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# Convalescent plasma for COVID-19

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## ■ ABSTRACT

Convalescent plasma has been used for over a century to treat various infections. Given the lack of currently available effective treatment for COVID-19, it has re-emerged as a potential therapeutic option. A direct antiviral effect of virus-neutralizing antibodies in convalescent plasma is believed to be main mechanism of action, but indirect effects may also contribute to improved viral clearance, inflammation, and organ function. While convalescent plasma therapy is proven safe and historical evidence suggests it may be effective, it has not been proven to be of benefit in acute COVID-19. Many clinical trials are currently underway to evaluate convalescent plasma for treatment of COVID-19, but the vast majority of plasma is currently administered as compassionate use of an experimental therapy through an expanded access program. While promising, convalescent plasma remains experimental and is not proven effective. In addition to its unproven efficacy, many questions remain regarding the accuracy and predictive value of antibody testing of donors and patients, optimal donor selection, and optimal timing and selection of patient most likely to benefit. Until these questions are answered, convalescent plasma should ideally be used in the context of well-designed clinical trials.

## ■ INTRODUCTION

COVID-19 convalescent plasma is plasma collected from donors who have recently recovered from acute COVID-19 infection. This plasma is likely to contain high levels of neutralizing antibodies against the SARS-CoV-2 virus, which, when transfused to patients with acute COVID-19 infection, can confer a degree of passive immunity.

Convalescent plasma has been used for over a

century as treatment and postexposure prophylaxis for various infections. Case series from prior viral outbreaks suggest it can reduce viral load and cytokine levels and may improve clinical outcomes. Clinical trials to assess its effectiveness for the treatment of COVID-19 are ongoing.

## ■ MECHANISM OF ACTION AND POTENTIAL SIDE EFFECTS

The presumed mechanism of action of convalescent plasma is through direct binding and inactivation of the SARS-CoV-2 virus by neutralizing anti-SARS-CoV-2 antibodies. Antibody-dependent complement activation, cytotoxicity, and phagocytosis may also contribute to the therapeutic effect of neutralizing antibodies in convalescent plasma. In addition to improved viral clearance, neutralizing and nonneutralizing antibodies may also lessen disease severity and facilitate recovery by modulating the exaggerated immune response—the cytokine storm—associated with severe disease and multiorgan failure.<sup>1-4</sup>

Convalescent plasma differs from standard plasma only in that it contains anti-SARS-CoV-2 antibodies. The risk of transfusion-related adverse events is therefore likely identical to the risk associated with standard plasma, namely transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), and allergic reactions.<sup>5</sup>

In the largest safety study, which reported the safety outcomes of 5,000 transfusions of convalescent plasma, there were 15 deaths within 4 hours of transfusion (0.3%), of which only 4 (0.08%) were judged as possibly or probably related to the transfusion of COVID-19 convalescent plasma. In addition, 21 serious nonfatal adverse events were reported (0.4%): 7 cases of TACO, 11 cases of TRALI, and 3 cases of allergic transfusion reactions.<sup>6</sup>

An increased risk of thrombotic events has been reported for treatment with hyperimmune immunoglobulin.<sup>7</sup> COVID-19 is a highly prothrombotic disease, and the impact of plasma transfusion on the

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coagulation system and the rate of thrombotic complications in COVID-19 is unknown but likely minimal, since plasma contains a balance of all coagulation factors, both coagulant and anticoagulant.

Theoretical risks unique to anti-SARS-CoV-2 antibodies within convalescent plasma are antibody-dependent enhancement of infection (ADE) and attenuated immune response with increased risk of future infection.

ADE is a phenomenon in which the presence of antibodies exacerbates the severity of the current infection. ADE is well described for other viral infections, such as dengue fever, and is usually due to prior infection with a virus of a different serotype. One proposed mechanism of ADEs is that nonneutralizing antibodies bound to the virus surface facilitate viral entry into host cells by anchoring the virus with host cells through host cell receptors to the Fc portion of the antibody. ADE has been cited as a potential reason for regional differences in severity of illness of COVID-19, but evidence for ADE in coronavirus infection stems mostly from in-vitro studies. It is unclear if this is truly contributing to the clinical manifestation of COVID-19 or if it is relevant to treatment with convalescent plasma with high titers of neutralizing antibodies. Unfortunately, currently available antibody tests lack accuracy to determine if SARS-CoV-2 antibodies present in convalescent plasma are truly neutralizing in vivo.<sup>5,8</sup>

Convalescent plasma may also blunt the recipient immune response and lead to decreased formation of anti-SARS-CoV-2 antibodies, leaving patients at potentially increased risk for future infections.<sup>5</sup>

## ■ HISTORICAL PRECEDENCE

Convalescent plasma or “serum therapy” has a storied history dating back to the 1900s, when Emil Adolf von Behring was awarded the first Nobel Prize in medicine for its use for the treatment of diphtheria. It was the only targeted therapy for acute infections until the advent of antibiotics in the 1940s and was used to treat various bacterial infections from pneumonia to meningitis and botulism, as well as viral infections such as mumps, measles, polio, and influenza.<sup>1,2</sup> A meta-analysis of 8 studies involving 1,703 patients from the 1908 H1N1 influenza outbreak concluded, despite many methodologic limitations, that patients treated with convalescent plasma may have experienced a clinically significant reduction in the risk of death.<sup>9</sup>

More recently, during the 2009–2010 H1N1 pandemic, the use of convalescent plasma or hyperimmune globulin from convalescent plasma for the treatment of critically ill patients was reported to be associated with improved viral clearance and decreased cytokine levels, particularly decreased inflammatory cytokines. Subgroup analysis of patients treated within 5 days or earlier showed improved survival if treated with convalescent plasma-derived hyperimmune globulin compared with placebo.<sup>10,11</sup>

Convalescent plasma was also used in the 2013 West African Ebola epidemic and in the 2 Ebola patients transferred to the United States (both of whom survived).<sup>1,2</sup>

Evidence supporting the use of convalescent plasma in the treatment of coronavirus-associated disease stems from the outbreaks of SARS-CoV-1 in 2003 and Middle Eastern Respiratory Syndrome (MERS) in 2012. The largest study<sup>12</sup> involved 80 critically ill patients treated with convalescent plasma during the SARS-CoV-1 outbreak in 2003 in Hong Kong. Compared with control patients (who were offered convalescent plasma but declined to give consent for experimental treatment), those who received it were reported to have higher rates of “good outcomes” if treated within 14 days of hospital admission. “Good outcome” was defined as alive and discharged from the hospital by day 22.

A meta-analysis<sup>13</sup> of 32 studies of convalescent plasma for the treatment of SARS and severe influenza concluded, despite weak evidence, that treatment with convalescent plasma led to statistically significant reduction in the pooled odds of mortality (odds ratio 0.25; 95% confidence interval [CI] 0.14–0.45).

## Convalescent plasma for COVID-19

To date, evidence on the effectiveness of convalescent plasma for the treatment of COVID-19 is limited to several small case series from China,<sup>14–16</sup> a series of 25 patients treated with convalescent plasma in Houston, Texas,<sup>17</sup> a matched cohort of 39 patients treated with convalescent plasma at a single institution in New York City,<sup>18</sup> and a single randomized controlled trial.<sup>19</sup> All patients in the Chinese case series were alive at the time of publication, with improved viral clearance, decreased cytokines levels, improved chest imaging, and stable or improved oxygenation after treatment with convalescent plasma.<sup>14–16</sup> Similarly, 74% of the patients from Houston showed clinical improvement by day 14, and 24 of the 25 patients were

alive at the time of publication.<sup>17</sup> Liu et al<sup>18</sup> report stable to improved oxygenation of patients treated with convalescent plasma compared with matched controls, with improved survival for nonintubated patients (hazard ratio 0.19, 95% CI 0.05–0.72,  $P = .015$ ), but not for intubated patients (hazard ratio 1.24, 95% CI 0.33–4.67,  $P = .752$ ).

The first randomized controlled trial of convalescent plasma in COVID-19 was stopped early due to slow enrollment, as local infection rates declined thanks to strict lockdown measures in Wuhan, China.<sup>19</sup> The study was therefore underpowered to demonstrate statistically significant differences in either the primary (time to clinical improvement) or secondary endpoints (28-day mortality, time to hospital discharge, and rate of negative polymerase chain reaction [PCR] testing at 72 hours). Although not statistically significant, the results appear to signal a more favorable outcome for patients treated with convalescent plasma. An analysis stratified by disease severity showed patients without the need for mechanical ventilation or multiorgan failure had significantly shorter time to clinical improvement when treated with convalescent plasma than with placebo. Clinically significant improvement at day 28 was also more likely to occur in the convalescent plasma group (91.3%) than in the control group (68.2%).

Taken together, the limited evidence available today suggests treatment with convalescent plasma may improve viral clearance, decrease inflammation, and improve oxygenation, which may translate into a lower mortality rate for select patients. Treatment with convalescent plasma appears to be of greatest benefit when given early in the course of the disease, during active viral replication and before progression to multisystem organ failure.

While promising, convalescent plasma is not proven effective in the treatment of COVID-19, and the quality of available evidence in support of it is weak. The Infectious Diseases Society of America therefore recommends its use only within the context of well-controlled clinical trials.<sup>20</sup>

## ■ CURRENT USE OF CONVALESCENT PLASMA IN THE UNITED STATES

Given the extraordinary circumstances of this global pandemic and the lack of effective treatment, the US Food and Drug Administration (FDA) has allowed the use of convalescent plasma as an investigational product through 1 of 3 pathways:

- Clinical trials
- Expanded access program

- Single-patient emergency investigational new drug (IND) application.

### Clinical trials of COVID-19 convalescent plasma

On July 23, 2020 there were 72 clinical trials listed on [ClinicalTrials.gov](https://clinicaltrials.gov) that were recruiting patients for clinical trials of the use of convalescent plasma for prevention and treatment of COVID-19.

### Expanded access program

The FDA<sup>21</sup> describes an expanded access program as follows: “Sometimes called “compassionate use,” expanded access is a potential pathway for a patient with an immediately life-threatening condition or serious disease or condition to gain access to an investigational medical product (drug, biologic, or medical device) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available.”

The FDA and Mayo Clinic have collaborated to create the US Convalescent Plasma Expanded Access Program.<sup>22</sup> This program allows any physician treating COVID-19 patients to register and request convalescent plasma for individual qualifying patients. Patient inclusion criteria are as follows, and there are no specified exclusion criteria:

- At least 18 years of age
- Laboratory-confirmed COVID-19
- Admitted to acute care facility for treatment of COVID-19
- Patient has or is at risk of developing severe or immediately life-threatening COVID-19
- Informed consent provided by patient or proxy.

Severe disease is defined as 1 or more of the following: shortness of breath (dyspnea), respiratory frequency 30 per minute or higher, blood oxygen saturation 93% or less, partial pressure of arterial oxygen to fraction of inspired oxygen ratio less than 300, and lung infiltrates greater than 50% within 24 to 48 hours. Life-threatening disease is defined as 1 or more of the following: respiratory failure, septic shock, and multiple organ dysfunction or failure.

The physician registering a patient is required to complete all necessary documentation including consent, patient history, posttransfusion follow-up data, and adverse event reporting in a centralized electronic database administered by Mayo Clinic. Mayo Clinic also serves as a central institutional review board and safety monitoring board for this program. A detailed description of the process of enrolling a patient, ordering plasma, and necessary documentation is outlined in detail on their web site.<sup>22</sup>

The Expanded Access Program is designed as a

registry study aimed to facilitate rapid application of convalescent plasma in clinical practice and monitor its safety. Given the broad inclusion criteria, no exclusion criteria, and lack of a control group, conclusions on the effectiveness of convalescent plasma from this study may be limited.

At the time of this report over 2,500 sites and more than 11,000 physicians have registered and over 43,000 units of convalescent plasma have been transfused through this program.

### Single-patient emergency investigational new drug application

For patients unable or ineligible to participate in clinical trials of the Expanded Access Program, the FDA allows the use of convalescent plasma for “serious or immediately life-threatening” COVID-19 infections through the process of a single-patient emergency IND application under Title 21, Code of Federal Regulations 312.310. This process allows the use of an investigational drug for the treatment of an individual patient by a licensed physician upon FDA authorization. A licensed physician seeking to administer convalescent plasma to an individual patient must request permission from the FDA through the emergency IND process.<sup>23</sup>

### ■ DONOR SELECTION

Convalescent plasma is collected by registered and licensed blood establishments that collect plasma, such as the American Red Cross. Once manufactured, it is distributed by blood centers for investigational use under the 3 pathways outlined above.

All donors must meet standard blood donation eligibility requirements and are tested for relevant transfusion-transmissible infections. The FDA<sup>23</sup> has set the following criteria for COVID-19 convalescent plasma donors:

- Laboratory confirmation of COVID-19 infection, either by nasopharyngeal PCR at the time of illness, or a positive serological test for SARS-CoV-2 antibodies after recovery, if PCR was not performed at the time COVID-19 was clinically suspected.
  - Complete resolution of symptoms at least 14 days before the donation. A negative result for COVID-19 by a diagnostic test is not necessary.
  - Male donors, or female donors who have never been pregnant or who have tested negative for HLA antibodies since their most recent pregnancy.
- SARS-CoV-2 neutralizing antibody testing has

not been a requirement, but samples from each unit of convalescent plasma are stored for future testing once reliable antibody testing is available.

Based on studies of antibody kinetics showing immunoglobulin G seroconversion around day 10 and peak antibody titers around day 28, the optimal timing for convalescent plasma donation appears to be approximately 4 weeks after symptom onset. Older, male patients with more severe illness appear to develop higher antibody titers than those with minimal symptoms and may be more suitable donors.<sup>24–26</sup>

If antibody titers are available, the FDA suggests the viral neutralizing antibody titers should be at least 1:160, but titers of 1:80 are considered acceptable if an alternative matched unit is not available.

However, assays to determine viral neutralizing antibody titers are not widely available, in part because they are labor-intensive and require a biosafety level 3 laboratory if live virus is used. Viral neutralizing titers are therefore not known for the vast majority of donor plasma units, and a substantial portion of convalescent plasma donors may have titers below the FDA-recommended threshold.<sup>24,27</sup>

Antibody titers determined by commercially available enzyme-linked immunosorbent assay may correlate with viral neutralizing antibody titers, but have poor specificity.<sup>24</sup>

Until reliable antibody testing is widely available, convalescent plasma is collected solely on the basis of the FDA criteria above, resulting in unpredictable and likely heterogeneous viral neutralizing antibody titers across all donations.

### ■ SUMMARY

Transfusion of convalescent plasma may benefit patients with acute COVID-19 by direct antiviral effect of neutralizing antibodies and possible non-specific anti-inflammatory properties. Convalescent plasma is likely most effective when given early in the course of the disease. The optimal donor has high titers of neutralizing antibodies against SARS-CoV-2, although optimal testing for these antibodies is not yet established. Convalescent plasma has been used for over a century, is proven to be safe, and is supported by anecdotal evidence from prior viral outbreaks; however, its effectiveness is yet to be established in well-designed clinical trials. While clinical trials are ongoing, the vast majority of convalescent plasma is currently being used through the Expanded Access Protocol.



## REFERENCES

1. Casadevall A, Dadachova E, Pirofski L. Passive antibody therapy for infectious diseases. *Nat Rev Microbiol* 2004; 2(9):695–703. doi:10.1038/nrmicro974
2. Casadevall A, Pirofski L-A. The convalescent sera option for containing COVID-19. *J Clin Invest* 2020; 130(4):1545–1548. doi:10.1172/JCI138003
3. Blanco-Melo D, Nilsson-Payant BE, Liu WC, et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. *Cell* 2020; 181(5):1036–1045.e9.
4. Rojas M, Roriguez Y, Monsalve DM, et al. Convalescent plasma in COVID-19: possible mechanisms of action. *Autoimmun Rev* 2020; 19(7):102554. doi:10.1016/j.autrev.2020.102554
5. Bloch EM, Shoham S, Casadevall A, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. *J Clin Invest* 2020; 130(6):2757–2765. doi:10.1172/JCI138745
6. Joyner MJ, Wright RS, Fairweather D, et al. Early safety indicators of COVID-19 convalescent plasma in 5,000 patients. *J Clin Invest* 2020; 140200. doi:10.1172/JCI140200
7. Menis M, Sridhar G, Selvam N, et al. Hyperimmune globulins and same-day thrombotic adverse events as recorded in a large healthcare database during 2008–2011. *Am J Hematol* 2013; 88(12):1035–1040. doi:10.1002/ajh.23559
8. Kadkhoda K. COVID 19: are neutralizing antibodies neutralizing enough? *Transfusion* 2020; 60(7):1602–1603. doi:10.1111/trf.15897
9. Luke TC, Kilbane EM, Jackson JL, Hoffman SL. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? *Ann Intern Med* 2006; 145(8):599–609. doi:10.7326/0003-4819-145-8-200610170-00139
10. Hung IFN, To KKW, Lee C-K, et al. Hyperimmune IV immunoglobulin treatment: a multicenter double-blind randomized controlled trial for patients with severe 2009 influenza A (H1N1) infection. *Chest* 2013; 144(2):464–473. doi:10.1378/chest.12-2907
11. Hung IFN, To KKW, Lee C-K, et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. *Clin Infect Dis* 2011; 52(4):447–456. doi:10.1093/cid/ciq106
12. Cheng Y, Wong R, Soo YOY, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur J Clin Microbiol Infect Dis* 2005; 24(1):44–46. doi:10.1007/s10096-004-1271-9
13. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis* 2015; 211(1):80–90. doi:10.1093/infdis/jiu396
14. Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci U S A* 2020; 117(17):9490–9496. doi:10.1073/pnas.2004168117
15. Zeng F, Chen X, Deng G. Convalescent plasma for patients with COVID-19. Letter. *Proc Natl Acad Sci U S A* 2020; 117(23):12528. doi:10.1073/pnas.2006961117
16. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA* 2020; 323(16):1582–1589. doi:10.1001/jama.2020.4783
17. Salazar E, Perez KK, Ashraf M, et al. Treatment of coronavirus disease 2019 (COVID-19) patients with convalescent plasma. *Am J Pathol* 2020 May 27;S0002-9440(20)30257-1. doi:10.1016/j.ajpath.2020.05.014
18. Liu STH, Lin H-M, Baine I, et al. Convalescent plasma treatment of severe COVID-19: A matched control study. *medRxiv* 2020 May 22. doi:10.1101/2020.05.20.20102236
19. Li L, Zhang W, Hu Y, 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 Jun 3;e2010044. doi:10.1001/jama.2020.10044
20. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the treatment and management of patients with COVID-19. Recommendation 7: Convalescent plasma vs. no convalescent plasma for hospitalized patients. Accessed July 23, 2020. <https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#toc-7>
21. FDA. Expanded access. Information for physicians. Accessed July 22, 2020. <https://www.fda.gov/news-events/expanded-access/expanded-access-information-physicians#ExpandedAccess>
22. Joyner M. COVID-19 expanded access program. Accessed July 22, 2020. <https://www.uscovidplasma.org>
23. FDA. Recommendations for investigational COVID-19 convalescent plasma. Accessed July 23, 2020. <https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma#Pathways%20for>
24. Klein SB, Pekosz A, Park H-S, et al. Sex, age, and hospitalization drive antibody responses in a COVID-19 convalescent plasma donor population. *medRxiv* 2020 Jun 20;2020.06.26.20139063. doi:10.1101/2020.06.26.20139063
25. Li L, Tong X, Chen H, et al. Characteristics and serological patterns of COVID-19 convalescent plasma donors: optimal donors and timing of donation. *Transfusion* 2020 Jul 6;10.1111/trf.15918. doi:10.1111/trf.15918
26. Lynch KL, Whitman JD, Lacanienta NP, et al. Magnitude and kinetics of anti-SARS-CoV-2 antibody responses and their relationship to disease severity. *Clin Infect Dis* 2020 Jul 14;ciaa979. doi:10.1093/cid/ciaa979
27. Salazar E, Kuchipudi SV, Christensen PA, et al. Relationship between anti-spike protein antibody titers and SARS-CoV-2 in vitro virus neutralization in convalescent plasma. *bioRxiv* 2020 Jun 9;2020.06.08.138990. doi:10.1101/2020.06.08.138990

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