**COVID-19 and Convalescent Plasma and Antibody Therapies: Frequently Asked Questions**

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<https://www.hematology.org/covid-19/covid-19-and-convalescent-plasma>

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Note: Please review [ASH's disclaimer](https://www.hematology.org/covid-19#disclaimer) regarding the use of the following information.

**What is the evidence for or against the use of convalescent plasma therapies in COVID-19?**

The use of convalescent plasma (CP) collected from previously infected individuals to passively transfer antibodies in order to protect or treat humans dates back almost 100 years. Results from small case series during the prior MERS and SARS coronavirus outbreaks suggested that CP is safe and may confer clinical benefits, including faster viral clearance, particularly when administered early in the disease course.1 The vast majority of patients who recover from COVID-19 illness develop circulating antibodies to various SARS-CoV-2 proteins as early as one to three weeks following infection, which are detectable by ELISA or other quantitative assays and often correlate with the presence of neutralizing antibodies. Immunity appears to be protective, based on primate studies showing that animals could not be experimentally re-infected with SARS-CoV-2 weeks to months later, detection of memory B cells able to produce neutralizing antibodies in patients following infection, and the very infrequent occurrence of recurrent COVID-19 in recovered patients at least for the first six months following natural infection.

Multiple studies have now reported the use of COVID-19 convalescent plasma (CCP) to treat COVID-19 patients, without unexpected or serious adverse events (see below). Many of the early studies were observational and nonrandomized, in patients with severe or critical disease, complicated by evolution of additional treatment interventions over time such as steroids, antivirals, and other drugs; patient heterogeneity; and a lack of detailed analyses of neutralizing antibody content of infused units. More than 90,000 patients were enrolled in a [U.S. Food and Drug Administration (FDA) –sponsored expanded access program coordinated by Mayo Clinic](https://www.medrxiv.org/content/10.1101/2020.08.12.20169359v1.full.pdf). While many patients improved clinically, the specific role of CCP was unclear given treatment with other therapies including antivirals and/or corticosteroids. In a retrospective study of a subset of these patients with data available on titer of neutralizing antibodies in the administered CPP, the relative risk of mortality was lower in hospitalized but non-ventilated patients receiving high-titer versus low-titer CPP.2

Data are accumulating from randomized controlled trials (RCTs) carried out around the world, differing with respect to target population, disease severity, outcome measures, and characterization of antibody status and titers in donors and recipients. Trials focused on severely ill hospitalized patients around the world have failed to show benefit,3,4 which is not surprising based on theoretical considerations that support administration of CCP early relative to symptom onset. Use of high-titer CCP within three days of symptom onset in older Argentinian patients with mild COVID-19 yielded less progression to severe respiratory disease, with the most benefit conferred by CCP units with the highest titers.5 However, the NIH [halted accrual](https://www.nih.gov/news-events/news-releases/nih-halts-trial-covid-19-convalescent-plasma-emergency-department-patients-mild-symptoms) to the [C3PO trial](https://clinicaltrials.gov/ct2/show/NCT04355767) for futility after enrolling 511 of 900 planned participants. This trial administered CPP or placebo to patients presenting to the emergency department with mild to moderate symptoms within one week of onset. A retrospective observational study in patients with cancer did report improved 30-day mortality in those receiving CCP, even in those requiring mechanical ventilation.6

Current NIH [treatment guidelines do not recommend](https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/summary-recommendations/) use of CCP in hospitalized patients and state that there is insufficient evidence recommending for or against CCP use in nonhospitalized or immunocompromised patients. These guidelines instead focus on the use of passive monoclonal antibody therapies in some subsets of patients (see below).

**What are the potential risks of convalescent plasma therapies for COVID-19?**

More than 500,000 people have received CCP in the United States, and many more worldwide; in the United States, safety data were published for 20,000 patients who received CCP via the expanded access program.7 CCP was observed to confer comparable risk to that of nonimmune plasma. The incidence of severe adverse events was less than 1 percent, most of which were deemed to be unrelated to CCP. Known general risks of plasma transfusion more generally include allergic reactions, transfusion-associated circulatory overload, and transfusion-associated acute lung injury. Specific additional concerns were raised regarding CCP prior to deployment, including worsening of immune-mediated tissue damage via antibody-dependent enhancement, blunting of endogenous immunity, and transfusion transmission of SARS-CoV-2. These have not been demonstrated with CCP.

**What mechanisms exist for providers to access CCP therapy clinical trials or other mechanisms to deliver this treatment to patients? What is emergency use authorization?**

On August 23, 2020, the U.S. FDA first granted emergency use authorization (EUA) of [CCP in hospitalized individuals with COVID-19](https://www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-convalescent-plasma-potential-promising-covid-19-treatment), and updated the EUA recently to [reflect new information](https://www.fda.gov/news-events/fda-brief/fda-brief-fda-updates-emergency-use-authorization-covid-19-convalescent-plasma-reflect-new-data). The EUA continues to be limited to hospitalized patients, but now suggests treatment “early” in the hospital course and the use of “high titer” CCP units as measured by specific antiviral Ig testing and titer threshold criteria given in the EUA.

Some countries have authorized use of CCP more broadly. Clinical trials continue for indications not covered by the EUA. These include RCTs for prophylaxis following high-risk exposure or at onset of first symptoms, in patients with impaired immunity, and in pediatric patients. Early administration of any passive antibody therapy to nonhospitalized patients, including CCP, hyperimmune globulin, and monoclonal antibodies, makes sense given the potential to mitigate viral replication and tissue damage, thus preventing progression to severe disease. Since many patients improve on their own, large numbers of subjects will be required to show a benefit for CCP. To date, accrual to these RCTs has been a major challenge, particularly in regions of the world with high rates of vaccine administration.

**How is CCP collected?**

CCP is procured from recovered patients (e.g., prospective donors), including those who have been vaccinated after a natural SARS-CoV-2 infection. These prospective donors can donate at blood collection organizations. CCP is collected through plasmapheresis and then the plasma is tested for SARS-CoV-2 antibody levels and undergoes standard donor and infectious disease screening before releasing the plasma for clinical use. Plasmapheresis is desirable as a means to collect larger volumes of plasma. Donations can occur as frequently as weekly for several months before antibody titers begin decreasing. Allowed donation frequency varies between blood centers. Clinical assays that measure the level of antibodies reacting against various SARS-CoV-2 proteins are widely available and may correlate, albeit imperfectly, with neutralizing antibody titers, and thus might be used to predict the potency of CCP units. It is important to consider the assay platform as well as the specificity (e.g., reactive with spike protein vs. nucleocapsid) and the class of antibody (IgG vs. total) when [evaluating results](https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/antibody-serology-testing-covid-19-information-patients-and-consumers), given major differences reported for available commercial serologic assays regarding correlations with neutralizing antibody activity.

Listed below are some sites for referral of potential donors:

* [AABB:](https://covidplasma.org/) Information about convalescent plasma donation and a feature that helps potential donors locate AABB-accredited donation sites.
* [FDA Donate COVID-19 Plasma:](https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/donate-covid-19-plasma) Lists information regarding donation of CP for transfusion or for manufacturing of hyperimmune globulin.

**What other passive immune therapies are available for COVID-19?**

A variety of passive antibody therapies are available for COVID-19, including hyperimmune globulin (concentrating neutralizing antibody activity up to tenfold) and engineered monoclonal antibodies. Interim analyses of early-phase clinical trials8 reporting decreased viral shedding, symptoms and hospitalizations with passive antibody treatment. One preparation, bamlanivimab, consists of a single antibody, and the second preparation is a combination of two antibodies, casirivimab and imdevimab, all directed against the SARS-CoV2 spike protein. However, [NIH guidelines](https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/summary-recommendations/) currently recommend *against*the use of bamlanivimab and etesevimab due to their lack of efficacy against emerging SARS-CoV-2 viral variants now prevalent worldwide,9 and instead recommend use of casirivimab and imdevimab or sotrovimab, also available under an EUA in the United States. There is also concern that variants are arising and being selected for in immunocompromised patients being treated with CCP or antibody therapies.

**In what settings should treatment with monoclonal antibody therapies be considered?**

Initial clinical trials focusing on hospitalized patients were stopped due to futility or lack of benefit, and this is not surprising given that accelerating viral clearance via antibodies is unlikely to improve clinical status in patients already making their own antibodies a week or more after infection.10 In contrast, a trial administering bamlanivimab to older nursing home residents and staff soon after infectious exposure was effective in decreasing the incidence of infection and death.11 Additional clinical trials of these and other purified or engineered antibody therapies are ongoing, with most focusing on treatment of very high-risk exposed but not yet PCR-positive individuals, immunocompromised patients, or high-risk patients early following confirmed infection — settings more likely to be beneficial for any passive antibody therapy. The [U.S. EUA for monoclonal antibodies](https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19) restricts administration to those nonhospitalized patients at risk for severe disease, or those hospitalized for other reasons who become infected. Logistical challenges in administering intravenous antibodies to SARS-CoV-2 infectious outpatients has limited widespread use.

The NIH treatment guidelines [recommend](https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/summary-recommendations/) the use of casirivimab/imdevimab or sotrovimab to treat outpatients within 10 days of symptom onset with mild to moderate COVID-19 who are at high risk of clinical progression, including patients with hematologic malignancies, sickle cell disease, or acquired or inherited immunodeficiencies. The panel recommended against use in patients hospitalized for COVID-19, except as part of a clinical trial.

**References**

1. Casadevall A, Pirofski L. The convalescent sera option for containing COVID-19. *J Clin Invest*, [10.1172/JCI138003](https://doi.org/10.1172/JCI138003).
2. Joyner MJ et al. Convalescent plasma antibody levels and the risk of death from COVID-19, *New Eng J Med*, 2021. 10.1056/NEJMoa2031893.
3. Agarwal A, et al. Convalescent plasma in the management of moderate COVID-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID trial), *Brit Med J*, 2020 371:m3939 <http://dx.doi.org/10.1136/bmj.m3939>.
4. Simonovich VA et al. A randomized trial of convalescent plasma in severe COVID-19 pneumonia. *New Eng J Med*, 2020. 10.1056/NEJMoa2031304.
5. Libster R, et al. Early high titer plasma therapy to prevent severe COVID-19 in older adults. *New Eng J Med*, 2021. 10.1056/NEJMoa2033700.
6. Thompson MA, et al. Association of convalescent plasma therapy with survival in patients with hematological cancers and COVID-19. JAMA Oncology, 2021. [10.1001/jamaoncol.2021.1799](https://jamanetwork.com/journals/jamaoncology/fullarticle/2780916).
7. Joyner MJ, et al. Early safety indicators of COVID-19 convalescent plasma in 5000 patients. *J Clin Invest*, [10.1172/JCI140200](https://www.jci.org/articles/view/140200/pdf).
8. Chen et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. *N Engl J Med*, 2020: [10.1056/NEJMoa2029849](https://www.nejm.org/doi/full/10.1056/NEJMoa2029849).
9. Wang P et al. Antibody resistance of SARS-CoV-2 Variants B.1.351 and B.1.1.7. Nature, 2021. <https://doi.org/10.1038/s41586-021-03398-2>
10. Lundgren et al A neutralizing monoclonal antibody for hospitalized patients with COVID-19. NEJM, 2021, [10.1056/NEJMoa2033130](https://doi.org/10.1056/nejmoa2033130)
11. Cohen et al JAMA 2021, Effect of bamlanivimab vs placebo on incidence of COVID-19 among residents and staff of skilled nursing and assisted living facilities: a randomized clinical trial. [0.1001/jama.2021.8828](https://doi.org/10.1001/jama.2021.8828)