium > 6.5 mmol/L or rapidly rising potassium); 6) progressive and uncontrolled severe dysnatremia; and/or 7) clinically significant, diuretic-unresponsive organ edema (especially lung edema). RRT application might be considered earlier, especially in patients with more severe volume overload, progressive metabolic alkalosis with diuretic use, suboptimal diuretic response or refractoriness, and oliguric AKI [19].

End-Stage Renal Disease (ESRD) is also a potential indication for CRRT in patients presenting with COVID-19. CRRT should be initiated when dialysis-dependent patients have not received hemodialysis for more than two days or be administered as a quarantined renal support service in the isolation ward for suspected and/or diagnosed cases who may have increased viral exposure during transportation or at the hemodialysis center [20]. For non-dialysis-dependent ESRD patients with systemic edema (especially acute pulmonary edema), chronic heart failure, and severe metabolic disorders, CRRT must be performed in a timely manner [21].

Non-renal indications

Immunodysregulation, presented as high inflammatory markers and cytokines, such as a five-fold increase or daily doubling of serum IL-6 levels [2], is a major non-renal indication for blood purification in severe and critical COVID-19 cases, and should be early recognized and intervened. Besides, blood purification should also be considered in severe hemodynamic instability and organ dysfunction, which can be evaluated through the IRRIV score, developed by International Renal Research Institute Vicenza (IRRIV) (Table 1) [22].

Variable	Thresholds	Single AUCs	Points added
Mean arterial pressure Lowest on the first day of ICU	≤ 65 mmHg	0.61	1
Temperature Highest in first day of ICU	≥ 38.2°C	0.57	2
HCO_3 Lowest on the first day of ICU	≤ 23 mmol/L	0.60	1
Urinary output Lowest on the first day of ICU	≤ 40 ml/h	0.60	1
SOFA renal Highest on the first day of ICU	≥ 2	0.73	2
Invasive mechanical ventilation On the first day of ICU	No MV	0.52	1.5
Change of SCr during ICU stay, mg/dl (Hospital stay - admission)	≥ 0.3 mg/dl	0.63	1.5
Fluid accumulation	≥ 10%	0.47	1
IRRIV score			
To predict RRT and define late initiation	≥3.5 pt. (including one of the renal dysfunction)	0.81	Total: 0-11

Table 1: *International renal research institute Vicenza score [21].*

CRRT clinical practice

Vascular access

A jugular double-lumen catheter of adequate size to allow sufficient bleed flow is recommended [23], and insertion into the right internal jugular vein or femoral vein is preferred according to the KDIGO guidelines [17]. For the management of severe COVID-19 patients in the ICU setting, however, access via the right internal jugular vein is preferred for the prone position, as the dialysis catheter needs to be secured and monitored to avoid dislocation or kinking [24].

In patients on ECMO, CRRT can be provided either via an integrated approach or independently via parallel systems [25]. Parallel systems may be preferred to minimize clot formation in the latter [24]; however, an integrated approach can also be used to avoid multiple vascular access points if anticoagulation is well-managed [2].

Modality and dosage

In COVID-19 patients with marked hemodynamic instability and/or refractory fluid overload, initial support with CRRT to offer greater hemodynamic tolerance, consistency in ultrafiltration, and less metabolic and osmotic fluctuations, in most circumstances, continuous veno-venous hemofiltration (CVVH) is recommended, with an effluent dose of 20 - 25 mL/kg/h for post-dilution or 25 - 30 mL/kg/h for pre-dilution [21]. Continuous veno-venous hemodiafiltration (CVVHDF) offers a better balance between dialysis and filter performance if high clotting risk is a concern. Maintaining a low filtration fraction is key to prolonging circuit integrity and patency. This can typically be achieved via the administration of predilution dialysis fluid in CVVH or CVVHDF. However, prolonged intermittent sessions (PIRRT) may be implemented to allow nursing maneuvers owing to frequent mobilization and pronation [23]. Slow continuous ultrafiltration (SCUF) is recommended with an ultrafiltration volume of 2 - 5 mL/min to manage fluid overload and can be adjusted according to patients' volume and hemodynamic status, and the total ultrafiltration volume should not exceed 4 L for each treatment [2,21].

To effectively remove cytokines, CRRT with an adsorptive membrane of ≥ 35 mL/kg/h is recommended [2]. Hemoperfusion [1], plasma exchange, and plasma adsorption are also recommended for cytokine removal [2]. The recommended volume for plasma exchange is as follows: (L) = body weight (kg) × 1/13 × (100-hematocrit); a minimum volume of 2000 mL should be exchanged in case of plasma shortage. Hemoperfusion is recommended for a duration of 2 - 3 hours per session [26], while plasma adsorption is recommended for a duration of 2 - 4 hours per session, with a volume of 1.5 - 2.0 times the patient's plasma volume, calculated as: 1) plasma volume (mL) = (1-hematocrit) * [b + (c * body weight (kg))], b = 1530 for males and 864 for females, c = 41 for males and 47.2 for females; 2) plasma volume (L) = 0.065 * body weight (kg) * (1-hematocrit). The blood flow rate should be increased gradually from 50 to 80 mL/min to 100 - 150 mL/min during therapy, with the separated plasma passing through the adsorption device and returning to the body at a rate of 25 - 50 [2].

For different stages of COVID-19, sequential extracorporeal therapy (SET) within the golden hour may be guaranteed based on accurate monitoring and biological markers. In the cytokine storm stage, hemoperfusion or CRRT with highly adsorptive hemodiafilters could be the treatment of choice to remove cytokines, followed by regular CRRT if AKI occurs concomitantly during hemoperfusion. When organ failure develops, extracorporeal therapies may become a broad-spectrum support replacement or support the function of several organs such as the heart, kidney, liver, and lungs, which is the rationale for extracorporeal organ support (ECOS), a new form of therapy for MODS [27]. Since acidosis, which mainly results from metabolic disorders and lung-protective ventilation, is common in COVID-19, extracorporeal CO_2 removal (ECCO2R) in combination with RRT has the potential to facilitate reduction in tidal volume (< 6 ml/kg) during lung-protective ventilation strategies [23].

Anticoagulation

Hypercoagulability is common in COVID-19 patients, with activated partial thromboplastin time (APTT) and prothrombin time (PT) reduced by 16% and 30%, respectively, while 36% of patients have an elevated D-dimer level [12]. Therefore, regional citrate anticoagulation is more efficacious than other anticoagulation methods in terms of prolonging the extracorporeal circuit lifespan and reducing the risk of bleeding among these patients [24], with a pre-filter citrate concentration of 3 - 5 mmol/L to maintain a post-filter ionized calcium concentration of 0.25 - 0.35 mmol/L and a venous ionized calcium concentration of 1.0 - 1.35 mmol/L [2,24]. In situations that regional citrate anticoagulation is not feasible due to contraindication or limited resources, where there is no protocol in place, or the staff is not well trained in a protocol, low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) can also be conducted with proposed anticoagulation strategy [2]: 1) LMWH: 60 - 80 U/kg bolus injection followed by 30 - 40 U/kg every 4 - 6 hours to maintain the activity of Factor X at 0.25 - 0.35 U/ml; 2) UFH: 2000 - 2500 IU bolus injection followed by 12.5 - 25 IU/kg/h incremental dose in pre-dilution CRRT, or 2500 - 3500 IU bolus injection followed by 20 - 37.5 IU/kg/h incremental dose in post-dilution CRRT, stopped 30 - 60 minutes before the end of the treatment. A modest increase in heparin dose may be required during hemoperfusion to maintain the APTT level at 1.5 - 2.0 times higher than normal or to keep the activated clotting time (ACT) at 200 - 250 seconds. Other anticoagulation strategies include the use of heparin-coated membranes or regional heparin anticoagulation [2]. Anticoagulation should be provided to maintain circuit patency in all cases, and a blood flow rate higher than 120 ml/min should be prescribed with a minimal filtration fraction (less than 20% [28]) to help avoid circuit clotting [23].

Equipment and filter selection

Healthcare professionals on the frontline of the COVID-19 pandemic are faced with an elevated risk of exposure and limited staff resources. To help minimize infection risk and maintain individual and team performance over the long-term, it is important to have blood purification devices that are easy to use and compatible with different treatment modalities.

CRRT equipment with quick and easy operation is important because of the limited number of trained staff [29], as well as reducing setup time and being more user friendly. Certain CRRT machines have features that make it easier to manage and decontaminate, such as completely closed systems and the use of disposable dialysate and saline supplies. The possibility of blood contamination of the internal machine components through pressure monitors is also much less likely with these machines than with others. Later generation CRRT machines with the possibility of modifying circuit characteristics during treatment should be used if possible [23].

Using a CRRT machine that is familiar to the staff who will perform dialysis and that minimizes variations in prescriptions is recommended. Because staff are usually redeployed to the highest-risk sites, the provision of self-learning modules or facilitation of remote training may help reduce operational anxiety.

For the management of elevated cytokine levels in patients with severe COVID-19, synthetic membrane filters with sufficient ultrafiltration coefficients and adsorption capacity are preferred for CRRT. Novel membranes, such as AN69ST or Oxiris (acrylonitrile and sodium methallyl sulfonate plus polyethyleneimine), are recommended [2,6,21], supported by several clinical reports showing a reduction in TNF-α, IL-2, IL-6, and IL-10, hemodynamic improvement, and potential improvements in all-cause mortality in COVID-19 patients undergoing invasive mechanical ventilation [30]. High-cut-off dialyzers can also be used to remove cytokines; however, they may also increase the removal of large essential molecules such as albumin, and close monitoring is recommended so that supplementation can be provided as necessary [2]. Other extracorporeal therapies, including hemoadsorption and hemoperfusion, can be considered, with new sorbent cartridges such as HA380 and CytoSorb designed to remove cytokines and other circulating mediators [1]. Based on bench performance testing and reported clinical experience [30,31], in April 2020, the FDA authorized the emergency use of Oxiris and CytoSorb in the U.S. to reduce pro-inflammatory cytokine levels in the blood for confirmed COVID-19 cases admitted to the ICU with confirmed or imminent respiratory failure and, in turn, provide clinical benefit to these patients [32].

Fluid management during CRRT

Patients with severe COVID-19 can present with right ventricular dysfunction due to increased pulmonary circulation resistance, which is attributed to alveolar exudation, pulmonary edema, and pulmonary consolidation. Left ventricular dysfunction, as a result of damage to cardiomyocytes and decreases in effective circulating volume due to increased vascular permeability (considered to be mainly caused by cytokine storm), is also common in COVID-19. All of these factors result in a decreased tolerable volume range; thus, tertiary fluid management should be carried out to maintain both mean arterial pressure for tissue and organ perfusion and decrease fluid load to relieve pulmonary edema [33].

Goal-oriented tertiary fluid management is preferred for daily review of fluid balance in COVID-19 due to the contradiction of effective circulating volume and pulmonary edema. The fluid balance should be calculated every hour based on close hemodynamic monitoring and adjusted in a timely manner. In particular, insensible fluid loss from the respiratory tract in patients with respiratory distress should be closely monitored [2].

Drug adjustment during CRRT

As severe cases of COVID-19 can be treated with antiviral and/or antimicrobial therapy, careful dosing is essential in the CRRT setting. CRRT is associated with significant modifications in several pharmacokinetic parameters, including protein binding, volume of distribution, and total body clearance. For example, the antiviral drugs lopinavir/ritonavir and arbidol are mostly eliminated by non-renal processes and, with protein binding typically over 90%, are not likely to be removed during CRRT and do not require dose adjustment [2]. However, for antimicrobials known for their narrow therapeutic range, therapeutic drug monitoring is strongly recommended to guide dosing adjustment in complex clinical settings, such as in COVID-19 patients with sepsis and AKI undergoing CRRT.

Weaning time of blood purification

There has been no consensus on the timing of stopping blood purification in patients with severe COVID-19 symptoms; the following guidance is proposed for clinical consideration.

For CRRT, stabilization of vital signs and hemodynamics, ventilator settings reduced to a lower level, correction of any electrolyte/acid-base disturbances, and daily urine output of ≥ 500 - 1000 mL without diuretics or ≥ 1500 - 2000 mL with diuretics [2]. It should be noted that for some patients with partial recovery of renal function or preceding chronic kidney disease, RRT may be continued outside the ICU when discharged. Plasma exchange and plasma perfusion/adsorption: severity of SIRS eased; respiratory function improved; substantial improvement in any prognosis of acute liver failure and reduction of serum inflammatory mediators such as IL-6 to within two times the normal value [2,34].

Infection prevention and control management

Infection prevention and control management, including sterilization of equipment [35], use of PPE for operators [36], and medical waste disposal [37]. Efforts to minimize direct exposure of healthcare personnel to blood and blood contaminants are of principal importance. All other dialysis-related supplies, including dialyzer membranes, should be disposed of after use in accordance with local, state, and federal regulations.

Although SARS-CoV-2 should not be able to cross an intact dialyzer membrane, small leaks in the membrane may not be apparent, and effluents should always be handled with care, including appropriate PPE to avoid contact and splashes. Machine decontamination and terminal disinfection of external machine surfaces should be performed following local Centers for Disease Control (CDC) guidance [35].

Conclusion

A goal-oriented blood purification technique is recommended for both renal and non-renal indications; therefore, early recognition and intervention strategies should be applied in the management of patients with severe COVID-19. The femoral vein is preferred over the right internal jugular vein for catheter insertion. Given the specific coagulopathy presents in COVID-19 patients, system heparin anticoagulation as a popular anticoagulation strategy is considered to be due to hypercoagulability in patients without bleeding risk. Adsorptive blood purification techniques designed to remove circulating cytokines may display remarkable benefits in terms of hemodynamic support and organ function recovery. Goal-oriented tertiary fluid management is preferred for daily review of fluid balance in COVID-19 due to the contradiction of effective circulating volume and pulmonary edema. Infection prevention and control management are also vital to prevent the spread of infectious diseases, including PPE for operators, sterilization of equipment, and medical waste disposal. Other aspects, including operational ease, flexibility, and training, should be considered to optimize intensive care operations and performance, despite limitations in staffing and resources.

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