



# COVID-19 Convalescent Plasma

Last Updated: November 2, 2023

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.<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 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 outpatients or inpatients with COVID-19 who have immunosuppressive disease or who are receiving immunosuppressive treatment. The testing criteria used to identify high-titer CCP 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

### *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. Without definitive data, 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

See [Special Considerations in People Who Are Immunocompromised](#) for a broader discussion on the therapeutic management of COVID-19 in people who are immunocompromised.

### *Patients Who Are Immunocompetent*

- The Panel **recommends against** the use of CCP for the treatment of COVID-19 in hospitalized patients who are immunocompetent (**AI**).
- 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.<sup>3,4</sup> 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.<sup>2</sup>

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 evaluating 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 from the use of CCP in this population.<sup>5-7</sup> However, subgroup analyses need to be interpreted with caution. In the overall trial populations, there was no evidence of benefit from the use 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.<sup>8-16</sup>

The emergence of SARS-CoV-2 variants further complicates assessment of benefit from the use of CCP. Although results from some in vitro studies suggest that CCP collected from vaccinated individuals who recovered from Omicron infection exhibits neutralizing activity against certain Omicron subvariants,<sup>17-23</sup> extrapolation of these results to the clinical setting is challenging for the following reasons:<sup>24</sup>

- 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.<sup>20-23,25-27</sup>
- 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 for a definitive recommendation for 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 documented the treatment of these patients with additional antiviral treatments, prolonged courses of antiviral treatments, high-titer CCP, or combination therapy.<sup>28-32</sup> 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](#).

Results from the 3 largest randomized controlled trials that evaluated CCP in hospitalized patients—RECOVERY,<sup>33</sup> CONCOR-1,<sup>34</sup> and REMAP-CAP<sup>6</sup>—found no evidence of benefit from the use of high-titer CCP in hospitalized patients with COVID-19. All 3 were open-label trials that were stopped early due to futility.

The Panel **recommends against** the use of CCP for the treatment of COVID-19 in hospitalized patients who are immunocompetent (AI).

### ***Nonhospitalized Patients Who Are Immunocompetent***

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.

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, and some used non-SARS-CoV-2 plasma), and CCP manufacturing and testing methods may have contributed to the disparate outcomes and difficulty in reconciling results across these clinical trials. The emergence of SARS-CoV-2 variants further complicates the assessment of benefit from the use of 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.

### **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>35</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>36,37</sup> 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. 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 FDA for use in patients who are immunocompetent.

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 therapies in children may be considered on a case-by-case basis. See [Special Considerations in Children](#) and [Therapeutic Management of Hospitalized Children With COVID-19](#) for more information.

## 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.<sup>2,33,38</sup>

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 IgG were associated with worse outcomes, suggesting that the use of CCP with nonfunctional anti-SARS-CoV-2 antibodies may be harmful.<sup>34</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>6</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.

## References

1. Wang X, Guo X, Xin Q, et al. Neutralizing antibody responses to severe acute respiratory syndrome coronavirus 2 in coronavirus disease 2019 inpatients and convalescent patients. *Clin Infect Dis*. 2020;71(10):2688-2694. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32497196>.
2. Food and Drug Administration. Fact sheet for health care providers: Emergency Use Authorization (EUA) of COVID-19 convalescent plasma for treatment of coronavirus disease 2019 (COVID-19). 2021. Available at: <https://www.fda.gov/media/141478/download>.
3. Cattaneo C, Masina L, Pagani C, et al. High mortality in fully vaccinated hematologic patients treated with anti-CD20 antibodies during the “Omicron wave” of COVID-19 pandemic. *Hematol Oncol*. 2023;41(1):205-207. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35933702>.
4. Shahzad M, Chaudhary SG, Zafar MU, et al. Impact of COVID-19 in hematopoietic stem cell transplant recipients: a systematic review and meta-analysis. *Transpl Infect Dis*. 2022;24(2):e13792. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35030267>.
5. Denking CM, Janssen M, Schäkel U, et al. Anti-SARS-CoV-2 antibody-containing plasma improves outcome in patients with hematologic or solid cancer and severe COVID-19: a randomized clinical trial. *Nat Cancer*. 2023;4(1):96-107. Available at: <https://pubmed.ncbi.nlm.nih.gov/36581734>.
6. Writing Committee for the REMAP-CAP Investigators. Effect of convalescent plasma on organ support-free days in critically ill patients with COVID-19: a randomized clinical trial. *JAMA*. 2021;326(17):1690-1702. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34606578>.
7. Lacombe K, Hueso T, Porcher R, et al. COVID-19 convalescent plasma to treat hospitalised COVID-19 patients with or without underlying immunodeficiency. *medRxiv*. 2022;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2022.08.09.22278329v2>.
8. Thompson MA, Henderson JP, Shah PK, et al. Association of convalescent plasma therapy with survival in patients with hematologic cancers and COVID-19. *JAMA Oncol*. 2021;1167-1175. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34137799>.
9. Lanza F, Monaco F, Ciceri F, et al. Lack of efficacy of convalescent plasma in COVID-19 patients with concomitant hematological malignancies: an Italian retrospective study. *Hematol Oncol*. 2022;40(5):857-863. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35932208>.
10. Lang-Meli J, Fuchs J, Mathé P, et al. Case series: convalescent plasma therapy for patients with COVID-19 and primary antibody deficiency. *J Clin Immunol*. 2022;42(2):253-265. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34893946>.

11. Rodionov RN, Biener A, Spieth P, et al. Potential benefit of convalescent plasma transfusions in immunocompromised patients with COVID-19. *Lancet Microbe*. 2021;2(4):e138. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33817676>.
12. Franchini M, Focosi D, Percivalle E, et al. Variant of concern-matched COVID-19 convalescent plasma usage in seronegative hospitalized patients. *Viruses*. 2022;14(7):1443. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35891421>.
13. Ljungquist O, Lundgren M, Iliachenko E, et al. Convalescent plasma treatment in severely immunosuppressed patients hospitalized with COVID-19: an observational study of 28 cases. *Infect Dis (Lond)*. 2022;54(4):283-291. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34878955>.
14. Ripoll JG, Gorman EK, Juskewitch JE, et al. Vaccine-boosted convalescent plasma therapy for patients with immunosuppression and COVID-19. *Blood Adv*. 2022;6(3):5951-5955. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/36156121>.
15. Senefeld JW, Klassen SA, Ford SK, et al. Use of convalescent plasma in COVID-19 patients with immunosuppression. *Transfusion*. 2021;61(8):2503-2511. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34036587>.
16. Beraud M, Goodhue Meyer E, Lozano M, et al. Lessons learned from the use of convalescent plasma for the treatment of COVID-19 and specific considerations for immunocompromised patients. *Transfus Apher Sci*. 2022;61(3):103355. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35063360>.
17. Lusvardi S, Pollett SD, Neerukonda SN, et al. SARS-CoV-2 BA.1 variant is neutralized by vaccine booster-elicited serum but evades most convalescent serum and therapeutic antibodies. *Sci Transl Med*. 2022;14(645):eabn8543. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35380448>.
18. Yu J, Collier AY, Rowe M, et al. Neutralization of the SARS-CoV-2 Omicron BA.1 and BA.2 variants. *N Engl J Med*. 2022;386(16):1579-1580. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35294809>.
19. Richardson SI, Madzorera VS, Spencer H, et al. SARS-CoV-2 Omicron triggers cross-reactive neutralization and Fc effector functions in previously vaccinated, but not unvaccinated, individuals. *Cell Host Microbe*. 2022;30(6):880-886.e4. Available at: <https://pubmed.ncbi.nlm.nih.gov/35436444>.
20. Li M, Beck EJ, Laeyendecker O, et al. Convalescent plasma with a high level of virus-specific antibody effectively neutralizes SARS-CoV-2 variants of concern. *Blood Adv*. 2022;6(12):3678-3683. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35443020>.
21. Khan K, Karim F, Ganga Y, et al. Omicron BA.4/BA.5 escape neutralizing immunity elicited by BA.1 infection. *Nat Commun*. 2022;13(1):4686. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35948557>.
22. Wang W, Lusvardi S, Subramanian R, et al. Antigenic cartography of well-characterized human sera shows SARS-CoV-2 neutralization differences based on infection and vaccination history. *Cell Host Microbe*. 2022;30(12):1745-1758.e7. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/36356586>.
23. Di Germanio C, Simmons G, Thorbrogger C, et al. Vaccination of COVID-19 convalescent plasma donors increases binding and neutralizing antibodies against SARS-CoV-2 variants. *Transfusion*. 2022;62(3):563-569. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35129839>.
24. Rijnders BJA, Huygens S, Mitjà O. Evidence-based dosing of convalescent plasma for COVID-19 in future trials. *Clin Microbiol Infect*. 2022;28(5):667-671. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35150881>.
25. Qu P, Faraone J, Evans JP, et al. Neutralization of the SARS-CoV-2 Omicron BA.4/5 and BA.2.12.1 subvariants. *N Engl J Med*. 2022;386(26):2526-2528. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35704428>.
26. Richardson SI, Kgagudi P, Manamela NP, et al. Antibody-dependent cellular cytotoxicity against SARS-CoV-2 Omicron sub-lineages is reduced in convalescent sera regardless of infecting variant. *Cell Rep Med*. 2023;4(1):100910. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/36603577>.
27. Tuekprakhon A, Nutalai R, Dijokaite-Guraliuc A, et al. Antibody escape of SARS-CoV-2 Omicron BA.4 and

- BA.5 from vaccine and BA.1 serum. *Cell*. 2022;185(14):2422-2433.e13. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35772405>.
28. Huygens S, Gharbharan A, Serroukh Y, et al. High-titer convalescent plasma plus nirmatrelvir/ritonavir treatment for non-resolving COVID-19 in six immunocompromised patients. *J Antimicrob Chemother*. 2023;78(7):1644-1648. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/37248664>.
  29. Brosh-Nissimov T, Ma'aravi N, Leshin-Carmel D, et al. Combination treatment of persistent COVID-19 in immunocompromised patients with remdesivir, nirmaltrevir/ritonavir and tixegavimab/cilgavimab. *medRxiv*. 2023;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2023.04.07.23288144v1>.
  30. Mikulska M, Sepulcri C, Dentone C, et al. Triple combination therapy with two antivirals and monoclonal antibodies for persistent or relapsed SARS-CoV-2 infection in immunocompromised patients. *Clin Infect Dis*. 2023;Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/36976301>.
  31. Graziani L, Gori L, Manciuoli T, et al. Successful use of nirmatrelvir/ritonavir in immunocompromised patients with persistent and/or relapsing COVID-19. *J Antimicrob Chemother*. 2023;78(2):555-558. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/36544352>.
  32. Trottier CA, Wong B, Kohli R, et al. Dual antiviral therapy for persistent coronavirus disease 2019 and associated organizing pneumonia in an immunocompromised host. *Clin Infect Dis*. 2023;76(5):923-925. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/36281907>.
  33. RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. *Lancet*. 2021;397(10289):2049-2059. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34000257>.
  34. Bégin P, Callum J, Jamula E, et al. Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial. *Nat Med*. 2021;27(11):2012-2024. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34504336>.
  35. Franchini M, Prefumo F, Grisolia G, et al. Convalescent plasma for pregnant women with COVID-19: a systematic literature review. *Viruses*. 2021;13(7):1194. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34206468>.
  36. Revello MG, Lazzarotto T, Guerra B, et al. A randomized trial of hyperimmune globulin to prevent congenital cytomegalovirus. *N Engl J Med*. 2014;370(14):1316-1326. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24693891>.
  37. Hughes BL, Clifton RG, Rouse DJ, et al. A trial of hyperimmune globulin to prevent congenital cytomegalovirus infection. *N Engl J Med*. 2021;385(5):436-444. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34320288>.
  38. Nguyen FT, van den Akker T, Lally K, et al. Transfusion reactions associated with COVID-19 convalescent plasma therapy for SARS-CoV-2. *Transfusion*. 2021;61(1):78-93. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33125158>.