

# Cytokine Blood Filtration Responses in COVID-19

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## Keywords

COVID-19 · Coronavirus · Cytokine adsorption · Blood filtration devices · Membranes

## 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.

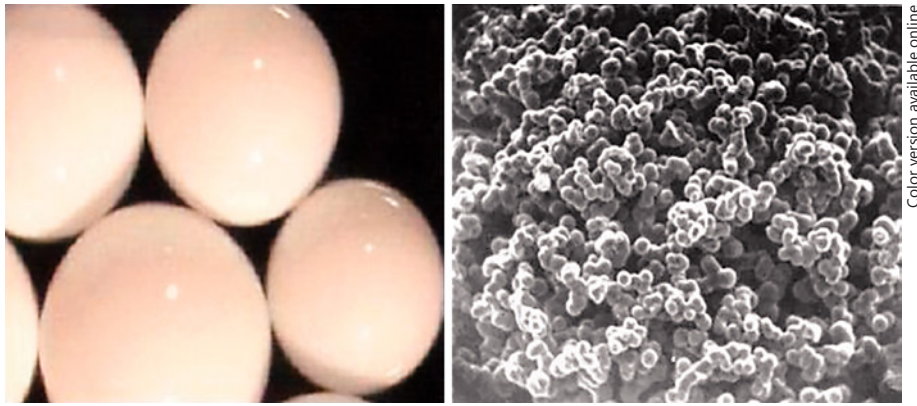
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## Introduction

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

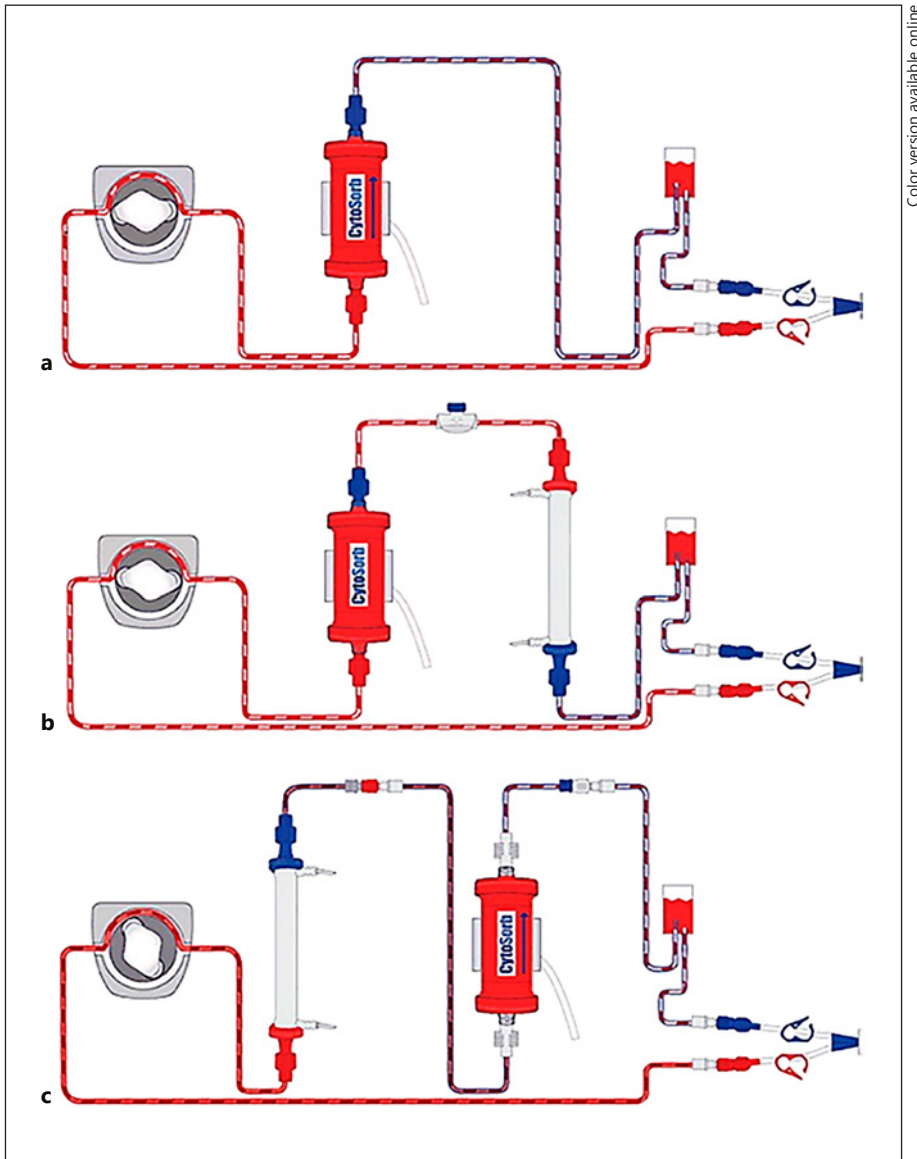
other countries from Wuhan City in China [2]. In contrast to the 2 other coronavirus targets of the WHO, SARS-CoV and MERS-CoV, SARS-CoV-2 is lethal. The Chinese National Health Commission survey of February 25, 2020, recorded a total of 2,663 deaths in China due to SARS-CoV-2 [3, 4]. Patients with COVID-19 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



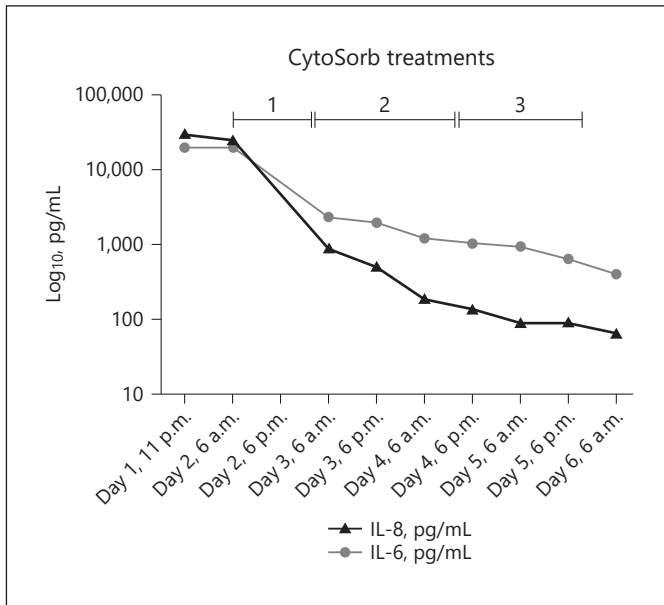
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**Fig. 1.** CytoSorb beads under a microscope [13].



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**Fig. 2.** CytoSorb configuration. **a** Stand-alone; **b** Pre-dialyzer; **c** Post-dialyzer [14].

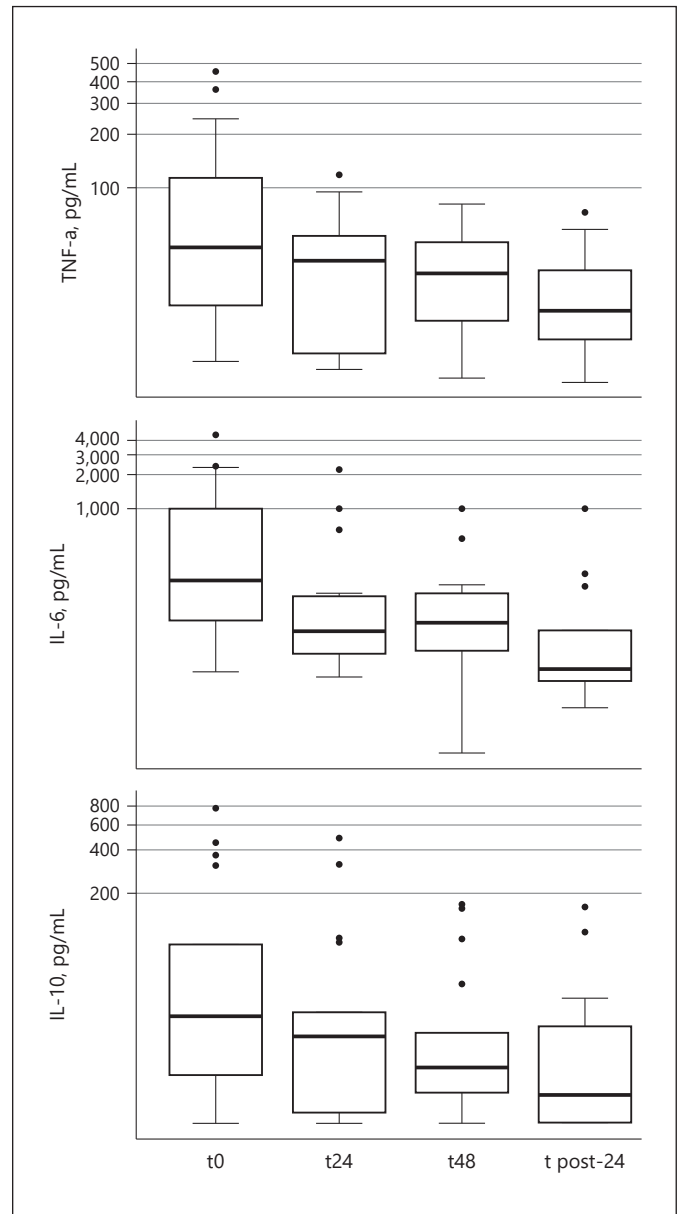


**Fig. 3.** Cytokine level after adding CytoSorb [15].

lung lesions due to its ability to speed up the degradation of messenger RNA in blood cells and thus reduce tumor necrosis factor- (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.

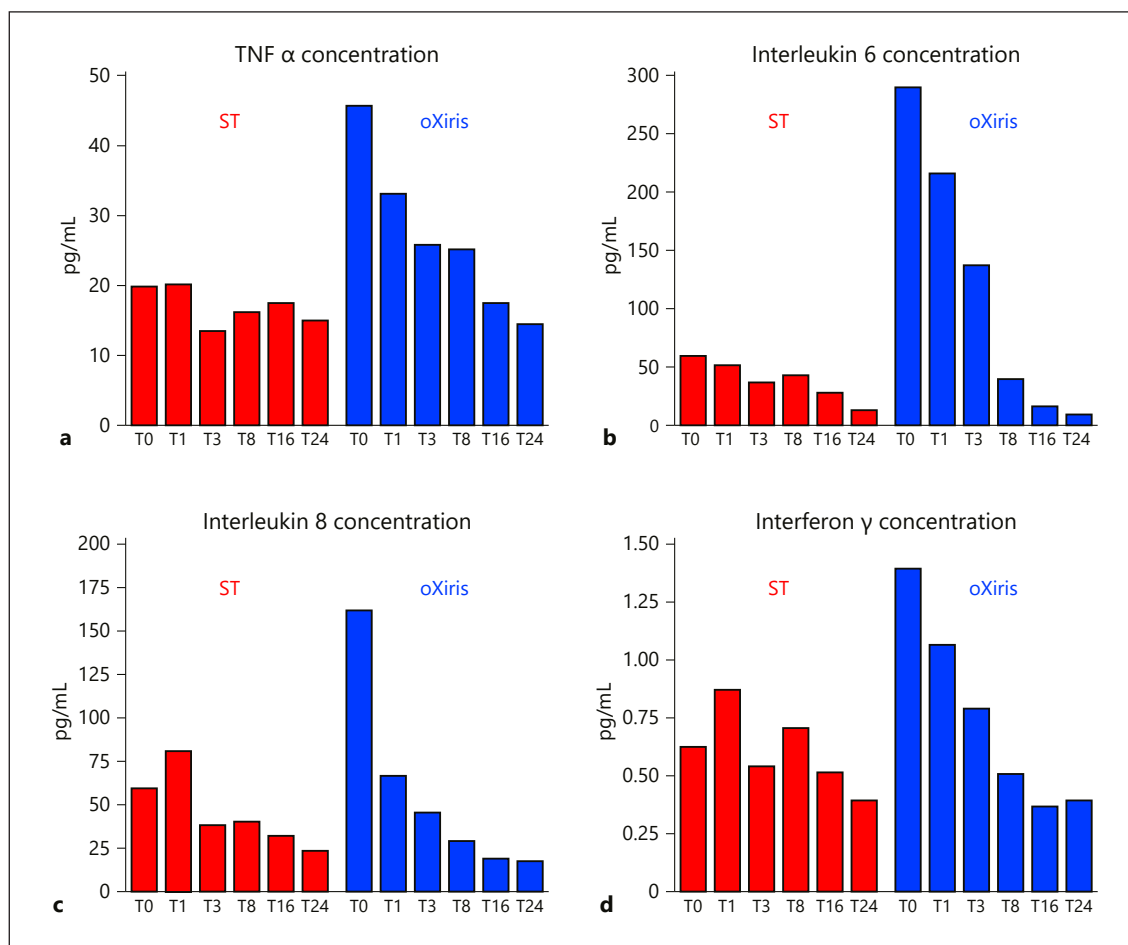
The main concern during the COVID-19 pandemic is that severely diseased patients in Italy and China are flooding hospitals, overwhelming the capacity of the healthcare systems. Although ICU rooms are well equipped, in some cases, infection breaks out between the limited number of patients with COVID-19, 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



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

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. 5.** Cytokine level before initiation and during the treatment [21]. **a** TNF- $\alpha$  concentration; **b** Interleukin-6 concentration; **c** Interleukin-8 concentration; **d** Interferon- $\gamma$  concentration.

## Blood Filtration Devices

### Blood Perfection Technologies

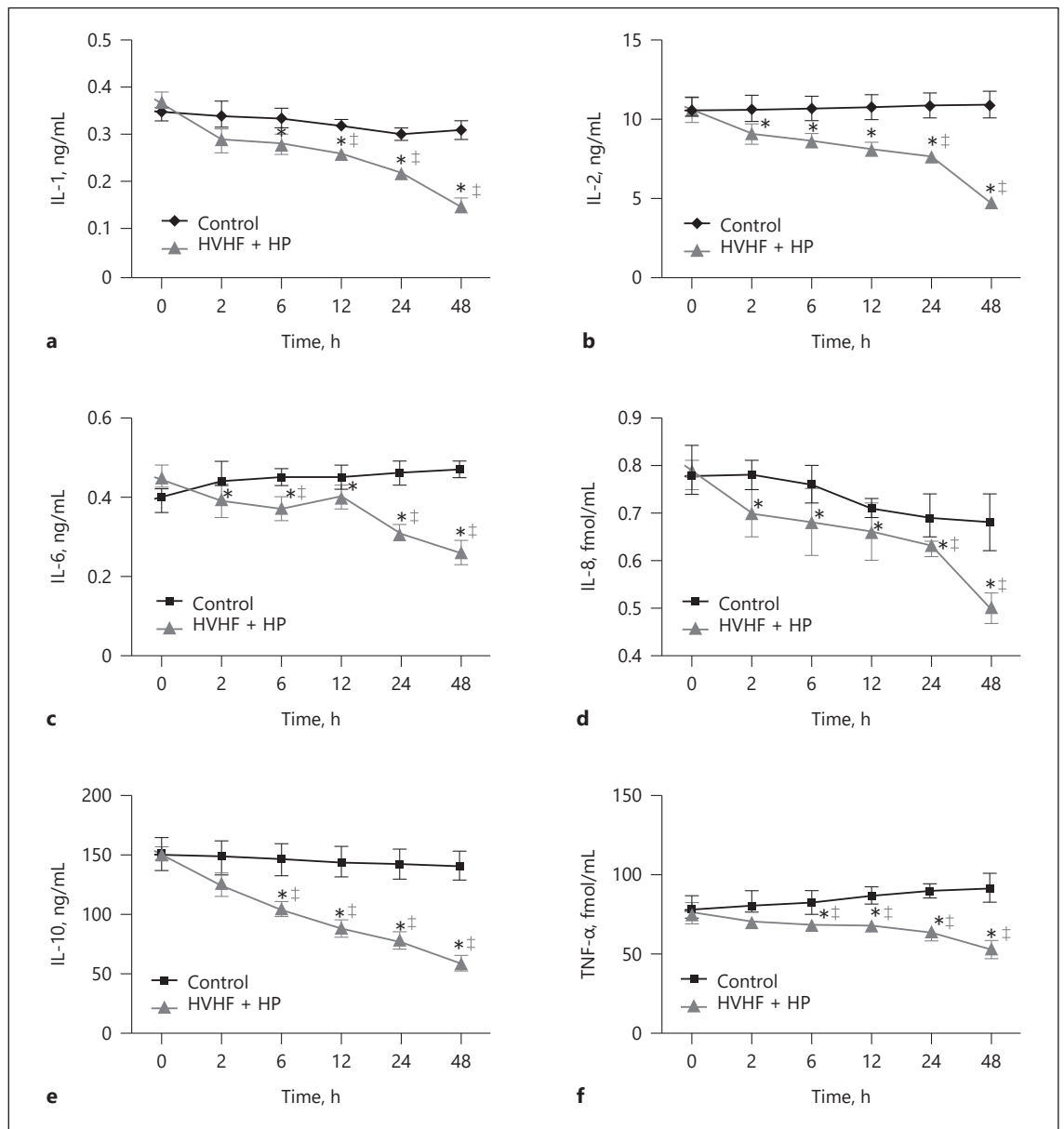
Using the extracorporeal circuit was suggested as a solution to remove inflammatory mediators from plasma, thus reducing their effects [12]. There are many extracorporeal techniques, but this article focuses on CytoSorb and high cutoff membranes.

### 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



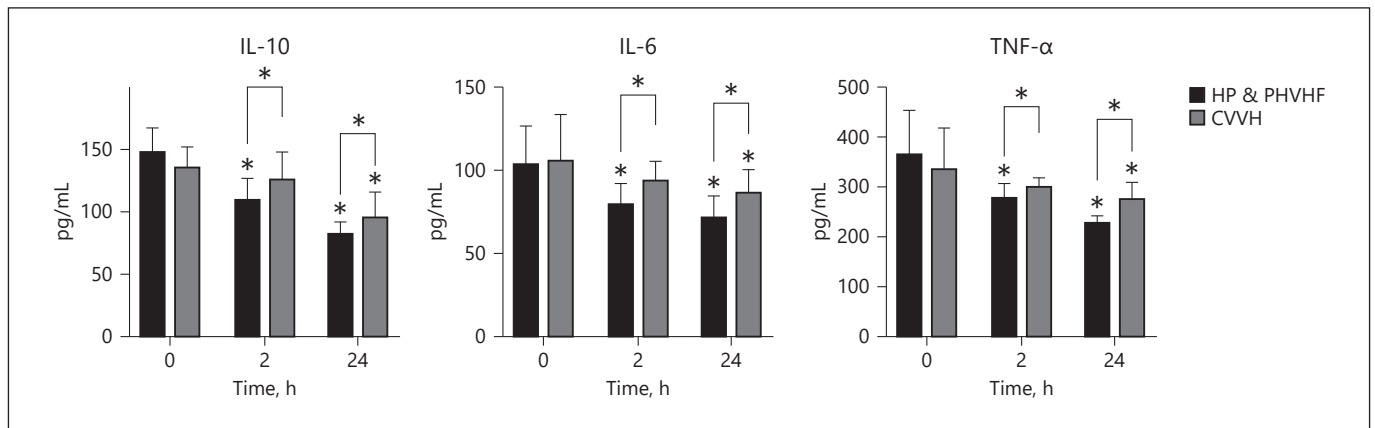
**Fig. 6.** Cytokine level before initiation and during the treatment [25]. **a** IL-1 (ng/mL); **b** IL-2 (ng/mL); **c** IL-6 (ng/mL); **d** IL-8 (ng/mL); **e** IL-10 (ng/mL); **f** TNF- $\alpha$  (fmol/mL).

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. 7.** Cytokine level in combined and CVVH groups [26].

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 an-

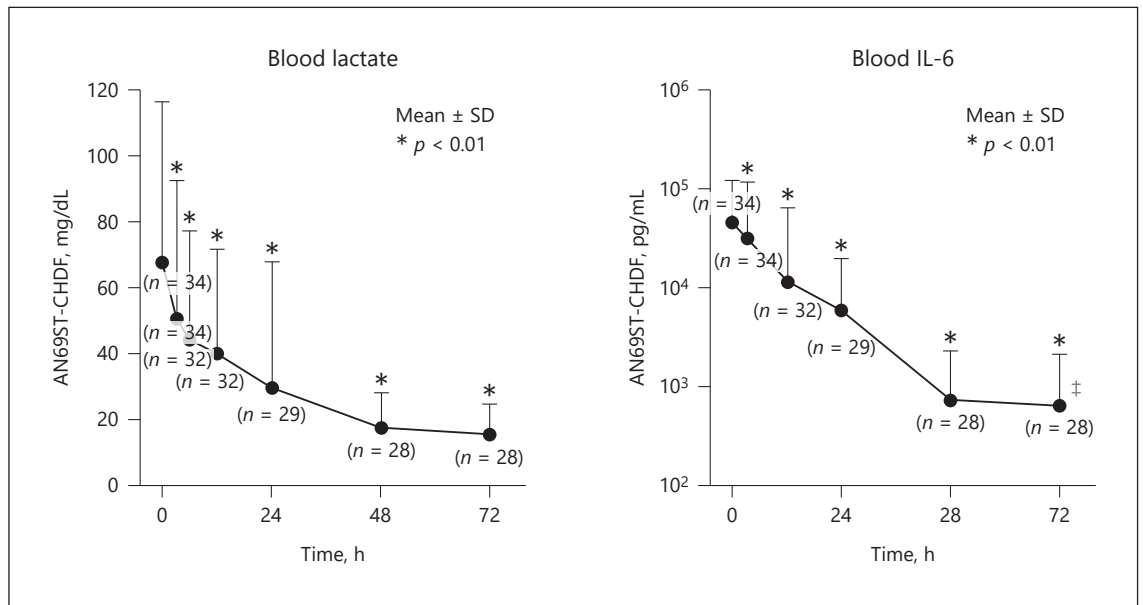
other 24 h; the other group was treated with the reverse order of treatment. In the first 24 h, there was a significant reduction in inflammatory mediators (Fig. 5) [20].

#### Polymethyl Methacrylate Membrane

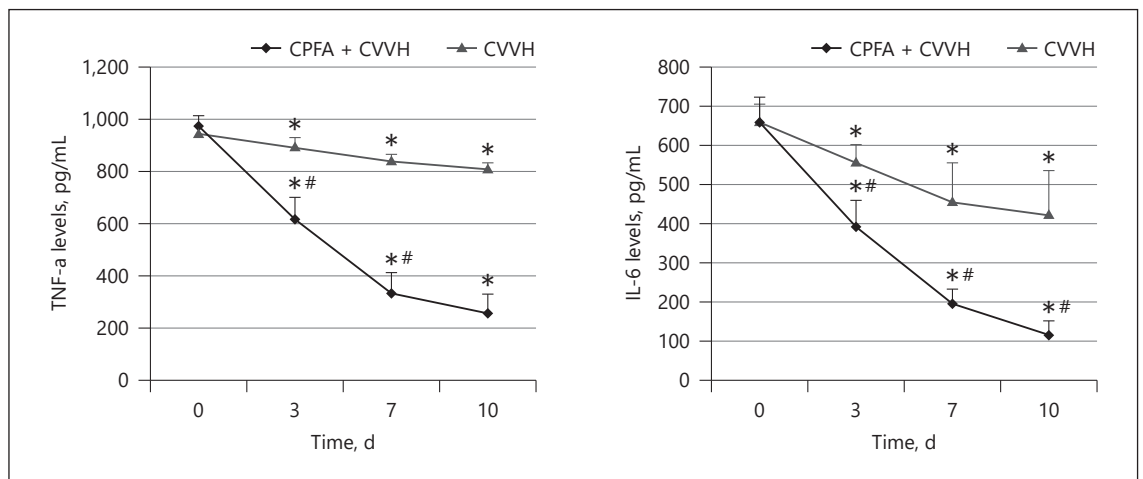
Polymethyl methacrylate (PMMA) membrane's ability to remove inflammatory cytokines has been studied. A 19-year-old patient was admitted to the ICU due to septic shock caused by an infected giant venous malformation. Despite conventional treatment that includes infusion of fluids and blood transfusion, 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-



**Fig. 8.** Inflammatory mediators' level for AN69ST-CHDF treatment [27].



**Fig. 9.** TNF- $\alpha$  and IL-6 level removal using CPFA + CVVH group and CVVH group [31].

atitis patients. Twenty patients were divided into 2 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. In addition, both groups were treated based on the international sepsis guidelines. The cytokine level decreased in both groups; however, it was significant in the combined treatment group, as illustrated in Figure 7 [25].

#### AN69ST

AN69ST membrane is an acrylonitrile/methallyl sulfonate copolymer membrane that has the ability to remove cytokines. This membrane with continuous hemo-

diafiltration (CHDF) was used to treat 34 septic shock patients in addition to the conventional treatment according to the Surviving Sepsis Campaign guidelines. The duration of CHDF with AN69ST membrane was more than 72 h. The IL-6 level before the initiation of treatment procedure was 44,800 pg/mL, and that of lactate was 69 mg/dL. After the treatment, the inflammatory mediators decreased significantly: IL-6 was 1,200 mg/mL and lactate was 16.5 mg/mL, as demonstrated in Figure 8 [26]. A patient with hemophagocytic lymphohistiocytosis was admitted to the hospital and treated, yet the patient's conditions did not improve and the patient developed ARDS, AKI, and multiple organ dysfunction syndrome that led the patient to be admitted to the ICU. The inflammatory mediators were elevated: TNF- $\alpha$  was 27.6 pg/mL and interferon- $\gamma$  was 7,600 mg/mL. The patient received AT69ST-CHDF that resulted in a reduction in the cytokine level: TNF- $\alpha$  was 8.21 pg/mL and interferon- $\gamma$  was 16.9 mg/mL. Moreover, the patient's multiple organ dysfunction syndrome condition improved [27].

#### 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- $\alpha$ , 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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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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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.

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