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Background

Convalescent plasma refers to the plasma in the blood of a patient who has recovered from 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 SARS-CoV-2, the pathogen that causes COVID-19.³ 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. Antibodies present in the plasma can help boost the recipient's immune response. Convalescent plasma therapy is also known as passive immunization, as the recipient is not producing 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 can 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 are 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, registered or licensed blood establishments must test plasma donations for SARS-CoV-2 antibodies as a manufacturing step using one of several tests designated by the US Food and Drug Administration (FDA).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. The FDA states a preference for “high” neutralizing antibody levels, or titers, as defined by the results of several acceptable tests designated in Appendix A of the March 9, 2021, Convalescent Plasma EUA Letter of Authorization.⁷

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.⁸ Neutralizing antibodies are also known to be higher in severe cases and to peak 31 to 60 days after symptom onset.⁹⁻¹¹ Specific assays are required to determine the titer of neutralizing antibodies, but these generally require laboratory-based assays.¹² On November 6, 2020, the



FDA issued an emergency use authorization (EUA) for the cPass SARS-CoV-2 Neutralization Antibody Detection Kit, which specifically detects this type of antibody.¹³ The agency notes the effect of neutralizing antibodies for SARS-CoV-2 in humans it is still being researched.

- 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 and up to 92 days.^{14,15} While IgG levels can decline over time, levels seem to persist for months after symptoms.^{6,15} Specific tests are required to detect IgG levels.⁷

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.^{16,17} 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).¹⁶ 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.¹⁸

Eligibility for receipt of convalescent plasma therapy

In the United States, there are currently 3 ways for a patient to receive convalescent plasma therapy:¹⁹

- 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 32 clinical trials actively recruiting in the United States for convalescent plasma therapy.²⁰
- 2. Emergency use authorization:** On August 23, 2020, the FDA authorized an EUA for convalescent plasma therapy. Since then, the FDA has updated the EUA based on the latest clinical trial results, including RCTs. The updated EUA permits only the use of high-titer COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19 who early in the course of disease and those hospitalized with impaired humoral immunity. The use of low-titer COVID-19 convalescent plasma is not authorized under the EUA.⁷ The FDA requests hospitals maintain careful records of who receives the treatment, conduct a thorough investigation of adverse reactions after transfusion of convalescent plasma, and report fatalities related to transfusion, as required under 21 CFR §606.170.²¹ The EUA states that convalescent plasma therapy should not be considered a standard of care, as data from additional 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 specify an age range for use of convalescent plasma therapy.⁷
- 3. 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).²² The physician must complete Form FDA 3926, which allows patients access to an investigational drug.¹⁹

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 were 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 been free from 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).²³ Plasma is currently recommended to match blood type; therefore, type AB donors are optimal.²⁴

Evidence supporting use of convalescent plasma for COVID-19 treatment

Clinical trials provide data that can inform the use of COVID-19 convalescent plasma (CCP) therapy and can assess the utility of CCP 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.²⁵

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.²⁶ 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. Although this study was not randomized, it provided results from an expanded access program that involved more than 2,800 acute care centers and more than 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.

In the Mayo Clinic study,²⁶ 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%. The



researchers also looked at mortality rates 30 days after CCP was given. Mortality rates were lowest in patients who received high-titer CCP within 3 days of diagnosis, compared to those who received low-titer CCP 4 days or more after diagnosis—a reduction from 30% to 20%.

While some RCTs using CCP are ongoing, others have published results and several have halted enrollment after independent data safety and monitoring boards concluded the treatment likely would show no benefit in the groups under study. The US National Institutes of Health on March 2, 2021, halted enrollment of the Clinical Trial of COVID-19 Convalescent Plasma of Outpatients, which was evaluating the safety and effectiveness of CCP in treating emergency department patients who developed mild to moderate symptoms of COVID-19.²⁷ In January 2021, 2 other randomized international clinical trials (RECOVERY in the United Kingdom, CONCOR-1 in Canada) closed recruitment for their CCP treatment groups due to an unlikely benefit of the intervention.^{28,29}

Studies with published results show mixed outcomes for patient populations. A randomized, double-blind, placebo-controlled study of high-titer CCP among 160 older adult patients in Argentina treated within 72 hours of mild symptoms, and equally split between intervention and placebo, showed a 48% relative risk reduction of progress to severe disease.³⁰ In a retrospective study based on 3,082 patients in a US national registry, researchers determined that hospitalized patients treated with high-titer CCP had a lower risk of death at 30 days versus those in the low-titer group, but there was no difference between titers among patients who received mechanical ventilation.³¹ Another randomized, placebo-controlled trial using high-titer CCP among 228 hospitalized adult patients with severe COVID-19 showed no significant difference in clinical outcomes or mortality between those who received CCP and those in the placebo group.³²

Previously, a matched, prospective study in Houston examined outcomes of 316 patients, with 136 who received CCP and 251 who did not.³³ This study also found that CCP administered within 3 days of diagnosis significantly reduced mortality at 28 days posttransfusion. Another matched cohort study,³⁴ with 64 patients receiving CCP and 177 matched controls, found there was no significant reduction in in-hospital mortality or time to discharge between groups, overall. When subgroups were analyzed, patients aged 65 years and older receiving CCP did have a significantly greater rate of hospital discharge.

Gaining more insight into the efficacy of CCP 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.³⁵ 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 and among various patient populations, 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%).³⁶ 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.²¹

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.³⁷ 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, with the latter 2 requiring 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 outcomes in some patients. RCTs on this treatment will be necessary to fully characterize its safety and efficacy for COVID-19.

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