



## Review Article



# Convalescent Plasma Therapy for Coronavirus Disease 2019

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### Conflict of Interest

No conflicts of interest.

### Author Contributions

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## ABSTRACT

Convalescent plasma has been used for decades to prevent and treat a wide range of infectious diseases for which no specific treatment is available. The use of convalescent plasma involves transfusing plasma collected from patients who have recovered from a viral illness, in an attempt to transfer virus-neutralizing antibodies and confer passive immunity. In addition to the antiviral mechanisms of neutralizing antibodies, the immunomodulatory effects of plasma components could have benefits. Several small and large-scale studies have shown the effects of convalescent plasma for the treatment of severe coronavirus disease 2019 (COVID-19). In addition to transfusion-related side effects, unexpected side effects such as antibody-dependent enhancement (ADE) may occur during convalescent plasma therapy, but early safety studies have not found any cases of ADE among more than 5,000 participants. With historical precedents and recent clinical studies, convalescent plasma therapy should be considered as a candidate therapy for COVID-19 given the limited effectiveness of antiviral drugs and lack of a vaccine. A system to secure safe collection and use of convalescent plasma should be developed as a response to the pandemic. Further clinical trials should be conducted to determine the safety and efficacy of convalescent plasma therapy concurrently with its clinical use.

**Keywords:** Coronavirus disease 2019; Severe acute respiratory syndrome coronavirus 2; COVID-19 serotherapy; Plasma

## INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has become a global concern, and the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a Public Health Emergency of International Concern on January 30, 2020, and a pandemic on March 11, 2020 [1]. Between December 31, 2019 and July 29, 2020, more than 16 million cases of COVID-19 were reported worldwide, including more than 660,000 deaths. Most patients with COVID-19 have mild disease and recover without any treatment. However, older individuals with comorbidities such as diabetes mellitus, hypertension, and respiratory or cardiovascular disease are at greater risk of complications and mortality [2, 3].

To overcome the COVID-19 pandemic, the development of effective therapeutic agents and vaccines is crucial. However, as of August 3, 2020, there are few therapeutic agents that have been approved for the treatment of COVID-19, and there are no vaccines [4]. Remdesivir is the only antiviral agent that showed efficacy in a randomized controlled trial [5], and dexamethasone is another medication that showed efficacy in severe COVID-19 patients [6]. However, having these medications is not enough to overcome the COVID-19 pandemic. Given the lack of therapeutic options for COVID-19 and vaccines, historical interventions for emerging infectious diseases have reemerged as options for disease control. Given its rapid acquisition, convalescent plasma therapy has been considered as an emergency intervention in several pandemics, including the Spanish flu, severe acute respiratory syndrome coronavirus (SARS-CoV-1), and West Nile virus, and more recently, Ebola virus [7-9].

During the current COVID-19 pandemic, multiple studies of varying sizes have been conducted on convalescent plasma therapy for COVID-19. The purpose of this review is to provide the theoretical rationale, summarize the evidence of safety and effectiveness, and discuss considerations for clinical application of convalescent plasma therapy.

## HISTORICAL PRECEDENTS

In the early twentieth century, convalescent sera were used to stem epidemics of viral diseases such as poliomyelitis, measles, mumps, and influenza [10]. A retrospective meta-analysis of eight studies on the use of convalescent sera involving 1703 patients during the 1918 H1N1 influenza virus pandemic suggested that those who received serum had lower mortality [11]. During the 2009 - 2010 H1N1 influenza pandemic, convalescent plasma was used to treat patients with severe H1N1 infection requiring critical care [12]. A study with 93 participants showed that treatment of severe H1N1 2009 infection with convalescent plasma reduced respiratory tract viral load, serum cytokine response, and mortality. During the 2013 Ebola epidemic in West Africa, a nonrandomized study showed significantly longer survival for those treated with convalescent whole blood compared to those who received standard treatment [13]. However, another nonrandomized study on Ebola virus disease did not show the survival benefit of convalescent plasma therapy [14].

Convalescent plasma therapy has also been used for treating coronavirus diseases such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). A study from a hospital in Hong Kong evaluated the efficacy of convalescent plasma therapy in the treatment of patients with SARS in 2003 [15]. A higher day-22 discharge rate was observed among patients who were given convalescent plasma before Day 14 of illness and among those who were PCR positive and seronegative for coronavirus at the time of plasma infusion. During the MERS epidemic in South Korea, convalescent plasma therapy was performed for several MERS patients, and a study suggested that donor plasma with a neutralization activity of a plaque reduction neutralization test (PRNT) titer  $\geq 1:80$  should be used for convalescent plasma therapy [16].

Although large-scale randomized controlled trials have not yet been performed, and most studies did not evaluate neutralizing activities of used convalescent plasma, previous experiences on convalescent plasma therapy for the treatment of emerging infectious diseases provide us with important historical precedents that this intervention might be useful for confronting the COVID-19 epidemics.

## POSSIBLE MECHANISM OF ACTION

Convalescent plasma therapy is a passive antibody therapy that involves the administration of antibodies against a given pathogen to a susceptible individual for the purpose of preventing or treating an infectious disease. Neutralizing antibodies have been considered essential in the effects of convalescent plasma therapy, and the efficacy of this therapy was associated with the titer of neutralizing antibodies in the convalescent plasma [17, 18]. In addition to the antiviral mechanisms of neutralizing antibodies, immunomodulatory effects of plasma components could have additional benefits [18]. During apheresis, in addition to neutralizing antibodies, other proteins such as anti-inflammatory cytokines, clotting factors, natural antibodies, defensins, pentraxins, and other undefined proteins are obtained from donors [19]. In this sense, transfusion of convalescent plasma in infected patients may provide further benefits such as immunomodulation via amelioration of severe inflammatory response.

## CLINICAL STUDIES ON COVID-19

Several uncontrolled case series of convalescent plasma therapy for the treatment of patients with COVID-19 have suggested a possible benefit [20-23]. Multiple studies have evaluated the effects of convalescent plasma therapy for patients with COVID-19 (Table 1) [20, 23-27]. The reports showed that convalescent plasma therapy induced reduction in viral loads and improvement of laboratory markers and clinical signs. Most studies were non-randomized, non-controlled studies, and the participants had severe or life-threatening disease. Given encouraging historical precedents and the lack of proven effective therapy for COVID-19, clinical studies on the use of convalescent plasma as a treatment option for COVID-19 are ongoing in many countries. As of August 3 2020, a total of 132 studies evaluating the role of convalescent plasma in COVID-19 are registered on ClinicalTrials.gov. The first randomized trial of convalescent plasma therapy for COVID-19 patients was conducted in China [28]. To evaluate the efficacy and adverse effects of convalescent plasma therapy for patients with COVID-19, an open-label, multicenter, randomized clinical trial was performed in seven medical centers in Wuhan, China. The study included 103 participants with severe or life-threatening COVID-19.

**Table 1.** Studies of convalescent plasma therapy for treating COVID-19

Authors, Year of publication	Country	Study design	Number of participants		Clinical outcomes		Adverse events	Reference
			Cases	Controls	Cases	Controls		
Abolghasemi et al., 2020	Iran	Nonrandomized, controlled study	115	74	14.8% died	24.3% died	Not reported	[27]
Ahn et al., 2020	Korea	Nonrandomized, non-controlled study	2		100% improved		None	[23]
Duan et al., 2020	China	Nonrandomized, non-controlled study	10		100% improved within 3 days		1 evanescent facial red spot	[20]
Li et al., 2020	China	Randomized, controlled study	53	51	51.9% improved within 28 days	41.1% improved within 28 days	2 adverse events within hours after transfusion	[28]
Perotti et al., 2020	Italy	Nonrandomized, non-controlled study	46		6.5% died within 7 days		5 serious adverse events	[26]
Salazar et al., 2020	US	Nonrandomized, non-controlled study	25		76% improved within 14 days		None	[25]
Shen et al., 2020	China	Nonrandomized, non-controlled study	5		100% improved		None	[21]
Zeng et al., 2020	China	Nonrandomized, non-controlled study	6	15	83% died	93% died	None	[24]
Zhang et al., 2020	China	Nonrandomized, non-controlled study	4		100% improved		None	[22]

COVID-19, coronavirus disease 2019.

To ensure the therapeutic potency of the convalescent plasma, only the plasma units with a spike protein receptor-binding domain (S-RBD)-specific immunoglobulin G (IgG) titer of at least 1:640 were used in the study. However, because the COVID-19 epidemic in China was contained while enrolment was in progress, the trial was terminated before it reached its targeted sample size of 200 patients. Hence, it was underpowered and many comparisons between the convalescent plasma group and the control group were not statistically significant. The primary endpoint of time to clinical improvement within 28 days (defined as being discharged alive or having a reduction of 2 points on a 6-point disease severity scale) was 2.15 days shorter (95% confidence interval [CI], -5.28 to 0.99 days; hazard ratio [HR]: 1.40, 95% CI: 0.79 - 2.49;  $P = 0.26$ ) in the intervention group compared to the control group, and 27 (51.9%) patients in the intervention group experienced a clinical improvement within 28 days, compared to 22 patients (43.1%) in the control group (difference: 8.8%; 95% CI: -10.4% to 28%; odds ratio [OR]: 1.20, 95% CI: 0.80 - 1.81;  $P = 0.37$ ). In analyses stratified by disease severity, among patients with severe disease (23 in the convalescent plasma group and 22 in the control group), the time to clinical improvement was 4.94 days shorter (95% CI: -9.33 to -0.54 days; HR: 2.15, 95% CI: 1.07 - 4.32;  $P = 0.03$ ,  $P = 0.03$ ) in the intervention group, and clinical improvement at 28 days occurred in 21 patients (91.3%) in the intervention group *vs.* 15 patients (68.2%) in the control group (OR: 1.34, 95% CI: 0.98 - 1.83;  $P = 0.07$ ). Although the study was underpowered, the study results showed convalescent plasma therapy was associated with some clinical improvement in severely ill patients, but not in critically ill patients. Because antibody therapies generally work when administered earlier stage of disease, the efficacy might be better in patients with severe (respiratory distress and/or hypoxemia) than life-threatening (shock, organ failure, or requiring mechanical ventilation). Some of the patients with life-threatening disease might have had irreversible disease at the time that plasma therapy was initiated.

Although a recent systematic review showed uncertainty regarding the effectiveness of convalescent plasma for individuals with COVID-19 [29], ongoing studies including randomized controlled trials will provide further evidence of the effectiveness and safety of convalescent plasma therapy for COVID-19.

## SAFETY

There are several concerns about the use of convalescent plasma therapy for COVID-19 patients. Transfusion of plasma may cause transfusion-related adverse events, including minor adverse events such as fever, nausea, allergic reactions, transmission of blood-borne pathogens, and some severe adverse events such as transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), and antibody-dependent enhancement (ADE) [10, 30].

TACO and TRALI are the leading causes of transfusion-related fatalities, and specific therapies are unavailable [31]. TACO and TRALI are syndromes of acute respiratory distress that occur within 6 hours of blood transfusion. The pathophysiology of both syndromes is not fully understood. In TACO, cardiac or renal impairment and positive fluid balance may precede circulatory overload. TRALI often presents as bilateral pulmonary edema with little evidence of circulatory overload. TRALI may be caused by preceding inflammation, antileukocyte antibodies, and biological response modifiers. Because COVID-19 itself can induce lung injury, the underlying lung injury associated with COVID-19 further complicates

the differential diagnosis of TACO and TRALI, and may increase the risk of TACO and TRALI in critically ill patients.

ADE may occur when antibodies to the virus fail to efficiently neutralize the virus. Previous studies showed that the binding of virions to non-neutralizing or sub-neutralizing antibodies could lead to more efficient viral uptake into the target cell in Fcγ receptor or through complement-mediated mechanisms, leading to enhanced viral replication [32, 33]. ADE has been reported for various viral diseases including dengue, Zika, influenza, and respiratory syncytial virus infection. The ADE phenomenon has been demonstrated for SARS-CoV-1 using in vitro and animal models [34]. However, to date, there has been no evidence of ADE in reported cases and clinical trials on coronaviruses [7, 20-23, 28].

A United States (US) study of 5,000 hospitalized adults with severe or life-threatening COVID-19, with 66% in the intensive care unit, provided safety data on convalescent plasma therapy [30]. The incidence of all serious adverse events (SAEs) in the first four hours after transfusion was <1%, including a 0.3% mortality rate. Of the 36 reported SAEs, 25 were assessed as possibly or definitely transfusion related, including mortality (4 cases), TACO (7 cases), TRALI (11 cases), and severe allergic transfusion reactions (3 cases). However, only 2 (of 36) SAEs were judged as definitely related to the convalescent plasma transfusion by the treating physician. The study suggested that convalescent plasma therapy for hospitalized patients with COVID-19 was relatively safe.

## PATIENT AND DONOR ELIGIBILITY

Most patients with COVID-19 have mild disease and recover with conservative treatment only. Clinical studies on convalescent plasma therapy for COVID-19 have been conducted in patients with severe or life-threatening disease.

According to the US Food and Drug Administration (FDA) guidelines, investigators in the US wishing to study the use of convalescent plasma in a clinical trial should submit requests to the FDA for investigational use under the traditional investigational new drug (IND) regulatory pathway [35]. The suggested patient eligibility criteria are as follows: (1) Laboratory confirmed COVID-19; (2) severe or immediately life-threatening disease; and (3) Informed consent provided by the patient or a healthcare proxy.

The US FDA also provide suggested donor eligibility criteria which stipulate that donors should satisfy the following conditions:

- (1) Evidence of COVID-19 documented by a laboratory test either by a diagnostic test (*e.g.*, nasopharyngeal swab) at the time of illness or a positive serological test for SARS-CoV-2 antibodies after recovery, if prior diagnostic testing was not performed at the time that COVID-19 was suspected.
- (2) Either one of the following (i) Complete resolution of symptoms at least 28 days prior to donation; or (ii) Complete resolution of symptoms at least 14 days prior to donation, and negative results for COVID-19 either from one or more nasopharyngeal swab specimens or by a molecular diagnostic test from blood.
- (3) Male donors, or female donors who have not been pregnant, or female donors who have been tested since their most recent pregnancy and results were interpreted as negative for human leukocyte antigen (HLA) antibodies.

- (4) SARS-CoV-2 neutralizing antibody titers, if available (when measurement of neutralizing antibody titers is available, the US FDA recommends neutralizing antibody titers of at least 1:160. A titer of 1:80 may be considered acceptable if an alternative matched unit is not available. When measurement of neutralizing antibody titers is not available, it is suggested that a retention sample from the convalescent plasma donation be stored so that the antibody titers can be determined at a later date.

The Korea Centers for Disease Control (KCDC) has also developed donor eligibility criteria as detailed below [36]:

- (1) An individual who has recovered from COVID-19 can donate plasma at least 14 days after being cured of COVID-19. Negative results of real-time reverse transcription polymerase chain reaction for SARS-CoV-2 using a respiratory specimen should be confirmed if the plasma collection is performed less than 28 days after the donor has been cured of COVID-19. Infectious disease specialists and laboratory medicine specialists should confirm that the donor is completely cured of COVID-19 at the point of plasma collection.
- (2) Before plasma collection, the donor's body weight, medical history, social history, physical examination, and laboratory tests must be evaluated to determine whether the individual is suitable to serve as a plasma donor. The minimum standard for age (17 to 69 years old, donors over 65 years of age who have experience of blood donation from 60 to 64 years old), body weight (50 kg or more for men, 45 kg or more for women), and hemoglobin level 12 g/dL or more) should be met.
- (3) A repeat donation of plasma can be performed 14 days after apheresis if the doctor confirms that the health condition of the donor is suitable for a repeat donation of plasma.
- (4) Other donor screening criteria, blood collection procedures, donor safety matters, and handling of side effects should be in accordance with the current blood management laws and guidelines for general blood management.
- (5) Pregnant women are not suitable to serve as plasma donors because of the high probability of TRALI due to anti-HLA antibodies.

## MEASURING NEUTRALIZING ANTIBODY TITERS IN CONVALESCENT PLASMA

Some patients who recover from viral diseases may not have high titers of neutralizing antibodies, which are crucial for the effectiveness of convalescent plasma therapy [13, 14]. A study showed that virus-specific IgG levels in asymptomatic COVID-19 patients were significantly lower than those in symptomatic patients in the acute phase [37]. Of asymptomatic individuals, 93.3% and 81.1% had reductions in IgG and neutralizing antibody levels, respectively, during the early convalescent phase, as compared to 96.8% and 62.2% of symptomatic patients, respectively. Forty percent of asymptomatic individuals, and 12.9% of symptomatic individuals, became seronegative for IgG in the early convalescent phase. Another study showed that SARS-CoV-2-specific neutralizing antibody titers were low for the first 7 – 10 days after symptom onset and increased after 2 – 3 weeks [38]. The median peak time for neutralizing antibodies was 33 days after symptom onset. The titers in 93.3% of the patients declined gradually over the 3-month study period. Another study evaluated serological reactivity in plasma from 436 convalescent plasma donors with a history of disease compatible with COVID-19 in England [39]. The study showed that antibody levels declined over 3 months following the diagnosis.

Because historical experience of the use of convalescent plasma therapy suggests that the neutralizing activity may correlate with the efficacy of convalescent plasma, the measurement of SARS-CoV-2 neutralizing antibody titers should be considered, if available. However, laboratory methods for evaluating neutralizing antibody titers, such as the PRNT, microneutralization assay, and pseudovirus neutralization assay, are not routinely performed in hospital settings. However, as several reports suggest that SARS-CoV-2 specific IgG titers correlate with neutralizing antibody titers [38, 40], the SARS-CoV-2-specific IgG titer should be measured in the convalescent plasma.

## SYSTEM DEVELOPMENT FOR CONVALESCENT PLASMA THERAPY

To perform convalescent plasma therapy for COVID-19, development of a system with an adequate infrastructure is required. A population of donors who have recovered from the disease and can donate convalescent serum need to be recruited. Blood banking facilities to process apheresis are necessary. Essential assays, including serological assays to detect SARS-CoV-2 antibodies in serum, and virological assays to measure viral neutralization, should be performed. To perform the assays for neutralization antibodies, the necessary laboratory support to perform these assays should be implemented. Protocols for safe collection and use of convalescent plasma should be developed. Clinical trials to assess the efficacy, safety, and immunologic responses should be combined with clinical use. Regulatory review and approval should be performed in a timely manner. Pharmaceutical companies should try to develop highly purified preparations containing a high titer of neutralizing antibodies against SARS-CoV-2, which is preferable to convalescent plasma. The preparation may be safer and have higher neutralization activity; however, the development of the hyper-immunoglobulin preparation takes many months.

## CONCLUSION

With historical precedents and recent clinical studies, convalescent plasma therapy should be considered as a candidate intervention for COVID-19, given the limited evidence of effectiveness of antiviral agents and the lack of a vaccine. A system to secure safe collection and use of convalescent plasma should be developed as a response to the pandemic. Further scientific studies on the safety and effectiveness of convalescent plasma therapy should be explored through clinical trials that can be established concurrently with the clinical use of convalescent plasma therapy.

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