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Application of Extracorporeal Apheresis in Treatment of COVID-19: a Rapid Review

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Abstract
Spread of a novel coronavirus infection in 2019 caused by SARS-CoV-2 virus has become a real threat to public health all around the world. The new pandemic required the mobilization of all resources for effective treatment of COVID-19 patients. Extracorporeal apheresis methods were suggested as an addition to the therapy of severe COVID-19 patients, especially when there is a threat of cytokine storm. Cytokine storm has a complex and not fully understood mechanism, and it can result in the multiple organ failure syndrome, associated with high mortality. The main cytokines that play the key role in the cytokine storm are IL-6, IL-10, and TNF-alpha. Removal of the target pro-inflammatory cytokines from the bloodstream can be beneficial in reducing the risk of complications as well as the mortality rate. We describe and compare different methods of extracorporeal apheresis: hemoadsorption, selective plasma filtration, and plasma exchange therapy in the context of their potential use in COVID-19 treatment.

Keywords COVID-19 · Extracorporeal apheresis · Hemoadsorbtion · Selective plasma filtration · Therapeutic plasma exchange

1 Background

New coronavirus infection is currently the most frequent etiological cause of hospital patient mortality. According to The World Health Organization (WHO), 195 million coronavirus infection incidents were detected from 2020 to 2022 including almost 2 million of hospital patient mortality rate [1]. The main danger of coronavirus infection is the respiratory distress syndrome and multiple organ failure (MOF) [2, 3] caused by a cytokine storm [4]. Cytokine storm — is the state of uncontrollable system hyperinflammation developed in response to the excess secretion of cytokines [5]. It is noteworthy that death from coronavirus infection occurs in the first 14 days from the first symptoms manifestation, the current mortality rate is estimated from 1.36 to 5% of total patients [6, 7].

There is currently no single effective strategy of treatment COVID-19 patients, with vaccination being an important method of infection control. However, to date 10% of population have not been vaccinated in 23 countries, 73 countries have not achieved 40% of vaccinated population, and many other countries have a prognosis to be unable to achieve the target 70% by the middle of 2022 [1]. Slow vaccination rate as well the ongoing infection spread call for development new and effective methods of treating COVID-19 patients.

The necessity of extracorporeal apheresis use, directed at the inflammatory mediator elimination and different systems of organs support, arises based on the pathophysiological failures shown in coronavirus infection patients. Extracorporeal therapy can help to prevent a multiple organ failure and increase the survival rate. Therefore, exploring the possibilities of various therapeutic apheresis methods of treating severe COVID-19 patient is still of a great importance.

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2 COVID-19: Pathophysiology and Role of Cytokines

Novel coronavirus infection (NKI) caused by SARS-CoV-2 virus was first reported in Wuhan (China) and widely spread all over the world [8]. The disease caused by the new coronavirus was officially named COVID-19 («Coronavirus disease 2019») [9]. On 11th of March 2021, WHO declared COVID-19 a pandemic [10].

The main sites of entry of SARS-CoV-2 are the upper airways epithelium and gastric and intestinal epitheliocytes. SARS-CoV-2 enters the target cells through the ACE2 receptor binding. However, because SARS-CoV-2 is able to affect different organs and tissues, there are likely other receptors and coreceptors, like CD147, involved in virus entrance [9]. An important role in coronavirus infection pathophysiology is assigned to an inadequate immune system reaction and cytokine hyperproduction that can result in cytokine storm [11]. The mechanism of cytokine storm in COVID-19 is still not fully explored. SARS-CoV-2 spike protein binding activates various signal pathways, resulting in increased proliferation of T lymphocytes, macrophages, and NK cells [12, 13] as well as cytokine hyper production [14].

Cytokine storm syndrome provokes DIC and cardiovascular dysfunction, and eventually, can lead to a multiple organ failure syndrome [7]. Liu et al. provide evidence that the following cytokines play a major role in severe COVID-19 symptoms: IL-6, IL-1β, IP10, and MCP-1. IL-6 and IL-1β are the main targets for monoclonal antibodies therapy [15]. IL-6 is the key cytokine in severe COVID-19 pathogenesis and cytokine storm progress. It is involved in Janus kinase–activated transmembrane transport of signals into the cell [16]. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV)–infected pneumonia (China) published on 30th of January 2020 first recommended to monitor cytokines for faster recovery and decrease of mortality rate [17].

High patient mortality rate is caused by the lack of a targeted antiviral therapy; therefore, a targeted treatment of the key pathogenic factors is of a major significance for patients' lifesaving [18]. Liu et al. claim that the most perspective and promising way is to inhibit the IL-6 [15]. A major retrospective study has shown that IL-6 is the predictor of adverse outcome and mortality in severe COVID-19 patients [19].

IL-6 plays a key role in different lymphocyte population interaction and their activation. Animal models show that the inhibition of nuclear factor κB, which is also a key transcription factor of IL-6, or infecting animals with SARS-CoV strain with lacking envelope protein E that activates nuclear factor κB increase the infected animal survival rate through the decrease of IL-6 production [20]. These findings confirm the key role of IL-6 in pathogenesis of severe coronavirus infection and COVID-19 cytokine storm.

Therapeutic apheresis methods can benefit patients with severe COVID-19 symptoms by eliminating pro-inflammatory cytokines that play the key role in COVID-19 pathogenesis [15, 21].

3 Therapeutic Apheresis Application in COVID-19 Treatment: an Overview

Therapeutic apheresis (EA) is a method of extracorporeal hemocorrection that plays an important role in patient management and treatment with different renal, hematological, rheumatological, and neurological disorders. During the procedure, different pathogenic components circulating in blood are eliminated from the blood of patients with various diseases [22]. Therapeutic apheresis methods are used to treat complex autoimmune diseases, allergic conditions, metabolic failures, sepsis and infectious diseases, hematological, hepatic and gastrointestinal diseases, neurologic conditions, and acute exogenous poisoning [23]. Therapeutic apheresis methods can be subdivided on the basis of what is the driving force of different molecule elimination: sorption and filtration [24].

A number of countries (China, Japan, USA, Italy, Russian Federation, etc.) have already included extracorporeal apheresis methods in COVID-19 treatment clinical guidelines [9, 11, 23, 25, 26]. Chinese clinical guidelines (expert recommendations on blood purification treatment protocol for patients with severe COVID-19) in particular describe in great detail the process of blood purification treatment for patients with severe COVID-19 with further patient monitoring [11].

Extracorporeal apheresis methods application guidelines can also be found in ASFA-2019 (the American Society for Apheresis). According to ASFA-2019 guidelines, the possibility of plasma exchange in patients with infections fall under category III, degree 2B, which means that the optimal role of apheresis therapy in patient treatment is unknown, and currently, there is only a moderate evidence supporting the efficiency of this method [23]. Methods of AE were included into Russian Federation temporal clinical guidelines for new coronavirus disease (COVID-19) prevention, diagnosis, and treatment, version 14. Indications for use are progressive respiratory failure and/or multiple organ failure [9].

The main effects of EA in severe COVID-19 patients are blocking the cytokine storm; reducing inflammation in lungs and improving respiratory function; improving kidney and

liver functions; and most importantly, decreasing of the mortality rate of severe COVID-19 patients [27].

It should be noted that to date, there has not been enough clinical data to fully understand the role of EA methods in the survival and mortality of COVID-19 patients. This is due to the lack of large randomized trials, and most information available is based on the description of a single clinical case or a series of cases, allowing to only assessing the individual patient's recovery rate and laboratory parameters before and after the procedure.

Currently, the most relevant SARS-CoV-2 variant of concern is Omicron (B.1.1.529 lineage), first identified in South Africa in November 2021 [28]. However, it should be noted that the Omicron variant is less clinically severe compared to the Delta variant. Patients with Omicron variants have fewer admissions to hospitals and especially to the intensive care department, and as a result, the mortality rate caused by Omicron is lower compared to other SARS-CoV-2 variants of concern (Delta variant, Gamma variant) [29]. It may be due to this that we were unable to find any information on the use of therapeutic apheresis for the treatment of Omicron variant, and most of the studies were related to Alpha, Beta, Gamma, and Delta variants.

Not much information was found about the possibility of using therapeutic apheresis in pediatric patients. Raina et al. [30] used CytoSorb absorber or oXiris filters when treating pediatric patients with COVID-19 who also required renal replacement therapy. A higher clearance was achieved through incorporation of CytoSorb or oXiris into the continuous kidney replacement therapy (CKRT) circuit. However, FDA has not yet officially approved the use of these devices for pediatric patients.

According to the latest published data, another important problem today is the development of a so called "post-COVID syndrome" or "long-COVID" in patients after COVID-19 infection recovery [31]. It is supposed that autoantibodies against the M1 acetylcholine receptors (AChR) [32] and autoantibodies against β1 and β2 adrenergic receptors (AdR) [33] play the key role in the pathophysiology of these syndromes. Therefore, more and more information is published about the possibility of including therapeutic apheresis methods, especially sorption methods, in the treatment of "post-COVID syndrome" [34, 35].

4 Hemoadsorption

4.1 Brief Description and Application in Clinical Practice

Hemoadsorption is a type of extracorporeal detoxification therapy, when the target component is selectively extracted as a result of blood perfusion through the sorbent [36]. The active component of the adsorption column is a sorbent with granules with different size pores. When blood passes through the sorbent, the targeted molecules of certain size get absorbed by sorbent granules due to hydrophobic and ionic interactions [37]. This procedure does not have a high level of specificity, since removal of the molecules is only based on the size of these molecules [38]. However, there are also sorbents with a maximum level of specificity, where sorbent granules are linked with a specific ligand on their surface that have a molecule specific affinity from the circulating blood [39]. For example, hemoadsorption using an immobilized LPS–selective ligand makes it possible to remove only target molecules from blood — lipopolysaccharide molecules of Gram-negative bacteria [40]. Then the purified blood is returned to the patient. The schematic overview of hemoadsorption is given in Fig. 1.

There are a lot of hemoadsorbers that have been proposed for hemoperfusion. For example, a disposable sterile cartridge of the HA 330 series (Jafron Biomedical, Co. LTD, China) removes excess inflammatory mediators, pro-inflammatory cytokines (IL-6, IL-10, TNF-alfa), metabolites and other pathogenic blood components, and residual drug concentrations. The neutral absorber, due to its macroporous structure and high specific surface area, binds excess pro-inflammatory factors from blood [41]. Cytosorb is a more expensive version of the similar type absorber (CytoSorbents Inc., Monmouth Junction, NJ, USA) [42]; there is also a Russian device for hemoabsorption—Efferon CT (Russia) [43].

The main advantages of hemoadsorption are the following: alongside of a cytokine removal, there is also an elimination of pathogen-associated molecular patterns or damage factors, substances that can provoke and maintain a generalized inflammatory response in the body [44]; decrease in the level of vasopressors such as catecholamine in blood [45]; reducing the need for anticoagulant therapy compared with other extracorporeal methods; decrease in the level of lactate in the blood serum [44]; the highest selectivity compared to other ECH methods [36]. However, there are also some disadvantages: the need to control the doses of administered medications, as antibiotics are also removed during the procedure, for example, hydroxychloroquine and azithromycin due to the low molecular weight can be removed, but tocilizumab (148 kDa), antibodies (> 150 kDa), and other molecules of similar size are not removed [46]. Despite the higher selectivity of hemoadsorption compared to other methods, nonspecific binding of molecules to the sorbent is also possible. Patients may develop thrombocytopenia and leukopenia as side effects [47]. There is also a restriction on consumption of lipid or fat emulsions in food before the procedure [46].

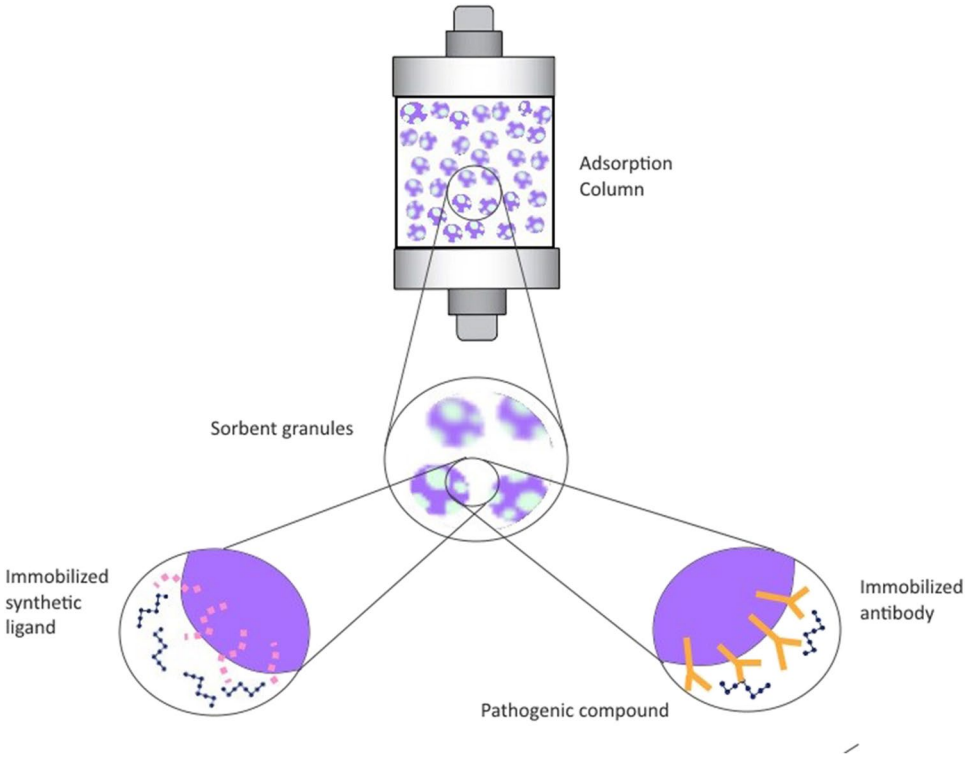

Fig. 1 Adsorption process in the hemoadsorber. Blood goes through the hemoadsorption device, composed of specific porous sorbent beads. Molecules that are smaller than the pores in diameter are captured and removed from the bloodstream. The highest level of removing specificity is achieved by sorbent granules with synthetic ligands or antibodies that bind only targeted molecules from the bloodstream

Hemoadsoption is indicated for intensive care patients and patients in critical conditions (acute pancreatitis and peritonitis; respiratory distress syndrome; septic, burn, traumatic shock, and poisoning, etc.) and for patients with complex chronic diseases (allergies, especially with the phenomena of allergic diseases: intoxication, etc.) [48].

4.2 Application in COVID-19 Treatment

Hemoadsorber used to remove inflammatory mediators from the bloodstream include CytoSorb, Cytosorbents, NJ, USA, and HA330, Jafron, China [37, 49, 50]. CytoSorb absorbers have become widely used for the COVID-19 treatment. In April 2020, FDA temporarily approved the emergency use of CytoSorb device for the treatment of cytokine storm in patients with COVID-19 [21].

Prevention of cytokine storm syndrome associated with COVID-19 using EA treatments has been successfully used in China and Europe. As mentioned above, the most commonly used absorber is Cytosorb (Cytosorbents Inc, Monmouth Junction, NJ). CytoSorb hemoadsorption was also included in the national clinical guidelines in Italy [25]. In several observational studies and a randomized controlled trial involving patients with septic shock, CytoSorb was reported to reduce excess levels of inflammatory mediators, and required low need for vasopressors [51–54]. CytoSorb demonstrated capacity to adsorb many of the mediators associated with severe COVID-19.

Stockmann et al. [55] noted that the removal of cytokines using CytoSorb in critically ill COVID-19 patients with suspected generalized inflammation and shock can be an excellent way of stabilizing hemodynamics and improving the clinical outcome. However, in a large open-label randomized controlled trial involving patients with severe COVID-19, they showed that the use of CytoSorb did not prevent the development of Vasoplegic shock; moreover, mortality level in the CytoSorb and control groups was almost the same at 78% and 73%, respectively [56].

In an open-label randomized controlled study led by Supady et al. [57], resulted indicated that CytoSorb decreased the level of IL-6 from 357.0 to 98.6 pg/ml. However, the number of survived patients after 30 days was 3 (18%) out of 17 in CytoSorb group and 13 (76%) out of 17 in control group ($p = 0.0016$). Thus, the authors concluded that an early cytokine adsorption in patients with severe COVID-19 and veno-venous ECMO did not reduce the level of IL-6 and had a negative effect on survival rate. Therefore, cytokine adsorption should not be used in the first days of ECMO for COVID-19 patients.

On the contrary, in March 2020, Damiani et al. [58] demonstrated successful experience of using the CytoSorb in the treatment of patients with COVID-19 at Papa Giovanni XXIII Hospital, Bergamo, Italy. There was a shown decrease in the concentration of cytokines with a significant decrease in IL-6, IL-8, IL-10, and IL-1β; clinical improvement was reported in most patients. Peng et al. [44] described a series

of cases where CytoSorb hemoadsorption was successfully applied to critically ill patients. CytoSorb also showed a great effect in the treatment of septic shock with a significant decrease in IL-6 levels [59] and in the treatment of cytokine storm [49].

An important advantage of hemoadsorption compared to the other EA methods is its ability to integrate with most extracorporeal circulation systems, such as continuous renal replacement therapy (CRRT) or extracorporeal membrane oxygenation (ECMO), being a useful addition in combination with other EA methods [58]. For example, Dastan et al. [60] demonstrated the possibility of combining hemosorption using the HA330 cartridge (Jafron Biomedical Co., China) with continuous veno-venous hemofiltration (CVVH) treatment. This resulted in an increased saturation, improvement of CT scans, and a decrease of IL-1, IL-6, IL-8, and TNF-a. The authors also noted the benefits of adding tocilizumab to the complex therapy; however unlike hemoadsorption, it is a monoclonal antibody against the interleukin-6 receptor.

It should be noted that there is less data available on the use of Jafron absorbers than of CytoSorb; however, there are studies describing HA330 cartridges (Jafron Biomedical, China) in the COVID-19 treatment. Mikaeili et al. [61] conducted a comparative study to determine the effectiveness of the hemoadsorption procedure using HA 330 (Jafron Biomedical Co., China) compared to the standard COVID-19 therapy. Analyzing the obtained data, the authors concluded that there was a significant decrease in mortality among patients who had hemosorption with a P/F ratio above 75 (mortality rate of 84.7% with a P/F ratio <75 vs. 15.4% with a P/F ratio ≥ 75, $p=0.02$). It means that early initiation of hemoadsorption can be extremely effective in patients with severe COVID-19. Surasit et al. [62] conducted a prospective cohort study to compare 2 groups: patients with standard therapy and patients who received at least 3 hemoadsorption procedures using an HA 330 (Jafron Biomedical Co., China). The result of this study was that in the group of patients who had the hemoadsorption procedure, there was a marked improvement in laboratory parameters, and the 28-day mortality rate was significantly lower in the hemoperfusion group compared to the control group (6.67% vs 85.71%, $p<0.001$). Thus, the authors noted that adding a hemoperfusion procedure at early stages of the disease may be beneficial in improving patient's condition and preventing death. However, it must be noted that the study results were influenced by external confounding factors associated with the initial state of the patients, as well as the small sample size.

In addition to CytoSorb and Jafron, Stephen et al. provided an example of a successful use of Seraph-100 Microbind Affinity Blood Filter column (Seraph-100; Exthera Medical Corporation, Martinez, CA) for the treatment of severe COVID-19. The results showed: restoration of hemodynamic parameters, temperature normalization, and a decrease in pro-inflammatory markers in the blood [63]. The authors claimed that this column was unique, as it directly bound SARS-CoV-2 and other pathogens due to specific sorbent particles, which mimics the natural heparin sulfate molecules of the endothelial cells [64]. At the same time, the column did not bind drugs [65]. Also, compared to other methods, there was no hypercoagulation reported, perhaps due to the internal heparin fragments present in the device. Previous reports of other hemoadsorbers that non-specifically bind endotoxins and cytokines suggested that hypercoagulation might be a significant problem [21, 66, 67]. This distinguishes Separah-100, for example, from CyroSorb, where there was no evidence of virus-binding properties. In this respect, Separah-100 has a selectivity advantage over the other absorption devices [63].

According to Krenn et al., CytoSorb hemoadsorption is by far the most studied and clinically recommended method. The authors compared CytoSorb (CytoSorbents Inc., Monmouth Junction, NJ, USA), HA 330 (Jafron Biomedical Co., Guangdong, China), and Biosky MG (Biosun Medical Technology Co., Foshan, Guangdong, China). As for the latter, there are no specific recommendations available for its use. The pre-treatment process is more complicated in the case of HA-330, while CytoSorb does not require a prewash. Another attractive advantage of CytoSorb over HA-330 is its compatibility with other EA methods, whereas the incorporation of HA-330 is limited. It is worth noting, however, that Jafron and Biosky are less expensive than CytoSorb [68]. The price difference is quite impressive: CytoSorb is almost twice as expensive as HA 330 [69]. However, the capacity for continuous use of CytoSorb for several days negates this cost advantage [68].

The data from a comparative study led by Magomedov et al. suggested that the use of Efferon — a Russian made absorber in addition to the standard therapy, in contrast to the standard therapy alone, lead to a statistically significant decrease in IL-6 and ferritin, while statistically there was no statistically significant differences in mortality between the two comparison groups [43].

Thus, according to Koc et al., comparing the available data on the use of hemoadsorption for the treatment of severe forms of COVID-19, hemoadsorption therapy is an alternative method of treatment in critically ill patients with COVID-19: mortality, mean intubation time, and length of stay in the intensive care unit and hospital were 29%, 14.93 days, 17.21 days, and 31.7 days, respectively [70].

5 Plasmapheresis

5.1 Overview of the Method

Plasmapheresis is a method of separating plasma from blood cells with the return of the patient's own cells [65]. This

technique is designed to remove pathogenic antibodies and lipoproteins. Plasmapheresis can be carried out either by membrane separation or centrifugation [71]. The main disadvantages are low selectivity, activation of complement, and leukocytes by an artificial membrane, and the need for a large vein catheter to obtain adequate blood flow [72]. Another important disadvantage is the need to replace the plasma volume. The low selectivity of plasmapheresis can lead to adverse side effects: plasmapheresis-associated coagulopathy [73], hypogammaglobulinemia [27], and hypotension [73]. All these factors must be taken into account during the procedure. Plasmapheresis based on the centrifugation technique is more common in the USA, whereas membrane separation is more popular in Russia, Germany, and Japan [74].

The first plasma exchange filter was a flat parallel plate membrane (Centry TPE; Cobe) approved in the USA: plasma filters Prismaflex TPE-2000 (Baxter) and Plasmaflo OP-05 W (Asahi Kasei Medical Company Ltd. Japan). Their technical characteristics are very similar, but they differ from a conventional dialyzer intended for hemodialysis with higher selectivity [75]. In Russia, plasma filters PFM-800 consisting of flat "track" porous membranes manufactured by AO "Optika" and plasma filters manufactured by "Gemos-PFS" are used [76].

Clinical indications for plasmapheresis are neurological, autoimmune diseases, when rapid removal of antibodies is necessary; in multiple sclerosis when there is no effect of glucocorticoids; opticomyelitis, neuropathy, systemic lupus erythematosus, and autoimmune hemolytic anemia [77]. Pathological factors that can be removed by plasmapheresis include autoantibodies, complement products, lipoproteins, immune complexes, cryglobulin, myeloma protein, ADAMTS-13, protein-bound toxins, platelets, and leukocytes [78].

5.2 Application in COVID-19 Treatment

There are two medical terms that can be found in the literature: plasmapheresis and plasma exchange. Plasma exchange is plasmapheresis with a plasma exfusion volume of 70–150% of the circulating blood volume (CBV). Therefore, adjusted for the volume of plasma exfusion, these two terms can be considered synonymous. It should be noted that due to the widespread use of the plasma exchange method [36], we will mainly describe the experience of plasma exchange use for the COVID-19 treatment; however, it must be remembered that the plasmapheresis method is the basis of plasma exchange.

Khamis et al. [79] conducted a small comparative study to assess the effect of therapeutic plasma exchange (TPE) in patients with severe COVID-19 compared with the control group. Authors concluded that there was a lower 14-day (0 versus 35%, $p = 0.033$) and 28-day (0 versus 35%, $p = 0.033$) mortality after TPE compared to the control group. However, all-cause mortality was only slightly lower in the TPE group than in the non-plasmapheresis group (9.1% vs. 45%; $p = 0.055$). Laboratory and ventilation parameters also improved after therapeutic plasma exchange.

Shi et al. demonstrated the successful use of PE for the treatment of severe COVID-19 patient. PE led to an improvement in the patient's condition, no further episodes of diarrhea, return of an appetite, improvement in CT, and an increase in PaO2/FiO2 [78]. Keith et al. used quadruple plasma exchange, after which the patient's general condition and lung radiographic picture improved [80]. Adeli et al. [81] and Ma et al. [82] described a series of clinical cases of successful plasma exchange method application. As a result, there was a recovery of patients, a decrease in the titer of anti-phospholipid antibodies and inflammatory markers, followed by withdrawal from mechanical ventilation [82], and an increase in the survival of severe COVID-19 patients [81]. Duong-Quy et al. give an example of the successful use of therapeutic apheresis in a pregnant woman at 17 weeks gestation admitted to the intensive care unit with severe COVID-19. The patient received 3 cycles of plasma exchange, and as a result, her condition improved and the level of pro-inflammation cytokines normalized. Authors says that plasma exchange therapy may be very beneficial in situations when other therapies are failing. The possibility of using plasma exchange in pregnant is possible because of the high level of the procedure's safety [83]. The plasmapheresis can also be used for the combined therapy of COVID-19 complications. For example, successful experience in the treatment of COVID-19–associated meningoencephalitis in ventilated patients was demonstrated [84].

Patidar et al. tried to explore the main advantages and disadvantages of PE treatment. There are a lot of data confirming the effectiveness of plasma exchange in sepsis, and it is clear that this method can be useful during the initial stages of the disease to prevent the syndrome of multiple organ failure. However, the clinical evidence for its effectiveness in COVID-19 is extremely low. In addition, the method has no absolute contraindications that is why there is a widespread use of plasma exchange therapy [85].

It is not always possible distinguish which treatment led to a particular result. That is why various comparative studies are required. For example, Luo et al. [86] tried to compare the effects of tocilizumab therapy and plasma exchange. After plasma exchange, in contrast to tocilizumab, there was a pronounced decrease in the levels of CRP, IL-6, reconstitution of the number of lymphocytes, and return of PTI to the initial level. Thus, the authors concluded that plasma exchange was more preferable in patients with severe COVID-19.

Nowadays, there are a lot of data on the combination of various EA techniques to achieve the best results. Yang et al. noted that plasmapheresis could be performed both as a separate procedure and in combination with other methods of blood purification, including immunoadsorption, two-volume plasma filtration, continuous plasma filtration and adsorption, multifiltration systems, continuous veno-venous hemofiltration, and slow continuous ultrafiltration [11].

6 Selective Plasma Filtration

6.1 Overview of the Method and Application in Clinical Practice

Selective plasma filtration (SPF) is a semi-selective extracorporeal hemocorrection method from the group of therapeutic apheresis membrane technologies [36]. This method is based on the principle of water molecules and substances dissolved in it being transferred through a semi-impermeable membrane [87]. The main driving force in this case is the pressure gradient. It can be useful for removing various medium- and low-molecular-weight components (cytokines or immunoglobulin group G [87], bilirubin, bile acids, urea [88]), the size of which is approximately equal to the size of an albumin molecule, from the blood, while maintaining bigger components [36] (immunoglobulins M, coagulation factors and fibrinogen [89]).

Special devices, which are called plasma fractionators, are used for the SPF procedure. The most popular fractionators today are Evaclio M (Kawasumi Laboratories Inc., Japan) [90]. It noteworthy, that until 2005, this type of plasma fractionators were called Evacure, and they were used exclusively in Japan. Later, SPF method and plasma separators became widely used all over the world, and from that on have been produced under the trade name Evaclio [88]. Separators are divided into different types depending on the pore sizes and each separator has its own level of selectivity towards certain molecules. The marker molecule for SPF is the albumin molecule (66 kDa) [90]. A simplified scheme of plasma filtration is shown in Fig. 2.

The main feature of SPF is the need to restore a plasma volume equal to the removed blood filtrate (fresh frozen plasma or albumin are used). Due to the structural features of the filter, all the necessary coagulation factors remain in the blood stream, so there is no need to add them [87]. Thus, the main advantages of SPF are a large extraction volume (up to 10 l) and minimal protein loss. Depending on the goals and objectives of the therapy, filters with different pore diameters can be selected [91]. The main disadvantage of the procedure is the semi-selectivity of the method, since only the pore size can be controlled [90].

Clinical indications for the SPF procedure on EVACLIO are sepsis, liver failure, rhabdomyolysis, multiple myeloma (Bence-Jones), metabolic syndrome, and focal segmental glomerulosclerosis [23, 92]. The ability to remove IgG using the SPF allows the use of EC-4A fractionators for various immunological disorders. The use of SPF is also effective for the treatment of autoimmune blistering skin disorder and thrombocytopenia [87]. The experience of using SPF in transplantation as a pre-transplantation preparation for AB0-incompatible donor and recipient has also been described [93]. Nakamoto et al. give examples of the successful use of SPF as part of the complex therapy of autoimmune conditions and kidney diseases [94]. Nakae et al. demonstrated the possibility of using the SPF method for the complex treatment of thrombocytopenia [95].

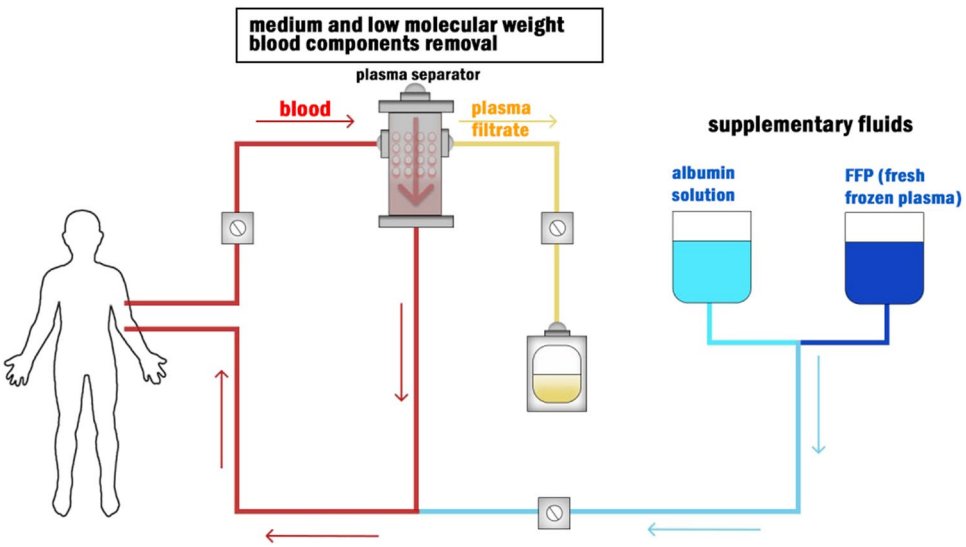

Fig. 2 A simplified scheme of selective plasma filtration. The arrows indicate the direction of a blood flow. Blood from a patient goes through the plasma separator where medium and low-weight molecules are removed from the bloodstream according to the diameter of the pores. After the procedure, the amount of fresh frozen plasma or albumin solutions equal to the amount of filtrate that had been withdrawn is added. Blood with the supplementary fluids and without the removed molecules is returned to the patient

Table 1 Comparison of different methods of extracorporeal apheresis in COVID-19 treatment: brief description, main advantages and disadvantages, possible effect

Method (device name)	Brief description	Advantages/disadvantages	Application in COVID-19 therapy	References
1. Selective plasma filtration (Evaclio)	Removes components from the blood of medium to low molecular weight; the size of the molecules is approximately equal to the size of an albumin molecule. Larger components (for example coagulation factors) remain in blood. The pore size allows controlling the selectivity of the method [36]	- High-molecular compounds, such as coagulation factors and IgM, do not pass through the pores of the filter; - Large volume of plasma passing through the column; - "Protein-preserving" procedure — minimal loss of albumin [90]	Removes cytokines from plasma due to their small molecular weight: they pass through the pores of the filter [11] Can be performed on patients with macrophage activation syndrome, the development of DIC, and thrombotic microangiopathy [9] Effect on patients with severe COVID-19: temperature normalization, a decrease in CRP levels, a decrease in liver enzymes (ALT and AST), and the absence of a clinically significant increase in creatinine levels [97]	Molochkov AV, Terpigorev SA, Belousova EA, Vatazin AV, Dreval AV, Zulkarnaev AB, Karateev DE, Kildyushevsky AV, Kotov SV, Kulikov DA, Likhvantsev VV, Ovezov AM, Ogneva EYu, Smirnova EV, Faenko AP, Filippovskaya ZhS, Fomin AM (2020) Features Of Complex Treatment Of Patients With New Coronavirus Infection (Covid-19): Methodological Recommendations For The Management Of In-Site Patients. Almanac of Clinical Medicine 48: 91–142. https://doi.org/10.18786/2072-0505-2020-48-041 Samoylov AS, Udalov YuD, Kruglyakov NM, Terekhov DA, Bazhanov GI, Ochkin SS (2020) A Clinical Case of Successful Application of a New Treatment Method for Severe COVID-19. Journal of Clinical Practice 11(2):93–100. https://doi.org/10.17816/clinpract34529 Yang X–H, Ren-Hua S, Ming-Yan Z, Er-Zhen C, Jiao L, Hong-Liang W, Rong-Li Y, De-Chang C (2020) Expert recommendations on blood purification treatment protocol for patients with severe COVID-19. Chronic Diseases and Translational Medicine 2/9 https://doi.org/10.1016/j.cdtm.2020.04.002 Avetisyan EA, Merkulova IA, Pevsner DV, Donskikh VV, Pokrovskiy SN (2020) Combined extracorporeal blood purification by means of cytokine sorption and selective plasma exchange in patients with severe COVID-19 — clinical case series, from Russia. Jafron Oversea clinical cases collection

Table 1 (continued)

Method (device name)	Brief description	Advantages/disadvantages	Application in COVID-19 therapy	References
2. Hemoadsorption (CytoSorb, Jafron, Eferon, Separah)	The cartridges contain biocompatible polystyrene-divinylbenzene polymer particles that adsorb medium molecular weight molecules using a combination of pore size and hydrophobic interactions Remove a wide range of molecules from blood: cytokines, bilirubin, myoglobin, exotoxins, and medicinal substances [100]	- Reduce excessive levels of inflammatory mediators of severe COVID-19 symptoms [51–54]; - Do not affect the electrolyte balance; - Do not remove immunoglobulins, coagulation factors [101] - However, it is important to remember about drugs elimination	Cytosorb (Cytosorbents Inc, Monmouth Junction, NJ) Removes cytokines in critically ill COVID-19 patients with suspected development of generalized inflammation and shock [55] The treatment resulted in a decrease of key pro- inflammatory cytokines, and improvement in the general condition of patients [44, 51–54, 58] CytoSorb is significantly more expensive than HA380 [79], but it is approved for a 24 h long use [68]	Friesecke S, Stecher SS, Gross S, Felix SB, Nierhaus A. (2017) Extracorporeal cytokine elimination as rescue therapy in refractory septic shock: a prospective single-center study. J Artif Organs 20 (3):252–259. https://doi.org/10.1007/s10047-017-0967-4 Kogelmann K, Jarczak D, Scheller M, Druner M (2017) Hemoadsorption by CytoSorb in septic patients: a case series. Crit Care 21 (1):74. https://doi.org/10.1186/s13054-017-1662-9 Schädler D, Pausch C, Heise D, Meier-Hellmann A, Brederlau J, Weiler N, Marx G, Putensen C, Spies C, Jörres A, et al. (2017) The effect of a novel extracorporeal cytokine hemoadsorption device on IL-6 elimination in septic patients:a randomized controlled trial. PLoS One 12 (10):e0187015. https://doi.org/10.1371/journal.pone.0187015 Hawchar F, Laszlo I, Oveges N, Trasy D, Ondrik Z, Molnar Z (2019) Extracorporeal cytokine adsorption in septic shock: a proof of concept randomized, controlled pilot study. J Crit Care 49:172–178. https://doi.org/10.1016/j.jcrc.2018.11.003 Stockmann H, Keller T, Büttner S, Jörres A, Kindgen-Milles D, Kunz JV, Leebmann J, Spies C, Träger K, Treskatsch S, Uhrig A, Willam C, Enghard P, Slowinski T (2020) CytoResc Trial Investigators. CytoResc—"CytoSorb" Rescue for critically ill patients undergoing the COVID-19 Cytokine Storm: A structured summary of a study protocol for a randomized controlled trial. Trials 21(1):577 https://doi.org/10.1186/s13063-020-04,501-0
			HA 330 (Jafron, Biomedical Co, China) Due to the macroporous structure and high specific surface area removes target molecules from the bloodstream [11]. Two comparative studies demonstrated a decrease in the pateints' mortality, compared with the control group [51, 62] When used in the early stages of the disease may have a beneficial effect on improving the patient's condition and decreasing mortality [62]	Yang X–H, Ren-Hua S, Ming-Yan Z, Er-Zhen C, Jiao L, Hong-Liang W, Rong-Li Y, De-Chang C (2020) Expert recommendations on blood purification treatment protocol for patients with severe COVID-19. Chronic Diseases and Translational Medicine 2/9 https://doi.org/10.1016/j.cdtm.2020.04.002 Surasit K, Srisawat N (2022) The Efficacy of Early Additional Hemoperfusion Therapy for Severe COVID-19 Patients: A Prospective Cohort Study. Blood Purif. https://doi.org/10.1159/000521713 Seffer MT, Cottam D, Forni LG, Kielstein JT (2021) Heparin 2.0: A New Approach to the Infection Crisis. Blood Purif. 50: 28–34. https://doi.org/10.1159/000508647
			Seraph-100 Microbind Affinity Blood Filter (Seraph-100; Exthera Medical Corporation, Martinez, CA) Showed a good result in treatment of severe COVID-19 patients. Has the highest selectivity, binds the SARS-CoV 2 pathogen directly [63]	Stephen WO, Oliver JD, Collen J et al. (2020) Treatment for Severe Coronavirus Disease 2019 With the Seraph-100 Microbind Affinity Blood Filter. Crit Care Explor. 2(8): e0180 https://doi.org/10.1097/CCE.0000000000000180
			Efferon CT (Russia) When used in addition to a standard therapy, leads to a statistically significant decrease in IL-6 and ferritin, but did not alter mortality rate [43]	Magomedov M, Kim T, Masolitin S, Yaralian A, Kalinin E, Pisarev V (2021) Hemoperfusion with the Efferon CT extracorporeal adsorbers containing mesoporous styrene–divinylbenzene copolymer (SDC) in patients with severe COVID-19. Critical Care 25(1): P041

Table 1 (continued)

Method (device name)	Brief description	Advantages/disadvantages	Application in COVID-19 therapy	References
3. Plasmapheresis	Removes autoantibodies, complement products, lipoproteins, immune complexes, cryoglobulin, myeloma protein, ADAMTS-13, protein-bound toxins, cell platelets and leukocytes from the bloodstream [102]	Advantages: - Cheaper than the selective plasma filtration; - Widely used all over the world; - Part of a therapy of a wide range of diseases - Disadvantages: - Lacks selectivity of the removed plasma components and can result it: hypogammaglobulinemia, coagulopathy, thrombocytopenia, hypotension [72, 74]	Helps to reduce the "cytokine storm" induced by endotheliopathy and microthrombosis associated with COVID-19. Shows the greatest efficiency when used at 2–3 weeks from the disease onset [103, 104] Successful application resulted in recovery of patients and decrease in the levels of pro-inflammatory cytokines [78, 80–82, 84] There was a pronounced decrease in the levels of CRP, IL-6, restoration of the number of lymphocytes and return of PTI to the initial level, when compared to the standard monoclonal antibody drug treatment (tocilizumab) [86]	Kaplan AA (2013) Therapeutic plasma exchange: A technical and operational review. J Clin Apher 28:3–10. https://doi.org/10.1002/jca.21257 Brian G, Weinshenker MD, Peter C. O'Brien PhD,Tanya M. Petterson MSc,John H. Noseworthy MD,Claudia F. Lucchinetti MD,David W. Dodick MD,Alvaro A. Pineda MD,Lorna N. Stevens RN,Moses Rodriguez MD (2001) A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. Ann Neurol. 46(6):878–86. https://doi.org/10.1002/1531-8249(199,912)46:6%3C878::AID-ANA10%3E3.0.CO;2-Q Mokrzycki MH, Balogun RA (2011) Therapeutic apheresis: A review of complications and recommendations for prevention and management. J Clin Apher. 26:243–248. https://doi.org/10.1002/jca.20303 Wood L, Jacobs P (1986) The effect of serial therapeutic plasmapheresis on platelet count, coagulation factors, plasma immunoglobulin, and complement levels. J Clin Apher. 3:124–8. https://doi.org/10.1002/jca.2920030209 Sonawane S, Kasbekar N, Berns JS (2006) The safety of heparins in end-stage renal disease. Semin Dial. 19:305–310. https://doi.org/10.1111/j.1525-139X.2006.00177.x Keith P, Day M, Choe C, Perkins L, Moyer L, Hays E, et al. (2020) The successful use of therapeutic plasma exchange for severe COVID-19 acute respiratory distress syndrome with multiple organ failure. SAGE open medical case reports. 10.1177%2F2050313X20933473 Shi H, Zhou C, He P, Huang S, Duan Y, Wang X, et al. (2020) Successful treatment with plasma exchange followed by intravenous immunoglobulin in a critically ill patient with COVID-19. Int J Antimicrob Agents 2020:105,974. https://doi.org/10.1016/j.ijantimicag.2020.105974

6.2 Application of SPF in COVID-19 Treatment

This method resembles the plasmapheresis method; however, in the case of SPF, it is possible to select the appropriate filter pore size, thereby controlling selectivity [90]. However, there are not much data on the use of this method for the COVID-19 treatment. Samoylov et al. proposed introducing SPF, using Evaclio 2C20 plasma fractionator to treat patients with severe COVID-19. According to the author, this would effectively remove inflammatory mediators circulating in blood, while almost completely preserving large protein molecules, such as immune globulins and coagulation factors [96]. Avetisyan et al. reported a successful use of SPF as a part of a complex therapy of a patient with a severe form of COVD-19. Selective plasma filtration was carried out using Evaclio 2C separator. The results of the procedure were temperature normalization, a decrease of CRP levels more than in a half, a decrease in liver enzymes (ALT and AST), and an absence of a clinically significant increase in creatinine levels [97].

Avetisyan et al. did a comparative study of hemoperfusion and SPF methods in the context of their use for COVID-19 treatment. The research indicated that SPF was more beneficial for patients with hepatic and renal dysfunction, signs of multiple organ failure. It was noted that the selectivity of this method made it possible to remove predominantly hydrophilic molecules with a molecular weight of less than 65 kDa. The total loss of albumin in that case was 30% due to the use of an appropriate filter size [97].

Selective plasma filtration may also be part of a combination of EA methods used to treat COVID-19. For example, Lin et al. [98] described a clinical case when high-volume hemofiltration and the subsequent performance of three plasma filtration procedures were used. The authors

described a significant improvement of patient's condition after plasma filtration. Zashezova et al. [99] demonstrated a successful application of a combination of cytokine sorption using an HA330 absorber (Jafron) and selective plasma filtration using an Evaclio 2C plasma filter. The combination treatment resulted in the temperature normalization and positive dynamics of laboratory parameters, primarily CRP and IL-6.

A brief description and application of EA methods for COVID-19 treatment are presented in Table 1.

7 Conclusion

Methods of extracorporeal apheresis are becoming an important addition to combination therapy for COVID-19. EA methods demonstrate the greatest efficiency for patients with severe forms of COVID-19, when there is a threat of the cytokine storm development. Among all methods of apheresis in COVID-19 treatment, the methods of hemoadsorption, plasma filtration, and plasma exchange are most widely used.

Based on the available published data, it can be concluded that hemoadsorption using Cytosorb (Cytosorbents Inc, Monmouth Junction, NJ) and HA 330 (Jafron, Biomedical Co, China) is the most widely utilized method. In view of a larger evidence-based data for CyroSorb and the possibility of its use in patients with septic shock, CytoSorb is more preferable to remove mediators responsible for the development of a cytokine storm from the circulating blood of patients. However, as shown by comparative studies, HA330 can also be used for treatment of severe forms of COVID-19, significantly reducing mortality compared to control groups. Less information can be found regarding Seraph-100 Microbind Affinity Blood Filter columns (Seraph-100; Exthera Medical Corporation, Martinez, CA) and Efferon TsT (Russia).

A large number of clinical cases are also available, describing the successful use of a plasma exchange method for treatment of patients with severe forms of COVID-19. Selective plasma filtration method, despite being rarely mentioned in the literature, also showed good results as part of a combination treatment of severe forms of COVID-19.

Perhaps, due to a lesser severity of symptoms caused by a new SARS-CoV-2 variant Omicron (B.1.1.529 lineage) and fewer admissions to hospitals, especially to the intensive care unit, there were no current studies available, describing the use of therapeutic apheresis for the treatment of Omicron variant, but only focused on Alpha, Beta, Gamma, and Delta variants.

As more people start to experience the so called "post-COVID syndrome" or "long-COVID", more studies focus on the application of therapeutic apheresis methods, especially sorption methods, in the treatment of "post-COVID syndrome".

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Declarations

Conflict of Interest The authors declare no competing interests.

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