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Plasma exchange and COVID 19

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1. Introduction

Coronaviruses (CoVs) were first described in the 1960s as a broad subfamily of RNA viruses affecting both human and animals. In humans, infections caused by members of this family primarily involve respiratory and/or gastrointestinal system, with a wide range of clinical manifestations [1]. Since the beginning of the 21st century, there have emerged two highly pathogenic and, at times, fatal in humans, members of the corona-family: Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) that was the etiological agent of a severe respiratory endemic disease in China during 2002–2003 and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) that was responsible for a similar outbreak in the Middle East during 2012-today [2].

By November 2019 a novel viral infection appeared in Wuhan China, caused by a new variant of coronaviruses. The infection was first reported on December 31, 2019, and has since spread rapidly worldwide, leading the World Health Organization (WHO) to officially declare it as a pandemic disease on March 11, 2020 [3]. The outbreak of the novel coronavirus disease had enormous impact on global health and created panic, forcing the medical community to search rapidly for answers. As of May 29, 2022, more than 525 million infections of COVID-19 have been reported, including more than 6.28 million deaths globally [4]. These staggering numbers prove undoubtedly that the COVID-19 pandemic constitutes the toughest challenge of the century to mankind, rendering the struggle for effective therapy a global necessity of high priority for all healthcare systems and physicians. Disease is caused by a new betacoronavirus variant called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), classified to the subfamily of Orthocoronavirinae. It is a single-stranded, positive-sense, enveloped RNA virus, spherical in shape with a diameter 80–220 nm and a crown-like appearance under the microscope [5]. A common characteristic of RNA viruses is that while adapting to their new human hosts, they are prone to genetic evolution, resulting in development of mutations over time that may differ from ancestral strains. New mutations can potentially change infectiousness and virulence, as well as the virus' ability to evade adaptive immune responses developed by the host [6]. Since December 2020, the World Health Organization (WHO) decided to identify in Greek letters all emerging mutations of SARS-CoV-2 and define as a variant of concern (VOC) those variants exhibiting certain features, such as increased transmissibility or virulence, change in clinical presentation and ability to overcome the body's immune response or decrease effectiveness of current therapeutic strategies [7]. On November 2021, the Omicron variant was designated as a VOC and, since then, has rapidly spread and finally dominated across the world. The Omicron mutation is more transmissible than other variants and not susceptible to certain anti-SARS-CoV-2 antibodies used at the time for treatment and prevention of the viral infection [8].

All individuals are at risk for COVID-19 infection and severe disease. However, it was evident from the outbreak of the pandemic, that the most important risk factor for serious illness was the patient's increasing age (especially $\geq$ 60 years). In addition, other comorbid medical conditions, such as cardiovascular or chronic respiratory disease, diabetes mellitus, obesity or other immunocompromised conditions lead to a high probability of a serious outcome in COVID-19 infection [9]. The median estimated incubation period of the virus infection is 4–5 days from the time of exposure and clinical manifestations vary, ranging from asymptomatic, or mild flu-like symptoms to severe or fulminant and quite often fatal disease. Most analyses of the coronavirus clinical spectrum report a rate of about 81 % for mild disease (defined as no respiratory involvement or mild pneumonia), 14 % for severe (defined as respiratory involvement with dyspnea, oxygen saturation $<$ 93 % and/or lung infiltrations $>$ 50 %) and 5 % for critical illness, which may require Intensive Care Unit (ICU) admission [10,11]. When serious life-threatening disease occurs, the risk of mortality is high and attributed mainly to an excessive immune response typically called the Cytokine Storm or Release Syndrome (CSS), that clinically may result in Acute Respiratory Distress Syndrome (ARDS), sepsis and/or Multiple Organ Failure (MOF). Cytokine Storm Syndrome is a condition of uncontrolled systemic hyper-inflammation caused by cytokine excess leading to multi-organ failure and frequently even death [12]. The phenomenon is not unique to COVID-19 nor is it observed for the first time. It is an umbrella term that includes pathogenetic pathways of host maladaptive response to infection, observed and described nearly two decades before [13]. It was initially recognized in the process of hematopoietic stem cell transplantation as an acute graft-versus-host disease and, subsequently, researchers revealed that it may also occur in various diseases [14]. Since the recognition of the syndrome, research on autoimmune disorders, malignancies, sepsis syndrome and specific iatrogenic causes established the concept that an excessive immune response can seriously damage the body, leading rapidly to clinical

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deterioration, multi-organ failure, and finally, death. Major progress in understanding pathogenetic mechanisms of the Cytokine Storm has been made by studying Hemophagocytic Lymphohistiocytosis (HLH) Familial or Secondary by specific viral infections, typical diseases accompanied by a deficiency in cytotoxic cell function [15]. Research has yet to reveal whether the syndrome results from abnormalities in innate or adaptive immunity, although there are clues that suggest problems in both branches [12]. This overly systemic reactive response is a condition of uncontrolled systemic hyper-inflammation caused by cytokine excess. It involves multiple inciting events mediated by complex interactions of cytokine storm, inflammation, endothelial dysfunction and pathologic coagulation system [16,17]. However, evidence demonstrates, that in the development of Cytokine Storm Syndrome a variety of cytokines are involved, including interleukin 1 (IL-1) family, IL-6, IL-8, IL-10, TNF-α and interferon (IFN-γ). The key pathogenic substance appears to differ depending on the underlying disease. For example, IFN-γ plays the key role in Primary HLH, IL-1β is the key cytokine in Systemic Juvenile Idiopathic Arthritis, whereas in sepsis multiple factors are involved [16]. Therefore, even if the clinical symptoms caused by Cytokine Storm Syndrome exhibit a common pattern, treatment must be individualized. Soon after the onset of the pandemic, it became apparent that critically ill COVID-19 patients died mostly because of the pathological inflammatory response following infection rather than infection itself. This group of patients exhibited elevated levels of a wide range of cytokines, including multiple interleukins (IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10), granulocyte colony-stimulating factor, monocyte chemoattractant protein-1, interferon γ-induced protein 10, tumor necrosis factor-α, macrophage inflammatory protein-1 α and a variety of chemokines [18]. This hyperinflammatory condition can induce complement activation, endothelial damage, increased vascular permeability and pathological activation of the coagulation system [19]. Many researchers tried to identify certain biomarkers to differentiate, early in the course of COVID-19 infection, between patients with or without severe disease. According to systematic revisions high levels of C-Reactive protein (CRP), Lactate Dehydrogenase (LDH) and D-dimer, along with decreased T-lymphocyte cells may help physicians predict the progression of coronavirus disease to a critical illness [20]. In addition, other trials reveal interleukins and in particular high levels of IL-6, IL-8 and IL-10 to be independent risk factors for the severity of COVID-19 pneumonia and correlate with disease progression, ARDS and mortality [21,22]. Similar phenomena were described during the previous SARS and MERS epidemics, when respiratory involvement correlated with significant high levels of serum cytokines [23,24].

Despite the fact that the international medical and political community came together against a threatening enemy and the substantial progress that has been made to better understanding of the pathophysiology of SARS-CoV-2, COVID-19 disease continues to concern mankind having enormous impact of every aspect on everyday living. Worldwide political authorities primarily had to take public health measures, in an effort to prevent and contain the infection from spreading. Subsequently, there was a significant struggle to develop, with unprecedented speed, a preventive anti-viral vaccine. When this happened, the global community rallied on performing a robust vaccination effort worldwide. During this effort and to date, direct treatment for the virus itself was certainly desired and various therapeutic agents were researched. Nowadays, there are a number of anti-viral agents on the market (e.g. molnupiravir, paxlovid, remdesivir) showing some level of effectiveness, as well as anti-SARS-CoV-2 monoclonal antibodies (e.g. bamlanivimab/etesevimab, casirivimab/imdevimab). Nevertheless, currently there is still no specific effective treatment against COVID-19 disease. In addition, due to the above mentioned characteristics of severe COVID-19 infection, coronavirus disease should be defined, understood and consequently managed as a systemic disease. Therefore in severe COVID-19 cases it is essential, in addition to targeting virus activity with existing antiviral agents, to effectively modulate the innate and restore the adaptive immune response, breaking the cycle of coronavirus infection. Consequently, besides antiviral agents and supportive care, management of severe COVID-19 patients might also include efforts to timely control CSS in order to prevent disease deterioration and reduce mortality [18,25]. In this regard, a variety of therapeutic options were tested and are still available, such as anti-inflammatory drugs (e.g. dexamethasone), immunomodulators agents (e.g. baricitinib, tocilizumab) and cytokine antagonists [25,26]. Most of these potential complementary therapeutic options often need time (days or weeks), in order to remove pro-inflammatory factors and exhibit their beneficial action which, in critically ill patients, is always difficult to obtain. Blood purification methods and notably therapeutic plasma exchange have been included as possible therapeutic options targeting this systemic hyperinflammation status, since they are unique treatment approaches that act instantly at multiple levels of this cascade phenomenon [27].

Therapeutic Plasma Exchange, is an extracorporeal blood purification method designed for the removal of large-molecular weight substances (MW > 15000 Da), reversing pathological processes related to their presence [28]. It's defined as "a therapeutic procedure in which the blood of the patient is passed through a medical device which separates out plasma from other blood components. Plasma is removed and replaced with a replacement solution potentially a colloid solution (e.g. human albumin and/or plasma) or a combination of crystalloid/colloid" [29]. The method was developed by Dr Dau in the 1970s and was first used to control severe hyperviscosity related to multiple myeloma. Nowadays, it is often used as a primary or adjunct therapy to treat severe and critical diseases mediated by pathogenic antibodies, immune complexes, cryoglobulins, paraproteins, endotoxins, lipoproteins and inflammatory mediators like cytokines. Consequently, TPE is usually applied to manage critical diseases such as Thrombotic Microangiopathies, Thrombotic Thrombocytopenic Purpura, Guillain-Barre Syndrome, Myasthenia Gravis, Glomerulonephritis and others [29]. The American Society for Apheresis (ASFA) regularly publishes updated evidence-based guidelines, the most recent edition in 2019, supporting indications for applying TPE [29]. These guidelines contain all the diseases for which there are adequate evidence in the literature to support or refute the use of apheresis procedures. For plasma exchange to be a rational treatment of choice, at least one of the three following conditions concerning the substance to be removed should be fulfilled: sufficiently large substance mostly dissolved in the intravascular compartment, with a comparatively prolonged half-life and acutely toxic and/or resistant to conventional therapy [28]. TPE is one of the most common therapeutic apheresis procedures performed globally [30] by either centrifugation or membrane filtration methods. The type of anticoagulant selected to achieve the extracorporeal circuit depends on the apheresis device, with citrate solutions most commonly used. According to numerous studies, exchange of 1–1.5-plasma volume is considered sufficient to achieve adequate substance removal without high risk for procedural complications. Most frequently the replacement fluids used for the method are 5 % albumin, normal saline, a combination of the above or Fresh Frozen Plasma (FFP). The time interval between sessions and the number of sessions required are generally based on the underlying disease and its clinical course. Most of the procedure's adverse effects are mild and easily resolved, rendering the method relatively safe [31].

In the course of using TPE, the procedure was applied in diseases with similarities to COVID-19 infection, such as sepsis due to various causes, influenza infection and Secondary Hemophagocytic Lymphohistiocytosis (HLH). Therapeutic plasma exchange has been used as an alternative treatment in severe sepsis for several decades, with conflicting results. Although there is no clear evidence to recommend plasma exchange in severe sepsis, there are a few studies supporting the role of TPE in this entity, suggesting improvement in hemodynamic stability and coagulation disbalance in septic patients receiving the treatment [32–34]. Based on this growing evidence and currently available clinical data, the American Society for Apheresis (ASFA) in the

eight special issue offers plasma exchange a category III, 2B recommendation for sepsis with multiple organ failure (MOF). This is an overall weak recommendation, meaning that currently the peer-reviewed evidence does not establish the optimum role of plasma exchange in these patients [29]. Therefore, decision-making for patients with infection and MOF should be individualized and it remains a challenge for every clinician to identify those patients most likely to benefit from the method and apply it on a case-to-case basis as an adjunct therapy. Furthermore, there are several studies that support the helpful role of therapeutic plasma exchange in severe cases of influenza infection [35,36]. For example, during the H1N1 influenza pandemic, TPE was performed as a rescue therapy on three pediatric patients with ARDS on mechanical ventilation and hemodynamic instability. All of them received three TPE sessions on consecutive days, with no reported side effects and after that dramatically improved the organ dysfunction score and survived with good functional recovery [35]. Finally, Hemophagocytic Lymphohistiocytosis constitutes a typical disease accompanied by an hypercytokinemic status, characterized by excessive elaboration of IL-2, IL-7, TNF and macrophage inflammatory protein 1-alpha, at times fatal. Although HLH is not included in the indications for applying TPE, a few studies have suggested a promising role for the method [37–39].

2. Possible mechanisms of TPE beneficial action in severe COVID-19 patients

The scientific community eagerly awaits the discovery of effective and specific antiviruses agents. Until then, a variety of immunosuppressive measures on the cytokine storm syndrome and coagulopathy which accompany serious COVID-19 cases, are under investigation, in order to reduce the likelihood of progressive organ damage. Although currently used anti-inflammatory and immunomodulator agents have shown some therapeutic benefit, complementary approaches for critically ill COVID-19 patients with ARDS and MOF are needed in order to save more lives.

Despite the lack of solid evidence for the usefulness of plasma exchange in severe infectious conditions including sepsis, practical experience with the application of the method in various clinical diseases provides clues for using TPE as an alternative treatment in serious covid-19 cases. Several researchers considered TPE not only as a rescue therapy, but also as an alternative treatment option highly justified to apply earlier in the clinical course of serious coronavirus cases with signs of rapid deterioration and features of Cytokine storm Syndrome [40]. As soon as this hyperinflammation status in severe coronavirus infections was understood, it became apparent that removing large amounts of cytokines and blocking the development of CSS before substantial endothelial or end-organ damage occurred, were potentially beneficial therapeutic options. Therapeutic plasma exchange is a procedure that can reduce plasma components, such as antibodies, proteins and inflammatory mediators, and thus act as an adjunctive therapy option for the treatment of severe COVID-19 infections. In this regard, there are various strengths that could support the rational of TPE being a non-pharmacological treatment strategy for more effective management of critically ill coronavirus patients, although to date few high-quality studies have evaluated the role of plasma exchange in severe COVID-19 management.

At least four mechanisms of TPE action support the role of the method in modifying the course and outcome of coronavirus disease. First and foremost, plasma exchange has a direct clinical effect, through direct removal of inflammatory cytokines, especially in rapidly deteriorating cases of CSS, attenuating the phenomenon thus giving the required time for other possible therapeutic approaches to act. Therapeutic plasma exchange has a cut-off of 1.000.000 Da and thus inflammatory mediators such as CRP (120.000 Da), ferritin (474.000 Da), LDH (144.000 Da), D-dimers (180.000 Da) and IL-6 (21.000 Da), should be removed. In addition, TPE is a non-selective method of removing cytokines, which seems to be a more appropriate treatment option for a complex phenomenon as CSS involving various inflammatory factors [41]. Finally, mass removal of cytokines could prevent or reduce adverse effects on immune cells, reversing the observed immune paralysis and, by that, increasing susceptibility to co-administered immunosuppressant agents [26]. The above application of TPE could attenuate the cytokine release syndrome and stabilize the endothelial membrane. A second mechanism proposes that, simultaneously with cytokine removal, a decrease in levels of antifibrinolytic mediators, fibrin degradation products, toxic free radicals and other viscous substances, is observed, helping the organism adjust aberrations in the coagulation pathway [42,43]. Furthermore, part of the viral load is eliminated, since the viral particles' diameter is 60–140 nm, large enough to be removed, which theoretically constitutes a third mechanism for beneficial action of the method towards controlling the infection with severe lung injury [44–46]. Finally, it has been postulated that using fresh frozen plasma as replacement fluid in the application of TPE in COVID-19 patients may replenish consumed protective factors (such as ADAMTS-13, protein C and angiopoietin-1). Through this forth mechanism plasma exchange could help maintain the microcirculation and prevent vascular leakage [47,48]. Furthermore, enhancement of the positive effects could be gained by using immune plasma containing antibodies that can neutralize the pathogen's infectivity either by direct binding or through other antibody-mediated pathways (e.g. complement activation, cellular cytotoxicity) [49]. The effectiveness of using convalescent plasma in treatment of viral infections in general was first noted during the outbreak of Spanish influenza (1918–20) and continued to be considered as a possible preventive and/or therapeutic approach against various other infectious diseases that emerged over the years (e.g. West Africa Ebola, West Nile, MERS-CoV, SARS-CoV-1) [50].

The corresponding experience of TPE application in diseases similar to COVID-19 strengthens the possible beneficial role of the method in the management of severe coronavirus cases. Severe COVID-19 infection constitutes a cause of sepsis and MOF and, therefore, based on the similarities in pathophysiology and clinical course TPE may be considered as a supportive adjunct therapy just like in other septic patients. Furthermore, COVID-19 is a viral disease, more similar to influenza infection, both of which are characterized by acute lung injury followed by multiple organ failure. As mentioned above, application of TPE in severe cases of influenza proved to be beneficial [35,36]. Additionally, a number of neurologic complications have been associated with severe COVID-19 infection [51], including Guillain Barre syndrome and Myasthenia Gravis [52,53]. For these two diseases ASFA's most recent guidelines accepts plasma exchange as fist-line therapy either alone or in combination with other treatment modalities (indication category I) [29]. Finally, severe coronavirus patients may exhibit a number of complex and varied coagulation abnormalities that create a general hypercoagulable state. The pathogenetic mechanisms of this hyperviscosity status and its role in the patient's outcome is not completely understood. Nonetheless, plasma exchange has been suggested as a potential option in the management of COVID-19 related hyperviscosity [42,54].

3. Concerns and clinical issues for the use of TPE in severe COVID 19 patients

As opposed to advantages for using therapeutic plasma exchange in severe COVID-19 patients there were also several clinical issues that aroused great concern. A primary clinical consideration, from the beginning of the hypothetical use of plasma exchange as a novel therapeutic option against coronavirus, was the possibility of reducing protective anti-viral immune factors. Therefore, immediately after the first publications on the prospect of using the method, there were a few researchers that pointed out the risk of the removal of already formulated SARS-Cov-2-specific IgG and IgA antibodies and their protective action. According to Stahl et al., these antibodies were detected in the

waste plasma bag, when they performed a TPE session as a rescue therapy on a septic COVID-19 patient. Additionally, they found out that the titer of the patients circulating antibodies was also reduced during plasma exchange. This letter to the editor concludes that TPE might be an optional therapeutic approach, only if the method uses plasma collected from convalescent COVID-19 survivors (CCP) that carries specific neutralizing antibodies as the substitution fluid. In this way we secure the fundamental principal of all physicians from the Hippocratic Oath: FIRST DO NO HARM [46]. Due to the limited supply of CCP, it is proposed to use this enriched plasma if available at the end of the procedure [55]. Other plasma proteins that are being removed via plasma exchange are anti-inflammatory mediators, such as complement, that protect against secondary infections [56]. Additionally, the efficacy of TPE to attenuate CSS has been questioned due to the marked short half-time of most cytokines involved (approximately 5 min) along with their continuous production [57]. As long as cytokine production continues, within minutes after the completion of a TPE session they are reactivated. A way to overcome this limitation is to combine TPE with agents blocking cytokine action (e.g., IL-6 receptor antagonists). Thus, we ensure prolonged blocking of action as well as intermittent removal of cytokines with possible better outcomes.

Another concern with the use of TPE is that side effects that may occur. As for all interventions that require catheterization, plasma exchange poses risk of bleeding or catheter infection. In addition, it can cause electrolyte imbalances or anaphylactic shock. The most common electrolyte abnormalities are hypocalcemia and hypokalemia, whose extent depends on the type of anti-coagulating agents or replacement fluid used. Occasionally, unpredicted shock may be induced due to the use of blood materials. Another problem that may arise with the application of plasma exchange in severe COVID-19 patients is that they are usually already in hypotensive shock. All these complications or any other technical issue can be prevented or avoided, if TPE is applied early, when blood pressure is maintained, in experienced centers with active involvement of specialized medical staff. There are no absolute contraindications for performing plasma exchange in COVID-19 patients. However, various features should be taken into account in order to distinguish patients who may be at higher risk for TPE complications. For example, these patients with severe hemodynamic instability, coagulopathy or hypocalcemia, unable to tolerate central line placement and allergic to plasma or albumin.

A third critical consideration regarding TPE use is that, as all blood purification methods, it is an expensive, time and resource consuming treatment modality. Performing TPE demands the presence of high technology equipment with expensive supplies and specially trained health workers, which are not available everywhere, especially in rural settings and low- or middle-income countries. It is a procedure that cannot be performed simultaneously on a number of patients, lasts several hours and demands strict protocols for the personal safety of the operators involved and decontamination of equipment involved.

All the above-mentioned advantages and disadvantages for applying TPE in severe coronavirus cases (Table 1) should be assessed and evaluated for each patient individually, in order to identify those patients most likely to benefit from the method and apply it on a case-to-case basis as an adjunct therapy.

Table 1
Strengths of and restrictions for using TPE in severe COVID-19 patients.

Strengths	Considerations
Studies suggesting potential role in CSS	Current studies for TPE in COVID-19 are of low-moderate level of evidence, suggesting a weak recommendation for using the method
Studies suggesting supportive role in sepsis and MOF	Expensive, time and recourse consuming method – not available everywhere
Studies suggesting potential role in influenza	Demands specialized equipment and trained personnel not readily available
Likely effective in early stage to reduce severity and prevent MODS progression	Inability to apply simultaneously to a number of patients – patients must be triaged
No absolute contraindications	Adverse events of TPE (rare but may contribute to hemodynamic instability)
Use as adjunct therapy in combination with other treatment modalities	Removing other therapeutic agents
Direct removal of viral particles	Removing patients neutralizing antibodies
Using FFP as replacement fluid potentially helpful in coagulation abnormalities	Using FFP as replacement fluid may increase risk of complications
Using CCP as replacement fluid towards the end of TPE session provides neutralizing antibodies	Using albumin or normal saline as replacement fluid may increase risk of coagulation abnormalities

TPE: Therapeutic Plasma Exchange, CSS: Cytokine Storm Syndrome, MOF: Multiple Organ Failure, MODS: Multiple Organ Dysfunction Syndrome FFP: Fresh Frozen Plasma, CCP: Covid Convalescent Plasma.

4. Review of the literature

In view of the globally ever-increasing number of critically ill coronavirus infected patients, especially during the first year of the pandemic, physicians all over the world tried many experimental therapeutic options in order to save as many lives as possible. Consequently, after nearly two and a half years of trying to tackle the COVID-pandemic, the world literature contains a number of case reports, case series and a few reviews that investigate the role of TPE in serious COVID-19 infection. It all started with the simple and reasonable hypothesis that in a severe viral infection like COVID-19 disease that may lead to Cytokine Storm Syndrome and Multiple Organ Failure, it is worth considering a method that can eliminate cytokines and viruses by exchanging plasma. Chinese authorities were the first to report success treating COVID-19 seriously infected patients with plasma-related therapies, using either plasma donated from survivors of the illness or blood purification methods [58]. Therefor the first publication using therapeutic plasma exchange in a COVID-19 patient with respiratory failure and anti-phospholipid syndrome comes from China by Ma et al. on 04/2020. In this case report, the researchers describe the effect of 3 TPE sessions on the patient, who after the treatment showed clinical and laboratory improvement, with reducing titers of antiphospholipid antibodies and other inflammatory markers [59]. At the same time in Taiwan, another research group applied plasma exchange in combination with CVVH in a Cytokine Storm-complicated COVID-19 patient. After 3 sessions, the patient presented with clinical, radiographic and laboratory improvement [48]. Almost simultaneously, Keith and colleagues from Lexington Medical Center in Columbia, USA, published an editorial in Critical Care, proposing plasma exchange as a possible novel treatment approach for fulminant COVID-19 [40]. Their group had recently conducted a retrospective single-center observational study concerning TPE in sepsis with Multiple Organ Failure. Their results, although limited, were very encouraging supporting the therapeutic efficacy of adjunct plasma exchange for these patients [60]. Under the existing environment of an outspreading pandemic, they changed their therapeutic approach based on their clinical experience and started to more often utilize TPE earlier in the clinical course of septic shock, rather than as a rescue therapy [40]. One month later they published a case report referring to a COVID-19 patient with respiratory involvement who developed septic shock and MOF. Given the continued clinical deterioration, the patient underwent a session of TPE and showed rapid improvement after. Researchers suggested a potential role of plasma exchange in severe coronavirus infection with MOF [61]. During 2020 there were increasing published data suggesting the usefulness of TPE in severe coronavirus patients, consisting mainly of case reports or case series from clinicians that could afford to use the method in their clinical practice (Table 2). Consequently, by the end of 2020, several case reports and series from different countries were published concerning the use of TPE in COVID-19 patients with respiratory involvement, ARDS and/or CSS and/or shock. Overall, these case studies indicate a

Table 2
Case studies on the effects of TPE in coronavirus disease.

Authors	Publication Date/ Country	Study type	Number of Subjects/Condition	TPE Prescription (number/volume/ replacement fluid)	Clinical outcome
Ma et al	04/2020 China	Case Report	3 CRS (1PE/2CRRT)	3/ND/ND	1died/2 improved
Lin et al	04/2020 Taiwan	Case Report	1 CSS	3/ 35 ml/KgrBW/h/ FFP	Improved
Keith et al	05/2020 USA	Case Report	1 pneumonia + MOF	1 / 4.5 L /FFP	Improved
Adeli et al	05/2020 Iran	Single-group case series	8 respiratory invol.	3–5 /2 L/FFP, albumin	1 died/7 Improved
Luo et al	05/2020 China	Matched case-control series	6 (3TPE/3 tocilizumab)	ND	TPE better
Wang et al	05/2020 China	Case report	1 Respiratory +CRS	3/2 L/ND	Improved
Khamis et al.	06/2020 Oman	Matched case-control series	11 ARDS + pneumonia vs 20 controls	5/BWX(1/13)X(100-Hct)/FFP	TPE better
Dogan et al	07/2020 Turkey	Single-group case series	6 meningoencephalitides	1–5 / ND/albumin	1 died/ 5 improvement
Zhang et al	08/2020 China	Single-group case series	3 respiratory invol	1/3 L/FFP	Improved
Faqihi et al	08/2020 USA /Saudi Arabia	Case report	1 respiratory + CRS	5/1,5XPV/albumin	Improved
Morath et al	08/2020 Germany	Single-group case series	5 respiratory invol.	1–2/3.39 L/FFP	Improved 2died/3 improved
Shi et al.	08/2020 China	Case Report	1 respiratory invol. +diarrhea	4 / 6 L /FFP	Improved
Hua et al.	09/2020 China	Case Report	1 respiratory+ shock	3/3 L/FFP	Improved
Altmayer et al	09/2020 France	Case Report	1 ARDS	4/1,2 L/albumin	Improved
Granger et al	09/2020 USA	Case Report	1 Guillian-Barre	5/ND/ND	Improved
Ragab et al	10/2020 Egypt	Case Report	1 ARDS+CSS	1/1XPV/FFP	Improved
Akkoyunlu et al	12/2020 Turkey	Case Report	1 respiratory	1/ND/FFP	Improved
Fernandez et al	12/2020 Spain	Single-group case series	4 respiratory	2–6/1,2XPV/ Albumin	Improved
Marco et al	02/2021 Italy	Case Report	1 liver transplanted	ND	Improved
De Prost et al	02/2021 France	Single-group case series	4 pneumonia	3–4/ND/FFP	Removed autoantibodies
Krajewski et al	04/2021 Poland	Case Report	1 toxic epidermolysis	5/ND/FFP	Improved
Truong et al	04/2021 USA	Single-group case series	6 Hyperviscosity	2–3/1XPV/FFP	4/6 Improved
Saleh et al.	05/2021 Iran	Case Report	1 Child with Respiratory inv.	4/ND/FFP	Improved
Lemarquis et al.	07/2021 Sweden	Case Report	1 Child with Respiratory inv.	5/ND/ND	Improved
Diaz et al	07/2021 Spain	Case Report	1 Child with MOF	3/1,5XPV/FFP	Improved
Ahmet et al	07/2021 Canada	Case Report	1 Respiratory + cold agglutimin	ND	Improved
Matsushita et al	08/2021 Japan	Single-group case series	5 ARDS	6/2,5–3 L/FFP	2/5 Improved
Zaid et al	10/2021 Morocco	Single-group case series	7 ARDS+CSS	3–5/1,5×30ml XKgrBW/FFP	Improved
Kiprov et al	11/2021 USA	Case Report	1 Long-haul	3/1XPV/albumin	Improved
Hashemian et al	12/2021 Iran	Single-group case series	15 CSS+ Risk of ARDS	ND/40 ml/KgrBW/ Albumin + N/S	Improved cytokines
Hassianiazad et al	12/2021 Iran	Single-group case series	22 Respiratory +CSS	3/30–40 ml/KgrBW/ albumin or FFP	Improved
Laaribi et al	02/2022 Morocco	Case Report	1 CRS respiratory	5/40mlXKgrBW/	Improved
Janikowska et al	02/2022 Germany	Case Report	2 Respiratory (avoid intubation)	5–6/3 L/albumin	1non-intubated/2 survived

ARDS=Acute Respiratory Distress Syndrome CSS = Cytokine Storm Syndrome CRS=Cytokine Release Syndrome MOF = Multiple Organ Failure ND=Non-available Data BW = Body Weight PV = Plasma Volume FFP = Fresh Frozen Plasma N/S = Normal Saline.

beneficial effect of plasma exchange in clinical condition and inflammatory markers, even If the patient number overall is small [62–72]. Another case study demonstrated that plasma exchange was helpful on treating critically ill patients with COVID-19-related autoimmune meningoencephalitis [73]. To the best of our knowledge this was the first case series (overall 6 patients) to present severe COVID-19 patients with nervous system involvement. Four patients regained consciousness and were extubated after an average of 3 TPE sessions, one worsened dramatically after one TPE cycle and died of cardiac arrest and the last one completed 5 TPE sessions and remained in the ICU for complementary infection treatment. Five out of six patients exhibited laboratory improvement, with the most striking reduction observed in serum ferritin levels [73].

At that period, to be published studies comparing plasma exchange to other treatment modalities started. For example, in an article originally written in Chinese by Luo et al., we understand by the abstract available in English, that the beneficial effect of plasma exchange on severe COVID-19 patients with excessive inflammatory reaction was better than administration of tocilizumab [74]. Simultaneously, Khamis et al. published an observational cohort study to evaluate the therapeutic use of plasma exchange in adults with severe COVID-19 infection compared to controls. A total of 31 COVID-19 patients admitted to the Intensive Care Unit (ICU) with ARDS or severe pneumonia were included. 35 % of them (n = 11) received TPE as a mode of treatment and this group was associated with higher extubation rates and a lower mortality rate at 28-days [47]. A similar study with relatively larger number of patients (overall 73) was conducted by Cegolon and colleagues recruiting patients in Iran [75]. They divided COVID-19 patients with respiratory involvement into two groups, a control group receiving standard treatment and a second group additionally receiving 1–5 TPE sessions. The primary end-point was all cause mortality, which appeared to be significantly lower among patients receiving TPE, but there were major differences between the two groups [75].

As research added knowledge in the understanding of the pathophysiology of COVID-19 infection and the clinical experience from patients' individual treatment contributed to more effective management

of severe cases, studies started to report overviews of treatment modalities with a potential beneficial role for severe coronavirus patients. Some of them proposeed plasma exchange as an effective way to remove inflammatory cytokines and improve patients' outcomes. For example, on January 2021 Kim et al. recommended initiation of TPE in COVID-19 patients with signs of respiratory failure requiring mechanical ventilation. In identifying these patients, in addition to clinical deterioration, highly elevated ferritin and/or high-sensitivity cardiac troponin levels were proposed as useful markers. They also pointed out the need of early initiation of the method, with daily or every other day the suggested schedule, as long as there was no particular complication. Discontinuation of TPE was to be considered if the critical clinical condition of patient could be handled by another therapeutic agent. The most preferable TPE technique was the centrifugal method, although filtration was also useful. The recommended prescription was considered as exceeding 1 calculated plasma volume per session, using Fresh Frozen Plasma (FFP) as replacement fluid, ideally convalescent plasma when available. This review concluded by describing TPE as a realistic alternative in the treatment of Cytokine Storm Syndrome associated with COVID-19, with clinical benefits when initiated promptly based on rapid clinical deterioration and high inflammatory parameters of the patient, ideally using convalescent plasma, and always in combination with other effective options [76]. Early initiation of plasma exchange in COVID-19 patients with cytokine release syndrome is recommended in a retrospective matched control study from Pakistan because it was associated with improved overall survival and better time to discharge [77]. In any case, early initiation of TPE should be considered, since waiting until specific parameters or markers of MOF and ARDS are present or reach certain levels may limit the efficacy of the method [60]. Furthermore, the current literature contains a number of case reports and case series that applied TPE between 2 and 20 days from PCR diagnosis of COVID-19 infection and found improvement in different clinical and laboratory parameters (PaO2/Fi02 ratio, extubation rate, CRP, neutrophil/lymphocyte ratio) along with mortality at 14 or 28 days [47,62]. A variety of laboratory parameters and healthcare scoring systems were tested as markers capable of predicting COVID-19 patient outcomes and consequently assist in decision-making for best therapeutic management (Table 3). For example, changes in Pediatric Logistic Organ Dysfunction (PELOD) or Sequential Organ Failure Assessment (SOFA) scores were found to correlate relatively well with patients outcome and consequently used to assess them [78,79].

All of these studies point out the need to conduct Randomized Clinical Trials (RCT) in order to attain relevant clinical evidence supporting this hypothesis. The first published RCT comes from Saudi Arabia by Faqihi et al. aiming to evaluate the efficacy and safety of TPE in serious and/or life-threatening COVID-19 patients. The study was terminated after enrollment of 87 ICU admitted coronavirus patients, who were randomized into two groups: one group received standard empirical treatment and TPE (n = 43), whereas the other received just standard therapy based on the evolving Saudi Ministry of Health treatment protocol at the time (n = 44). Primary outcomes of the trial were 35-day mortality and safety of the intervention procedure. This randomized control clinical trial concluded that TPE could be a safe adjunct rescue therapy in critically ill COVID-19 patients. Although survival did not reach a statistically significant difference between the two groups, the intervention group had a significant decrease in SOFA scores compared with controls. Overall, TPE appeared to be associated with better clinical recovery and less time on mechanical ventilation (MV) and ICU length of stay compared with the control group [80]. On March 2022 preliminary results of a matched control study aiming to evaluate the impact of plasma exchange therapy on survival of patients with severe COVID-19 were published. The study included hospitalized patients in Mexico with coronavirus infection and Cytokine Storm Syndrome, selected to receive either two sessions of plasma exchange and standard treatment or just standard therapy. Primary outcome was 60-days mortality and secondaries were requirement of mechanical ventilation, reduction of pro-inflammatory biomarkers, changes in severity scores and hospital length-of-stay. The preliminary report supports the application of plasma exchange in selected severe COVID-19 patients since the method reduced mortality and cleared pro-inflammatory mediators without significant adverse events [81].

There are currently at least 30 ongoing clinical trials referring to plasma therapies in COVID-19 management. From them at least 15 different clinical trials deal with TPE use in severe coronavirus infections alone or as adjunct therapy and are performed all over the world [82] Most of them are still enrolling patients, six have been completed, two haven't started recruitment yet, whereas one had been terminated on March 2022 probably due to lack of patients (Table 4).

Of the completed studies two evaluate the role of TPE on COVID-19 related Cytokine Storm and another two compare TPE's efficacy with other therapeutic options. In detail, a prospective study from Egypt included 10 coronavirus patients with resistant to tocilizumab, Cytokine Storm Syndrome. All of them underwent TPE using a filtration technique and the results reported improvement in oxygenation parameters and most of the laboratory markers, suggesting a potential helpful role of plasma exchange [83]. The other is a retrospective single-center study from Pakistan with 90 participants comparing use of TPE plus standard treatment with a control group receiving only standard therapy. The study concludes that an earlier use of TPE was associated with improved overall survival and early resolution of the Cytokine Syndrome [84]. Of the studies comparing TPE with other therapeutic options only one, performed in the USA by Gluck and colleagues, reported results. In this study 20 COVID-19 positive patients with CRS and respiratory failure were enrolled and divided into two groups: Group 1 received TPE alone and Group 2 received TPE in combination with ruxolitinib. The aim of the study was to document the efficacy of plasma exchange alone or in conjunction with a JAK/STAT pathway inhibitor that suppress production of cytokines, on Cytokine Storm and to evaluate therapy related adverse events. Five TPE sessions were performed in both study arms over 7 days (first two on a daily basis and the remaining three on an every other day schedule) using 5 % human albumin as replacement fluid. Primary endpoints were a decrease in levels of CRP and others cytokines (IL-6, IL-10, TNF) from baseline to study day 14. Application of TPE exhibited improvement in cytokines levels and the addition of ruxolitinib resulted in a statistically significant reduction of all measured parameters. Oxygenation index and median time on a mechanical ventilation were similar for patients of both study groups and there were no serious adverse events related to either of two study arms [85].

Nonetheless, high level evidence is still needed. Although it seems difficult to perform prospective, randomized controlled clinical trials are necessary to evaluate the application of plasma exchange alone or in combination with other therapeutic options in severe COVID-19 patients.

Table 3
Various parameters proposed as markers determining TPE treatment.

Measured parameter	Level to initiate TPE	Target level
SOFA score	≥ 3	≤ 2
PiO2/FiO2	< 150	≥ 150
Oxygen saturation	≤ 93 %	≥ 98 %
Respiratory rate	> 30 /min	< 20 /min
Lymphocyte count	≤ 0.6 (1,1–3,2 $\times 10^9$/L)	> 1.1 (1,1–3,2 $\times 10^9$/L)
Neutrophil/lymphocyte ratio	≥ 3.3	< 3.3
CRP	≥ 100	< 50
LDH	≥ 250	< 250
Ferritin	≥ 600	< 300
D-dimmers	≥ 1	< 1
IL-6	≥ 30	< 30

Table 4
Ongoing Clinical Trials on the use of TPE in COVID-19 on 05/2022.

Title	Status	Study results	Conditions	Interventions	Locations
Therapeutic plasma exchange in resistant Cytokine Storm of COVID-19	Completed	No available	COVID-19	Procedure: TPE	Egypt
Rescue plasma exchange in severe COVID-19 (RELAX)	Recruiting	No available	TPE COVID-19	Other: TPE	Germany
Plasma exchange in Covid-19 patients with anti-interferon autoantibodies	Recruiting	No available	COVID-19	Drug: TPE	France
Randomized study of Plasma exchange in severe COVID-19	Recruiting	No available	COVID-19	Drug: OCTAPLAS	Great Britain
Therapeutic Plasma Exchange for COVID-19-assocciated Hyperviscosity	Completed	No available	COVID-19	Biological: TPE Other:standard of care	USA
Therapeutic Plasma Exchange followed by Convalescent plasma transfusion in severe and critically ill COVID-19 patients	Completed	No available	COVID-19 pneumonia, respiratory infection, ARDS	Other: TPE	Romania
Therapeutic Plasma Exchange to alleviate hyperinflammatory conditions during severe COVID-19 infections	Recruiting	No available	COVID-19, ARDS, ICU	Other: TPE[3] Other: standard ICU therapy	France
Plasma exchange in patients with COVID-19 disease and invasive mechanical ventilation: a randomized control trial	Terminated	No available	Coronavirus	Biological: TPE Drug: standard care	Spain
Therapeutic plasma exchange alone or in combination with ruxolitinib in COVID-19 associated CRS	Completed	Has results	COVID-19, Cytokine Release Syndrome	Procedure: TPE Drug: Ruxolitinib	USA
Plasma exchange (PLEX) and convalescent plasma (CCP) in COVID-19 patients with multiorgan failure	Recruiting	No available	COVID-19, respiratory and renal failure	Procedure: TPE and convalescent plasma	Denmark
Therapeutic Plasma Exchange for coronavirus disease-2019 triggered Cytokine Release Storm	Completed	No available	COVID-19, Cytokine release Syndrome	Procedure: TPE	Pakistan
Measurement of IL-6 and secondary inflammatory markers before and after Therapeutic Plasma Exchange (TPE) in hospitalized patients	Recruiting	No available	COVID-19	Device: TPE	USA
Therapeutic Plasma Exchange as an adjunctive strategy to treat coagulopathy and inflammation in severe COVID-19	Not yet recruiting	No available	Severe COVID-19	Device: TPE	
Therapeutic plasma exchange in critically ill adult patients with COVID-19 confirmed diagnosis	Not yet recruiting	No available	COVID-19	Biological: convalescent plasma	Colombia
Investigational treatments for COVID-19 in tertiary care Hospital of Pakistan	Completed	No available	COVID-19, Cytokine release Syndrome, Critical illness, ARDS	Procedure: TPE Biological: convalescent plasma Drug: tocilizumab Drug: remdesivir Biological: mesenchymal stem cell therapy	Pakistan

TPE: Therapeutic Plasma Exchange, ARDS=Acute Respiratory Distress Syndrome CSS = Cytokine Storm Syndrome CRS=Cytokine Release Syndrome. MOF = Multiple Organ Failure, ICU: Intensive Care Unit.

5. Recommendation – conclusion

In the course of fighting against the pandemic, many researchers tried, at different time periods, to overview therapeutic options and to formulate specific recommendations on which drug should be used for which patient and when. In some of these reviews plasma exchange therapy is included and suggested under specific conditions, as included in the following recommendations:

5.1. Indication

All studies agree that Therapeutic Plasma Exchange should be considered as a treatment option for COVID-19 patients with sepsis and MOF, similar to the ASFA-2019 guidelines for septic patients from various causes of infections and MOF.

5.2. Optimal time to initiate method

in general, early initiation of TPE is thought to be more helpful, especially for COVID-19 patients with symptoms of MOF and ARDS. The short half-life of pro-inflammatory cytokines which we wish to remove and an attempt at blocking the development of CSS before substantial endothelial or end-organ damage exists, constitute the main arguments in favor of early initiation of plasma exchange.

5.3. Vascular access

As for all patients admitted in ICU, temporal central venous access is preferred, since they undergo multiple interventions. Generally, a dialysis double lumen central venous catheter is recommended for applying all blood purification methods. Ultrasound-guided insertion in femoral or right internal jugular vein is preferred in order to reduce risk of bleeding or infection [86].

5.4. Anticoagulation

Acid Citrate Dextrose formula-A (ACD-A) is the first-choice agent used as anticoagulant for performing TPE in COVID-19 patients. It has been proven safe and efficient with a potential immunosuppressive role in septic patients [87]. The only consideration is the possible induction of hypocalcemia, most frequently in patients with liver or renal failure, for which close calcium monitoring and oral or intravenous supplementation are strongly recommended [88]. In cases where citrate is contraindicated heparin may be considered despite prevailing side effects.

5.5. Replacement fluid

Although COVID-19 convalescent donor plasma has been considered as the ideal option for critically ill patients [49,50], there are practical issues that make this option almost impossible to accomplish in every-day practice. Alternatively, Fresh frozen plasma (FFP) is

recommended in order to avoid a high risk of bleeding or thrombosis from depleting coagulation proteins caused by other iso-oncotic replacement solutions (normal saline and 5 % albumin). A combination of all types of replacement fluid could be used and, in this case, is preferable to end the session with FFP in an effort to restore pre-treatment levels of coagulation factors [89].

5.6. Exchange volume

as in most diseases where TPE is applied exchanging 1–1.5 of patient's plasma volume is recommended, since, this way, nearly 65–70 % of a toxic substance present in the intravascular space is removed. However, if there is shortage in FFP a minimum volume of 2 L is suggested to be exchanged [86].

5.7. Optimal number of TPE sessions – Optimal time to end the intervention

there is no general formula. Each case should be assessed and monitored as to whether the parameters that led to the initiation of plasma exchange exhibit improvement or not. The current literature reports cases where patients improved after only one TPE session [48, 64], along with studies where patients underwent three to nine procedures to accomplish the desired effects [73,62,47].

5.8. Adverse events

All commonly known adverse events of plasma exchange can occur in COVID-19 patients. Most of them are mild, and transient and could be controlled if there is close monitoring of the patient's vital signs and laboratory parameters (especially calcium and hemostasis) [29]. Although severe and potentially life-threating complications have been reported, especially when TPE is performed in critically ill patients [90], a review of the current literature regarding plasma exchange in severe COVID-19 patients doesn't show any serious complication of the method.

Prospective randomized controlled clinical trials regarding TPE are missing and the effect of the method on mortality of severe COVID-19 patients remains unclear. Up to date, current data support the possibility of a beneficial action of TPE in life-threatening COVID-19 disease as an adjunct treatment modality when performed in specialized medical centers by experienced health-care sta+ff. Additionally, it appears to be a safe procedure for coronavirus patients in terms of side effects. However, given the absence of robust evidence-based data and the lack of guidelines regarding treatment conditions and features, further and extensive research is still needed.

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