

# Blood Hemoperfusion Therapies in COVID-19

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## Summary

COVID-19 is the term used to define the disease caused by a new beta coronavirus (SARS-CoV-2), consisting of pneumonia with a highly variable clinical course, ranging from mild and asymptomatic cases to severe clinical conditions with acute Respiratory Distress Syndrome (ARDS) and multiple organ dysfunction, as a consequence of poorly regulated proinflammatory activity, also known as “cytokine storm”. Given the above, blood hemoperfusion therapies are proposed as a treatment alternative with possible clinical benefits in patients with severe COVID-19.

**Materials and Methods:** A search of the literature was performed in the ClinicalKey, Embase, PubMed and Ovid databases with the terms “COVID-19; Hemoperfusion; sepsis”. We found 88 publications and after applying the filters, 16 articles with relevant content were selected for the present review.

**Keywords:** COVID-19; Hemoperfusion; sepsis. (MeSH)

## Introduction

COVID-19 is a disease caused by a new beta coronavirus (SARS-CoV-2), which can present with severe cases, showing multiple organ dysfunction and whose central axis is an exaggerated and poorly regulated inflammatory response, with a consequent state procoagulant and endothelial dysfunction. Current treatment strategies for severe cases are aimed at stopping this inflammatory

cascade. Within this arsenal of options, hemoperfusion therapies are a promising alternative, considering the successful results in other similar scenarios, such as sepsis of bacterial origin.

## Discussion

COVID-19 is an infectious disease caused by a new beta coronavirus: SARS-CoV-2; named for its great similarity

and relationship with the SARS-CoV virus reported in the early 2000s [1].

SARS-CoV-2 is a single-stranded RNA virus, which has the ability to bind to carboxypeptidase receptors related to the Angiotensin-Converting Enzyme (ACE2), which is widely distributed in many tissues (cardiopulmonary and renal), and even cells of the immune system (macrophages and monocytes, among others) [2]. This explains the great multisystem compromise and the formation of an exaggerated inflammatory response, called “cytokine storm” [3].

### Cytokine Storm

Poorly regulated proinflammatory response with very high levels of Interleukin 6 (IL-6), Interleukin 10 (IL-10), ferritin, tumor necrosis factor alpha (TNF- $\alpha$ ), and procoagulant factors are responsible for endothelial damage and multiple organ dysfunction in patients with COVID-19 [3, 4]. In turn, IL-6 works through two signaling pathways, a Cis and a Trans [3, 5].

Cis signaling is generated from binding to the mIL-6R receptor, which uses JAK (Janus kinases) and STAT3 dependent intracellular pathways, participating in the function of T and B lymphocytes, and cells of the immune system innate [4].

Trans signaling is generated by binding of soluble IL-6 with its soluble sIL-6R receptor. In this way, large amounts of endothelial vascular growth factor, monocyte chemoattractant protein -1 (MCP-1), IL-8 and more IL-6 are produced, generating a vicious circle and perpetuating the systemic inflammatory response [3, 4].

### Hemoperfusion Therapies

Considering that the systemic complications derived from COVID-19 are a direct consequence of the exaggerated activation of an inflammatory cascade composed of cytokines and cells of the immune system, hemoperfusion therapies are a promising treatment alternative for severe cases [3].

In this extracorporeal technique, we seek to eliminate endotoxins and inflammatory cytokines through an adsorption mechanism based on the use of specialized filters [6]. This adsorbent agent attracts solutes using different types of forces, including: hydrophobic interactions, ionic attraction, hydrogen bonds, and Van

der Waals interactions [3]. The elimination of the solutes will depend on the size of the solutes and their capacity to cross the pores of the absorbent membranes [7].

Adsorbent membranes such as polymethyl methacrylate and AN69ST have been used within hemoperfusion therapies, with excellent clinical results [8]; but there are also membranes with Polyxin B fixed in a polystyrene fiber, which have been shown to reduce the levels of endotoxins, IL-6, TNF- $\alpha$  and proinflammatory cells [3]. However, its use is still controversial in septic patients, due to the results of the EUPHRATES study, which showed hemodynamic and paraclinical improvement, but there was no impact on mortality at 28 days compared to conventional treatment [9].

There is also a device called CytoSorb<sup>®</sup> (CytoSorbents Corporation, Monmouth Junction, NJ, USA), which has a porous polymer material, allowing irreversible binding of molecules with variable size (5–60 kDa) such as TNF- $\alpha$ , IL-1 $\beta$ , IL-6 and IL-10 [10].

The international registry of CytoSorb in the intensive care unit (currently recruiting patients), showed in its preliminary results, a significant reduction in IL-6 levels in patients with sepsis after the use of CytoSorb technology [11]. Current indications for the use of this technology include: active systemic inflammatory response, septic shock, IL-6 levels > 300–500 pg/mL, metabolic acidosis with pH < 7.20, refractory hyperlactatemia, rhabdomyolysis and myoglobin >10,000 U/L and hyperbilirubinemia (>200  $\mu$ mol/L) [3, 12].

Another available technology is oXiris, derived from AN69ST membrane. The use of this therapy demonstrated a reduction in mortality, hemodynamic improvement and a decrease in serum lactate, in patients with sepsis of abdominal origin and for gram negative bacilli [13–15].

Despite the fact that hemoperfusion therapies are a promising treatment strategy in patients with COVID-19, little literature has been published regarding the benefits of hemoperfusion in this type of patient.

The Colombian consensus on recommendations informed in the evidence for the prevention, diagnosis and management of acute kidney injury by SARSCoV-2 / COVID-19, suggests considering the use of extracorporeal purification therapies (including hemoperfusion), in severe patients with COVID -19, as cytokine clearance

therapy in cytokine storm syndrome, when conventional therapies are failing or insufficient, and evaluating individual patient prognosis [16].

## Conclusion

Hemoperfusion therapies are a promising treatment alternative in patients with severe COVID-19, due to their great capacity to eliminate proinflammatory cytokines and improve clinical status in patients with sepsis. However, clinical trials are required in patients with COVID-19 and cytokine storm.

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