

## BRIEF REVIEW

## Convalescent Plasma Therapy in Coronavirus Disease 2019 (COVID-19) Patients: A Brief Review

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**Recommended Citation:** Khan MA, Ullah I. Convalescent plasma therapy in coronavirus disease 2019 (COVID-19) patients: A brief review. *Univ Louisville J Respir Infect* 2020; 4(1):Article 47. doi: 10.18297/jri/vol4/iss1/47.

### Abstract

The recent outbreak of the COVID-19 pandemic has caused a re-evaluation of the effectiveness of convalescent plasma therapy (CPT). This review was carried out to assess the usefulness of CPT in critically ill COVID-19 patients based on the published data to date. To the best of our knowledge, this is the second review of the usefulness of CPT in COVID-19 patients. PubMed, Google Scholar, MEDLINE, and Embase databases were searched for relevant reports up to June 21, 2020. Records of published data were analyzed according to eligibility criteria. Five different studies on CPT for critically ill COVID-19 patients were included in this review. The sig-

nificant findings from these records are: (a) CPT may help to reduce mortality in the critically ill patients (b) administration of CPT increased antibody titers and reduced the level of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) RNA to below the detection limit (c) transfusion of convalescent plasma (CP) caused clinical symptoms to subside. Based on the currently available data, CPT in COVID-19 patients seems effective and safe and reduces mortality. There is an urgent need to perform well-designed, multicenter clinical trials to establish the efficacy of CPT in COVID-19 patients.

### Introduction

Coronavirus is one of the major pathogens that predominantly affect respiratory system of human beings. Epidemics of the coronaviruses in the past include SARS-CoV and the Middle East respiratory syndrome coronavirus (MERS-CoV) have been identified as agents that are threat to the public health.[1] Many patients having pneumonia like symptoms of unknown cause were admitted to hospitals in late December 2019. Epidemiological studies linked these patients to a wet animals and seafood wholesale markets in the Wuhan city of Hubei (Province) of China, and spread to other parts of China and now it has become a global threat.[1, 2] As of 24 June 2020, World Health Organization (WHO) reported 9,129,146 confirmed cases of COVID-19 and 473,797 deaths worldwide.[3]

The potential outbreak of the coronavirus was predicted in the early reports, which had given estimate of reproduction number for the SARS-CoV-2 significantly greater than one (2.24–3.58).[4] Most of the COVID-19 patients are either asymptomatic or presents with mild symptoms, and in some patients it progresses to severe acute respiratory syndrome (SARS) which is

the main cause of mortality.[5] Until now, no specific antiviral drugs and vaccine have been found to cure and prevent the infection. Therefore, it is necessary to discuss scientifically and ethically all the therapeutic options for the lethal COVID-19 infections.[5] Several treatment options such as favipiravir and remdesivir are under investigation, but their antiviral efficacy is not yet known.[6]

In the past, the passive immunotherapy (PIT) has been used as a possible treatment option when no proven drugs or specific vaccine was available for the emerging infections.[7, 8] It has been used as an empirical therapy during the Ebola virus outbreak in 2014, and a treatment protocol of MERS-CoV with convalescent therapy was developed in 2015.[9] This therapeutic approach with convalescent plasma (CP) for other viral infections such as H1N1 influenza, H5N1 avian influenza and SARS-CoV has also suggested that the transfusion of CP had good results.[10, 11] As a result, transfusion of CP has gotten attention particularly in large-scale epidemics.[12] The Food and Drug Administration has recently suggested that the transfusion of the CP may be effective for the treatment of the COVID-19 patients amidst this public health emergency.[13]

We conducted this review to assess the available reports for the effectiveness of the CP in COVID-19 patients. It may provide scientific evidence of the potential treatment options to scientists and clinicians for the better management of the severe ill COVID-19 patients.

## What is Convalescent Plasma (CP)?

Most people who recover from COVID-19 develop antibodies (glycoproteins that are produced by the immune system in reaction to infections) to SARS-CoV-2. Antibodies are found in plasma. The plasma is collected from the COVID-19 recovered patients through a process called apheresis. This plasma is called CP. [14]

## Who Can Become a CP Donor?

Currently, people recovered from COVID-19 who had a confirmed positive test result can donate plasma after they have been symptom free for at least 14 days. People who recover from suspected COVID-19 but never had a confirmed positive test result can also become donors if tests show they have SARS-CoV-2 antibodies. All donors must meet other blood donation criteria.[14]

## Dosage of the CP

Different doses of the CP have been for the treatment of severe ill COVID-19 patients as evident from different studies. A study from China has reported a single dose of CP (200mL) with the neutralizing antibody titers above 1:640. Another study by reported a maximum dose of CP (2,400mL) for 73 year old male patient.[15] The doses of CP varies in different reports, the optimal dose of the convalescent is yet to be determined. The CP was administered to all the survivors between days 6 to 50 days after admission to the hospitals or symptoms onset.

## Potential Benefits of CP

CP has been used to treat other infections and may be beneficial for COVID-19 as well. The researchers hope that the administration of CP to severe COVID-19 patients may enhance the immune system capability to fight the virus. Studies are underway to evaluate use of CP as treatment for patients with severe COVID-19 and to prevent infection (prophylaxis) in certain high-risk patients exposed to COVID-19. CP might provide immunity by giving patients neutralizing antibodies for SARS-CoV-2. Although there is a lot that is unknown, CP may work best for patients earlier in the disease

course. Currently, CP is being given to small numbers of hospitalized patients with severe or life-threatening COVID-19 illness. Several case reports suggest treatment is helpful, but larger studies are still needed.[14]

## Potential Risks of CP

Plasma transfusions are safe and well tolerated by most patients. Side effects of CP are similar to those of regular plasma transfusions. The most common side effect is a mild allergic reaction. Rare but serious side effects include problems with the heart or lungs, or infection. As with all blood products, CP is thoroughly tested before use. All donated blood is screened for blood type compatibility as well as infections like hepatitis B and C, HIV, and many other less common infections. SARS-CoV-2 is not spread by blood, and there is no risk of transmission from recovered donors.[14]

## Conclusion

COVID-19 has posed the greatest threat to the globe and there is urgent need to control it. Currently, no reliable drugs or vaccines are available for curing and preventing COVID-19. Data of the 27 critically ill COVID-19 patients in five different studies suggests that in addition to the antimicrobial/antiviral drugs, the CPT can be an effective therapeutic option (**Table 1**). It is evident from data that CPT is safe, improves symptoms and reduces mortality. We recognize that definitive conclusions cannot be obtained on the optimal dose and administration time of CPT to critically ill COVID-19 patients; large clinical trials studies are needed to urgently tackle the COVID-19 pandemic.

In summary, administration of CP can provide an immediate therapeutic option while assessing the efficacy of the existing drug and developing new therapies and specific vaccine. There is urgent need of the following:

1. Identification of donor's criteria and the eligible donors.
2. Installing and maintaining blood testing and processing facilities in healthcare settings.
3. Developing serologic assays for screening.
4. Identification of the optimal dose of CP from apheresis collection for critically ill COVID-19 patients. As data of the natural history of the SARS-CoV-2 is scarce, the Pandemic Response and Recovery Team (PRT) should be considered to add a layer of safety for protection of the recipients of CP.

**Table 1.** Five different studies on convalescent plasma therapy for critically ill COVID-19 patients included in this review. All studies were case series.

Reference	No. of patients	Timing of administration	Volume transfused	Antibody titer	Patient outcomes
16	5	10–22 days	200 mL (×2)	>1:1,000	Body temperature was normalized in 4/5 patients within 3 days of CP administration. PaO <sub>2</sub> /FiO <sub>2</sub> increased and SOFA score decreased within 12 days. ARDS resolved in 4 patients at 12 days.
17	10	16.5 days (median)	200 mL (×1)	>1:640	Improved oxygenation; reduced viral loads and inflammation.
15	4	15.5 days (mean)	200–2,400 mL (1–8 infusions)	—	All 4 patients recovered.
18	2	6–10 days (range)	250 mL (×2)	—	Removed from mechanical ventilators; tracheostomy done; extubated and then discharged on the 24th day.
19	6	33–50 days after symptoms	500 mL (×2)	—	Symptoms improved; GGOs resolved by 37th–54th day; cured and ready to discharge.

**Abbreviations:** CP, convalescent plasma; GGOs, ground glass opacities; SOFA, sequential organ failure assessment.

**Received:** June 26, 2020

**Accepted:** July 9, 2020

**Published:** July 16, 2020

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**Funding Source:** The author(s) received no specific funding for this work.

**Conflict of Interest:** All authors declared no conflict of interest in relation to the main objective of this work.

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