**Blood Purification Treatments in COVID-19**

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**ABSTRACT**

Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) emerged for the first time in Wuhan, China, in December 2019. These viruses mainly cause respiratory and intestinal infections and induce a variety of clinical manifestations (1, 2). High virus titer and the subsequent strong inflammatory cytokine and chemokine responses are related to the high morbidity and mortality observed during the pathogenic HCoV infection. Blood purification system including plasma exchange, adsorption, perfusion, blood/plasma filtration, etc., can remove inflammatory factors, block the "cytokine storm", to reduce the damage of inflammatory response to the body. This therapy can be used for severe and critical patients in the early and middle stages of the disease (3). We recommend not using Extracorporeal treatments based on cytokine and / or endotoxin removal routinely in patients infected with COVID-19 due to insufficient studies (4).

**Keywords:** COVID-19, Blood purification therapy, sepsis, SARS-CoV-2

**Introduction**

Coronaviruses (CoVs) are single-stranded, positive-strand RNA viruses belonging to the Coronaviridae family, Nidovirales order. The International Committee on Taxonomy of Viruses (ICTV) classifies the CoVs into four categories: α, β, γ, and δ. under the electron microscope, the virus particles display a rough spherical or multi-faceted crystal shape. The surface of the viruses has prominent club-shaped projections composed of its spike protein. Inside the virus particle is the viral genome wrapped in a nucleocapsid. The viral genome contains approximately 26000 to 32000 bases. CoVs are the largest known RNA viruses. CoVs can infect a variety of host species, including birds, humans and some other vertebrates. These viruses mainly cause respiratory and intestinal infections and induce a variety of clinical manifestations (1, 2).

Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) emerged for the first time in Wuhan, China, in December 2019. It is a type of highly pathogenic human coronavirus (HCoV) that causes zoonotic diseases and poses a major threat to public health. The vast majority of patients with the coronavirus disease 2019 (COVID-19) have had a good prognosis, but there were still some critical individuals and even deaths (5).

**Pathogenesis of cytokine storm in COVID-19**

The pathophysiology of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced ARDS has similarities to that of severe community-acquired pneumonia caused by other viruses or bacteria(6). The relevant evidences from severely ill patients with HCoVs suggest that pro-inflammatory responses play a role in the pathogenesis of HCoVs. The first step of the infectious process is the recognition of the pathogen by the immune system. All pathogens exhibit on their surface specific components, known as pathogen-associated molecular patterns (PAMPs), such as the endotoxins expressed by Gram-negative bacteria. During infection, PAMPs are recognized by the pattern recognition receptor expressed at the surface of immune cells. This signal activates the leukocytes and induces the synthesis of pro- and anti-inflammatory cytokines, including tumor necrosis factor-alpha, interleukin-1 (IL-1), IL-6, IL-8, and IL-10(7, 8). In vitro cell experiments show that delayed release of cytokines and chemokines
occurs in respiratory epithelial cells, dendritic cells (DCs), and macrophages at the early stage of SARS-CoV infection. Later, the cells secrete low levels of the antiviral factors interferons (IFNs) and high levels of proinflammatory cytokines (interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)) and chemokines (C-C motif chemokine ligand (CCL)-2, CCL-3, and CCL-5) (9). The overproduction of early response proinflammatory cytokines (tumor necrosis factor [TNF], IL-6, and IL-1β) results in what has been described as a cytokine storm, leading to an increased risk of vascular hyperpermeability, multiorgan failure, and eventually death when the high cytokine concentrations are unabated over time (10).

The theory of blood purification with inflammatory cytokine storm

High virus titer and the subsequent strong inflammatory cytokine and chemokine responses are related to the high morbidity and mortality observed during the pathogenic HCoV infection. The experience from treating SARS and MERS shows that reducing viral load through interventions in the early stages of the disease and controlling inflammatory responses through immunomodulators are effective measures to improve the prognosis of HCoV infection (11).

Extracorporeal Blood Purification Therapies

In addition, the blood purification treatments currently used in clinic practice can remove inflammatory factors to a certain extent. Blood purification system including plasma exchange, adsorption, perfusion, blood/plasma filtration, etc., can remove inflammatory factors, block the “cytokine storm”, to reduce the damage of inflammatory response to the body. This therapy can be used for severe and critical patients in the early and middle stages of the disease (3).

1-Therapeutic plasma exchange

Therapeutic plasma exchange (TPE) refers to the extracorporeal technique performed in an apheresis device were patient’s plasma is separated from whole blood and removed, while the cellular blood components are returned to the patient together with a replacement fluid. The separation of blood can be performed either by centrifugation or by filtration (12).

According to American Society for Apheresis (ASFA) guidelines, over 30 diseases may be treated with TPE. In all of them, the rational for TPE is the removal of a pathological substance in plasma that is responsible for the disease, i.e. autoantibodies, immune complexes, cryoglobulins, toxins or lipids (13).

In a single TPE procedure the amount of plasma removed varies according to the volumes of plasma (PV) exchanged following an exponential function. Thus, usually 1–1.5 PV is exchanged, because larger volumes do not add much benefit but increase the risk of side-effects. The removal of the pathogenic substance also depends on its distribution between the intravascular and extravascular compartment. For example, in the case of IgM antibodies, which are predominantly in the intravascular space, a significant decrease is achieved after one or two consecutive

procedures. On the contrary, IgG antibodies that are distributed in both the intravascular and extravascular compartments, require multiple exchanges to decrease total body stores, and are usually performed every other day to allow redistribution between both compartments. Lastly, TPE efficiency is also influenced by the speed of production and clearance of the pathogenic substance. Therefore, in immune-mediated diseases, immunosuppressive treatment should be given together with TPE in order to obtain a sustained response (14).

Hemophagocytic lymphohistiocytosis and macrophage activating syndrome

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening immune mediated disease caused by genetic defects or reactive to some triggers. This results in an acute cytokine storm triggering an avalanche of hyperinflammation with a severe sepsis-like clinical picture. Macrophage activating syndrome refers to the same picture secondary to juvenile idiopathic arthritis. The basis of treatment of HLH is supportive intensive care, the elimination of the trigger, and the suppression of inflammatory response and cell proliferation or both with immunosuppressive and cytotoxic drugs. Although TPE benefits controversial, extracorporeal removal of cytokines with daily TPE with 5% albumin (or other methods) may be part of the supportive care used to stabilize organ function in severe patients (15).

Therapeutic plasma exchange can affect many steps such as clearing cytokines, stabilization of endothelial membranes, and correction of hypercoagulable condition in sepsis patients (16). It has been claimed in a limited number of small studies that therapeutic plasma exchange may reduce mortality in patients with sepsis (17). We recommend not routinely using therapeutic plasma exchange in patients infected with COVID-19 due to insufficient studies.

2-Removing Cytokines and Endotoxins

AN69 Membrane

It is composed of a copolymer combining acrylonitrile and sodium methallylsulfonate molecules. Due to the sulfonate groups, the membrane is highly negatively charged and able to adsorb the cytokines via their cationic residues. This membrane exhibits a symmetric microporous architecture with a hydrogel structure. The latter allows cytokine adsorption within the entire bulk of the membrane, enhancing the overall adsorption capacity. This membrane has been claimed to heal hemodynamically, but studies are inadequate (18, 19).

The oXiris® Membrane

The improvement of industrial processes led to the development of the oXiris® membrane, a heparin-grafted membrane specifically designed for cytokine and endotoxin adsorption, alongside RRT. More recently, Malard et al. conducted an in vitro experiment, comparing endotoxin and cytokine adsorption with 3 different devices: oXiris®, CytoSorb®, and Toraymyxin®; oXiris® was found to combine high endotoxin adsorption capacity, similar to Toraymyxin®, with a removal rate of inflammatory mediators comparable to CytoSorb® (20).
Toraymyxin® Membrane

One of the most widely used endotoxin removal therapies is adsorption with polymyxin B-immobilised fiber column (Toraymyxin®, Toray, Tokyo, Japan). Numerous RCTs comparing polymyxin B adsorption to a standard treatment found conflicting results, suggesting that the positive effect of Toraymyxin® could be greater in particular subgroups of patients such as severe patients, patients with endotoxin activity levels (as evaluated by the endotoxin activity assay) between 0.6 and 0.9, or those presenting a particular genetic profile (21, 22).

The Alteco® LPS adsorber

The Alteco® LPS adsorber (Alteco Medical AB; Lund, Sweden) contains a synthetic peptide developed for endotoxin adsorption. The peptide covers the surface of a porous polyethylene matrix designed to provide an optimal binding surface. A few case series in critically ill adults have reported a decrease in endotoxin levels and a hemodynamic improvement (23, 24). However, the ASSET (abdominal septic shock – endotoxin adsorption treatment) multicenter RCT evaluating the feasibility of Alteco® LPS adsorber was terminated early because of patient recruitment issues (25).

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