Cytokine Blood Filtration Responses in COVID-19

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Abstract
The real issue with the COVID-19 pandemic is that a rapidly increasing number of patients with life-threatening complications are admitted in hospitals and are not well-administered. Although a limited number of patients use the intensive care unit (ICU), they consume medical resources, safety equipment, and enormous equipment with little possibility of rapid recovery and ICU discharge. This work reviews effective methods of using filtration devices in treatment to reduce the level of various inflammatory mediators and discharge patients from the ICU faster. Extracorporeal technologies have been reviewed as a medical approach to absorb cytokines. Although these devices do not kill or remove the virus, they are a promising solution for treating patients and their faster removal from the ICU, thus relieving the bottleneck.

Introduction
The new coronavirus disease (COVID 19) caused by SARS-CoV-2 virus has been identified by the World Health Organization (WHO) as an international public health emergency [1]. The disease is rapidly spreading to other countries from Wuhan City in China [2]. In contrast to the 2 other coronavirus targets of the WHO, SARS-CoV and MERS-CoV, SARS-CoV-2 is lethal. The Chinese National Health Commission survey of February 25, 2020, recorded a total of 2,663 deaths in China due to SARS-CoV-2 [3, 4]. Patients with COVID-19 can develop mild to severe symptoms following infection. Symptoms such as fever, cough, dyspnea, myalgia, fatigue, and dehydration develop in patients with mild infection. This can lead to severe pneumonia, acute respiratory distress syndrome (ARDS), or multi-organ failure in some patients [5]. SARS-CoV-2 infection is also associated with inflammatory cytokine storms, primarily characterized by elevated interleukin (IL)-6 levels in most dying patients. Interestingly enough, several recent clinical trials of COVID-19 have shown a higher level of IL-6 in the extreme community than in a moderate group. Nevertheless, the relationship between IL-6 and mortality remains unclear in dying patients [6, 7].

Many COVID-19 patients were also affected by anxiety, especially in the intensive care unit (ICU). Nonetheless, currently, minimally invasive treatment options are urgently needed as no vaccine has yet been developed for COVID-19. In recent clinical trials, several antivirals have been tested to study the effect of inhibitors such as remdesivir, favipiravir, and ritonavir on this new coronavirus [8]. In general, Thalidomide has anti-inflammatory activity, suppresses cell proliferation, reduces pulmonary fibrosis, and has a protective effect on
**Fig. 1.** CytoSorb beads under a microscope [13].

**Fig. 2.** CytoSorb configuration. **a** Stand-alone; **b** Pre-dialyzer; **c** Post-dialyzer [14].
lung lesions due to its ability to speed up the degradation of messenger RNA in blood cells and thus reduce tumor necrosis factor-α (TNF) [9]. The protective effect of thalidomide, combined with the use of antiviral medications and low-dose glucocorticoids, on lung lesions and immunological stress due to COVID-19 pneumonia [8] is still under investigation. Clearly the efficacy of therapies used in COVID-19 management needs to be better identified. The evidence of any further research must be validated by broad randomized controlled clinical trials and submitted to rigorous peer review prior to publication.

The main concern during the COVID-19 pandemic is that severely diseased patients in Italy and China are flooding hospitals, overwhelming the capacity of the healthcare systems. Although ICU rooms are well equipped, in some cases, infection breaks out between the limited number of patients with COVID-19, such as ARDS, trauma, kidney failure, acute heart damage, and secondary bacterial infection. The leading cause of these complications is usually cytokine storms, which contribute to a significant systemic inflammatory reaction, leading to damage in many instances to the vital organs, including the lung, heart, and kidney [2, 10].

Currently, cytokine filtration is a proposed way to mitigate the overwhelming admission of patients in the ICU. In contrast, CytoSorb is a potentially useful way to handle these patients more effectively and discharge them from the ICU to alleviate the bottleneck. While CytoSorb does not destroy or remove the virus, it has been used in more than 80,000 EU procedures as an approved treatment for cytokine storms. It has been distributed worldwide to 58 countries, helping doctors control severe inflammation, help reverse shocks, and improve breathing and other functions of the heart, which are some of the primary reasons patients suffer from COVID-19 infection [3, 11].

Fig. 3. Cytokine level after adding CytoSorb [15].

Fig. 4. Cytokine level before, during and after treatment with CVVHD-HCO membrane [18].
Blood Filtration Devices

Blood Perfection Technologies

Using the extracorporeal circuit was suggested as a solution to remove inflammatory mediators from plasma, thus reducing their effects [12]. There are many extracorporeal techniques, but this article focuses on CytoSorb and high cutoff membranes.

CytoSorb

CytoSorb is a hemoadsorption column able to remove inflammatory mediators from the blood. It contains highly absorbent coated beads, as shown in Figure 1. The beads are coated with polyvinylpyrrolidone to enhance biocompatibility [13]. Since CytoSorb is a column, it can be configured as standalone, or added to the extracorporeal circuit, pre-dialyzer, or post-dialyzer, as shown in Figure 2 [14]. There were 2 medical reports that CytoSorb was used for the removal of inflammatory mediators. The first case was a patient with septic shock who developed MOF that was connected to continuous veno-venous hemodiafiltration due to AKI. The IL-6 level was above 5,000 pg/mL, and a CytoSorb column was added to the hemodiafiltration circuit. The duration of filtration lasted for 60 h, and IL-6 was reduced significantly. Hemodiafiltration was discontinued because the kidney was functioning normally, and the patient fully recovered [13].

The second case was a patient who developed severe and progressive respiratory failure during laparotomy even though the patient was mechanically ventilated. As a result, the patient was connected to veno-venous ECMO. Unfortunately, the patient’s condition deteriorated as he developed right ventricular failure, so the patient was switched to veno-arterial ECMO. Despite that, the patient

Fig. 5. Cytokine level before initiation and during the treatment [21]. a TNF-α concentration; b Interleukin-6 concentration; c Interleukin-8 concentration; d Interferon-γ concentration.
developed ARDS. Due to AKI, the patient was connected to continuous renal replacement therapy (CRRT). Moreover, inflammatory cytokines increased rapidly: IL-6 20,000 pg/mL and IL-8 24,656 pg/mL. Antibiotics were given to the patient in addition to the previous treatment. The patient’s condition did not improve. As a result, a CytoSorb column was attached in series with the CRRT combined with antibiotics. The duration of CRRT and CytoSorb therapy was 85 h. Following the treatment, the level of cytokines IL-6 and IL-8 decreased and continued to decrease in the following days, as demonstrated in Figure 3. In the end, the patient’s kidney function returned to normal, and the patient was weaned off the mechanical ventilator [15].

**High Cutoff Membrane**

**High cutoff (HCO) membrane is a type of membrane that is able to remove substances with molecular weight**

**Fig. 6.** Cytokine level before initiation and during the treatment [25]. a IL-1 (ng/mL); b IL-2 (ng/mL); c IL-6 (ng/mL); d IL-8 (ng/mL); e IL-10 (ng/mL); f TNF-α (fmol/mL).
in the range of 20–50 kDa [12]. HCO membrane was able to remove inflammatory cytokines in several studies. A patient was admitted to the ICU with inflammation, severe rhabdomyolysis, and AKI, and was placed on renal replacement therapy with the HCO membrane. After 3 sessions, with each session lasting 4 h, except the second session which lasted 6 h, IL-6 decreased significantly [16]. Another study involved 38 patients with septic shock associated with AKI who were treated with CVVHD with HCO membrane for 72 h. The inflammatory mediator levels were collected at different time points: before the start of the treatment, 24 h and 48 h after the initiation of the treatment procedure, and 24 h after the termination of CVVHD. In the end, 30 patients survived, while 8 patients died during the CVVHD. However, the level of cytokines in both groups was reduced significantly, especially in the survival group (Fig. 4) [17].

oXiris Membrane
oXiris membrane is an AN69 membrane with the surface treated with polyethylenimine and grafted with heparin [18]. The oXiris membrane has been investigated in septic shock patients for cytokine reduction. Sixty patients were examined in an observational study, where the patients were received CVVHD with the oXiris membrane for a mean duration of 72 h. At the end of the treatment, there was a significant reduction in cytokines: IL-6 decreased from 506 pg/mL to 126 pg/mL, and IL-10 decreased from 106 pg/mL to 28 pg/mL [19]. A crossover randomized double-blinded study was conducted to investigate the effect of the oXiris membrane on 16 septic shock patients with AKI. The patients were divided into 2 groups: the first group received CRRT with the oXiris membrane for 24 h and CRRT with standard filter for another 24 h; the other group was treated with the reverse order of treatment. In the first 24 h, there was a significant reduction in inflammatory mediators (Fig. 5) [20].

Polymethyl Methacrylate Membrane
Polymethyl methacrylate (PMMA) membrane’s ability to remove inflammatory cytokines has been studied. A 19-year-old patient was admitted to the ICU due to septic shock caused by an infected giant venous malformation. Despite conventional treatment that includes infusion of fluids and blood transfusion, the patient’s hemodynamics did not improve. The patient received hemodiafiltration using the PMMA membrane due to AKI. After 3 days, the IL-6 concentration significantly decreased (from 18,200 pg/mL to 582 pg/mL) [21]. Cardiopulmonary bypass surgery causes inflammation due to different factors, such as the blood being exposed to the extracorporeal circuit and ischemia. In another study, 19 patients were on maintenance hemodialysis before surgery and 7 patients were not on maintenance hemodialysis. The 19 patients were randomized into 2 groups: 10 patients received CRRT with polysulfone (PS) membrane, while 9 patients were treated with CRRT with PMMA membrane. The maintenance hemodialysis group was the control group. The PMMA and PS groups were treated with CRRT before, during, and after the surgery. The cytokine level post-surgery was lower in the PMMA membrane group (IL-6: 292 pg/mL, IL-8: 54.7 mg/mL) than in the PS membrane group (IL-6: 616 pg/mL, IL-8: 154.3 pg/mL) [22].

HA330
HA330 is a synthetic resin hemofilter used for cytokine removal [23]. The effect of HA330 on cytokine removal was investigated in hyperlipidemic severe acute pancre-
Coronavirus disease 2019 (COVID-19) is a respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has been demonstrated that severe COVID-19 patients exhibit abnormal levels of inflammation. Therefore, patients with severe COVID-19 infection were divided into two groups: the control group and the study group. The study group received 2 cycles of high-volume hemofiltration (HVHF) and hemoperfusion (HP) using HA330. Each cycle consists of 24 h of HVHF and 2 h of HP. The combination of the treatments resulted in a significant reduction in inflammatory cytokines, as illustrated in Figure 6 [24].

HP using HA330 combined with pulse HVHF was used to investigate their effect on septic shock patients. Fifteen patients were treated with the combined treatment, while the other group received CVVH. The cytokine level decreased in both groups; however, it was significant in the combined treatment group, as illustrated in Figure 7 [25].

AN69ST membrane is an acrylonitrile/methallyl sulfonate copolymer membrane that has the ability to remove cytokines. This membrane with continuous hemofiltration
Coupled Plasma Filtration Adsorption

Coupled plasma filtration adsorption (CPFA) is a method of extracorporeal filtration that removes plasma from blood, passes the removed plasma into a sorbent, and returns the plasma to blood. The sorbent is nonspecific, where it removes inflammatory mediators from the plasma [28]. Severe sepsis patients with AKI were categorized into 2 groups: the CPFA group (35 patients) and the control group (35 patients). Both groups received standard treatment that includes antimicrobials, fluid resuscitation, and vasopressors. The duration of CPFA was 10 h for 3 days. After the treatment procedure, the cytokine levels, such as IL-6, TNF-α, IL-8, and IL-10, decreased significantly in the CPFA group compared to the control group [29]. Severe acute pancreatitis patients (the study group) were treated with a combination of CPFA and CVVH, while the control group received CVVH. There was a significant reduction in inflammatory cytokines with combined treatment compared with the CVVH, as illustrated in Figure 9 [30].

Conclusion

The number of deaths from COVID-19 has increased rapidly, and IL-6 is one of the significant inflammatory factors in cytokine storms, which mainly increases vascular permeability and affects heart function. The authors recommend using blood filtration devices in addition to current treatment to reduce the number of patients admitted to ICUs.

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Author Contributions

Conceptualization, M.B.; methodology, K.A.; review and analysis, K.A.; writing – original draft preparation, all authors equally contributed to this; writing – review and editing, M.B. All authors contributed equally to the manuscript and approved submission.

References

1 Ruan Q, Yang K, Wang W, Jialew L, Song J. Correction to: clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020 Mar 3;46:846–8. https://doi.org/10.1007/s00134-020-05991-x.
2 Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 11;395(10229):1054–62. https://doi.org/10.1016/S0140-6736(20)30566-3.
3 Ronco C, Reis T, De Rosa S. Coronavirus epidemic and extracorporeal therapies in intensive care: si vis pacem para bellum. Blood Purif. 2020 Mar 13;49(3):255–8.
4 Gong J, Dong H, Xia SQ, Huang YZ, Wang D, Zhao Y, et al. Correlation analysis between disease severity and inflammation-related parameters in patients with COVID-19 pneumonia. medRxiv. 2020 Jan 1.
5 Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: lessons learned from SARS and MERS epidemic. Asian Pac J Allergy Immunol. 2020 Feb 27;38(1):1–9.
6 Chen X, Zhao B, Qu Y, Chen Y, Xiong J, Feng Y, et al. Detectable serum SARS-CoV-2 viral load (RNAemia) is closely correlated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients. Clin Infect Dis. 2020 Jan 1;ciaa449:1058–4838.
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Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L, et al. Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). *Front. Immunol.* 2020 May 1;11:827. https://doi.org/10.3389/fimmu.2020.00827.

Deng X, Yu X, Pei J. Regulation of interferon production as a potential strategy for COVID-19 treatment. arXiv:2003.00751 [preprint]. 2020 Mar 2.

Clinical trials on drug repositioning for COVID-19 treatment. *Revista Panamericana de Salud Pública.* 2020;8(44):e40. https://doi.org/10.26633/RPSP.2020.40.

Rothen HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun.* 2020 Feb 26:109:102433.

Kang JH. Multiscale biofluidic and nanobiotechnology approaches for treating sepsis in extracorporeal circuits. *Biochip J.* 2020 Mar 12;14(1):63–71.

Villa G, Zaragoza JJ, Sharma A, Neri M, De Gaudio AR, Ronco C. Cytokine removal with high cut-off membrane: review of literature. *Blood Purif.* 2014;38(3–4):167–73.

Morris C, Gray L, Giovannelli M. Early report: the use of Cytosorb® haemabsorption column as an adjunct in managing severe sepsis: initial experiences, review and recommendations. *J Intensive Care Soc.* 2015 Aug;16(3):257–64.

Ankawi G, Xie Y, Yang B, Xie Y, Xie P, Ronco C. What have we learned about the use of cytosorb adsorption columns? *Blood Purif.* 2019;48(3):196–202.

Träger K, Schütz C, Fischer G, Schröder J, Skrabal C, Liebold A, et al. Cytokine reduction in the setting of an ARDS-associated inflammatory response with multiple organ failure. *Case Rep Crit Care.* 2016;2016:9852073.

Goubella A, Gankam-Kengne F, Baudoux T, Fagnoul D, Husson C, Delforge ML, et al. Severe myoglobinuric acute kidney injury in a kidney recipient: rapid recovery after hemodialysis with the super high-flux membrane ‘Theralite’. *Clin Nephrol.* 2017 Dec 1;88(12):359–63.

Villa G, Chelazzi C, Morettini E, Zamidei L, Valente S, Caldini AL, et al. Organ dysfunction during continuous veno-venous high cut-off hemodialysis in patients with septic acute kidney injury: a prospective observational study. *PLoS One.* 2017;12(2):e0172039.

Shum HP, Chan KC, Kwan MC, Yan WW. Application of endotoxin and cytokine adsorption haemofilter in septic acute kidney injury due to Gram-negative bacterial infection. *Hong Kong Med J.* 2013;19(6):491–7.

Turani F, Barchetta R, Falco M, Busatti S, Welte A. Continuous renal replacement therapy with the adsorbing filter oXiris in septic patients: a case series. *Blood Purif.* 2019;47(Suppl 3):1–5.

Broman ME, Hansson F, Vincent JL, Bohdanski M. Endotoxin and cytokine reducing properties of the oXiris membrane in patients with septic shock: a randomized crossover double-blind study. *PloS One.* 2019;14(8):e0220444.

Tomita K, Watanabe E, Sadahiro T, Tateishi Y, Shinozaki K, Rikihisa N, et al. Septic shock due to infected giant venous malformation complicated by massive bleeding. *Acute Med Surg.* 2016 Jul;3(3):279–82.

Mukaida H, Matsushita S, Inotani T, Nakamura A, Amano A. Continuous renal replacement therapy with a polymethyl methacrylate membrane hemofilter suppresses inflammation in patients after open-heart surgery with cardiopulmonary bypass. *J Artif Organs.* 2018 Jun 1;21(2):188–95.

Xu X, Jia C, Luo S, Li Y, Xiao F, Dai H, et al. Effect of HA330 resin-directed hemoadsorption on a porcine acute respiratory distress syndrome model. *Ann Intensive Care.* 2017 Dec 1;7(1):84.

Sun S, He L, Bai M, Liu H, Li Y, Li L, et al. High-volume hemofiltration plus hemoperfusion for hyperlpidemic severe acute pancreatitis: a controlled pilot study. *Ann Saudi Med.* 2015 Sep;35(5):352–8.

Chu L, Li G, Yu Y, Bao X, Wei H, Hu M. Clinical effects of hemoperfusion combined with pulse high-volume hemofiltration on septic shock. *Medicine.* 2020 Feb 1;99(9):e19058.

Shiga H, Hirasawa H, Nishida O, Oda S, Nakamura M, Mashiyo K, et al. Continuous hemodiafiltration with a cytokine-adsorbing hemofilter in patients with septic shock: a preliminary report. *Blood Purif.* 2014;38(3–4):211–8.

Ishikawa Y, Nishizawa H, Kasuya T, Fujiwara M, Ono F, Kimura Y, et al. Successful treatment of fatal macrophage activation syndrome and haemophagocytic lymphohistiocytosis by combination therapy including continuous haemodiafiltration with a cytokine-adsorbing haemofilter (AN69ST) in a patient with systemic lupus erythematosus. *Mod Rheumatol Case Rep.* 2018 Jan 2;2(1):25–9.

Ronco C, Brendolan A, d’Intini V, Ricci Z, Wrathen ML, Bellomo R. Coupled plasma filtration adsorption: rationale, technical development and early clinical experience. *Blood Purif.* 2003;21(6):409–16.

Netti GS, Sangregorio F, Spadaccino F, Staffieri F, Crovace A, Infante B, et al. LPS removal reduces CD80-mediated albuminuria in critically ill patients with gram-negative sepsis. *Am J Physiol Renal Physiol.* 2019 Apr 1;316(4):F723–31.

He C, Zhang L, Shi W, Liang X, Ye Z, Zhang B, et al. Coupled plasma filtration adsorption combined with continuous veno-venous hemofiltration treatment in patients with severe acute pancreatitis. *J Clin Gastroenterol.* 2013 Jan 1;47(1):62–8.