# 18. Effectiveness of convalescent plasma therapy for COVID-19

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NARRATIVE REVIEW CORONA EXPERIENCE

# Effectiveness of convalescent plasma therapy for COVID-19 patients infected with variants of concerns

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## Abstract

COVID-19 cases in Indonesia seemed to be increasing by each passing day at the time of writing this review, more positive cases discovered than the recovered ones. With the highest rank within all ASEAN countries, and also a home of many variants of COVID-19, Indonesia had become a break off destination to others. Along with the problem associated with the pandemic, which all people had to face, the purpose of this review is to elaborate the use of convalescent plasma therapy on treatment against COVID-19, especially its different variants. We overview the evidence that we obtained from several databases using specific keywords. A large amount of evidence points out that the convalescent plasma therapy has shown a promising outcome against COVID-19 infection, as it did for infectious diseases. Although in COVID-19 variants of concern, convalescent plasma therapy showed a reduction in neutralization ~ 3-fold against P.1, and 7-13 folds against B.1.351 variant, it still can be used as a treatment for COVID-19 and its variants.

**Abbreviations:** PPE - personal protective equipment; VoC - Variants of concern; VoI - Variants of interest; CPT - convalescent plasma therapy; RBD - receptor-binding domain; ARDS - Acute Respiratory Distress Syndrome; ICU - Intensive Care Unit; IQR - Interquartile Range; RCT - Randomized Clinical Trial; RT-PCR - Reverse Transcriptase-Polymerase Chain Reaction; NAbs - neutralizing antibodies

**Key words:** Convalescent plasma therapy; COVID-19, Variants of Concern

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## 1. Introduction

At this time, all countries around the globe, including Indonesia have been suffered from misery of COVID-19 since March, 2020.[1] As of August 7th, 2020 Indonesia surpassed People's Republic of China with the total of 121.226 cases, 5.593 deaths, and 77.557 recovered.[2] Indonesia has been and continues to struggle to overcome this pandemic, especially in the last few weeks with the variant of concern that hit Indonesia and caused the second wave. Recently, Indonesia has reached new record with total confirmed cases over 2,780,803 and 71,397 deaths which makes Indonesia become the epicenter in Asia. Notwithstanding, the government of Indonesia has initiated on using many ways and strategies to suppress the COVID-19 spread in the community since 2020. Ever since the first case was confirmed to be positive, measures taken included large scale social restrictions, strict stay-at-home orders, improvement in healthcare services, and provision of personal protective equipment (PPEs) to healthcare workers across the country.[3]

'Variants of concern' (VoCs) comprise of SARS-CoV-2 variants that meet the definition of a VoIs (variants of interest) and, through a comparative assessment, have been demonstrated to be associated with increases in transmissibility or detrimental change in COVID-19 epidemiology, increases in virulence or changes in clinical disease presentation, and/or decreases in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics at a degree of global public health significance.[4] As VoCs have been suspected for the massive spread and higher mortality cases, various studies had introduced the use of convalescent plasma therapy (CPT) as an adjuvant therapy to counter against it. CPT is a passive antibody therapy administered to the patients with a main purpose to treat and possibly prevent infectious diseases.[5,6] As SARS-CoV-2 VoC strains spread in human populations, the use of CPT was proposed as alternative therapy options. This provides an additional rationale for surveillance of virus strains, which is necessary to follow SARS-CoV-2 evolution, just as it is for influenza.[7]

A recent study showed that although the beta (B.1.351) and gamma (P.1) variants had similar mutations in their receptor-binding domain (RBD), administration of serum from recovered patients as well as recipients of mRNA vaccine showed a ~3 fold reduction in neutralization against P.1 and as much as 7-13 fold for B.1.351.[8,9] Another study also stated that the plasma generated by infection with the B.1.351 variant not only effectively neutralized the B.1.351 virus, but also succeeded in cross-neutralizing the previous variant.[10,11,12] We aimed to elaborate studies on how much efficacy CPT does have in order to neutralize the infection, to accelerate the recovery rate and lower the damages caused. The authors worked on descriptive research, collecting data from various published sources on CPT and also COVID-19, including its VoCs. The collected data was then compiled and describes how the CPT does work and how much it has proved effective against COVID-19 VoCs.

## 2. CPT in COVID-19 and its efficacy against VoCs

CPT has been used to prevent and possibly cure infectious diseases; this notion obviously includes SARS-CoV2 infection. Several studies evaluated the effects of therapy in COVID-19 patients, one of which looked at studies in China and one study in Korea involving a total of 27 patients with varying degrees of severity.[13 – 17] They concluded that CPT in COVID-19 patients shows promise as it has improved clinical symptoms, laboratory and imaging parameters, but it is too early to be sure it is purely from transfusion due to various underlying clinical conditions, other treatments received, comorbidities and several days of transfusion treatment after the patient's hospitalization.[18]

An uncontrolled case series of five ARDS-complicated COVID-19 patients were on mechanical ventilation, four of whom were ≥ 50 y of age. They received 400 mL of convalescent plasma infusion each immediately after being obtained by aphaeresis from ABO-compatible donors. Following plasma transfusion, with an IgG titter > 1000 and a neutralization titter > 40, the patient's high temperature returned to normal within 3 days and the range of their $PaO_2/FiO_2$ improved within 12 days. While it has shown and realized that the administration of convalescent plasma containing neutralizing antibody was followed by improvement in the patients' clinical status, they were faced with several limitations such as the uncontrollable status of the case. It is not clear if these patients would have improved without transfusion of convalescent plasma since they were also administered other medications. Hence, it is difficult to determine whether the improvement observed was in fact, related to CPT or other medications.[13,19]

The clinical benefits of CPT reported in various studies may include reduced mortality, improved $O_2$ saturation, reduced time for clinical improvement, reduced ventilator support requirement, increased $PaO_2/FiO_2$, improved radiologic finding, and improved respiratory distress symptoms. Plasma donor contains anti-inflammatory cytokines, neutralizing antibody, and other proteins which have immunomodulatory effects from anti-inflammatory cytokines and neutralizing antibody.[20,21] Neutralizing antibody is essential to prevent SARS-CoV-2 entering lung tissues which afterward causing activation of neutrophils and

 

macrophage in lung tissues. Pulmonary damage is associated with activation of neutrophils and macrophage.[22] Beside neutralizing antibody activity, CPT also increases lymphocyte count in infected patients and reduces neutrophils and macrophage activation.[23] Using CPT as adjuvant therapy has been suggested to help suppress the virus and modify the inflammatory response.[24,25]

Time is essential factor of antibodies production and the appropriate timing for CPT administration is crucial. Previous clinical trials have proved that CPT could be more beneficial and the efficacy reached its highest effect at early phase of disease before the patient is critically ill.[26,27] The reason might be that the antibody contained in CPT might have suppressed viremia which commonly peaked in the early phase of the disease.[26] Moreover, CPT could also prevent overactivity of immune system and also avert cytokine storm and lung damage.[27]

On the other hand, the most problematic COVID-19's VoC right now is the delta variant (B.1617.2.1), which was first discovered in India.[28] This delta variant has been designated as a 'variant of concern' thus it gets attention related to the risk to public health which is higher and has been mentioned if this type has shown increased transmission in the community. Some of the results showed that viruses with the B.1.617 spikes were 2.3 fold resistant to neutralization by convalescent sera and it were caused by the L452R and E484Q mutation.[29] Another study stated that the effect of CPT on the Delta variant showed a significantly decreased neutralization titer by 4-6 fold when compared to the Alpha and D614G strains. This study indicated that the Delta variant showed increased resistance to neutralization by serum from unvaccinated, recovered individuals, particularly one year after the infection.[30] Thus the Delta variant is declared less sensitive to the administration of CPT.

Chen et al. showed that samples taken on the third day likely reflect antibody titers from convalescent plasma donors, showing strong neutralization titers against the Alpha variant, but at the same time neutralizing antibody titers decreased abruptly from 3 days to 10 and persisted at low levels up to 19th day.[31] The decrease in neutralizing antibody could be partially explained by the reduced neutralizing activity after CPT. Interestingly, the neutralizing antibody titer increased after day 19 and reached the same level as day 3 on day 33 and day 56.[31] In another in-vitro study, the beta variant exhibited complete escape from therapeutically relevant monoclonal antibodies as well as neutralizing antibodies in COVID-19 convalescent plasma.[32] Another study showed that most sera had high activity against the parental spike protein of the virus and the α variant to a lesser extent.[33] Only 58% of serum samples could efficiently neutralize a spike protein derivative containing mutations present in the β variant.[33] Besides, only 43% of non-ICU hospitalized patients had neutralizing antibody activity greater than 50 serum dilution IC50 against the spike protein with the K417N/E484K/N501Y mutation found in the β variant. The γ variant has a similar mutation profile in the RBD, and some of these non-ICU patients would be predicted to be susceptible to infection by this SARS-CoV-2 variant. Individuals whose infection had required an ICU stay generally displayed higher neutralizing antibody activity against all tested spike protein variants, although they too were less effective against the β-γ triple mutant.[33]

## 3. Mechanism of action

It was then understood that passive immunomodulatory properties, along with pathogen neutralization can be provided by the immune plasma. Neutralizing antibodies are considered essential, saying that titered antibodies in the convalescent plasma were associated with the efficacy of this therapy.[5,18,43] It proved to decrease the viral load, cytokine response, and mortality rate.[44,45,46]

CPT involves collection of plasma from the recovered patients via apheresis and transfused to symptomatic patients, assuming the donor has developed antibodies against the causal agent of the disease.[47,48] During apheresis, neutralizing antibodies (NAbs) and other proteins such as clotting factors, anti-inflammatory cytokines, defensins, pentraxins, natural antibodies, and other undefined proteins are collected from donors. Convalescent plasma transfusion into a COVID-19 patient is expected to have an antiviral effect from the antibodies and other immunomodulation benefits in severe inflammatory response of COVID-19.[48] Here are several potential mechanism of CPT against COVID-19:

### 3.1. Neutralizing and suppresion of viremia

Study of CPT administration among severe COVID-19 patients was shown to be beneficial in reducing short-term mortality.[49] CPT also improved clinical outcomes in severe and critically ill COVID-19 patients.[13,15,49,50,51] Reduced mortality and morbidity in COVID-19 patients, who received CPT, may be explained by mechanisms involving neutralization and suppression of the viremia.[13,15,49,50,51,52] Several studies have shown that CPT can increase the cycle threshold (CT) value [13,15] or decrease viral load up to being undetectable.[13,5,49,50] As shown in an RCT conducted by Li *et al*., CPT was associated with negative conversion rate of viral PCR in 87.2% COVID-19 patients at 72 h post-infusion.[51] These should be good results because viral load was associated with the disease severity and progression.[53,54]

NAbs have been considered as the key factor of CPT mechanism of action in restricting virus infection.[15,52] NAbs was correlated with SARS-CoV-2-specific

 

antibody, targeting on different domains of spike (S) protein including RBD, S1, and S2 that mediate virus entry into host cells via the ACE2 receptor.[52,55,56] NAbs play a vital role as long-lasting humoral immune response in accelerating virus clearance and preventing entry into target cells, also critical for patient's survival and viral control.[13,15,52,55,56] It was known that NAbs titers significantly increased in COVID-19 patients after convalescent plasma transfusion and provide rapid neutralization in viremia.[13,15,49,50,51] This neutralizing mechanism was one of the reasons for CPT efficacy [50] and could be a promising ability in improving survival and clinical outcomes of COVID-19 patients.

### 3.2. Immunomodulation

CPT immunomodulation works through multiple different mechanisms. Antibodies in CPT increase antigen presentation to T cells. Marked increases in $CD8^+$ and $CD4^+$ SARS-CoV-2-specific T cells were found following CPT and simultaneously produced TNF-α and IFN-γ.[57] An immunoglobulin fragment, F(ab')2, provides high neutralization titers against different strains of SARS-CoV-2. However, the efficacy of F(ab')2 has not yet been determined against other recent mutants such as the Delta variant.[58] The Fc region of IgG isotype has been associated with inhibitory effects of the immune cells and may help the modulation of immune response in COVID-19 patients. FcRn receptor is a critical regulator of IgG half-life that works by preventing degradation and clearance of IgG and shortening autoantibodies lifetime in autoimmune conditions.[59,60] Some antibodies may limit the inflammatory cascade driven by pathogenic antibodies, as well as the cellular damage induced by the complement cascade (i.e., C3a and C5a) activation in excessive inflammatory environments, limiting the formation of immune complexes. IgG transferred by plasma also neutralize cytokines such as IL-1β and TNFα.[60]

CPT may enhance anti-inflammatory properties of dendritic cells by canceling the maturation of dendritic cells, reducing production of IL-12, enhancing production of IL-10, IL-4, IL-13, and IL-33 that expands IL-4-producing basophils and enhances Th2, activating β-catenin in an IgG-sialylation independent manner that is critical for reducing inflammation, and down regulation of HLA-II.[61–66] On cell B, CPT inhibits NF-κB signaling pathway, causes reduction of CD25 and CD40 expression and reduction of IL-6 and IL-10 production by B cells and it seems to be regulated by SH2 domain–containing phosphatase 1.[60] CPT also contains NAbs for B cell–activating factor (BAFF) that could cause a reduction in proliferation and increased rates of apoptosis of B cells. B-cell receptor (BCR) may also experience modulations by the interaction of BCR and CD22 resulted in a down-regulation of tyrosine phosphorylation of Lyn and the B-cell linker proteins which resulted in a sustained activation of Erk 1/2 and arrest of the cell cycle at the G/1 phase.[60]

CPT may also promote anti-inflammatory macrophage profile by increasing production of IL-10 cytokine and reducing IL-12/23p40. Administration of convalescent plasma in early stages of COVID-19 may prevent innate immune cells migration to lung tissues and prevent excessive cytokine production and pulmonary damage.[60] A study showed a significant drop of neutrophil counts 3 days after plasma infusion.[67] COVID-19 patients experienced lower eosinophil count and normal level of eosinophil count was correlated with better prognosis. However, a study found there were no significant differences in eosinophil counts in patients with CPT compared to conventional therapy, despite another case report showing a patient with eosinophilia following CPT. Therefore, the effect of CPT on eosinophil count still needs further investigation.[68,69]

### 3.3. Antibody-dependent cellular cytotoxicity

In terms of CPT mechanisms, it's worthy to note that, aside from neutralization, there are a number of additional probable direct and indirect humoral and cellular immunological processes through which convalescent plasma works against virus.[70] In addition to complement-mediated inactivation of viral particles and/or their phagocytosis, one of the key direct ways is Antibody-dependent cellular cytotoxicity (ADCC), in which convalescent plasma can destroy infected cells exhibiting viral antigens on their surface.[70] ADCC is a cell-mediated immune defense process in which an immune system effector cell purposefully lyses a target cell which membrane-surface antigens are bound by particular antibodies.[71] In ADCC, NK cells use their FcRIII receptor, CD16, to detect and attach to Ab-opsonized (targeted) cells, resulting in perforin and cytotoxicity granzyme degranulation of infected target cells.[72] ADCC is also considered to play an essential role in the body's response to COVID-19 infection which the elevated ADCC response has been linked to inflammation during viral infection.[73] According to a study, of 95 people infected with SARS-CoV-2 found an increase in ADCC activity in COVID-19 patients, especially those who were hospitalized.[74] This is also supported by another study that shown that the highest level of ADCC was about 2 weeks from the onset of the disease, that were early than the peak period of neutralizing antibodies (Nabs), which was around 3 weeks.[75] From 6 to 12 months after infection, ADCC activity remained generally steady until the last tested point at 462 days.[75] This data suggests that ADCC can be used as an infection marker instead of Nab, extending the window beyond what can be deduced from neutralizing activity.[75]

 

Table 1: Reports of convalescent plasma therapy in COVID-19 in 2021

| Author, Year | Location | Study Design | Total Sample and Characteristics | | Age | Timing and Dose | Prior or Current Treatments | Outcomes | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|
| | | | CPT patients | Control | CPT patients | | | | |
| Allahyari et al., 2021[27] | Iran | RCT | 32 patients, including severe (n=4), moderate (n=9), and mild (n=19) with ARDS | 32 patients, matched with intervention group | 58.74 ± 14.67 | 600 ml | N/A | decrease in the length of hospital stay<br>lower need for non-invasive mechanical ventilation and intubation and finally mortality rate<br>non significant decrease 28-days mortality | no adverse reactions related to plasma therapy were reported |
| AlQahtani et al., 2021[34] | Bahrain | RCT | 20 patients, including severe (n=19) and life-threatening (n=1) patients | 20 patients, including severe (n=18) and life-threatening (n=2) patients | 52.6 ± 14.9 | 200 ml , two times on 2 consecutive days | corticosteroid, Hydroxychloroquine, Lopinavir/ritonavir, Ribavirin, Azithromycin, Peginterfeon, Tocilizumab, antibiotics, anticoagulation | lower length of stay (p=0.12)<br>lower need of non-invasive ventilator (p=0.47)<br>lower time on ventilator (p=0.809)<br>lower death (p=0.55) | spontaneously settled diarrhoea and vomiting (n=1), desaturated transiently after the infusion (n=1) |
| Bandopadhyay et al., 2021[35] | India | RCT | 17 patients | 13 patients | 60.0 ± 11.5 | 200 ml , two times on 2 consecutive days | corticosteroid, anticoagulation, antibiotic, antidiabetic, antihypertensive , awake proning | faster mitigation of hypoxia<br>improvements in Spo2/Fio2 ratio which correlate with the neutralizing antibodies content | N/A |
| Bennett-Guerrero et al., 2021[36] | USA | double-blind RCT | 59 patients, including ICU (n=17) and severe (n=44) patients | 15 patients, including ICU (n=3) and severe (n=13) | 67 ± 15.8 | 480 mL, single unit | corticosteroid, immunosuppressant , Remdesivir, Hydroxychloroquine, Tocilizumab, Sarilumab | no difference ventilator-free days (p=0.86)<br>lower 90-days all-cause mortality (p=0.74)<br>lower 28-d all-cause mortality (p=0.80) | infusion related (2%), serious adverse event in 28 days (30%) |
| Cho et al., 2021[37] | USA | hypothetical randomized trial (using observational data) | 402 patients, including prior ICU (n = 153) | 10867 patients, including prior ICU (n = 2204) patients | 65.0 ± 11.3 | N/A | corticosteroid, Remdesivir | higher 30-Day Mortality (6.5% vs 6.2%)<br>30-Day mortality (risk difference 0.30%, 95% CI −2.30-3.60%)<br>higher 30-Day mortality (HR 1.04, 95% CI 0.64–1.62) | no adverse reactions related to plasma therapy were reported |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Gharbharan et al., 2021** [38] | The Netherlands | RCT | 43 patients, including ICU (n=5) patients | 43 patients, including ICU (n=8) patients | median 61 (IQR 56–70) | 300 ml , second dose after 5 days (only for persistent positive RT-PCR) | N/A | lower mortality (6 (14%) vs 11 (26%)) than standard care patients | no adverse reactions related to plasma therapy were reported |
| **Mahapatra et al., 2021** [39] | India | Case Control | 1189 patients, including precritical (n=959) and critical (n=230) patients | 1243 patients, including precritical (n=996) and critical (n=247) patients | range 18-85 | 200–250 mL | N/A | lower 28-day mortality 44.3% | no adverse reactions related to plasma therapy were reported |
| **O'Donnell et al., 2021** [40] | USA and Brazil | RCT | 147 patients, all severe and critical patients | 72 patients, all severe and critical patients | median 60 (IQR 48-71) | 200–250 mL, single unit | corticosteroids, Remdesivir, Hydroxychloroquine , antibiotics | higher clinical status at 28 days (OR 1.50, 95% [CI] 0.83–2.68, p=0.180)<br>lower 28-day mortality (OR 0.44, 95% CI 0.22–0.91, p=0.034)<br>shorter time to clinical improvement (sHR 1.21, 95% CI 0.89–1.65, p=0.231) | serious adverse events (26.5%), with cardiovascular (65.3%), endocrine (6.1%), gastrointestinal/hepatic (29.3% ), hematologic (18.4%), infectious (19.7%), inflammatory (4.1%), miscellaneous (3.4%), musculoskeletal/dermatologic (4.8%), pulmonary (22.4%), adverse events |
| **Rejeki et al., 2021** [41] | Indonesia | single-arm, clinical trial | 10 patients, including moderate (n=5) and severe (n=5) patients | N/A | median 56.6 (range 42-75) | 3 mL/kg, three times with 2-day intervals | corticosteroid, Oseltamivir / Favipiravir / Ritonavir / Lopinavir | largely alleviated symptoms within 1-3 days in all patients<br>improved PaO2/FiO2 ratio in 8 patients | no adverse reactions related to plasma therapy were reported |
| **Sekine et al., 2021** [42] | Brazil | parallel-arm, clinical trial. | 80 patients, including ICU (n=53) patients | 80 patients, including ICU (n=53) patients | median 60.5 (IQR 48-68) | 300 mL, two times with 2-day intervals | corticosteroid, immunomodulators, antibiotic agents, antiviral | lower clinical improvement at 28 days (p=0.623)<br>higher death at 14 days (p=0.186)<br>higher death at 2 days (p=0.321)<br>longer time from randomization to hospital discharge (p=0.869) | grade 3 or 4 adverse effects (63.3%) |

***Abbreviation:*** *ARDS: Acute Respiratory Distress Syndrome; CI : Confidence Interval; CPT : Convalescent Plasma Therapy; ICU : Intensive Care Unit; IQR : Interquartile Range; N/A : Not Applicable; RCT : Randomized Clinical Trial; RT-PCR : Reverse Transcriptase-Polymerase Chain Reaction*

According to several studies show that the efficacy of a CPT should be measured not just in terms of the quantity of neutralizing antibodies (nAb) produced, but also in terms of the totality of the SARS-CoV-2-specific humoral response produced. In such studies, the possible contribution and persistence of non-neutralizing antibodies' effector mechanism should be evaluated. Given the importance and urgency of establishing a successful CPT, a more extensive and in-depth examination is certainly required to have a better understanding.[72]

### 3.4. Restoration of Coagulation Factor

COVID-19 viral infection has direct effect on the endothelium, causing endothelial injury and inflammation that may lead to profound thromboses in COVID-19 patients.[76] Convalescent plasma treatment could be the solution for restoring the coagulation factor.[77] In a study conducted by Klompas et al.[78], low rates of thrombotic and thromboembolic events were found in COVID-19 patients, even in critically ill COVID-19 patients, who had convalescent plasma transfusion.[78]

Convalescent plasma provides procoagulant and antifibrinolytic factors that could restore the endothelium glycocalyx and prevent vascular leakage.[77] Steric hindrance between receptor and ligand that provides by plasma and proteins in plasma have important role in fixing the endothelium glycocalyx.[76] D-dimer levels, which is an important marker of thrombosis, was found decreased in following to the convalescent plasma transfusion. Convalescent plasma is a source of some plasma proteins that have important role in the hemostatic process, such as antithrombin and albumin.[79]

### 3.5. CPT on Variant of Concern

The use of CPT against VoCs will work depending on the strain-specific match between the antibody present in the donor plasma and the variant that infects the patient. For example, the Alpha variant which has changes in spike glycoprotein can be neutralized by CPT.[80,81] Meanwhile, the Beta variant also shows significant neutralization when given CPT, but CPT only works effectively if patients who receive CPT also get or have SARS-CoV2 IgG antibody that is high.[32,82] However, neutralization ability of CPT is reported less effective when introduced to Delta variant as much as threefold to fivefold less than wild-type D614G strain.[83] Moreover, Delta sub-lineages such as Delta+N501S or variants under monitoring such as C.1.2 are largely resistant to CPT.[83] Another study also reported that the effect of CPT for delta decreases compared to previous variants.[84] Surprisingly, the Omicron variant has shown extensive escape from CPT and it has not shown any improvement in outcomes.[85]

## 4. Limitations of CPT

Even though CPT has been stated to offer promising results in treating COVID-19 and its VoCs, there are still several limitations in its use. As declared that CPT is not authorized for non-hospitalized patients with COVID-19 under the Emergency Use Authorization (EUA), and it is still not recommended during pregnancy, because the safety and efficacy have not been evaluated.[86] Reported in other study, titer of neutralizing antibodies are not always high in all CPT donors and levels of these antibodies last only for short duration, estimated for weeks or months.[87,88] It also still requires special consideration to determine the effective timing for giving CPT to the recipient.[89] For treatment purpose, it is needed in large volumes, e.g., between 200-2400 mL of plasma.[15,17,90] There are several probable adverse effects that may lead to life-threatening condition such as bronchospasm, transfusion related acute lung injury and circulatory overload in patients with cardiorespiratory disorders, renal impairment and aged individuals; also immunological reactions that could turn into serum sickness and anaphylaxis.[87,91]

Several studies in current recovery trials have shown contradictive results with the benefits of CPT in patients with COVID-19. In a clinical trial, the administration of high-titer CPT did not improve clinical outcome and survival of patients with severe to life-threatening COVID-19.[51] A meta-analysis of 10 RCTs also revealed that treatment with CPT was not associated with any benefit for clinical outcomes or with decrease in all-cause mortality, compared to placebo or standard treatment group.[92] This evidence showed that the use of CPT in COVID-19 still needs special concern and further studies to prove its clinical benefits, if any.

## 5. Conclusion

In conclusion, the effectiveness of the CPT is currently questionable in the treatment of COVID-19 and its variants of concern. It seems to have been abandoned because CPT does not work well against some variants of concern. In addition, there are still reservations about its use including not so much improvement in patient survival and other clinical outcomes.

### 6. Conflict of Interests

There is no conflict of interests declared by the authors.

### 7. Authors' contribution

EMK: concept, literature search, proofreading

ISP: concept, literature search, manuscript editing

DMW, VMP, V, MZ, FNP, AAW: concept, manuscript editing

FUP: concept, literature search, manuscript writing, bibliography editing

 

DN: concept, manuscript editing, bibliography editing

## 8. References


1. Djalante R, Lassa J, Setiamarga D, Sudjatma A, Indrawan M, Haryanto B, et al. Review and analysis of current responses to COVID-19 in Indonesia: Period of January to March 2020. Prog Disaster Sci. 2020;6:100091. [PubMed] DOI: 10.1016/j.pdisas.2020.100091
2. COVID-19 STP. Peta Sebaran Covid-19 di Indonesia; 2021. Available from: https://covid19.go.id/peta-sebaran-covid19
3. Nugraha D, Kloping NA, Yudhawati R, Purwandhono A, Hidayati HB. A current update in COVID-19 associated acute respiratory distress syndrome: Focus on mesenchymal stem cell therapy. Anaesth Pain Intensive Care. 2020;24(6). DOI: 10.35975/apic.v24i6.1404
4. Organization WH. Tracking SARS-CoV-2 variants [Internet]; 2021. Available from: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/
5. Choi JY. Convalescent plasma therapy for coronavirus disease 2019. Infect Chemother. 2020 Sep;52(3):307-316. [PubMed] DOI: 10.3947/ic.2020.52.3.307
6. Samad N, Sodunke TE, Banna H Al, Sapkota A, Fatema AN, Iskandar K, et al. Convalescent plasma therapy for management of covid-19: perspectives and deployment in the current global pandemic. Risk Manag Healthc Policy. 2020 Nov 23;13:2707-2728. [PubMed] DOI: 10.2147/RMHP.S281388
7. Casadevall A, Henderson JP, Joyner MJ, Pirofski LA. SARS-CoV-2 variants and convalescent plasma: reality, fallacies, and opportunities. J Clin Invest. 2021 Apr 1;131(7):e148832. [PubMed] DOI: 10.1172/JCI148832
8. Dejnirattisai W, Zhou D, Supasa P, Liu C, Mentzer AJ, Ginn HM, et al. Antibody evasion by the P.1 strain of SARS-CoV-2. Cell. 2021 May 27;184(11):2939-2954.e9. [PubMed] DOI: 10.1016/j.cell.2021.03.055
9. Garcia-Beltran WF, Lam EC, Denis K St., Nitido AD, Garcia ZH, Hauser BM, et al. Multiple SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity. Cell. 2021 Apr 29;184(9):2372-2383.e9. [PubMed] DOI: 10.1016/j.cell.2021.03.013
10. Xie X, Liu Y, Liu J, Zhang X, Zou J, Fontes-Garfias CR, et al. Neutralization of SARS-CoV-2 spike 69/70 deletion, E484K and N501Y variants by BNT162b2 vaccine-elicited sera. Nat Med. 2021 Apr;27(4):620-621. [PubMed] DOI: 10.1038/s41591-021-01270-4
11. Wang Z, Schmidt F, Weisblum Y, Muecksch F, Barnes CO, Finkin S, et al. mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants. Nature. 2021;592(7855):616–22. [PubMed] DOI: 10.1038/s41586-021-03324-6
12. Liu Y, Liu J, Xia H, Zhang X, Fontes-Garfias CR, Swanson KA, et al. Neutralizing Activity of BNT162b2-Elicited Serum. N Engl J Med. 2021 Apr 15;384(15):1466-1468. [PubMed] DOI: 10.1056/NEJMc2102017
13. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 Critically ill patients with covid-19 with convalescent plasma. JAMA. 2020;323(16):1582. [PubMed] DOI: 10.1001/jama.2020.4783
14. Ahn JY, Sohn Y, Lee SH, Cho Y, Hyun JH, Baek YJ, et al. Use of convalescent plasma therapy in two covid-19 patients with acute respiratory distress syndrome in Korea. J Korean Med Sci. 2020;35(14). [PubMed] DOI: 10.3346/jkms.2020.35.e149
15. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci. 2020;117(17):9490–6. [PubMed] DOI: 10.1073/pnas.2004168117
16. Ye M, Fu D, Ren Y, Wang F, Wang D, Zhang F, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. J Med Virol. 2020;92(10). [PubMed] DOI: 10.1002/jmv.25882
17. Zhang B, Liu S, Tan T, Huang W, Dong Y, Chen L. Treatment with convalescent plasma for critically ill patients with severe acute respiratory syndrome coronavirus 2 infection. Chest. 2020;158(1):e9–13. [PubMed] DOI: 10.1016/j.chest.2020.03.039
18. Putera DD, Hardianti MS. Efficacy and safety of convalescent plasma therapy in patients with COVID-19: a rapid review of case series. J thee Med Sci (Berkala Ilmu Kedokteran). 2020;52(03). [FreeFullText]
19. Alghamdi AN, Abdel-Moneim AS. Convalescent Plasma: A Potential Life-Saving Therapy for Coronavirus Disease 2019 (COVID-19). Front Public Health. 2020 Aug 6;8:437. [PubMed] DOI: 10.3389/fpubh.2020.00437
20. Garraud O, Heshmati F, Pozzetto B, Lefrere F, Girot R, Saillol A, et al. Plasma therapy against infectious pathogens, as of yesterday, today and tomorrow. Transfus Clin Biol. 2016;23(1):39–44. [PubMed] DOI: 10.1016/j.tracli.2015.12.003
21. van Griensven J, Edwards T, de Lamballerie X, Semple MG, Gallian P, Baize S, et al. Evaluation of convalescent plasma for ebola virus disease in Guinea. N Engl J Med. 2016;374(1):33–42. [PubMed] DOI: 10.1056/NEJMoa1511812
22. Cheng P, Li S, Chen H. Macrophages in lung injury, repair, and fibrosis. Cells. 2021;10(2):436. [PubMed] DOI: 10.3390/cells10020436
23. Huang S, Shen C, Xia C, Huang X, Fu Y, Tian L. A retrospective study on the effects of convalescent plasma therapy in 24 patients diagnosed with covid-19 pneumonia in february and march 2020 at 2 centers in Wuhan, China. Med Sci Monit. 2020;27. [PubMed] DOI: 10.12659/MSM.928755
24. Department of Health NI. COVID-19 Treatment Guidelines. Available from: https://www.covid19treatmentguidelines.nih.gov/
25. Wang X, Guo X, Xin Q, Pan Y, Hu Y, Li J, et al. Neutralizing antibody responses to severe acute respiratory syndrome coronavirus 2 in coronavirus disease 2019 inpatients and convalescent patients. Clin Infect Dis. 2020;71(10):2688–94. [PubMed] DOI: 10.1093/cid/ciaa721
26. Abolghasemi H, Eshghi P, Cheraghali AM, Fooladi AAI, Moghaddam FB, Imanizadeh S, et al. Clinical efficacy of convalescent plasma for treatment of COVID-19 infections: Results of a multicenter clinical study. Transfus Apher Sci. 2020;59(5):102875. [PubMed] DOI: 10.1016/j.transci.2020.102875
27. Allahyari A, Seddigh-Shamsi M, Mahmoudi M, Jamehdar SA, Amini M, Mozdourian M, et al. Efficacy and safety of


 

convalescent plasma therapy in severe COVID-19 patients with acute respiratory distress syndrome. Int Immunopharmacol. 2021;93:107239. [PubMed] DOI: 10.1016/j.intimp.2020.107239

28. Cherian S, Potdar V, Jadhav S, Yadav P, Gupta N, Das M, et al. SARS-CoV-2 Spike Mutations, L452R, T478K, E484Q and P681R, in the Second Wave of COVID-19 in Maharashtra, India. Microorganisms. 2021 Jul 20;9(7):1542. [PubMed] DOI: 10.3390/microorganisms9071542
29. Zhou H, Dcosta BM, Samanovic MI, Mulligan MJ, Landau NR. The Spike Proteins of SARS-CoV-2 B.1.617 and B.1.618 Variants Identified in India 1 Provide Partial Resistance to Vaccine-elicited and Therapeutic Monoclonal 2 Antibodies. bioRxiv. 2021. DOI: 10.1101/2021.05.14.444076
30. Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel-Benhassine F, Rajah MM, et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. Nature. 2021;596(7871). [PubMed] DOI: 10.1038/s41586-021-03777-9
31. Chen L, Zody MC, Germanio C Di, Martinelli R, Mediavilla JR, Cunningham MH, et al. Emergence of multiple SARS-CoV-2 antibody escape variants in an immunocompromised host undergoing convalescent plasma treatment. mSphere. 2021;6(4):e0048021. [PubMed] DOI: 10.1128/mSphere.00480-21
32. Wibmer CK, Ayres F, Hermanus T, Madzivhandila M, Kgagudi P, Oosthuysen B, et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. Nat Med. 2021;27(4):622-625. [PubMed] DOI: 10.1038/s41591-021-01285-x
33. Fenwick C, Turelli P, Pellaton C, Farina A, Campos J, Raclot C, et al. A high-throughput cell- And virus-free assay shows reduced neutralization of SARS-CoV-2 variants by COVID-19 convalescent plasma. Sci Transl Med. 2021;13(605):eabi8452. [PubMed] DOI: 10.1126/scitranslmed.abi8452
34. AlQahtani M, Abdulrahman A, Almadani A, Alali SY, Zamrooni AM Al, Hejab AH, et al. Randomized controlled trial of convalescent plasma therapy against standard therapy in patients with severe COVID-19 disease. Sci Rep. 2021;11(1):9927. [PubMed] DOI: 10.1038/s41598-021-89444-5
35. Bandopadhyay P, D'Rozario R, Lahiri A, Sarif J, Ray Y, Paul SR, et al. Nature and dimensions of systemic hyperinflammation and its attenuation by convalescent plasma in severe covid-19. J Infect Dis. 2021;224(4):565–74. [PubMed] DOI: 10.1093/infdis/jiab010
36. Bennett-Guerrero E, Romeiser JL, Talbot LR, Ahmed T, Mamone LJ, Singh SM, et al. Severe acute respiratory syndrome coronavirus 2 convalescent plasma versus standard plasma in coronavirus disease 2019 infected hospitalized patients in New York. Crit Care Med. 2021;49(7):1015-1025. [PubMed] DOI: 10.1097/CCM.0000000000005066
37. Cho K, Keithly SC, Kurgansky KE, Madenci AL, Gerlovin H, Marucci-Wellman H, et al. Early convalescent plasma therapy and mortality among us veterans hospitalized with nonsevere covid-19: an observational analysis emulating a target trial. J Infect Dis. 2021;224(6):967–75. [PubMed] DOI: 10.1093/infdis/jiab330
38. Gharbharan A, Jordans CCE, GeurtsvanKessel C, den Hollander JG, Karim F, Mollema FPN, et al. Effects of potent neutralizing antibodies from convalescent plasma in patients hospitalized for severe SARS-CoV-2 infection. Nat Commun. 2021;12(1):3189. [PubMed] DOI: 10.1038/s41467-021-23469-2
39. Mahapatra S, Rattan R, Mohanty CBK. Convalescent Plasma Therapy in the management of COVID-19 patients-The newer dimensions. Transfus Clin Biol. 2021;28(3):246–53. [PubMed] DOI: 10.1016/j.tracli.2021.04.009
40. O'Donnell MR, Grinsztejn B, Cummings MJ, Justman JE, Lamb MR, Eckhardt CM, et al. A randomized double-blind controlled trial of convalescent plasma in adults with severe COVID-19. J Clin Invest. 2021;131(13):e150646. [PubMed] DOI: 10.1172/JCI150646
41. Rejeki MS, Sarnadi N, Wihastuti R, Fazharyasti V, Samin WY, Yudhaputri FA, et al. Convalescent plasma therapy in patients with moderate-to-severe COVID-19: A study from Indonesia for clinical research in low- and middle-income countries. EClinicalMedicine. 2021;36:100931. [PubMed] DOI: 10.1016/j.eclinm.2021.100931
42. Sekine L, Arns B, Fabro BR, Cipolatt MM, Machado RRG, Durigon EL, et al. Convalescent plasma for COVID-19 in hospitalised patients: an open-label, randomised clinical trial. Eur Respir J. 2021;59(2):2101471. [PubMed] DOI: 10.1183/13993003.01724-2021
43. Piyush R, Rajarshi K, Khan R, Ray S. Convalescent plasma therapy: a promising coronavirus disease 2019 treatment strategy. Open Biol. 2020;10(9):200174. [PubMed] DOI: 10.1098/rsob.200174
44. Munir MA, Tandiabang PA, Setyawati T, Basry A, Cyio AD, Rahman N. Bioethical perspective of convalescent plasma therapy for COVID-19: A systematic review. Transfus Clin Biol. 2021;28(3):271-275 [PubMed] DOI: 10.1016/j.tracli.2021.03.005
45. Xi Y. Convalescent plasma therapy for COVID-19: a tried-and-true old strategy? Signal Transduct Target Ther. 2020;5(1):203. [PubMed] DOI: 10.1038/s41392-020-00310-8
46. Graham BS, Ambrosino DM. History of passive antibody administration for prevention and treatment of infectious diseases. Curr Opin HIV AIDS. 2015;10(3):129–34. [PubMed] DOI: 10.1097/COH.0000000000000154
47. Zhang Q, Xiang R, Huo S, Zhou Y, Jiang S, Wang Q, et al. Molecular mechanism of interaction between SARS-CoV-2 and host cells and interventional therapy. Signal Transduct Target Ther. 2021;6(1):233. [PubMed] DOI: 10.1038/s41392-021-00653-w
48. Moubarak M, Kasozi KI, Hetta HF, Shaheen HM, Rauf A, Al-kuraishy HM, et al. The Rise of SARS-CoV-2 Variants and the Role of Convalescent Plasma Therapy for Management of Infections. Life. 2021;11(8):734. [PubMed] DOI: 10.3390/life11080734
49. Perotti C, Baldanti F, Bruno R, Del Fante C, Seminari E, Casari S, et al. Mortality reduction in 46 patients with severe COVID-19 treated with hyperimmune plasma. A proof-of-concept, single-arm, multicenter trial. Haematologica. 2020;105(12):2834–40. [PubMed] DOI: 10.3324/haematol.2020.261784
50. Xia X, Li K, Wu L, Wang Z, Zhu M, Huang B, et al. Improved clinical symptoms and mortality among patients with severe or critical COVID-19 after convalescent plasma transfusion. Blood. 2020 Aug 6;136(6):755-759. [PubMed] DOI: 10.1182/blood.2020007079

 

51. Li L, Zhang W, Hu Y, Tong X, Zheng S, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening covid-19 a randomized clinical trial. JAMA. 2020;324(5):460-470 [PubMed] DOI: 10.1001/jama.2020.10044

52. Wu F, Wang A, Liu M, Wang Q, Chen J, Xia S, et al. Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. medRxiv. 2020. DOI: 10.1101/2020.03.30.20047365

53. Ng KT, Oong XY, Lim SH, Chook JB, Takebe Y, Chan YF, et al. Viral load and sequence analysis reveal the symptom severity, diversity, and transmission clusters of rhinovirus infections. 2018;67(2):261–8. [PubMed] DOI: 10.1093/cid/ciy063

54. Fajnzylber J, Regan J, Coxen K, Corry H, Wong C, Rosenthal A, et al. SARS-CoV-2 viral load is associated with increased disease severity and mortality. Nat Commun. 2020;11(1):5493. [PubMed] DOI: 10.1038/s41467-020-19057-5

55. Dispinseri S, Secchi M, Pirillo MF, Tolazzi M, Borghi M, Brigatti C, et al. Neutralizing antibody responses to SARS-CoV-2 in symptomatic COVID-19 is persistent and critical for survival. Nat Commun. 2021;12(1):2670. [PubMed] DOI: 10.1038/s41467-021-22958-8

56. Wanga C, Lia W, Drabek D, Okba NMA, Haperen R van, Osterhaus ADME, et al. A human monoclonal antibody blocking SARS-CoV-2 infection Running Head: A cross-neutralizing human antibody targeting SARS-CoV and SARS- CoV-2. BioRxiv. 2020. DOI: 10.1101/2020.03.11.987958

57. Bošnjak B, Odak I, Ritter C, Stahl K, Graalmann T, Steinbrück L, et al. Case Report: Convalescent Plasma Therapy Induced Anti-SARS-CoV-2 T Cell Expansion, NK Cell Maturation and Virus Clearance in a B Cell Deficient Patient After CD19 CAR T Cell Therapy. Front Immunol. 2021;12:721738. [PubMed] DOI: 10.3389/fimmu.2021.721738

58. Cunha LER, Stolet AA, Strauch MA, Pereira VAR, Dumard CH, Gomes AMO, et al. Polyclonal F(ab')2 fragments of equine antibodies raised against the spike protein neutralize SARS-CoV-2 variants with high potency. iScience. 2021;24(11):103315. [PubMed] DOI: 10.1016/j.isci.2021.103315

59. Erp EA Van, Luytjes W, Ferwerda G, Kasteren PB Van. Fc-mediated antibody effector functions during respiratory syncytial virus infection and disease. Front Immunol. 2019;10(MAR):548. [PubMed] DOI: 10.3389/fimmu.2019.00548

60. Rojas M, Rodríguez Y, Monsalve DM, Acosta-Ampudia Y, Camacho B, Gallo JE, et al. Convalescent plasma in Covid-19: Possible mechanisms of action. Autoimmun Rev. 2020;19(7). [PubMed] DOI: 10.1016/j.autrev.2020.102554

61. Bayry J, Lacroix-Desmazes S, Carbonneil C, Misra N, Donkova V, Pashov A, et al. Inhibition of maturation and function of dendritic cells by intravenous immunoglobulin. Blood. 2003;101(2):758–65. [PubMed] DOI: 10.1182/blood-2002-05-1447

62. Sharma M, Schoindre Y, Hegde P, Saha C, Maddur MS, Stephen-Victor E, et al. Intravenous immunoglobulin-induced IL-33 is insufficient to mediate basophil expansion in autoimmune patients. Sci Reports. 2014;4(1):1–6. [PubMed] DOI: 10.1038/srep05672

63. Tjon ASW, van Gent R, Jaadar H, van Hagen PM, Mancham S, van der Laan LJW, et al. Intravenous Immunoglobulin Treatment in Humans Suppresses Dendritic Cell Function via Stimulation of IL-4 and IL-13 Production. J Immunol. 2014;192(12). [PubMed] DOI: 10.4049/jimmunol.1301260

64. Karnam A, Rambabu N, Das M, Bou-Jaoudeh M, Delignat S, Käsermann F, et al. Therapeutic normal IgG intravenous immunoglobulin activates Wnt-β-catenin pathway in dendritic cells. Commun Biol. 2020;3(1):1–13. [PubMed] DOI: 10.1038/s42003-020-0825-4

65. Bayry J, Lacroix-Desmazes S, Delignat S, Mouthon L, Weill B, Kazatchkine MD, et al. Intravenous immunoglobulin abrogates dendritic cell differentiation induced by interferon-α present in serum from patients with systemic lupus erythematosus. Arthritis Rheum. 2003;48(12):3497–502. [PubMed] DOI: 10.1002/art.11346

66. Sharma M, Saha C, Schoindre Y, Gilardin L, Benveniste O, Kaveri S V, et al. Interferon-α Inhibition by Intravenous Immunoglobulin Is Independent of Modulation of the Plasmacytoid Dendritic Cell Population in the Circulation: Comment on the Article by Wiedeman et al. Arthritis Rheumatol. 2014;66(8):2308–9. [PubMed] DOI: 10.1002/art.38683

67. Xia X, Li K, Wu L, Wang Z, Zhu M, Huang B, et al. Improved clinical symptoms and mortality among patients with severe or critical COVID-19 after convalescent plasma transfusion. Blood. 2020;136(6):755–9. [PubMed] DOI: 10.1182/blood.2020007079

68. Esmaeili B, Esmaeili S, Pourpak Z. Immunological effects of convalescent plasma therapy for coronavirus: a scoping review. BMC Infect Dis. 2021;21(1):1–10. [PubMed] DOI: 10.1186/s12879-021-06981-0

69. Dai W, Wu J, Li T, Shen J, Pang R, Luo T, et al. Clinical outcomes for COVID-19 patients with diabetes mellitus treated with convalescent plasma transfusion in Wuhan, China. J Med Virol. 2021;93(4):2321–31. [PubMed] DOI: 10.1002/jmv.26712

70. Naranjo-Gomez M, Lambour J, Piechaczyk M, Pelegrin M. Neutrophils are essential for induction of vaccine-like effects by antiviral monoclonal antibody immunotherapies. JCI Insight. 2018 May 3;3(9):e97339. [PubMed] DOI: 10.1172/jci.insight.97339

71. Hashimoto G, Wright PF, Karzon DT. Antibody-dependent cell-mediated cytotoxicity against influenza virus-infected cells. J Infect Dis. 1983 Nov;148(5):785-94. [PubMed] DOI: 10.1093/infdis/148.5.785

72. Tso FY, Lidenge SJ, Poppe LK, Peña PB, Privatt SR, Bennett SJ, et al. Presence of antibody-dependent cellular cytotoxicity (ADCC) against SARS-CoV-2 in COVID-19 plasma. PLoS One. 2021 Mar 4;16(3):e0247640. [PubMed] DOI: 10.1371/journal.pone.0247640

73. Lu LL, Suscovich TJ, Fortune SM, Alter G. Beyond binding: Antibody effector functions in infectious diseases. Nature Reviews Immunology. 2018. [PubMed] DOI: 10.1038/nri.2017.106

74. Dufloo J, Grzelak L, Staropoli I, Madec Y, Tondeur L, Anna F, et al. Asymptomatic and symptomatic SARS-CoV-2 infections elicit polyfunctional antibodies. Cell Reports Med. 2021 May 18;2(5):100275 [PubMed] DOI: 10.1016/j.xcrm.2021.100275

75. Yu Y, Wang M, Zhang X, Li S, Lu Q, Zeng H, et al. Antibody-dependent cellular cytotoxicity response to SARS-CoV-2 in COVID-19 patients. Signal Transduct Target Ther. 2021 Sep


 

24;6(1):346. [PubMed] DOI: 10.1038/s41392-021-00759-1

76. Pati S, Fennern E, Holcomb JB, Barry M, Trivedi A, Cap AP, et al. Treating the endotheliopathy of SARS-CoV-2 infection with plasma: Lessons learned from optimized trauma resuscitation with blood products. Transfusion. 2021;61(S1):S336–47. [PubMed] DOI: 10.1111/trf.16452
77. Al-Riyami AZ. COVID-19 convalescent plasma: Mechanisms of action and rationale for use: A narrative review. Ann Blood. 2021;6(June). DOI: 10.21037/aob-2020-cp-01
78. Klompas AM, van Helmond N, Juskewitch JE, Pruthi RK, Sexton MA, Soto JCD, et al. Coagulation profile of human COVID-19 convalescent plasma. Sci Rep. 2022;12(1):1–7. [PubMed] DOI: 10.1038/s41598-021-04670-1
79. Focosi D, Franchini M, Pirofski L-A, Burnouf T, Fairweather D, Joyner MJ, et al. Covid-19 convalescent plasma is more than neutralizing antibodies: a narrative review of potential beneficial and detrimental co-factors. Viruses. 2021 Aug;13(8):1594. [PubMed] DOI: 10.3390/v13081594
80. Falcone M, Tiseo G, Valoriani B, Barbieri C, Occhineri S, Mazzetti P, et al. Efficacy of Bamlanivimab/Etesevimab and Casirivimab/Imdevimab in Preventing Progression to Severe COVID-19 and Role of Variants of Concern. Infect Dis Ther. 2021;10(4). [PubMed] DOI: 10.1007/s40121-021-00525-4
81. Menichetti F, Falcone M, Tiseo G. Management of COVID patients with convalescent plasma: Do we have the final word? Eur J Intern Med. 2022;95. [PubMed] DOI: 10.1016/j.ejim.2021.10.029
82. Aleem A, Akbar Samad AB, Slenker AK. Emerging Variants of SARS-CoV-2 And Novel Therapeutics Against Coronavirus (COVID-19). 2022 May 12. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022 [PubMed]
83. Focosi D, Franchini M, Joyner MJ, Casadevall A. Are convalescent plasma stocks collected during former COVID-19 waves still effective against current SARS-CoV-2 variants? Vox Sang. 2022 May;117(5):641-646. [PubMed] DOI: 10.1111/vox.13239
84. Dubey A, Choudhary S, Kumar P, Tomar S. Emerging SARS-CoV-2 Variants: Genetic Variability and Clinical Implications. Curr Microbiol. 2022;79(1):20. [PubMed] DOI: 10.1007/s00284-021-02724-1
85. Xu Z, Liu K, Gao GF. Omicron variant of SARS-CoV-2 imposes a new challenge for the global public health. Biosaf Health. 2022 Jun;4(3):147-149. [PubMed] DOI: 10.1016/j.bsheal.2022.01.002
86. National Institue of Health. No Title. 2021.
87. Sullivan HC, Roback JD. Convalescent Plasma : Therapeutic Hope or Hopeless Strategy in the SARS-CoV-2 Pandemic. Transfus Med Rev. 2020;34(3):145–50. [PubMed] DOI: 10.1016/j.tmrv.2020.04.001
88. Roback JD, Guarner J. Convalescent Plasma to Treat COVID-19: Possibilities and Challenges. JAMA. 2020 Apr 28;323(16):1561-1562. [PubMed] DOI: 10.1001/jama.2020.4940
89. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. J Med Virol. 2020 Oct;92(10):1890-1901. [PubMed] DOI: 10.1002/jmv.25882
90. Nagoba B, Gavkare A, Jamadar N, Mumbre S, Selkar S. Positive aspects, negative aspects and limitations of plasma therapy with special reference to COVID-19. J Infect Public Health. 2020 Dec;13(12):1818-1822. [PubMed] DOI: 10.1016/j.jiph.2020.08.011
91. Janiaud P, Axfors C, Schmitt AM, Gloy V, Ebrahimi F, Hepprich M, et al. Association of convalescent plasma treatment with clinical outcomes in patients with covid-19: a systematic review and meta-analysis. JAMA. 2021 Mar 23;325(12):1185-1195. [PubMed] DOI: 10.1001/jama.2021.2747

 

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20 Norma A. Valdez-Cruz, Enrique García-Hernández, Clara Espitia, Laura Cobos-Marín et al. "Integrative overview of antibodies against SARS-CoV-2 and their possible applications in COVID-19 prophylaxis and treatment", Microbial Cell Factories, 2021 <1%
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21 epidatum.com <1%
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22 Delphine Planas, David Veyer, Artem Baidaliuk, Isabelle Staropoli et al. "Reduced sensitivity of infectious SARS-CoV-2 variant B.1.617.2 to monoclonal antibodies and sera from convalescent and vaccinated individuals", Cold Spring Harbor Laboratory, 2021 <1%
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---

23 Juan G. Ripoll, Noud van Helmond, Jonathon W. Senefeld, Chad C. Wiggins et al. "Convalescent Plasma for Infectious Diseases: Historical Framework and Use in COVID-19", Clinical Microbiology Newsletter, 2021 <1%
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| | | |
|---|---|---|
| 24 | Bahrad A Sokhansanj, Zhengqiao Zhao, Gail L Rosen. "Interpretable and Predictive Deep Modeling of the SARS-CoV-2 Spike Protein Sequence", Cold Spring Harbor Laboratory, 2021<br>Publication | <1 % |
| 25 | Tihana Kurtović, Sanda Ravlić, Adela Štimac, Sanja Mateljak Lukačević, Ana Hećimović, Saša Kazazić, Beata Halassy. "Efficient and Sustainable Platform for Preparation of a High-Quality Immunoglobulin G as an Urgent Treatment Option During Emerging Virus Outbreaks", Frontiers in Immunology, 2022<br>Publication | <1 % |
| 26 | Zeinab Rafiee, Fereshteh Nejaddehbashi, Ava Nasrolahi, Fatemeh Khademi moghadam. "Stem cell ‐ based and mesenchymal stem cell derivatives for coronavirus treatment", Biotechnology and Applied Biochemistry, 2021<br>Publication | <1 % |
| 27 | www.covid19treatmentguidelines.nih.gov<br>Internet Source | <1 % |
| 28 | Amélia Carolina Lopes Fernandes, Adson José Martins Vale, Fausto Pierdoná Guzen, Francisco Irochima Pinheiro et al. "Therapeutic Options Against the New Coronavirus: Updated Clinical and Laboratory Evidences", Frontiers in Medicine, 2020 | <1 % |

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29 Denise Battaglini, Fernanda Cruz, Chiara Robba, Paolo Pelosi, Patricia R.M. Rocco. "Failed clinical trials on COVID-19 acute respiratory distress syndrome in hospitalized patients: common oversights and streamlining the development of clinically effective therapeutics", Expert Opinion on Investigational Drugs, 2022 <1%
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30 Kamal Kant Sahu, Vishal Jindal, Ahmad Daniyal Siddiqui, Jan Cerny, Jonathan M. Gerber. "Convalescent Plasma Therapy: A Passive Therapy for An Aggressive COVID‐19", Journal of Medical Virology, 2020 <1%
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31 Majid Khan, Lin Li, Laura Haak, Shannon Harger Payen et al. "Significance of Wastewater Surveillance in Detecting the Prevalence of SARS-CoV-2 Variants and Other Respiratory Viruses in the Community – A Multi-Site Evaluation", Cold Spring Harbor Laboratory, 2023 <1%
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32 Manuel Rojas, Juan-Manuel Anaya. "Why will it never be known if convalescent plasma is effective for COVID-19", Journal of Translational Autoimmunity, 2020 <1%
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| 33 | Marco Zaffanello, Giorgio Piacentini, Luana Nosetti, Massimo Franchini. "The use of convalescent plasma for pediatric patients with SARS-CoV-2: A systematic literature review", Transfusion and Apheresis Science, 2020<br>Publication | <1 % |
| 34 | Sylwester Drożdżal, Jakub Rosik, Kacper Lechowicz, Filip Machaj et al. "An update on drugs with therapeutic potential for SARS-CoV-2 (COVID-19) treatment", Drug Resistance Updates, 2021<br>Publication | <1 % |
| 35 | bmcinfectdis.biomedcentral.com<br>Internet Source | <1 % |
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| 39 | Chiraphat Kloypan, Matthanaporn Saesong, Juthamat Sangsuemoon, Prawat Chantharit, Pajaree Mongkhon. "Convalescent Plasma for COVID‐19: A Meta‐analysis of Clinical Trials | <1 % |

and Real - World Evidence", European Journal of Clinical Investigation, 2021
Publication

---

40 Manish Dhawan, Priyanka, Manisha Parmar, Steffy Angural, Om Prakash Choudhary. "Convalescent plasma therapy against the emerging SARS-CoV-2 variants: Delineation of the potentialities and risks", International Journal of Surgery, 2021 <1%
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---

41 Priyal Mistry, Fatima Barmania, Juanita Mellet, Kimberly Peta et al. "SARS-CoV-2 Variants, Vaccines, and Host Immunity", Frontiers in Immunology, 2022 <1%
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---

42 Alexander M Horspool, Chengjin Ye, Ting Y. Wong, Brynnan P. Russ et al. "SARS-CoV-2 B.1.1.7 and B.1.351 variants of concern induce lethal disease in K18-hACE2 transgenic mice despite convalescent plasma therapy", Cold Spring Harbor Laboratory, 2021 <1%
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---

43 Flordeluna Z Mesina, Maureen Via M Comia, June Marie P Ongkingco, Jimmy R Lafavilla et al. "Use of Convalescent Plasma Therapy with Best Available Treatment (BAT) among Hospitalized COVID-19 Patients: A Multi- <1%

Center Study", Cold Spring Harbor Laboratory, 2022
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| 44 | Milankumar Patel, Farah Shahjin, Jacob D Cohen, Mahmudul Hasan et al. "The Immunopathobiology of SARS-CoV-2 Infection", FEMS Microbiology Reviews, 2021<br>Publication | <1 % |
| 45 | Neima Briggs, Michael V. Gormally, Fangyong Li, Sabrina L. Browning et al. "Early but not late convalescent plasma is associated with better survival in moderate-to-severe COVID-19", PLOS ONE, 2021<br>Publication | <1 % |
| 46 | Ralf Duerr, Keaton M. Crosse, Ana M. Valero-Jimenez, Meike Dittmann. "SARS-CoV-2 Portrayed against HIV: Contrary Viral Strategies in Similar Disguise", Microorganisms, 2021<br>Publication | <1 % |

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