



Chinese Medical Association

Expert consensus on the Application of Special Blood purification Technology in severe COVID-19 pneumonia

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COVID-19 (COVID-19) epidemic prevention and control in China has entered the stage of actively treating severe patients and trying to improve the success rate of treatment and reduce the fatality rate. According to the sixth edition of COVID-19 's diagnosis and treatment Plan issued by the National Health and Health Commission (trial sixth edition), "for patients with high risk of inflammation, plasma exchange, adsorption, perfusion, blood / oar filtration and other in vitro blood purification

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techniques can be considered if there is a condition for the use of plasma exchange, adsorption, perfusion, blood / oar filtration, and so on." In order to better guide and standardize the application of blood purification technology in severe COVID-19, the expert group of nephrology committee of Chinese medical association and Chinese research hospital society has fully discussed how to carry out blood purification technology treatment for severe COVID-19 patients proposed in the above diagnosis and treatment plan, and formulated the following consensus.

1. Pathogenesis of severe COVID-19

1.1 Cytokine storms

At present, it is considered that cytokine storm (cytokine storm syndrome, CSS) is an important pathophysiological basis for the transformation of COVID-19 from mild to severe pneumonia and from single organ injury to multiple organ dysfunction (MODS). After infection with (SARS) coronavirus in severe acute respiratory syndrome (SARS), novel coronavirus may cause immune function out of control, excessive release of inflammatory cytokines, and form a series of self-magnifying cas

cade reactions of cytokines, resulting in disseminated alveolar injury, transparent eye formation, fibrin exudation and other injuries in the lungs. In severe cases, systemic cytokine storms invade the circulatory system. It further caused flow instability, body gram, disseminated intravascular coagulation and MODS (3). IL-6. in patients with severe COVID-19 The level of inflammatory cytokines such as IL-10, TNF-a is significantly increased, which may be related to poor prognosis (4).

1.2 Kidney damage

The study found that the new coronavirus (2019-nCoV) enters cells through the membrane protein angiotensin converting enzyme (angiotensin converting enzyme2, ACE2). The expression of ACE2 in kidney tissue is about 100 times that in lung tissue, and it is mainly present in proximal tubular epithelial cells. Therefore, we speculate that the direct damage of 2019-nCoV to kidney Wang is mainly renal tubule, which is clinically related to COVID-19 Patients often have mild proteinuria, and severe patients are more often associated with hypernatremia and metabolic alkalosis.

It has been reported that about 63% of COVID-19 patients have proteuria, 27% of COVID-19 patients have elevated blood

urea nitrogen, 19% of them have increased serum creatinine, and about 29% of severe patients with acute renal injury have a higher level of serum creatinine, suggesting that hypercreatinine level is a related factor for the poor prognosis of COVID-19 [5, 6].

2. The theoretical basis of the Application of Special Blood purification Technology in the treatment of severe COVID-19.

Blood purification technology plays an important role in the treatment of severe COVID-19 patients, and can be used in the treatment of severe COVID-19 and its complications. In addition to continuous renal replacement therapy ((CRRT)), hemoperfusion (HP), continuous plasma filtration adsorption (CPFA), plasma exchange (TPE) (including double plasma exchange), plasma dialysis filtration (PDF), dual plasma molecular adsorption system (DPMAS) and other blood purification techniques have also been used in the treatment of severe COVID-19 patients.

2.1 CRRT:

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CRRT refers to continuous blood purification therapy 24 hours or nearly 24 hours a day. At present, the commonly used treatment modes include continuous venous hemodiafiltration ((CVVHD)), continuous venous hemodiafiltration ((CVVHDF)) and continuous venous hemofiltration ((CVVH)). CRRT is beneficial to maintain volume balance, hemodynamics and internal environment stability, improve the clearance efficiency of medium and small molecular toxins, maintain body temperature stability and nutritional support treatment through long-term continuous treatment. Therefore, CRRT is not only simple renal support, but also the basis of systemic multiple organ support in critically ill patients.

2.2 Plasma / whole blood adsorption techniques:

CPFA and DPMAS are the representatives of plasma adsorption and toxin scavenging, and HP is the representative of whole blood adsorption and scavenging solute. These adsorption techniques are widely used in clinic. According to the different adsorption materials, the adsorber specifically or nonspecifically removes the substances from the blood through biological affinity and physicochemical affinity. In the treatment of severe COVID-19, plasma / whole blood adsorption technique was

applied to the adsorption and removal of inflammatory cytokines, and the curative effect was obtained.

2.3 Plasma dialysis filtration:

PDF is a non-biological artificial liver blood purification technology developed based on CVVHDF. It uses a special plasma separator to perform plasma diafiltration while separating plasma, which is better than CVVHDF to remove protein-binding toxins. Studies have shown that PDF can also clear the levels of IL-6, IL-18 and other cytokines in patients with macrophage activation syndrome, and alleviate the disease [7].

2.4 Plasma exchange:

Plasma exchange clears all kinds of toxins with large, medium and small molecular weight in patients by separating and abandoning the plasma or harmful plasma components of patients, which is the most comprehensive of all kinds of blood purification techniques. At the same time, supplementation of normal or recovered plasma is beneficial to improve coagulation ab

normalities, immune disorders and so on. Therefore, plasma exchange can also be used in patients with severe COVID-19 to remove inflammatory mediators with large molecular weight.

3. Selection and matters needing attention of special blood purification technology in the treatment of severe COVID-19

In the treatment of severe COVID-19 patients, the choice of blood purification technology should be based on the pathophysiological changes of the patients, take the clinical treatment objectives as the core, take into account the advantages and disadvantages of various treatment techniques, and choose the best treatment scheme for the patients at the right time [8].

3.1 In order to maintain the stability of the internal environment, it is suggested that the indications of CRRT treatment should be based on non-renal indications, and in order to prevent and cure cytokine storms, appropriate early intervention should be made.

It is not common for COVID-19 to combine AKI early. However, because severe COVID-19 patients have the characteristics of severe CSS and often complicated with MODS, the non-renal indications of CRRT should consider the following aspects: 1) persistent inflammatory fever, glucocorticoid treatment can not be controlled; 2) (ARDS); 3) complicated with acute respiratory distress syndrome complicated with right heart failure, 4) hypernatremia which can not be corrected by conservative treatment in internal medicine, 2) acute respiratory distress syndrome ((ARDS); 3) complicated with right heart failure, 4) hypernatremia which can not be corrected by conservative treatment in internal medicine. 5) volume overload, or urine volume could not meet the needs of drug infusion and energy supply; 6) diuretics resistance; 7) combined with epidural pulmonary oxygen combined with (ECMO) treatment [9].

In patients with severe COVID-19, due to massive viscous exudation of alveoli, pulmonary interstitial inflammation, pulmonary edema and pulmonary consolidation, pulmonary circulation resistance is increased, right ventricular insufficiency is prone to occur, and left ventricular dysfunction is often complicated with different degrees of left ventricular dysfunction, as well as the decrease of intravascular effective volume caused by the increase of vascular permeability. These factors lead to

the sharp reduction of tolerable volume window. Therefore, when ARDS, right heart failure and capacity overload occur at the initial stage, CRRT should be activated to implement three-level management capacity in order to better support cardiopulmonary function.

ECMO is an important means of respiratory support in critically ill patients with COVID-19, but there is evidence that it may promote cytokine release in vivo to aggravate the inflammatory response in patients [10, 11]. Clinical studies to observe whether early ECMO combined with CRRT can improve the prognosis of patients are under way. In view of the fact that CSS is one of the important pathophysiological changes in patients with severe COVID-19, it is suggested that ECMO treatment should be used as a non-renal indication for the initiation of CRRT in patients with severe COVID-19.

3.2. It is suggested that CRRT should choose a convective treatment mode and increase the amount of replacement appropriately.

In order to eliminate inflammatory cytokines more effectively, CVVH, CVVHDF or (HVHF) with high volume hemofiltration

on should be selected. In order to improve the clearance efficiency of cytokines, on the basis of sufficient and effective anticoagulant, even if the filtration fraction is more than 25%, it is suggested that the convective dose should be increased appropriately.

The dose of CRRT should be adjusted according to the clinical treatment target. If the main goal is to maintain the volume balance, the treatment dose should be equivalent to the post-dilution replacement dose 20-25mL/ (kg.h), and if the clearance of inflammatory cytokines is the main goal, the treatment dose should be greater than that of the post-dilution replacement dose 35mL/ (kg.h). ,

It should be noted that high convective dose can increase the removal of small and medium molecular nutrients and drugs, so it is necessary to adjust the use of drugs, especially antibiotics, and increase the replenishment of patients' calorie (20-30kcal/ (kg.d), protein ($1.5 \leq 1.7$ g (kg.d), amino acid ($1.5 \leq 1.7$ g (kg.d) according to the treatment mode.

3.3. It is recommended that CRRT should select membrane materials with good biocompatibility and apply bicarbonate repl

acement solution.

Membrane materials with poor biocompatibility may induce inflammatory reaction and should be avoided. Some studies have shown that AN69 membrane (including oXiris) hemofiltration has a definite adsorption of inflammatory cytokines, so the use of AN69 membrane hemofiltration or permission to better reduce the inflammatory response of patients, improve the prognosis [13].

In order to better play the role of filter membrane adsorption of inflammatory cytokines, without affecting hemodynamic stability, the use time of each CRRT blood filter should not exceed 12 hours.

The blood filter with appropriate membrane area should be selected according to the body surface area of the patient.

Severe COVID-19 patients are often complicated with abnormal liver function, and bicarbonate replacement solution should be used.

3.4. It is recommended that whole blood / plasma adsorption be started in the early stage of COVID-19 inflammation and when proinflammatory cytokines are dominant.

At present, the cytokine adsorption columns commonly used in clinic are non-specific adsorption columns, which cannot specifically remove proinflammatory cytokines.

When the patients showed proinflammatory cytokines, it was suggested that whole blood / plasma adsorption therapy should be initiated: 1) persistent inflammatory fever, glucocorticoid treatment could not be controlled; 2) IL-6/IL-10 ratio increased gradually, or IL-6 and other pro-inflammatory cytokines levels continued to rise [14, 15].

When the level of cytokines was high in the early stage of treatment, adsorption therapy could be performed every 12 hours, and gradually decreased to 24 hours per 24 hours with the improvement of inflammatory reaction.

When the body temperature of the patients gradually decreased to normal and the ratio of IL-6/IL-10 decreased gradually, it was suggested that anti-inflammatory cytokines would gradually replace proinflammatory cytokines and occupy a dominant position, and cytokine adsorption therapy should be stopped.

Because of the loss of quantitative albumin during cytokine adsorption therapy, it is recommended that albumin be supplemented after cytokine adsorption therapy.

3.5 When recommended conditions permit, plasma exchange therapy may be considered for patients with severe COVID-19. "COVID-19 diagnosis and treatment plan (trial sixth edition)" recommendation "for patients with high risk of inflammation, conditional can consider the use of plasma exchange and other treatments. Some medical centers in China use plasma exchange in the treatment of severe COVID-19, and have achieved good results. However, from other clinical data, neither hemophilia syndrome (including macrophage activation syndrome), which also takes cytokine storm as the core pathophysiological change, or sepsis complicated with MODS, plasma exchange can not clearly alleviate the disease or improve the prognosis. Therefore, the American Plasma Exchange Association classifies hemophilia syndrome (including macrophage activation syndrome) and sepsis with MODS as II indications for plasma exchange, that is, "the effectiveness of plasma exchange has not yet been determined and should be individually selected" [16]. This consensus does not recommend routine plasma exchange therapy for severe COVID-19, but in conditional centers, plasma exchange therapy can be carefully tried in patients with severe COVID-19.

Single plasma exchange was performed with 1.5 plasma volumes at a time, and 200mL-400mL recovery plasma or fresh frozen plasma could be infused after double plasma exchange.

In the application of plasma exchange, attention should be paid to the appropriate adjustment of the administration time and dose of the drug.

3.6 It is recommended to use a variety of CRRT-based blood purification techniques, such as CRRT plus whole blood adsorption or CRRT plus plasma adsorption.

Although high dose CVVH or CVVHDF has definite scavenging effect on inflammatory cytokines, the scavenging ability of a large number of inflammatory cytokines produced by severe COVID-19 patients is limited. Excessively increasing the dose of CVVH may increase the risk of coagulation and hemodynamic instability. Therefore, it is suggested that the whole blood or plasma adsorption technique should be combined on the basis of stable volume balance of CRRT in order to further increase the clearance of inflammatory cytokines [17, 18].

Plasma adsorption often requires the suspension of ultrafiltration, which may lead to volume imbalance during treatment. Therefore, the choice of CRRT plus whole blood adsorption may be more beneficial to hemodynamic stability than plasma adsorption, but we should be alert to the risk of destruction of blood cell components.

4. Vascular pathway

4.1 Selection of vascular pathways without ECMO

4.1.1 It is suggested that the central venous catheter should be used as the vascular pathway for the treatment of severe COVID-19 blood purification.

4.1.1.1 In patients with severe COVID-19 without well-functioning vascular pathway, it is suggested that (NCC) without tunnel and polyester sleeve dialysis catheter should be selected as vascular pathway.

Because of the critical condition of severe COVID-19 patients, the process of placing tunnel and polyester catheter (TCC) is more tedious than NCC, and the popularity of technology is not as much as that of NCC, which increases the exposure risk

of operators. Therefore, it is suggested that NCC should be the first choice in the treatment pathway of blood purification in patients with severe COVID-19. However, if the patient needs a longer period of blood purification treatment, if expected to exceed 1 month, it should be replaced with TCC when conditions permit [12, 19, 20].

4.1.1.2 Maintenance hemodialysis patients with well-functioning TCC complicated with severe COVID- at 19:00 could use TCC as a vascular pathway during the treatment of COVID-19, and attention should be paid to the standardized operation to reduce the incidence of infection.

4.1.1.3 Maintenance hemodialysis with (AVG) with self-functioning arteriovenous fistula ((AVF)) or artificial arteriovenous fistula ((AVG)) with severe COVID-19 is recommended. It is recommended that NCC be used as the vascular pathway during the treatment of COVID-19, and AVF or AVG is not recommended.

AVF or AVG is used as the vascular pathway of CRRT to increase the risk of acute thrombosis, infection, bleeding and so on, so it is not recommended to use it.

For patients who only need short-term day hemodialysis / filtration (treatment time 6-10 hours) or blood purification

treatments such as plasma exchange, hemoperfusion, blood / plasma adsorption, etc., AVF or AVG can be used as a blood vessel under the premise of ensuring safety path.

When using AVF or AVG, it is recommended to use dialysis casing needle as puncture needle.

4.1.2 Selection of catheter approaches

4.1.2.1 It is recommended that the femoral vein or the right internal jugular vein should be selected as the approach, and the left internal jugular vein or subclavian vein should be avoided as far as possible.

The choice of catheter approach in patients with severe COVID-19 should consider the influence of tracheotomy, endotracheal intubation, respiratory mask and other auxiliary ventilation devices, as well as the existing and previous vascular pathways, and choose the appropriate catheter approach.

The distribution of various vascular pathways in patients was reasonably distributed to avoid the unnecessary loss of drugs caused by central venous catheter for infusion and blood purification catheter and / or ECMO catheter located in inferior ven

a cava or superior vena cava, and to prevent the drug from flowing through CRRT filter and / or ECMO oxygen device first after entering circulation.

There was no difference in the effect of prone position ventilation on catheter function in different positions.

The risk of catheterization and the incidence of dysfunction of left internal jugular vein catheter are high and should be avoided as far as possible. Although the incidence of subclavian vein catheter infection is low, the risk of central vein stenosis is higher, which should be avoided as far as possible [21, 22].

4.1.3 Establishment of catheters

4.1.3.1 It is recommended that the operators should be protected by three levels to block the mouth and nose of the patients and reduce the exposure risk of the operators.

4.1.3.2 It is recommended that catheterization be carried out by skilled doctors in order to improve the success rate and redu

ce the risk of complications and exposure. .

4.1.3.3 It is recommended that central venous catheterization be performed under the guidance of ultrasound in real time.

Due to the interference of protective equipment, the difficulty of venous catheterization is increased. It is suggested that the central venous catheterization should be carried out under the guidance of ultrasound in real time.

4.1.4 It is recommended that radiography be performed before the catheter is used to observe the position of the catheter and to determine whether there are complications of catheterization.

4.2 Selection of vascular pathways in patients with ECMO

In the absence of ECMO-CRRT integrated machine, the vascular pathway for blood purification mostly chooses to connect the pipeline to the ECMO pathway, and can also choose to re-puncture and place the tube.

At present, there is no clear suggestion on the best connection method between CRRT and ECMO. In specific clinical practice, decision-making usually depends on the professional knowledge, familiarity, CRRT model and technical feasibility of field treatment staff and engineers. Regardless of the connection method, the CRRT circulating blood should return to the ECMO loop before the aerator [22, 23].

5. Anticoagulant technology

5.1 Selection of anticoagulant schemes without ECMO

CRRT anticoagulant therapy should be based on a full assessment of the potential risks and benefits of patients and select relatively safe and effective anticoagulant methods according to the experience of the unit. Although the AKI guidelines recommend local citrate anticoagulation as the preferred anticoagulant regimen for CRRT, they may need to be carefully considered in patients with severe COVID-19. Severe COVID-19 patients are often complicated with metabolic alkalosis, hypernatr

emia and different degrees of liver injury, which may limit the application of local citrate anticoagulation in severe COVID-19.

5.1.1 For patients without obvious risk of bleeding, basically normal coagulation function, or not receiving systemic anticoagulant therapy, it is recommended that low molecular weight heparin or heparin should be used in combination with citric acid if necessary, if there is no obvious anticoagulant taboo of citric acid.

Low molecular weight heparin can be injected intravenously into 60~80IU/kg. There is no need for additional dose for short-term treatment such as hemoperfusion, plasma adsorption or plasma exchange, and additional dose is needed for CRRT. When there are conditions, the activity of plasma anticoagulant factor Xa can be monitored and the dose can be adjusted according to the measured results. For patients who have received low molecular weight heparin or heparin systemic anticoagulation, low molecular weight heparin should be reduced or stopped when CRRT is performed or local citrate anticoagulation should be used.

5.1.2 For patients with active bleeding or increased risk of bleeding, it is recommended that the presence or absence of citrate anticoagulant taboos be assessed first, and then local anticoagulant or heparin-free treatment with citrate should be selected.

If there is no anticoagulant taboo of citric acid, local citrate anticoagulant is the first choice. When applying local citric acid anticoagulant, it is necessary to adjust the input rate of sodium citrate and calcium agent according to the actual blood flow of the patient, the concentration of calcium ion after the filter and the concentration of calcium ion in the body. If there is a contraindication of citric acid use, it can be treated with no heparin.

5.1.3 For patients with heparin allergy or heparin-induced thrombopenia, it is recommended that heparin should be stopped first, local citrate anticoagulant should be used in patients without citrate anticoagulant contraindication, or Agatroban anticoagulant should be used in patients with citrate anticoagulant contraindication [24].

5.2 Selection of anticoagulant methods in combination with ECMO

ECMO is mainly based on whole body heparin as the main anticoagulant mode, so it is generally believed that anticoagulant can no longer be used in the process of CRRT [25].

5.3 In order to prolong the service life of blood filter, it is suggested to choose the energy supply mode of glucose as the main factor and fat milk as the auxiliary in the heat supply. If fat milk must be used, it is recommended to monitor the level of blood lipid in the normal range to avoid shortening the service life of blood filter caused by hyperlipidemia.

6. Adjustment of drug dose during blood purification treatment

CRRT, plasma exchange, whole blood / plasma adsorption and other blood purification techniques have different degrees of scavenging effect on a variety of drugs in vitro, which may affect the therapeutic effect of these drugs. It is necessary to adju

st the frequency or single dose of these drugs. Under ideal conditions, the dose adjustment of blood drug concentration should be closely monitored in order to achieve the best therapeutic effect, but limited by objective factors, most hospitals receiving COVID-19 treatment have not yet carried out drug concentration monitoring.

6.1 When CRRT is performed in patients with severe COVID-19, it is recommended to determine whether the drug given needs dose adjustment.

When CRRT is carried out in patients with COVID-19, it is suggested that the renal excretion rate, apparent distribution volume, plasma protein binding rate and glomerular filtration rate of drugs should be comprehensively evaluated to determine whether the dose of a drug needs to be adjusted. Annex 1 lists the suggestions for dose adjustment of commonly used drugs in the treatment of COVID-19 in the process of CRRT.

For the drugs which can not give the exact dose in CRRT at this stage, we should evaluate it from the above aspects to judge

whether the drug dose needs to be adjusted. For concentration-dependent drugs, the drug concentration should reach the best therapeutic concentration by adjusting the frequency of administration, and for time-dependent drugs, the most suitable drug exposure time should be achieved by adjusting the dose of single drug administration.

6.2 In the course of plasma exchange and whole blood / plasma adsorption, it is recommended that the plasma protein binding rate and half-life of the drug be adjusted as appropriate.

Some plasma albumin will be discarded during plasma exchange treatment in patients with severe COVID-19, and the nonspecific adsorption of adsorbents will lead to the loss of some albumin when whole blood / plasma adsorption is carried out, so it has a definite degree of scavenging effect on some drugs with high binding rate of plasma protein. Therefore, after plasma exchange and whole blood / plasma adsorption, the plasma protein binding rate and half-life of the drug should be adjusted as appropriate.

7. Infection prevention and control measures

7.1 It is recommended that blood purification treatment be performed in intensive care unit (ICU) for patients with COVID-19, and infection prevention and control measures in intensive care unit (ICU) should be strictly implemented.

7.2. Prevention and control measures related to blood purification treatment

7.2.1 It is recommended that skilled doctors and nurses operate to deal with catheter dysfunction in a timely manner, reduce intervention during treatment and avoid unnecessary exposure.

7.2.2 It is recommended that chlorine disinfectant be used to wipe the surface of blood purification equipment machine and the surface of treatment vehicle, treatment table and so on.

7.2.3 It is recommended that the surface disinfection of the equipment in operation be carried out on a per-shift basis. When not contaminated by the patient's blood, body fluids and secretions, wipe and disinfect with 1000mg/L chlorine disinfectant for 30 minutes, clean with clean water; if polluted, remove visible pollution with hygroscopic material, wipe disinfection with 2000mg/L chlorine disinfectant, apply it for 30 minutes, and wipe clean with clean water.

7.2.4 It is recommended that the equipment be sterilized at the end of each treatment.

8. Medical waste management

8.1 It is recommended that CRRT waste liquid be controlled in accordance with the sewage of infectious disease medical institutions, and that the discharge of waste liquid directly or not up to standard should be prohibited.

8.2 It is suggested that the disposal of medical consumables such as blood purification and treatment of discarded pipelines, filters and perfusion devices should be carried out in accordance with the Technical guidelines for the Prevention and Control of novel coronavirus infection in Medical institutions (Edition).

After the blood purification treatment is completed, the medical consumables such as abandoned tubing, filters, and perfusion devices should be placed in a double yellow medical waste bag, layered with a gooseneck seal, and effectively sealed. The label on the outside of the package should be marked with the "new crown" warning sign.

Before leaving the contaminated area, the surface of the bag should be sterilized with 1000mg/L chlorine disinfection solution (pay attention to uniform spraying) or a layer of medical waste packing bag should be added to the outside of the bag [26, 27].

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