



Convalescent Plasma and Treatment

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Convalescent plasma refers to the plasma in the blood of a patient who has recovered from coronavirus disease 2019 (COVID-19).¹ Plasma is the yellow, translucent portion of whole blood that contains water, enzymes, salts, and antibodies. Plasma does not contain white or red blood cells, or platelets.² Convalescent plasma may contain antibodies specific to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).³ Patients who have recovered from COVID-19, regardless of disease severity, may donate their plasma in a process similar to blood donation.⁴ The plasma can then be tested for the levels and types of antibodies to SARS-CoV-2, purified, and given as a treatment to those with COVID-19. It is thought that these antibodies, which bind to the virus, may physically block SARS-CoV-2 virus from entering cells, limiting the infection.

How Convalescent Plasma Works

Convalescent plasma treatment is a transfusion of plasma components from a donor to a recipient. These antibodies present in the plasma help boost the recipient's immune response. Convalescent plasma therapy is also known as passive immunization, as the recipient is not producing the antibodies but is instead receiving them from someone who had an active immune response. Although passive immunization is short-lived, with antibodies typically persisting in naturally recovered patients for at least 2 to 3 months, it does provide an immediate benefit.^{5,6} In the context of COVID-19, convalescent plasma therapy refers to a treatment meant to transfer antibodies formed in a recovered patient to a patient currently suffering from the disease. Convalescent plasma is typically administered through an intravenous catheter.

For convalescent plasma treatment to be successful, there a few factors to be considered:

1. **The levels of antibodies present:** Research has shown that the levels of antibodies within convalescent plasma can widely vary. Therefore, convalescent plasma must be carefully tested to determine the levels of antibodies present. Higher levels of antibodies are best, and these must be detected with a quantitative serology assay. In the United States, current requirements for testing plasma uses the Ortho VITROS SARS-CoV-2 immunoglobulin G (IgG) test with a signal-to-cutoff (S/C) value of 12 or higher.⁷ If the S/C value is lower than 12, healthcare providers may make an individualized assessment of benefit-risk to determine if the plasma unit is acceptable.⁷
2. **Neutralizing antibody levels present:** While the overall presence of antibodies can indicate past exposure to SARS-CoV-2, neutralizing antibodies are those that can inhibit viral infection. Neutralizing antibody levels must be at least 1 to 160.⁸ These ratios, or titers, refer to the maximum dilution at which the sample can neutralize virus. In other words, the higher the concentration of antibodies, the more the plasma

can be diluted and still be effective. Neutralizing antibody levels have been shown to correlate well with total levels of IgG antibodies—one of the antibodies present during an immune response—in patients.⁹ Neutralizing antibodies are also known to be higher in severe cases, and peak 31 to 35 days post symptom onset.^{10,11} Specific assays are required to determine the titer of neutralizing antibodies, but these generally require laboratory-based assays.¹² No currently available commercial emergency use authorization (EUA) serology test detects neutralizing antibodies.

3. **The type of antibodies present:** Current convalescent plasma treatment relies on the presence of IgG, which seems to persist the longest out of all antibody types, lasting at least 75 days.¹³ While IgG levels can decline over time, levels seem to persist for months after symptoms.⁶ Specific tests are required to detect IgG levels.

Historical Use of Convalescent Plasma

Convalescent plasma treatment has been used to treat a variety of diseases, including during the 2009 H1N1 and the 1918 influenza pandemics.^{14,15} A prospective cohort study during the 2009 H1N1 pandemic found that convalescent plasma administered to patients with severe flu reduced mortality compared to a nontreatment group (20% versus 54.8%, respectively).¹⁴ In contrast, convalescent plasma treatment was attempted in a nonrandomized, comparative study with patients who had Ebola virus disease, however, it did not significantly improve patient outcomes.¹⁶

Eligibility for Receipt of Convalescent Plasma Therapy

In the United States, there are currently 3 ways for a patient to receive convalescent plasma therapy:⁸

1. **Enrollment in a clinical trial:** Clinical trials of convalescent plasma therapy are essential to understanding the health benefits of this therapy. Randomized controlled clinical trials (RCTs) allow for control of treatment, nontreatment, and monitoring of patients. They control for the biases inherent in simple observational studies that have no control group. Currently, there are 39 clinical trials (of which 20 are RCTs) actively recruiting in the United States for convalescent plasma therapy.¹⁷
2. **Emergency use authorization:** On August 23, 2020, the US Food and Drug Administration (FDA) authorized an EUA for convalescent plasma therapy.⁷ The FDA based this EUA on data from small clinical trials and a larger cohort from an observational study of an expanded access protocol based at the Mayo Clinic. This EUA permits the use of convalescent plasma in **hospitalized COVID-19 patients**, and requests hospitals to maintain careful records of who receives the treatment. Any adverse events must be reported to the US Department of Health and Human

Services Assistant Secretary for Preparedness and Response according to the fact sheet issued.¹⁸ The EUA states that convalescent plasma therapy should not be considered a standard of care, as randomized control trials are needed to establish this treatment as such. Healthcare providers are also encouraged to enroll patients in clinical trials. The EUA does not recommend an age range for use of convalescent plasma therapy.

4. **Single patient emergency investigational new drug:** This is another alternative pathway for convalescent plasma therapy for patients with severe or life-threatening COVID-19 who cannot participate in expanded access or a clinical trial. The use of convalescent plasma must be ordered by the patient's physician (under 21 CFR 312.310).¹⁹ The physician must complete Form FDA 3926, which allows patients access to an investigational drug. This may be suspended in the future due to recent EUA of convalescent plasma.

In the past, expanded access was also used. An expanded access protocol was an alternative pathway for convalescent plasma therapy for patients with severe or life-threatening COVID-19 who were not eligible/able to enroll in clinical trials. When expanded access protocols are in use, the treatment is available at designated acute care centers. However, as of August 28, 2020, all expanded access protocols have been discontinued because of the EUA issuance.

Eligibility for Donation of Convalescent Plasma

Individuals who have tested positive by molecular diagnostic or who have tested positive for SARS-CoV-2 specific antibodies are eligible to donate plasma. They must have resolved any symptoms at least 14 days before donation. Female donors must also test negative for human leukocyte antigen antibodies. Details of eligibility are also available in 21 CFR 630.15(b).²⁰ Plasma is currently recommended to match blood type; therefore, type AB donors are optimal.²¹

Evidence Supporting the Use of Convalescent Plasma for Treatment of COVID-19

Clinical trials provide data that can inform the use of COVID-19 convalescent plasma (CCP) therapy and can assess the utility of convalescent plasma for treatment of COVID-19. These trials are ongoing. The best trial to assess the success of convalescent plasma treatment is an RCT, which randomly assigns patients to either a treatment (experimental) or a placebo (control) group. This type of trial gives researchers the best chance to identify significant improvements in outcomes and reduces biases that may complicate the data. This is done by using a blinding process—where researchers and patients (and sometimes other groups) are unaware of which treatment each patient receives—to reduce the chance for bias in reporting of symptoms and outcomes. One such clinical trial is currently being conducted by the University of California San Francisco. This randomized study was designed as a triple-blind trial that blinds the patient, provider, and healthcare provider.²²

Previous studies have provided data on the use of convalescent plasma for COVID-19. One of the largest studies in the United States so far has been through an expanded access program with the Mayo Clinic. The primary finding from the study was that CCP treatment with plasma with high antibody levels

significantly reduced mortality relative to patients receiving CCP with low antibody levels.²³ Although this study was not a randomized or a clinical trial, it provided results from an expanded access program that involved over 2,800 acute care centers and over 35,000 patients with the majority in critical care. Because the Mayo Clinic study was meant to be exploratory, it did not have a nontreatment arm, therefore, there was no placebo/control group with which to compare results. However, the data are valuable because of the number of patients who participated.

The mortality rate of patients given CCP within 3 days of diagnosis was 8.7%; if patient treatment was initiated 4 days or more after diagnosis, the mortality rate was 11.9%. The importance of timing of CCP treatment underscores the need for rapid, efficient COVID-19 testing. The levels of IgG in the CCP were also important. Patients with who received CCP with the highest IgG levels (<18.45 S/C) had the lowest mortality (8.9%). At mid-levels (4.62 to 18.45 S/C), mortality was 11.9%. At low levels (<4.62 S/C), the mortality rate was 13.7%. They also looked at mortality rates 30 days after CCP was given. Mortality rates were lowest in patients who received high-antibody-level CCP within 3 days of diagnosis, compared to those who received low-antibody-level CCP 4 days or more after diagnosis—a reduction from 30% to 20%.

While all US clinical trials are ongoing, and have not yet published results, a small trial of 5 patients treated with CCP in China showed that all 5 had improved health outcomes, including time on ventilators.²⁴ A matched, prospective study in Houston examined outcomes of 316 patients, with 136 who received CCP and 251 who did not. This study also found that CCP administered within 3 days of diagnosis significantly reduced mortality at 28 days posttransfusion.²⁵ A recent matched cohort study, with 64 patients receiving CCP and 177 matched controls, found that there was no significant reduction in in-hospital mortality or time to discharge between groups, overall. When subgroups were analyzed, patients 65 and older receiving CCP did have a significantly greater rate of hospital discharge.²⁶

Gaining more insight into the efficacy of COVID-19 convalescent plasma therapy will depend on careful clinical trials. Some experts fear that recruitment for RCTs will diminish now that CCP is available through EUA because participants in an RCT could be assigned to a nontreatment arm and guaranteed treatment is likely a more attractive option.²⁷ Still, RCTs will yield important data on health outcomes in treatment groups relative to controls. We need more data on the performance of CCP relative to the current standard of care, so we can make the best decisions on how to treat patients with COVID-19 in the future.

Health Risks Associated with Convalescent Plasma Treatment

Convalescent plasma treatment can include several side effects, which can be exacerbated if a patient has a history of allergies or anaphylaxis. Allergic reactions to plasma, most mild, have been estimated to occur in about 1% to 3% of patients. Anaphylaxis reactions are estimated to occur in 1 in 18,000 to 1 in 172,000 transfusions (0.0006% to 0.005%).²⁸ Occasionally, transfusions may transmit viruses such as HIV and hepatitis C. Patients may also have febrile nonhemolytic reactions, transfusion-related

acute lung injury, transfusion-associated cardiac overload, and hemolytic reactions. Hypothermia, metabolic complications, and posttransfusion purpura (skin hemorrhages/lesions) have also been described.¹⁸

Important work by the Mayo Clinic with 20,000 patients has shown that in a diverse pool of patients, including Black and Hispanic patients, there are low safety risks.²⁹ In addition, there is a theoretical risk of antibody-dependent enhancement, in which low levels of nonneutralizing antibodies exacerbate infection by a virus (ie, dengue), which is thought to more likely occur in plasma with low antibody titers. However, there is no clear evidence to support antibody-dependent enhancement theory.

Conclusion

Convalescent plasma treatment is a potential treatment option for COVID-19 that should be further investigated. The success of CCP will depend on the levels of total antibodies, levels of neutralizing antibodies, and isotype of antibodies present in donated plasma. Patients may receive CCP through enrollment in a clinical trial or through emergency use or single-patient emergency investigational new drug use, the latter 2 require physician authorization. As understanding of CCP evolves, so will options for treatment. Initial results of trials and expanded access use of CCP show promise in improving patient outcomes. RCTs on this treatment will be necessary to fully characterize its safety and efficacy for COVID-19.

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