



# COVID-19 Convalescent Plasma

Last Updated: April 29, 2022

Plasma from donors who have recovered from COVID-19 may contain antibodies to SARS-CoV-2 that could help suppress viral replication.<sup>1</sup> In August 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for COVID-19 convalescent plasma (CCP) for the treatment of hospitalized patients with COVID-19. The EUA was revised in February 2021 to limit the authorization to the use of high-titer CCP for the treatment of hospitalized patients with COVID-19 who are early in their disease course or who have impaired humoral immunity.<sup>2</sup> In December 2021, the EUA was revised again to authorize the use of CCP only in outpatients or inpatients with COVID-19 who have immunosuppressive disease or who are receiving immunosuppressive treatment. The testing criteria used to identify CCP products that contain high levels of anti-SARS-CoV-2 antibodies (i.e., high-titer products) was also revised.<sup>2</sup>

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

## Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of CCP that was collected prior to the emergence of the Omicron (B.1.1.529) variant for the treatment of COVID-19 (**AIII**).
- The Panel **recommends against** the use of CCP for the treatment of COVID-19 in hospitalized, immunocompetent patients (**AI**).
- There is insufficient evidence for the Panel to recommend either for or against the use of high-titer CCP that was collected after the emergence of Omicron for the treatment of immunocompromised patients and nonhospitalized, immunocompetent patients with COVID-19.

## Rationale

### *Regarding the Use of COVID-19 Convalescent Plasma Collected Prior to the Emergence of the Omicron Variant*

The Omicron variant is the dominant SARS-CoV-2 variant currently circulating in the United States. Although in vitro data suggest that the CCP collected from vaccinated and unvaccinated individuals who have recovered from Omicron infection exhibits neutralizing activity against the Omicron variant,<sup>3-6</sup> it is not possible to extrapolate the potential clinical efficacy of CCP in the current clinical context. This is due in part to the following factors:

- The current supply of CCP products in the United States was not generated from donors who had recovered from Omicron infection.<sup>7</sup>
- Many CCP clinical trials were completed before the Omicron surge, and their results may not inform the current clinical context.
- The current approaches to testing CCP titers do not account for potential differences in the neutralizing activity of CCP products against currently circulating variants.

Furthermore, it is difficult to interpret the available data on the in vitro antiviral activity of CCP, since the published studies use a variety of assays to characterize the neutralizing activity of CCP, and the

level of immunity to COVID-19 can vary across different donor populations.

### ***For Hospitalized, Immunocompetent Patients***

Under the revised EUA, the use of CCP is no longer authorized for hospitalized patients 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, immunocompetent patients, including data from several randomized trials and the U.S. Expanded Access Program (EAP) for CCP, are summarized in [Table 5b](#).

The initial EUA for CCP for the treatment of hospitalized patients with COVID-19 was issued on the basis of retrospective, indirect evaluations of efficacy generated from the CCP EAP, which allowed CCP to be used regardless of titer. Several retrospective analyses of the EAP data have indicated that patients who received high-titer CCP had a lower relative risk of death than patients who received low-titer CCP.<sup>8,9</sup> The Panel reviewed the EAP analyses and determined that the data were not sufficient to establish the efficacy or safety of CCP due to potential confounding factors, the lack of randomization, and the lack of an untreated control group.

Data from the initial randomized clinical trials that evaluated CCP, which were all underpowered, did not demonstrate the product's efficacy for the treatment of hospitalized patients with COVID-19.<sup>10-17</sup>

Subsequently, results from the 3 largest randomized clinical trials that evaluated CCP in hospitalized patients—RECOVERY,<sup>18</sup> CONCOR-1,<sup>19</sup> and REMAP-CAP<sup>20</sup>—found no evidence of benefit for high-titer CCP in hospitalized patients with COVID-19. All 3 were open-label trials that were stopped early due to futility.

Although these trials and the EAP did not exclude patients with impaired humoral immunity, most of the patients enrolled did not report a history of an immunocompromising condition or receipt of chronic immunosuppressive therapy. After reviewing the collective results from these studies, the Panel **recommends against** the use of CCP for the treatment of COVID-19 in hospitalized, immunocompetent patients (**AI**).

### ***For Nonhospitalized, Immunocompetent Patients***

CCP is not authorized for the treatment of nonhospitalized patients with COVID-19 who do not have immunosuppressive disease or who are not receiving immunosuppressive treatment. Clinical data on the use of CCP for the treatment of nonhospitalized, immunocompetent patients are summarized in [Table 5b](#). The data from well-designed clinical trials that evaluated the use of CCP for the treatment of nonhospitalized patients with COVID-19 are conflicting. All of the following trials were conducted prior to the emergence of Omicron.

#### **Trials That Demonstrated Efficacy for COVID-19 Convalescent Plasma**

- A moderately-sized, double-blind, placebo-controlled, randomized trial evaluated the use of high-titer CCP in older, nonhospitalized adults with <72 hours of mild COVID-19 symptoms (n = 160). The patients were aged  $\geq 75$  years or aged 65 to 74 years with  $\geq 1$  comorbidity. The trial reported a reduction in the proportion of patients who developed severe respiratory disease within 14 days in the CCP arm (16% in the CCP arm vs. 31% in the placebo arm; relative risk 0.52; 95% CI, 0.29–0.94;  $P = 0.03$ ).<sup>9</sup>
- CSSC-004, a large (n = 1,181), double-blind, placebo-controlled trial that evaluated the use of high-titer CCP for the treatment of adults with  $\leq 8$  days of COVID-19 symptoms, demonstrated a reduction in the proportion of patients who experienced COVID-19-related hospitalization within

28 days in the CCP arm (2.9% in the CCP arm vs. 6.3% in the placebo arm; absolute risk reduction of 3.4 percentage points; 95% CI, 1.0–5.8;  $P = 0.005$ ). Eighty-two percent of the patients were not vaccinated against COVID-19, and 53 of the 54 hospitalizations that were reported during the study occurred in unvaccinated patients. No hospitalizations occurred in either arm among fully vaccinated patients.<sup>21</sup>

### **Trials That Demonstrated No Benefit of COVID-19 Convalescent Plasma**

- The SIREN-C3PO trial (n = 511) was a single-blind randomized trial that evaluated the use of high-titer CCP for the treatment of nonhospitalized patients with  $\leq 7$  days of mild or moderate COVID-19 symptoms and  $\geq 1$  risk factor for severe COVID-19. This study did not report a reduction in the proportion of patients who experienced disease progression in the CCP arm (30% in the CCP arm vs. 32% in the placebo arm; risk difference of 1.9 percentage points; 95% CrI, -6.0 to 9.8).<sup>22</sup>
- The CONV-ERT study (n = 376) was a double-blind, placebo-controlled randomized trial that evaluated the use of high-titer, methylene blue-treated CCP for the treatment of nonhospitalized patients aged  $\geq 50$  years with  $\leq 7$  days of mild or moderate COVID-19 symptoms. This study did not report a reduction in the proportion of patients who were hospitalized or died in the CCP arm (12% in the CCP arm vs. 11% in the placebo arm; relative risk 1.05; 95% CI, 0.78–1.41).<sup>23</sup>

Differences in patient populations, the placebo used (e.g., some studies used saline and some used non-SARS-CoV-2 plasma), and CCP manufacturing and testing methods may have contributed to the disparate outcomes of these clinical trials. Additional well-designed trials are necessary to establish evidence for a consistent benefit of using CCP in nonhospitalized patients during the current phase of the pandemic.

The emergence of SARS-CoV-2 variants further complicates the assessment of any potential benefit of CCP for this patient population. Most CCP products that are available in the United States are expected to have no or very little neutralizing activity against the currently circulating SARS-CoV-2 variants because they were collected from donors who had COVID-19 prior to the emergence of the Omicron variant. The Panel **recommends against** using CCP that was collected prior to the emergence of the Omicron variant for the treatment of COVID-19 (**AIII**).

Currently, nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease are eligible to receive several antiviral therapies with proven efficacy. See [Therapeutic Management of Nonhospitalized Adults With COVID-19](#) for the Panel's recommendations for this patient population.

### ***Hospitalized or Nonhospitalized Patients Who Are Immunocompromised***

This section pertains to people who are moderately or severely immunocompromised.<sup>24</sup> According to the Centers for Disease Control and Prevention, individuals who qualify as having moderately or severely immunocompromising conditions are those who:

- Are receiving active treatment for solid tumor and hematologic malignancies.
- Received a solid-organ transplant and are taking immunosuppressive therapy.
- Received chimeric antigen receptor T cell therapy or a hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy).
- Have a moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome).
- Have advanced or untreated HIV infection (defined as people with HIV and CD4 T lymphocyte counts  $< 200$  cells/mm<sup>3</sup>, a history of an AIDS-defining illness without immune reconstitution, or

clinical manifestations of symptomatic HIV).

- Are receiving active treatment with high-dose corticosteroids (i.e.,  $\geq 20$  mg prednisone or equivalent per day when administered for  $\geq 2$  weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor-necrosis blockers, and other immunosuppressive or immunomodulatory biologic agents (e.g., B cell-depleting agents).

Under the EUA issued on December 27, 2021, CCP is authorized for the treatment of COVID-19 in outpatients or inpatients who have immunosuppressive disease or who are receiving immunosuppressive treatment.

Although there are no definitive data to support using CCP in patients who are immunocompromised, there is a physiologic rationale for the use of CCP in this patient population. People who are immunocompromised are more likely to require hospitalization for breakthrough SARS-CoV-2 infection despite COVID-19 vaccination, become severely ill from COVID-19, and experience prolonged SARS-CoV-2 infection and shedding.<sup>25-27</sup> Although some of this vulnerability may be attributed to impaired cellular immune responses, numerous studies indicate that people who are immunosuppressed are at risk of having reduced antibody responses to SARS-CoV-2 infection and/or vaccination.<sup>28-30</sup> Furthermore, the subgroup analyses from several clinical trials suggest that anti-SARS-CoV-2 antibody products are more likely to be effective in patients who are SARS-CoV-2 seronegative than in patients who are seropositive.<sup>31,32</sup> Therefore, patients who are immunocompromised could potentially benefit from receiving antibody-based therapies in circumstances where patients without an immunocompromising condition might not.

There are limited clinical data to inform the use of CCP to treat COVID-19 in patients who are immunocompromised. No randomized, adequately controlled trials evaluating CCP in immunocompromised patients have been published to date. A prespecified subgroup analysis of 126 critically ill REMAP-CAP participants with immunodeficiencies suggested that CCP might offer a potential benefit of improved survival and/or more organ support-free days in this subgroup (OR 1.51; 95% CI, 0.80–2.92); however, this finding was not statistically significant.<sup>20</sup> Data from case reports, case series, and a retrospective case-control study also suggest a potential benefit of CCP in patients with primary and secondary humoral immunodeficiencies, including patients with hematologic malignancy, common variable immune deficiency, or agammaglobulinemia, and those who have received a solid organ transplant.<sup>33-46</sup>

As noted above, the emergence of SARS-CoV-2 variants further complicates the assessment of any potential benefit of CCP for patients who are immunocompromised. Studies have shown that prior infection with the Beta (B.1.351) or Delta (B.1.617.2) variants affords little protection and has reduced neutralizing antibody responses against the Omicron variant, raising doubts that CCP collected prior to the emergence of Omicron will be effective.<sup>47-50</sup> Thus, the Panel **recommends against** the use of CCP collected prior to the emergence of the Omicron variant for the treatment of COVID-19 (**AIII**).

There is insufficient evidence for the Panel to recommend either for or against the use of high-titer CCP that was collected after the emergence of Omicron for the treatment of COVID-19 in immunocompromised patients and nonhospitalized, immunocompetent patients. 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 COVID-19 in patients who are immunocompromised.

## Considerations in Pregnancy

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.<sup>51</sup> Pathogen-

specific immunoglobulins (Ig) are used clinically during pregnancy to prevent infection from varicella zoster virus and rabies virus and have been used in clinical trials of congenital cytomegalovirus infection.<sup>52,53</sup> Pregnancy is not a reason to withhold CCP from a patient if it is otherwise indicated.

## Considerations in Children

The safety and efficacy of CCP have not been systematically evaluated in pediatric patients. Published literature on its use in children is limited to case reports and case series. A few clinical trials that are evaluating the use of CCP in children are ongoing. The use of 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 FDA for use in immunocompetent patients.

As an alternative to CCP, several antiviral therapies are available for the treatment of children with COVID-19 who are at high risk of progressing to severe disease. The use of these products in children may be considered on a case-by-case basis. See [Special Considerations in Children](#) for more information.

## 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.<sup>2,18,54</sup>

Additional risks of CCP transfusion include a theoretical risk of antibody-dependent enhancement of SARS-CoV-2 infection and a theoretical risk of long-term immunosuppression. In the CONCOR-1 trial, higher levels of full transmembrane spike IgG were associated with worse outcomes, suggesting that the use of CCP with nonfunctional anti-SARS-CoV-2 antibodies may be harmful.<sup>19</sup> A subgroup analysis in the REMAP-CAP trial showed potential harm in patients who received CCP transfusions more than 7 days after being hospitalized.<sup>20</sup>

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.

## Clinical Trials

Several randomized clinical trials that are evaluating the use of CCP for the treatment of COVID-19 are underway. Please see [ClinicalTrials.gov](#) for the latest information.

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