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Current Perspectives of convalescent plasma therapy in COVID-19

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Summary. The outbreak of the coronavirus disease 2019 (COVID-19) has posed an unprecedented challenge to the health care communities across the globe. As of December 2020, a total of 69,874,432 confirmed COVID-19 cases with 1,553,000 deaths have been reported. Different regions of the world have reported varying intensity of COVID-19 severity. The disease burden for COVID-19 depends on multiple factors like the local infection rate, susceptible population, mortality rate, and so on. The COVID-19 pandemic is a rapidly evolving emergency and is a subject of regular debate and advanced research. As of today, there is a lack of definitive treatment options for COVID-19 pneumonia. In search of alternative options, few drugs are being tested for their efficacy and repurposing. Preliminary reports have shown positive outcomes with Remdesivir and tocilizumab, but this needs further confirmation. Recently, the therapeutic application of Convalescent Plasma therapy in critically ill patients suffering from COVID-19 has gained momentum. We hereby discuss the convalescent plasma as a potential therapeutic option, its challenges of finding the ideal donors, transfusion medicine responsibilities, and the current global experience with its use. (www.actabiomedica.it)

Keywords: Coronavirus; pandemic; plasma therapy; COVID-19

Introduction

The current coronavirus pandemic (COVID-19) started as a local outbreak in December 2019 at Wuhan, a densely populated city in Hubei Province in the People's Republic of China (1). In a short span of 6 months, most of the other parts of the world got affected thereby turning the local outbreak to a full-blown pandemic (2). Most of the data so far suggest that COVID-19 predominantly remains asymptomatic or in the milder form (3, 4). Only a smaller percentage of the population develops severe illness requiring a high level of care and trial of investigational therapies. Drugs like tocilizumab, remdesivir, hydroxychloroquine, lopinavir-ritonavir, and other investigational drugs are currently being used by various hospitals and health care institutes (5, 6). While many randomized clinical trials (RCTs) on these drugs are underway, researchers and health experts are constantly working towards finding an effective and immediate therapy (5, 7).

The collective data from patients receiving convalescent plasma therapy can provide more granularity to our current understanding in terms of the therapeutic value and about the effectiveness of the therapy and whether it can become an approved therapy to treat COVID-19. Preliminary data is encouraging, many people have benefited from convalescent plasma therapy. Convalescent plasma therapy (CPT) is one such therapy that has provided a ray of hope for faster recovery of critically ill patients with COVID-19(8-10). With this current perspective article we intend to highlight the available data with an anticipation the translational research in this field will result in meaning guidance to the treating physicians.

COVID-19, prognostic factors, and diagnostic tools

COVID-19 has involved numerous countries across the globe and the disease load, susceptible age group; mortality rate has been variable depending on the demographical profile, economic status, and health care infrastructure (11-14). Many studies have shown that factors like old age, pregnancy, cancer, individuals with HIV/AIDS are specifically at higher risk of have fatal outcome and severe disease (15-22). Respiratory system is the major system to be affected at least at beginning and the disease may or may not spread as a multi dysfunction syndrome with cytokine storm depending upon the viral load immune response (23). Serological studies, and Computed tomography are two major diagnostic tools, but results should be analyzed depending upon the test sensitivity and specificity, and clinical probability of having the disease (24, 25). At current times, due to the sudden rise in the number of cases, COVID-19 is being considered as one of the important differentials for the respiratory tract symptoms. It is important to consider the other common cardiopulmonary disorders especially with a positive history of comorbidities (26-34). It is beyond doubt that COVID-19 has been established as a multisystem pathology influencing outcome by affecting various organ system and eventually leading to multi-organ failure(35-38). Understanding the impact of SARS-CoV-2 virus infection on various vital organs and their functioning is also essential to aid researchers in their studies on newer and innovative treatment protocols for COVID-19 (39-42). Laboratory parameters like elevated d-dimers, thrombocytopenia, lymphopenia, high ferritin levels are prognostic factors which have suggested an overall poorer outcome, worse clinical features, and higher mortality (43).

Background and Past experience with convalescent plasma in previous viral outbreaks

CPT is a form of passive antibody therapy that has been previously used in a variety of infectious diseases. CPT is usually not a licensed product and its use only gets a periodical approval during a new epidemic or pandemic as a short-term remedy. In the past, CPT has been tried in coronavirus outbreaks as well; Severe Acute Respiratory Syndrome (SARS) in 2002–04 and Middle East respiratory syndrome (MERS) in 2012 (44-47). Results from SARS showed a positive response with the use of plasma therapy. Contrary to SARS, the clinical efficacy of using CPT in MERS had conflicting results. One of the major limitations of using CPT in MERS was low titers of neutralizing antibodies. Ko et al found that not all patients receiving CPT infusions developed adequate neutralization antibodies. They found that a higher plaque reduction neutralization test (PRNT) titer of 1:80 donor plasma demonstrated meaningful serological response after CPT infusion (48).

The data derived from observational literature is suggestive that allogeneic plasma infusion can modify the immune function in infected individuals. This is done by augmenting both innate and adaptive immunity (49-51). This comes with a cost of potential risks of pro-inflammatory effects, dysregulation of T cell immunity, and associations with increases in nosocomial infection, thrombosis, and organ failure.

Data on the use of CPT in COVID-19 is still maturing and the available results are mostly based on individual reports and institutional experiences (9, 52, 53). Although CPT use for COVID-19 seems promising, so far it has not been confirmed to be safe and effective. Hence, it is of utmost importance to pool in the data on COVID-19 patients receiving convalescent plasma.

Use of Investigational COVID-19 Convalescent Plasma

Currently, in the United States, CPT can be made available through any of the following ways [1] Clinical Trials [2] Expanded Access, and [3] Single Patient Emergency IND (54). COVID-19 expanded access program is an initiative by the U.S. Government, which coordinates with various national agencies, hospitals, and transfusion centers to collect and provide CPT to patients across the United States. Mayo Clinic, Rochester has been designated as a primarily responsible center. As of June 2, 2020, 2396 programs have enrolled themselves in this program. So far, a total of 24,513 patients have been registered and 18,543 CP transfusions have been done.

In cases when clinical trials or an expanded access program are unavailable due to various reasons, "Single Patient Emergency IND" is an alternative method through which any physician can request for CP for a single patient under emergency IND (eIND under 21 CFR 312.310. Specific patient eligibility criteria have been laid down to consider for eINDs for the use of COVID-19 convalescent plasma **(Supplement Table 1).**

There are various trials currently underway and in the various phases across the world. It is expected that these trials would provide enough evidence to evaluate the use of CPT in COVID-19**.**

Clinical details on Convalescent plasma in COVID-19.

In this comprehensive review, we included all the studies reporting the role of CP in patients with COVID -19. We did a literature search in PubMed, Medline, and Google scholar for the English articles reporting CP use in COVID 19 patients. We only included studies published from December 1st, 2019 through May 6th, 2020 with actual clinical, outcome-related data. We excluded reviews, opinions, commentaries, and letters without any clinical data. A total of 59 articles were identified.

An additional 10 articles were identified from the references. We excluded duplicate articles, preprints, abstracts as well. Six articles were identified to report clinical studies with the reported outcome (10, 55-58). **Table 1** summarizes the studies reporting the role of CP among patients with COVID -19. To date, 33

Supplementary Table 1. Patient Eligibility for eINDs for use of COVID-19 convalescent plasma to treat patients (Adapted from FDA)

Diagnostic criteria fulfillment	**Laboratory confirmed COVID-19**
Clinical/laboratory criteria	Severe disease is defined as one or more of the following: • Shortness of breath (dyspnea), • Respiratory frequency ≥ 30/min, • Blood oxygen saturation ≤ 93%, • Partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, • Lung infiltrates > 50% within 24 to 48 hours Life-threatening disease is defined as one or more of the following: • Respiratory failure, • Septic shock, • Multiple organ dysfunction or failure
Consent	• Informed consent provided by the patient or healthcare proxy.

Adapted from https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma (Accessed on 06-02-2020)

Table 1. Description of recent experience with convalescent plasma therapy in COVID-19.

Number	Study	Country	Patients	Indications	ARDS	Survival	Highlights
1	Duan et al	China	10	Severe COVID 19	All	100%	Prospective study (for safety) Dose: One Volume: 200 ml Titers: 1: 640 Median time of illness to transfusion: 16.5 days **No Severe Adverse effect** 70% undetectable viral load Improvement in oxyhemoglobin, clinical symptoms, lymphocyte count, radiological findings Reduction in C reactive protein
2	Shen et al	China	5	Severe COVID 19	All	100%	Prospective study (for efficacy) Dose: Twice Total volume: 400 ml Titers: 1:1000 Median time of illness to transfusion: 10-12 days Negative viral load in 12 days Increase in SARS-COV-2 specific ELISA and neutralizing antibody titer Improvement in fever (80%), ARDS (80%), PaO2/FiO2 ratio Weaning from ventilation (60%), discharge (60%) Reduction in SOFA score
3	Zhang et al	China	4	Severe COVID 19	All	100%	Case series Maximum dose: 8 and 3 respectively Maximum volume: 900 ml Reduction in viral load Documented RT PCR negative status after treatment at discharge Improvement in clinical condition, lung imaging finding, and respiratory status

4	Ahn et al	Korea	2	Severe COVID 19	All((	100%	Case reports Dose: 2 Volume: 500 ml On Hydroxychloroquine as well Measured Anti SARS – COV – 2 IgG antibody in donor plasma was: 0.586 Improvement in fever, imaging finding, respiratory parameters and clinical status Reduction in inflammatory markers including CRP, IL -6 and Viral load Documented negative viral RT PCR Weaned of ventilators and discharged
5	Ye et al	China	6	Moderate/Severe COVID 19	1	100%	Retrospective study Maximum doses: 3 Maximum volume: 600 ml Improvement in symptoms and radiological findings
6	Zeng et al	China	6	Severe COVID 19	All	16%	Retrospective study Median dose: 2 Median volume: 300 ml Adverse effect: None SARS –COV-2 clearance documented in all patients (100%) SARS –COV-2 clearance documented in all patients before death (100%) Longer survival in patients receiving CP

patients have been reported with clinical outcomes following administration of CP.

Majority of the results so far on convalescent plasma therapy is based on the observational studies and individual experiences. A review on the ongoing studies suggests that majority of them Interventional studies and allocating patients based on randomization (39 studies). The less common are the observational studies followed by the Expanded Access. However, none of the enrolled studies so far have results available as per clinicaltrials.gov (accessed on July 21st, 2020). Majority of these studies are being conducted in US, China, Mexico Italy, Mexico, and the Netherlands. It is expected that the outcome from these studies from different geographical locations would provide us with key outcome data. Various combinations of inclusion criteria is being used to select the patients eligible for convalescent plasma therapy such as:

[a] Duration of illness from onset of symptoms (e.g. NCT04333251)
[b] Development of ARDS (e.g. NCT04321421)
[c] Severity of disease (e.g. NCT04332380)
[d] Hypoxia (e.g. NCT04425915)
[e] Mechanical ventilation (e.g.NCT04327349) and so on.

A systematic meta-analysis combining results from all these studies would help us consolidating the data.

Below we summarize the crucial points of each study as follows:

Duan et al (55)

In this prospective study from China, 10 patients with severe COVID 19 were enrolled. Each of them received a single dose of 200 mL of CP.

CP was obtained from recently recovered COVID -19 donors with the neutralizing antibody titers above 1: 640. The median time to infusion of CP was 16.5 days from the onset of illness. CP was transfused to the patients as an addition to the maximal supportive care and antiviral agents. The study demonstrated that the level of neutralizing antibody increased rapidly to 50% of patients. It also showed improvement in clinical symptoms, oxyhemoglobin saturation, parameters including lymphocyte counts, decreasing inflammatory markers, and radiological findings of the lung. This study also established the safety of CP transfusion as its primary endpoint. In this study, the viral load was undetectable in 70% of patients after transfusion. The study reported survival in all the patients treated with CP.

Shen et al (10)

In this prospective case series, 5 critically ill patients with severe COVID-19 and acute respiratory distress syndrome (ARDS) were treated with CP within 10 to 22 days of admission to ICU. To be included patients had to have [1] severe pneumonia with rapid progression, [2] continuously high viral load despite antiviral treatment; [3] Pao2/Fio2 <300; and [4] need of mechanical ventilation. Each patient received a cumulative dose of 400 ml of CP. CP was obtained from the donors on the same day, was ABO compatible, and had a serum SARS-CoV-2–specific ELISA antibody titer higher than 1:1000 and a neutralizing antibody titer greater than 40. The study reported normalization of body temperature, improvement in SOFA score, improvement in Pao2/Fio2 ratio, reduction in viral load, increase in and SARS-CoV-2–specific ELISA and neutralizing antibody titers, and reduction in the inflammatory markers including C-reactive protein, Procalcitonin and, IL-6 following transfusion. No fatality was reported at the end of around 60 days follow up.

Zhang et al (56)

In this case series, authors reported four critically ill patients with severe COVID 19, ARDS requiring intensive care unit admission and mechanical ventilation. Administered CP dose was variable [median volume per dose: 300 ml]. Interestingly, the authors reported administration of 8 doses of CP [2400 ml] to a 73 -year-old gentleman with chronic renal failure and administration of a single dose of CP to a 31-year-old pregnant lady at 35+2 weeks of gestation. The median duration to CP administration was 19 days. In this study, the viral load was undetectable

in 3 [75%] patients. 3 of the 4 patients [including the pregnant patient] were extubated and discharged from the hospital. Persistent radiological improvement was reported, and no adverse events were noted.

Ahn et al (57)

In this case series, authors from Korea reported the successful administration of CP in two critically ill patients with severe COVID 19 pneumonia. Both these patients were older [> 60] and had ARDS requiring intensive care unit admission and mechanical ventilation. CP was administered within 10 days of onset of symptoms [Mean 8 days]. Both patients were reported to have significant clinical improvement, improvement in the Pao2/Fio2 ratio, resolution of x-ray findings, decline inflammatory markers following administration. Both patients were alive at the end of the study.

Ye et al (59)

In this case series, the authors included six moderates to severe COVID-19 patients requiring hospital admission. Only one patient had been reported to have a Pao2/Fio2 <300. Patients were administered CP in view of the clinical presentation, markers of inflammation, and radiological findings. Only three patients [50%] received a single dose of 200 ml of ABO compatible convalescent plasma, and the remaining 3 are received multiple doses. The study interestingly did not have patients sick enough to require intensive care unit admission. Following administration of CP clinical improvement, resolution of imaging findings was reported in all the patients. Negative viral load was documented in four patients [75%]. Mortality, any adverse event was not reported in any of the patients.

Zeng et al (58)

This retrospective, observational study compared the role of convalescent plasma therapy in patients with severe COVID 19. 21 patients with severe COVID -19 requiring intensive care admission were admitted into the study. 6 of them received 300 ml of convalescent plasma after the median duration of 21.5 days. Three of the six [50%] received a second dose of CP. Patients receiving plasma were a decade younger, and with fewer comorbidities as compared to the controls [61.5 vs 73 yrs.]. Case fatality was reported in 83.3% [5 of 6] of patients receiving plasma and 93.3% [14 of 15] of controls. Interestingly, clearance of viral shedding was reported in all [N =100%] the patients receiving convalescent plasma as compared to 26.7% of controls. No CP related adverse effects were reported. The authors concluded that CP was instrumental in achieving clearance of viral shedding, but no mortality benefit in patients with critically ill COVID -19. The strength of the study was in having a comparison arm. The authors did suggest that CP should be initiated earlier.

Role of Transfusion medicine services in convalescent plasma therapy

The existing compliance of the plasma usage world over is moderate to poor when compared with the published guidelines. Multiple loopholes exist in ordering this blood component (58, 60, 61). The use of plasma as a therapeutic tool is mainly justified in conditions such as bleeding with coagulopathy, prior to any invasive procedure and or reversal of the effect of the anticoagulants. The use of plasma as a convalescent therapy gets only temporary approval during emergency situations. Food and Drug Administration (FDA) has issued interim recommendations for recipients and donors of CP (54):

Facilitating Donor Recruitment and transportation: Who is eligible to donate?

CP currently is being collected from the recovered individuals once they are eligible to donate**.** Following are the criteria laid down by the FDA:

- Evidence of disease

Laboratory confirmed COVID-19 either by a nasopharyngeal swab or a positive serological test for SARS-CoV-2 antibodies.

PLUS

- Complete resolution of symptoms for at least 14 days before the apheresis.

It is important to note that female donors with a history of pregnancy must have a negative result for HLA antibodies before apheresis. This is to reduce the risk of TRALI reaction in a COVID-19 recipient which could occur due to the presence of antibodies to HLA in the donor plasma. A neutralizing antibody titer of at least 1:160 is likely to be more beneficial and hence FDA recommends checking for SARS-CoV-2 neutralizing antibody titers if the facility is available. Otherwise, a sample from the donated convalescent plasma should be retained for the calculation of antibody titers later.

Safety assessments and Reporting of Adverse events

CPT can have adverse events (AEs) which can range from fever, rash chills to serious untoward events at any point during the process. Broadly, these AEs can be classified as [1] **Donor-related AEs:** Hypotensive reactions, anticoagulant related reactions, hematomas, and allergy, [2] **Equipment related AEs:** Hemolysis, thrombus formation, air embolism, leakage, infection, improper mounting on the equipment, etc., and [3] **Recipient related AEs:** Majority are mild and medically treatable AEs. Commonly associated adversities associated with transfusion of plasma include transfusion-related acute lung injury (TRALI); transfusion-associated circulatory overload (TACO); allergic/anaphylactic reactions; transfusion-related transmission of infections (TTI); and febrile non-hemolytic transfusion reactions (FNHTR) (62, 63).

Future and the Road Ahead

Future of use of CP for treatment of serious SARS-CoV-2 infection appears promising, based on previous experience and the current data from retrospective studies. There are certain known risks that are associated with any blood product administration such as allergic reaction in transmission of viral infections. In the intensive care units, respiratory failure is one of the commonest conditions that require attention (30, 64-67). Transfusion of large volume of blood products and plasma could place these patients at risk of further complicating respiratory failure with transfusion related acute lung injury (TRALI) and transfusion related circulatory overload (TACO).

Despite all these advancing measures, there is still a possibility that treatment with CP may be ineffective. Various acute care facilities in the United States and worldwide have started using CP as an investigational new drug (IND). Houston Methodist hospital became the first hospital in the United States to make available CP with COVID-19 under emergency investigational new drug application (eIND). Robust data from clinical trials are needed to confirm its usefulness and therapeutic superiority in severe SARS-CoV-2 infection **(Table 2).**

Plasma may possibly be useful due to its properties of antibody neutralization in the initial phase of infection but deleterious when the inflammatory response is abundantly advanced. There is also a theoretical concern that antibodies active against one type of coronavirus could predispose against infection to another viral strain (68). The timing of resorting to this therapy is another point of contention with unclear objective data. Overall benefit in terms of mortality and duration of hospital and ICU admission and length of stay remains to be determined.

Anticipated hurdles in plasma therapy would be to provide the amount of convalescent plasma in large amounts to enable medical centers to use them routinely for an exponentially rising number of cases. Even if the upcoming clinical trials prove its effectiveness against COVID-19 disease, healthcare resource expansion to treat large numbers of patients may become an issue. Construction of a reserve of frozen CP would be an exquisite asset to tackle COVID-19. Funding and administrative support to scale up plasma collection abilities at the national and international levels could be crucial to advance these efforts.

Finally, the common connotation of infusing ABO non-identical, which is presumed to be

Table 2: Recent clinical trials on COVID-19 and convalescent plasma therapy

ClinicalTrials.gov Identifier	Status	Title	Study Design		Country
Study Type: Interventional (Clinical Trial)					
NCT04345679	Not yet recruiting	Anti-COVID-19 Convalescent Plasma Therapy	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Iterventional (Clinical Trial) 20 participants N/A Single Group Assignment	Hungary
NCT04345523	Recruiting	Efficacy of Convalescent Plasma Therapy in Severely Sick COVID-19 Patients	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 278 participants Randomized Parallel Assignment	India
NCT04345523	Recruiting	Convalescent Plasma Therapy vs. SOC for the Treatment of COVID19 in Hospitalized Patients	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 278 participants Randomized Parallel Assignment	Spain
NCT04380935	Not yet recruiting	Effectiveness and Safety of Convalescent Plasma Therapy on COVID-19 Patients With Acute Respiratory Distress Syndrome	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 60 participants Randomized Parallel Assignment	Indonesia
NCT04356534	Recruiting	Convalescent Plasma Trial in COVID -19 Patients	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 40 participants Randomized Parallel Assignment	Bahrain
NCT04359810	Recruiting	Plasma Therapy of COVID-19 in Critically Ill Patients	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 105 participants Randomized Parallel Assignment	United States
NCT04372979	Not yet recruiting	Efficacy of Convalescent Plasma Therapy in the Early Care of COVID-19 Patients.	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 80 participants Randomized Parallel Assignment	France
NCT04361253	Recruiting	Evaluation of SARS-CoV-2 (COVID-19) Antibody-containing Plasma thErapy	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 220 participants Randomized Parallel Assignment	United States
NCT04403477	Recruiting	Convalescent Plasma Therapy in Severe COVID-19 Infection	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 20 participants Randomized Parallel Assignment	Bangladesh
NCT04342182	Recruiting	Convalescent Plasma as Therapy for Covid-19 Severe SARS-CoV-2 Disease (CONCOVID Study)	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 426 participants Randomized Parallel Assignment	Netherlands
NCT04377568	Not yet recruiting	Efficacy of Human Coronavirus-immune Convalescent Plasma for the Treatment of COVID-19 Disease in Hospitalized Children	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 100 participants Randomized Parallel Assignment	Canada

ClinicalTrials.gov Identifier	Status	Title	Study Design		Country
NCT04389944	Recruiting	Amotosalen-Ultraviolet A Pathogen-Inactivated Convalescent Plasma in Addition to Best Supportive Care and Antiviral Therapy on Clinical Deterioration in Adults Presenting With Moderate to Severe COVID-19	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 15 participants N/A Single Group Assignment	Switzerland
NCT04358783	Recruiting	Convalescent Plasma Compared to the Best Available Therapy for the Treatment of SARS-CoV-2 Pneumonia	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 30 participants Randomized Parallel Assignment	Mexico
NCT04390178	Active, not recruiting	Convalescent Plasma as Treatment for Acute Coronavirus Disease (COVID-19)	Study Type: Actual Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 10 participants N/A Single Group Assignment	Sweden
NCT04377568	Enrolling by invitation	Convalescent Plasma in the Treatment of COVID 19	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 100 participants Randomized Parallel Assignment	United States
NCT04384497	Recruiting	Convalescent Plasma for Treatment of COVID-19: An Exploratory Dose Identifying Study	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 15 participants N/A Single Group Assignment	Sweden
NCT04383535	Not yet recruiting	Convalescent Plasma and Placebo for the Treatment of COVID-19 Severe Pneumonia	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 333 participants Randomized Parallel Assignment	Argentina
NCT04355897	Recruiting	CoVID-19 Plasma in Treatment of COVID-19 Patients	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 100 participants N/A Single Group Assignment	United States
NCT04385186	Not yet recruiting	Inactivated Convalescent Plasma as a Therapeutic Alternative in Patients CoViD-19	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 60 participants Randomized Parallel Assignment	Colombia
NCT04389710	Recruiting	Convalescent Plasma for the Treatment of COVID-19	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 100 participants N/A Single Group Assignment	United States
NCT04391101	Not yet recruiting	Convalescent Plasma for the Treatment of Severe SARS-CoV-2 (COVID-19)	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 231 participants Randomized Parallel Assignment	Colombia

ClinicalTrials.gov Identifier	Status	Title	Study Design		Country
NCT04343755	Recruiting	Convalescent Plasma as Treatment for Hospitalized Subjects With COVID-19 Infection	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 55 participants N/A Single Group Assignment	United States
NCT04393727	Recruiting	Transfusion of Convalescent Plasma for the Early Treatment of Patients With COVID-19	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 126 participants Randomized Parallel Assignment	Italy
NCT04395170	Not yet recruiting	Convalescent Plasma Compared to Anti-COVID-19 Human Immunoglobulin and Standard Treatment (TE) in Hospitalized Patients	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 75 participants Randomized Parallel Assignment	↑Colombia
NCT04383548	Not yet recruiting	Clinical Study for Efficacy of Anti-Corona VS2 Immunoglobulins Prepared From COVID19 Convalescent Plasma Prepared by VIPS Mini-Pool IVIG Medical Devices in Prevention of SARS-CoV-2 Infection in High Risk Groups as Well as Treatment of Early Cases of COVID19 Patients	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 100 participants N/A Single Group Assignment	Egypt
NCT04374149	Not yet recruiting	Therapeutic Plasma Exchange Alone or in Combination With Ruxolitinib in COVID-19 Associated CRS	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 20 participants Non-Randomized Sequential Assignment	United States
NCT04321421	Recruiting	Clinical Trial to Evaluate the Efficacy of Treatment With Hyperimmune Plasma Obtained From Convalescent Antibodies of COVID-19 Infection	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 72 participants Randomized Parallel Assignment	Spain
NCT04376034	Recruiting	Convalescent Plasma Collection and Treatment in Pediatrics and Adults	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 240 participants Non-Randomized Sequential Assignment	United States
NCT04321421	Completed	Hyperimmune Plasma for Critical Patients With COVID-19	Study Type: Actual Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 49 participants N/A Single Group Assignment	Italy

ClinicalTrials.gov Identifier	Status	Title	Study Design		Country
NCT04397757	Recruiting	COVID-19 Convalescent Plasma for the Treatment of Hospitalized Patients With Pneumonia Caused by SARS-CoV-2.	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 80 participants Randomized Parallel Assignment	United State
NCT04333355	Recruiting	Safety in Convalescent Plasma Transfusion to COVID-19	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 20 participants N/A Single Group Assignment	Mexico
NCT04357106	Recruiting	COPLA Study: Treatment of Severe Forms of COronavirus Infection With Convalescent PLAsma	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 10 participants N/A Single Group Assignment	Mexico
NCT04374565	Recruiting	Convalescent Plasma for Treatment of COVID-19 Patients With Pneumonia	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 29 participants N/A Single Group Assignment	United States
NCT04345991	Recruiting	Efficacy of Convalescent Plasma to Treat COVID-19 Patients, a Nested Trial in the CORIMUNO-19 Cohort	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 120 participants Randomized Parallel Assignment	France
NCT04385043	Recruiting	Hyperimmune Plasma in Patients With COVID-19 Severe Infection	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 400 participants Randomized Parallel Assignment	Italy
NCT04381858	Recruiting	Convalescent Plasma vs Human Immunoglobulin to Treat COVID-19 Pneumonia	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 500 participants Randomized Parallel Assignment	Mexico
NCT04340050	Active, not recruiting	COVID-19 Convalescent Plasma	Study Type: Actual Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 10 participants N/A Single Group Assignment	United States
NCT04362176	Recruiting	Passive Immunity Trial of Nashville II for COVID-19	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 500 participants Randomized Parallel Assignment	United States
NCT04356482	Not yet recruiting	Convalescent Plasma For Ill Patients By Covid-19	Study Type: Estimated Enrollment: Allocation: Intervention Model:	Interventional (Clinical Trial) 90 participants N/A Single Group Assignment	Mexico

ClinicalTrials.gov Identifier	Status	Title	Study Design		Country
Study Type: Observational					
NCT04292340	Recruiting	Anti-SARS-CoV-2 Inactivated Convalescent Plasma in the Treatment of COVID-19	Study Type: Estimated Enrollment: Observational Model: Time Perspective:	Observational 15 participants Case-Only Prospective	China
NCT04334876	Not yet recruiting	Rapid SARS-CoV-2 IgG Antibody Testing in High Risk Healthcare Workers	Study Type: Estimated Enrollment: Observational Model: Time Perspective:	Observational 340 participants Ecologic or Community Prospective	Indiana
NCT04360278	Recruiting	Plasma Collection from Convalescent and/or Immunized Donors for the Treatment of COVID-19	Study Type: Estimated Enrollment: Observational Model: Time Perspective:	Observational 1500 participants Cohort Prospective	United States
Study Type: Expanded Access (Compassionate Use)					
NCT04360486	Available	Treatment of coronavirus disease 2019 (COVID-19) With Anti-Sars-CoV-2 Convalescent Plasma (ASCoV2CP)	Study Type: Expanded Access Type:	Expanded Access Treatment IND/Protocol	U.S. Army Medical Research and Development Command
NCT04363034	Available	Arkansas Expanded Access COVID-19 Convalescent Plasma Treatment Program	Study Type: Expanded Access Type:	Expanded Access Intermediate-size Population	United States
NCT04338360	Available	Expanded Access to Convalescent Plasma for the Treatment of Patients With COVID-19	Study Type: Expanded Access Type:	Expanded Access Intermediate-size Population	United States
NCT04372368	Available	Convalescent Plasma for the Treatment of Patients With COVID-19	Study Type: Expanded Access Type:	Expanded Access Treatment IND/Protocol	United States

COVID -19: Corona virus disease 2019, SARS – COV -2: Severe Acute Respiratory Syndrome Corona virus 2, ELISA: Enzyme linked immunosorbent assay, ARDS: Acute respiratory distress syndrome, SOFA: Sequential organ function assessment, RT PCR: Reverse Transcriptase Polymerase chain reaction, IgG: Immunoglobulin G, CRP: C Reactive protein, IL 6: Interleukin 6.

"compatible plasma", is practically definitely not immunologically neutral. Infusion of large amounts of soluble antigen can create large amounts of circulating immune complexes. Downstream this can translate into increased bleeding, acute lung injury (ARDS), sepsis, and mortality. This has been learned from SARS-CoV-1, MERS-CoV, and COVID-19 experience (69). Unknowns that are still unknown will include its safety and efficacy, the most appropriate time for administration, preparedness for upscaling transfusion-related resources, and infrastructure. Food and Drug Administration (FDA) approval provides a ray of hope as an adjunct treatment for the seriously ill-affected by COVID-19 (62, 63, 70, 71).

Conclusion

It is very essential from the perspective of progressing research to isolate the associated antibodies with SARS-CoV-2 disease from the population of recovered patients. It would be even more beneficial if it is done keeping in line with the regional distribution of disease (in case there develops a suspicion for strain variance). Raised antibodies ought to be produced on an enormous scale for the treatment of SARS-CoV-2 patients. These antibodies could potentially provide an immediate strategy for emergency SARS-CoV-2 therapy until the alternative and more time-intensive process of vaccines and new drugs are ongoing.

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