

COVID-19 Convalescent Plasma

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Plasma from donors who have recovered from COVID-19 (regardless of vaccination status) may contain antibodies to SARS-CoV-2 that could help suppress viral replication.¹ In August 2020, the Food and Drug Administration issued an Emergency Use Authorization (EUA) for COVID-19 convalescent plasma (CCP) for the treatment of hospitalized patients with COVID-19. The EUA was subsequently revised. The current EUA limits the authorization to the use of CCP products that contain high levels of anti-SARS-CoV-2 antibodies (i.e., high-titer products) for the treatment of COVID-19 in outpatients or inpatients who have immunosuppressive disease or who are receiving immunosuppressive treatment. The testing criteria used to identify high-titer CCP products was also revised.²

The use of CCP should be limited to high-titer products. Products that are not labeled “high titer” should not be used.

Recommendations

Patients Who Are Immunocompromised

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of high-titer CCP for the treatment of COVID-19 in hospitalized or nonhospitalized patients who are immunocompromised.
- Some people who are immunocompromised have prolonged, symptomatic COVID-19 with evidence of ongoing SARS-CoV-2 replication. The data for these approaches are not definitive, but some Panel members would use 1 or more of the following treatment options:
 - Longer and/or additional courses of ritonavir-boosted nirmatrelvir (Paxlovid)
 - Longer and/or additional courses of remdesivir
 - High-titer CCP from a vaccinated donor who recently recovered from COVID-19 likely caused by a SARS-CoV-2 variant similar to the variant causing the patient’s illness

Patients Who Are Immunocompetent

- The Panel **recommends against** the use of CCP for the treatment of COVID-19 in hospitalized patients who are immunocompetent (**BIIa**).
- There is insufficient evidence for the Panel to recommend either for or against the use of high-titer CCP for the treatment of COVID-19 in nonhospitalized patients who are immunocompetent.

Rationale

Patients Who Are Immunocompromised

This section pertains to people who are moderately or severely immunocompromised. For examples of moderately or severely immunocompromising conditions and for a broader discussion on the therapeutic management of COVID-19 in people who are immunocompromised, see [Special Considerations in People Who Are Immunocompromised](#).

Patients who are immunocompromised are at risk of having reduced antibody responses to SARS-CoV-2 infection and COVID-19 vaccination, having suboptimal control of viral replication, and progressing to

severe disease.^{3,4} Despite the lack of definitive evidence, there is a physiologic rationale for the use of SARS-CoV-2 antibody-based therapies in these patients.

Under the revised EUA issued on December 27, 2021, CCP is authorized for the treatment of COVID-19 in nonhospitalized or hospitalized patients who have immunosuppressive disease or are receiving immunosuppressive treatment.²

Evidence to support the use of CCP for the treatment of COVID-19 in patients who are immunocompromised is limited. No randomized, adequately powered trials that evaluated the use of CCP for the treatment of COVID-19 in these patients have been published. Some subgroup analyses generated from clinical trials that enrolled patients who were immunocompromised suggested a potential benefit of using CCP in this population.⁵⁻⁷ However, subgroup analyses need to be interpreted with caution. In the overall trial populations, there was no evidence of a benefit of CCP. Other clinical data from case series, retrospective case-control studies, and meta-analyses have been cited as support for the potential benefit of CCP in patients who are immunocompromised. However, the patient populations differed across studies, and the studies had design limitations, making the findings difficult to interpret.⁸⁻¹⁶

The emergence of SARS-CoV-2 variants further complicates the assessment of the benefits of using CCP. Although results from some in vitro studies suggest that CCP collected from vaccinated individuals who recovered from COVID-19 caused by the Omicron variant exhibits neutralizing activity against certain Omicron subvariants,¹⁷⁻²³ extrapolation of these results to the clinical setting is challenging for the following reasons:²⁴

- COVID-19 immune responses across donor populations are heterogeneous; thus, CCP products are variable.
- The tests used to qualify high-titer CCP measure anti-SARS-CoV-2 antibody titers. They do not directly measure neutralizing activity or account for currently circulating subvariants.
- Published in vitro studies that evaluated the virologic activity of CCP against the currently circulating variants used a variety of assays that are difficult to compare and interpret.^{20-23,25-27}
- The pharmacokinetics and pharmacodynamics of individual CCP products are not clearly understood; therefore, determining the clinical relevance of a degree of in vitro neutralization activity is difficult.

In this context, the Panel has concluded that there is insufficient evidence to definitively recommend the use of CCP for the treatment of COVID-19 in people who are immunocompromised. For patients who are immunocompromised and have prolonged COVID-19 symptoms and evidence of ongoing viral replication (e.g., those with a low cycle threshold value, as measured by a reverse transcription polymerase chain reaction result or with a positive rapid antigen test result) despite receiving a course of antiviral therapy, the optimal management is unknown. Case reports and case series have described the treatment of these patients with additional antiviral treatments, prolonged courses of antiviral treatments, high-titer CCP, or combination therapy.²⁸⁻³⁴ The data for these approaches are not definitive, but some Panel members would use longer and/or additional courses of ritonavir-boosted nirmatrelvir or remdesivir, high-titer CCP, or combinations of these. If CCP is used, clinicians should attempt to obtain high-titer CCP from a vaccinated donor who recently recovered from COVID-19 likely caused by a SARS-CoV-2 variant similar to the variant causing the patient's illness.

Adequately powered, well-designed, and well-conducted randomized clinical trials are needed to provide more specific, evidence-based guidance on the role of CCP in the treatment of COVID-19 in patients who are immunocompromised.

Hospitalized Patients Who Are Immunocompetent

Under the revised EUA, the use of CCP is not authorized for hospitalized patients with COVID-19 who do not have immunosuppressive disease or who are not receiving immunosuppressive treatments.

Clinical data on the use of CCP for the treatment of COVID-19 in hospitalized patients who are immunocompetent, including data from several randomized trials and the U.S. Expanded Access Program for CCP, are summarized in [Table 4c](#).

Three large randomized controlled trials that evaluated the use of CCP in hospitalized patients—RECOVERY,³⁵ CONCOR-1,³⁶ and REMAP-CAP⁶—reported no benefit of using high-titer CCP in hospitalized patients with COVID-19. All 3 were open-label trials that were stopped early due to futility. However, an open-label randomized trial that enrolled patients with COVID-19–induced acute respiratory distress syndrome who required mechanical ventilation showed a lower mortality among patients who received high-titer CCP than among those who received standard care.³⁷ The benefit was primarily seen among patients who received CCP within 48 hours of mechanical ventilation. Almost all of the patients (98%) received corticosteroids during the trial, but only a few received a second immunomodulator or were previously vaccinated against COVID-19. Concomitant antiviral therapy use was low during the trial (<6% of patients received remdesivir) despite evidence of ongoing viral replication among the participants (i.e., low median cycle threshold values on nasopharyngeal SARS-CoV-2 polymerase chain reaction tests).

The Panel **recommends against** the use of CCP for the treatment of COVID-19 in hospitalized patients who are immunocompetent (**BIIa**). The rationale for this recommendation is based on the evidence from the 4 large randomized controlled trials, the widespread, pre-existing immunity to SARS-CoV-2 in the population, the continuously evolving SARS-CoV-2 variants, and the availability of other antiviral agents (e.g., remdesivir).

Nonhospitalized Patients Who Are Immunocompetent

CCP is not authorized for the treatment of COVID-19 in nonhospitalized patients who do not have immunosuppressive disease or who are not receiving immunosuppressive treatments.

Data from well-designed clinical trials that evaluated the use of CCP for the treatment of nonhospitalized patients with COVID-19 prior to the emergence of the Omicron variants are conflicting. These data are summarized in [Table 4c](#). Differences in patient populations, the placebo used (e.g., some studies used saline; some used non-SARS-CoV-2 plasma), and CCP manufacturing and testing methods may have contributed to the disparate outcomes and the difficulty in reconciling results across these clinical trials. The emergence of SARS-CoV-2 variants further complicates the assessment of the benefits of using CCP.

There is insufficient evidence for the Panel to recommend either for or against the use of high-titer CCP for the treatment of COVID-19 in nonhospitalized patients who are immunocompetent.

Monitoring and Adverse Effects

The available data suggest that serious adverse reactions following the administration of CCP are infrequent and consistent with the risks associated with plasma infusions for other indications. These risks include transfusion-transmitted infections (e.g., HIV, hepatitis B, hepatitis C), allergic reactions, anaphylactic reactions, febrile nonhemolytic reactions, transfusion-related acute lung injury, transfusion-associated circulatory overload, and hemolytic reactions. Hypothermia, metabolic complications, and post-transfusion purpura have also been described.^{2,35,38}

Additional risks of CCP transfusion include a theoretical risk of antibody-dependent enhancement

of SARS-CoV-2 infection. In the CONCOR-1 trial, higher levels of full transmembrane spike immunoglobulin G (IgG) were associated with worse outcomes, suggesting that the use of CCP with nonfunctional anti-SARS-CoV-2 antibodies may be harmful.³⁶ A subgroup analysis in the REMAP-CAP trial showed evidence of potential harm in patients who received CCP transfusions more than 7 days after being hospitalized.⁶

When considering the use of CCP in patients with a history of severe allergic or anaphylactic transfusion reactions, consultation with a transfusion medicine specialist is advised.

Considerations in Pregnant People

The safety and efficacy of using CCP during pregnancy have not been evaluated in clinical trials, and published data on its use in pregnant individuals with COVID-19 are limited to case reports.³⁹ Pathogen-specific immunoglobulins are used during pregnancy to prevent infection from varicella zoster virus and rabies virus and have been used in clinical trials of congenital cytomegalovirus infection.^{40,41} Pregnancy is not a reason to withhold CCP from a patient if it is otherwise indicated. The expected physiologic immunomodulation during pregnancy should not affect the decision to use CCP.

Considerations in Children

The safety and efficacy of CCP have not been systematically evaluated in pediatric patients. The published literature on its use in children is limited to case reports and case series. A few clinical trials evaluating the use of CCP in children are ongoing. The use of high-titer CCP may be considered on a case-by-case basis for hospitalized children who are immunocompromised and meet the EUA criteria for its use. CCP is not authorized by the Food and Drug Administration for use in patients who are immunocompetent.

Several other antiviral therapies are available for the treatment of children with COVID-19 who are at high risk of progressing to severe disease. See [Therapeutic Management of Nonhospitalized Children With COVID-19](#) and [Therapeutic Management of Hospitalized Children With COVID-19](#) for more information.

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