



# PLASMA CONVALESCENT THERAPY FOR COVID-19 PATIENTS: A LITERATURE REVIEW

TERAPIA DE PLASMA CONVALECIENTE PARA PACIENTES CON COVID-19: REVISIÓN DE LA LITERATURA

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## ABSTRACT

**Introduction:** The coronavirus disease 2019 (COVID-19) caused by novel coronavirus (SARS-CoV-2) infection has created a pandemic leading to a global struggle to cope with the sheer numbers of infected persons, many of whom require intensive care support. To date, there is no specific antiviral treatment for COVID-19. The use of convalescent plasma transfusions could be of great value in the current pandemic.

**Methods:** A Google Scholar and PubMed search was conducted between November 2019 and July 2020.

**Results:** We found 150 articles. After using the exclusion criteria and deleting duplicate articles, we reviewed 37 studies. We included 18 studies (5 case reports, 4 case-series, 2 systematic review, 7 article reviews) with 90 participants. Recovered SARS-CoV-2 patients who may be suitable donors undergo apheresis in order to obtain convalescent plasma containing high-titer antibodies, granted they meet blood donation criteria. **Conclusion:** The benefits and effectiveness of convalescent plasma far outweigh the possible side effects, since there is no specific pharmacological therapy or vaccine available. Convalescent plasma therapy use in the management of patients at different severity levels of COVID-19 disease has become a management pillar in global management and an accessible option in developing countries.

**Key words:** COVID-19; SARS-CoV-2; Plasma; COVID-19 serotherapy (source: MeSH NLM).

## RESUMEN

**Introducción:** La enfermedad por coronavirus 2019 (COVID-19) causada por la infección por el nuevo coronavirus (SARS-CoV-2) ha creado una pandemia que ha llevado a una lucha mundial para hacer frente a la gran cantidad de personas infectadas, muchas de las cuales requieren cuidados intensivos. Hasta la fecha, no existe un tratamiento antiviral específico para COVID-19. El uso de transfusiones de plasma de convalecientes podría ser de gran valor en la pandemia actual. **Métodos:** Se realizó una búsqueda en Google Scholar y PubMed entre noviembre de 2019 y julio de 2020. **Resultados:** Se encontraron 150 artículos. Después de utilizar los criterios de exclusión y eliminar los artículos duplicados, revisamos 37 estudios. Se incluyeron 18 estudios (5 informes de casos, 4 series de casos, 2 revisiones sistemáticas, 7 revisiones de artículos) con 90 participantes. Los pacientes con SRAS-CoV-2 recuperados que pueden ser donantes adecuados se someten a aféresis para obtener plasma de convalecencia que contenga anticuerpos de alto título, siempre que cumplan los criterios de donación de sangre. **Conclusión:** Los beneficios y la eficacia del plasma de convalecencia superan con creces los posibles efectos secundarios, ya que no existe una terapia farmacológica o vacuna específica disponible. El uso de la terapia con plasma de convalecencia en el manejo de pacientes con diferentes niveles de gravedad de la enfermedad COVID-19 se ha convertido en un pilar de manejo en el manejo global y una opción accesible en los países en desarrollo.

**Palabras clave:** COVID; COVID-19; SARS-CoV-2; Plasma de convalecencia; Terapia de tratamiento con plasma (fuente: DeCS BIREME).

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## INTRODUCTION

On March 11, 2020, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) caused by novel coronavirus (SARS-CoV-2) infection a pandemic. Since early December 2019 and up to July 2020, over 15 million COVID-19 infections with over 640,000 deaths are reported in 188 countries<sup>(1)</sup>. Coronaviruses are enveloped viruses, with a positive-stranded RNA and a nucleocapsid. Among its structural elements, spike glycoproteins composed of two subunits (S1 and S2) are of great importance<sup>(2,3)</sup>. Receptor-binding protein (RBD) is a peptide domain fundamental in the pathogenesis of infection; it represents a binding site for the human Angiotensin-Converting Enzyme 2 (ACE2) receptor<sup>(4)</sup>. COVID-19 presentation ranges from asymptomatic form to conditions characterized by respiratory failure requiring mechanical ventilation and ICU support, reaching multiorgan and systemic manifestations like sepsis and septic shock<sup>(4,5)</sup>. Virologic testing (i.e., using a molecular diagnostic or antigen test to detect SARS-CoV-2) should be done in all patients with symptoms consistent with COVID-19 and people with known high-risk exposures to SARS-CoV-2. The WHO recommends collecting specimens from the upper respiratory tract and lower respiratory tracts, such as expectorated sputum, endotracheal aspirate, or bronchoalveolar lavage<sup>(6)</sup>. In the laboratory, amplification of the genetic material extracted from the saliva or mucus sample is processed through a reverse polymerase chain reaction (RT-PCR) to confirm the diagnosis<sup>(7)</sup>. Despite the numerous studies reported on treatments, antiviral therapy for COVID-19 has not been approved, and vaccine development is still under clinical trials. Current treatment focuses on symptomatic management of hypoxemic patients ranging from conventional oxygen therapy to intubation and invasive mechanical ventilation<sup>(8)</sup>. Among the multiple treatments proposed, convalescent plasma therapy represents a therapeutic option currently under study<sup>(5,9)</sup>. The usage of plasma treatment has been

described in several immunoglobulin therapies in the past for pathogens like H1N1 and Ebola virus disease, severe acute respiratory syndrome, and thrombocytopenia syndrome<sup>(10)</sup>. Despite its use, COVID-19 history and the lessons learned from previous infections with SARS coronavirus and MERS-CoV, still raise concerns favoring careful surveillance by clinicians during human trials<sup>(11)</sup>. In this review, we aim to recognize when convalescent plasma usage is appropriate, its effect on improving clinical symptoms, and the safety of convalescent plasma for COVID-19 by measuring the severity of its adverse effects based on the current literature.

## METHODS

We performed a search in Google Scholar search and PubMed between November 2019 to July 2020, using the following terms: COVID, COVID19, SARS-CoV-2, convalescent plasma treatment, and plasma treatment therapy. The studies could be conducted worldwide and include participants of any gender, age, or ethnicity, with mild, moderate, or severe COVID-19.

### Selection criteria

We included all studies (case reports, case series, meta-analysis) evaluating convalescent plasma treatment in patients testing positive for COVID-19.

We excluded studies including articles that no involve plasma as a treatment description, articles currently being performed, a language other than English or Spanish, letters to the editors, editorials, and abstracts.

## RESULTS

We found 150 articles. After using the exclusion criteria and deleting duplicate articles, we reviewed 37 studies. We included 18 studies (5 case reports, 4 case-series, 2 systematic review, 7 article reviews) with 90 participants.

**Table 1.** Convalescent plasma administration during SARS-CoV-2 infection.

Reference	Study	Number of patients treated with convalescent plasma	Amount of CP plasma administrated	Efficacy	Safety
Zhang et al., Aging, 2020.	Case series	1	200 mL single dose	D-dimer remained increased Clinical recovery and transfer to general ward	No adverse effects observed
Zeng et al., J Infect Dis, 2020	Retrospective case-control	6	200–600 ml	All patients presented viral clearance achieved after convalescent plasma administration and one was discharged from hospital	5 of 6 patients in the treatment group and 14 of 15 patients in the control group died
Zhang et al., Chest, 2020	Case series	4	200–2,400 ml	Pulmonological improvement on CT Clinical recovery and discharge from hospital	No adverse effects observed
Duan et al., Proc Natl Acad Sci USA, 2020	Clinical trial	19	200 mL single dose	Clinical recovery Pulmonological improvement on CT Reduced viral load Laboratory improvement	Two showed an evanescent facial red spot
Olivares-Gazca et al., Rev Invest Clin, 2020	Case series	10	200 mL single dose	Clinical recovery Laboratory improvement Pulmonological improvement on X-ray (6 out of 10) and CT (7 out of 10)	No adverse effects observed
Shen et al., JAMA, 2020	Case series	5	400 ml	Clinical recovery Reduced viral load Pulmonological improvement	No adverse effects observed
Im et al., J. Korean Med. Sci, 2020	Case report	1	250 mL for 2 consecutive days	Clinical recovery for 3 days after convalescent plasma	Respiratory distress 4 days after achieving clinical improvement
Xu et al., Virol J, 2020	Case report	1	Unknown	Clinical recovery	No adverse effects observed
Ahn et al., J Korean Med Sci, 2020	Case report	2	Unknown	Clinical recovery Reduced viral load Pulmonological improvement	No adverse effects observed



## DISCUSSION

Since early December 2019 and up to July 2020, over 15 million COVID-19 infections with over 640,000 deaths are reported in 188 countries<sup>(1)</sup>. Former coronavirus epidemics, like severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), have caused numerous deaths. However, the scale and impact of the COVID-19 pandemic remain an unparalleled crisis for public health and the world economy challenging health facilities and healthcare workers worldwide<sup>(2,3,12)</sup>. Coronaviruses are enveloped viruses, with a positive-stranded RNA and a nucleocapsid. Among its structural elements, spike glycoproteins composed of two subunits (S1 and S2) are of great importance<sup>(2,3)</sup>. Characteristic findings in SARS-CoV-2 infection are severe fever, cough, fatigue, dyspnea, and chest radiographs, revealing invasive multilobed lesions that might lead to intensive care unit admission (ICU). In contrast, nasal congestion, runny, and diarrhea are noted in some patients<sup>(2)</sup>. Despite the numerous studies reported on treatments, antiviral therapy for COVID-19 has not been approved, and vaccine development is still under clinical trials. Current treatment focuses on symptomatic management of hypoxemic patients ranging from conventional oxygen therapy to intubation and invasive mechanical ventilation<sup>(8,13)</sup>. One study that evaluated the treatment with dexamethasone in patients hospitalized with COVID-19, show the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support, that mean patient that are not critical ill the improvement was not important<sup>(14)</sup>.

Lack of proven antiviral treatment has led hospitals and clinicians to treat COVID-19 infection with convalescent plasma, a strategy of passive immunization used in the prevention and management of infectious diseases since the early 20<sup>th</sup> century. Recently recovered SARS-CoV-2 patients who may be suitable donors undergo apheresis in order to obtain convalescent plasma containing high-titer antibodies, granted they meet blood donation criteria<sup>(15,16)</sup>. Continuous centrifugation of donor blood allows a selective plasma collection. From this method, single apheresis can yield 400-800ml of plasma, which needs to be stored in 250ml units and frozen within 24h<sup>(17)</sup>. During apheresis, in addition to neutralizing antibodies (NABs), proteins

such as clotting factors, anti-inflammatory cytokines, defensins, pentraxins, and other undefined proteins are also obtained. Rojas et al.<sup>(2)</sup> hypothesized that transfusion of convalescent plasma to infected patients might provide immunomodulation via decreasing a severe inflammatory response; thus, improving patient outcomes.

Considered convalescent plasma donors are asymptomatic individuals age 18-65, with a negative test for COVID-19 after 14 days of recovery and at the moment of the donation<sup>(2)</sup>. Donors' physical examination to establish good health and confirm the absence of respiratory symptoms and fever is essential<sup>(16)</sup>.

Based on the current findings, convalescent plasma treatment should be given to patients with COVID-19 at the right phase or severity of illness and at the right time point. During the first week after infection viremia usually peaks in most acute viral diseases, a primary immune response is found by day 10-14 following virus clearance. By the third week, inflammatory or hyperimmune attacks rather than direct virally caused tissue damage causes clinical deterioration. In theory, convalescent plasma should probably be administered early in the course of the disease (i.e., before day 14, or during the viremic and seronegative stage)<sup>(11,18)</sup>. Timing on convalescent plasma administration appears to be the key. Mild cases can resolve without treatment, yet convalescent plasma administration in critically ill patients with multiorgan failure does not reduce the mortality rate<sup>(11,18)</sup>.

On a systematic review<sup>(3)</sup> authors suggested that the effectiveness of convalescent plasma in reducing hospital length of stay depends on early administration of the therapy, and use as prophylaxis is more likely to be beneficial than treating severe disease. We do not know the optimal timing and dosage of convalescent plasma therapy<sup>(9,19)</sup>. So prompt recognition of COVID-19 patients that are likely to become critically ill is vital to the administration of convalescent plasma. Convalescent plasma treatment can significantly decrease the relative risk of patients' mortality, as shown by previous evidence<sup>(12)</sup>; this may be because the antibodies from convalescent plasma could suppress viremia. Hence, the convalescent plasma intervention's effectiveness could depend on the level of SARS-CoV-2 neutralizing antibodies in donor plasma<sup>(11,18)</sup>. On chest CT scans, different degrees of absorption of pulmonary lesions were observed after



transfusion<sup>(19)</sup>. Improvement of routine laboratory values and pulmonary function were among the laboratory findings: a significant increase in neutralizing antibody (NaBs) titers and lymphocyte count, and a decrease in C-Reactive protein, alanine aminotransferase, and aspartate aminotransferase after convalescent plasma transfusion<sup>(20,21)</sup>. Data from ten critically ill patients infected with COVID-19 from 3 different hospitals in Wuhan suggested high-titer convalescent plasma transfusion can effectively neutralize SARS-CoV-2, without severe adverse events. These patients showed improvement in clinical outcomes or were cured and discharged from the hospital<sup>(15,20)</sup>.

Convalescent plasma is a generally safe and well-tolerated therapy (Table 1); although, side effects can occur. Currently, there is little information about severe adverse effects due to convalescent plasma, but symptoms reported are similar to those found in other types of plasma blood component transfusion, including fever or chills, allergic reactions, and transfusion-related acute lung injury (TRALI). Plasma transfusions are also known to cause transfusion-associated circulatory overload (TACO)<sup>(3,12,21)</sup>. Convalescent plasma decreased viral load, and there were no reported side effects<sup>(21,22)</sup>. A case report<sup>(23)</sup> noted that respiratory distress developed in two patients four days after convalescent plasma therapy showed clinical improvement.

## CONCLUSION

Convalescent plasma provides the potential to render an immediate promising treatment option

while evaluating existing drugs and developing new specific vaccines and therapies. It is important to note that in theory, convalescent plasma should probably be administered early in the course of the disease (i.e., before day 14, or during the viremic and seronegative stage). Still, appropriate timing on convalescent plasma administration and the severity of its adverse effects needs to be further studied. Furthermore, the benefits and effectiveness of convalescent plasma far outweigh the possible side effects, since there is no specific pharmacological therapy or vaccine available. Convalescent plasma therapy use in the management of patients at different severity levels of COVID-19 disease has become a management pillar in global management and an accessible option in developing countries.

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