Convalescent Plasma

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Plasma from donors who have recovered from COVID-19 may contain antibodies to SARS-CoV-2 that could help suppress viral replication. In August 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for convalescent plasma for the treatment of hospitalized patients with COVID-19. On February 4, 2021, the FDA revised the convalescent plasma EUA to limit the authorization to high-titer COVID-19 convalescent plasma and only for the treatment of hospitalized patients with COVID-19 early in their disease course or hospitalized patients who have impaired humoral immunity. Use of convalescent plasma should be limited to those products that contain high levels of anti-SARS-CoV-2 antibodies (i.e., 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 **COVID-19 convalescent plasma** for the treatment of COVID-19 in hospitalized patients without impaired humoral immunity (AI).
- There is insufficient evidence for the Panel to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19 in:
  - Nonhospitalized patients without impaired humoral immunity; and
  - Nonhospitalized or hospitalized patients with impaired humoral immunity.

**Rationale**

For Hospitalized Patients Without Impaired Humoral Immunity

Clinical data on the use of convalescent plasma for the treatment of COVID-19, including data from several randomized trials and the U.S. Expanded Access Program (EAP) for Convalescent Plasma, are summarized in **Table 3b**.

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

Data from the initial randomized clinical trials evaluating convalescent plasma, which were all underpowered, did not demonstrate the product’s efficacy for the treatment of hospitalized patients with COVID-19.

Subsequently, results from the 3 largest randomized clinical trials evaluating convalescent plasma in hospitalized patients—RECOVERY, CONCOR-1, and REMAP-CAP—found no evidence of benefit from high-titer convalescent plasma in hospitalized patients with COVID-19. All 3 were open-label trials that were stopped early due to futility.

In the RECOVERY trial, patients were randomized to receive convalescent plasma (n = 5,795) or usual care (n = 5,763). The trial demonstrated no significant difference in the primary endpoint of 28-day
mortality between the convalescent plasma arm and the usual care arm (24% in each arm; risk ratio 1.00; 95% CI, 0.93–1.07). Additionally, there were no differences between the arms in the secondary endpoints of time to hospital discharge and receipt of mechanical ventilation or death.

In the CONCOR-1 trial, patients were randomized to receive convalescent plasma or standard of care. The primary endpoint of intubation or death by Day 30 occurred in 199 of 614 patients (32%) in the convalescent plasma arm and 86 of 307 patients (28%) in the standard of care arm (relative risk 1.16; 95% CI, 0.94–1.43). There were no differences between the arms in secondary endpoints, including time to intubation or death, mortality, or intensive care unit and hospital length of stay. Serious adverse events occurred in 33% of the patients in the convalescent plasma arm and 26% of those in the standard of care arm, including 35 transfusion-related complications reported in the convalescent plasma arm.

The REMAP-CAP trial evaluated convalescent plasma in hospitalized patients. Although noncritically ill patients participated in the study, the reported outcomes are only for those who were critically ill at enrollment (1,084 patients in the convalescent plasma arm and 916 patients in the control arm). There was no difference in the primary endpoint of organ support-free days up to Day 21 between the arms (median of 0 days in the convalescent plasma arm [IQR -1 to 16 days] vs. 3 days in the control arm [IQR -1 to 16 days]). There were also no differences between the arms in secondary endpoints, including in-hospital mortality (401 of 1,075 patients [37.3%] in the convalescent plasma arm died vs. 347 of 904 patients [38.4%] in the control arm). The study showed a potential for harm (90.3% posterior probability) in 126 patients who were randomized to convalescent plasma after >7 days of hospitalization.

Although these trials 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. Based on the collective results from these studies, the Panel recommends against the use of COVID-19 convalescent plasma for the treatment of COVID-19 in hospitalized patients who do not have impaired humoral immunity (AI).

**For Nonhospitalized Patients Without Impaired Humoral Immunity**

Current data are insufficient to establish the safety or efficacy of convalescent plasma in nonhospitalized patients with COVID-19. Convalescent plasma is not authorized for nonhospitalized patients with COVID-19 under the EUA.

Data from a double-blind, placebo-controlled, randomized trial of high-titer convalescent plasma in older, nonhospitalized adults with <72 hours of mild COVID-19 symptoms demonstrated benefit in reduced progression of respiratory disease. However, the trial included relatively few participants (80 participants in each arm).

The C3PO study was a single-blind randomized trial that evaluated high-titer convalescent plasma for the treatment of nonhospitalized patients with ≤7 days of mild or moderate COVID-19 symptoms and at least 1 risk factor for severe COVID-19. Trial participants (n = 511) were randomized to receive convalescent plasma or a placebo transfusion. The trial was halted after a second interim analysis indicated a priori futility criteria were reached. There was no difference in the occurrence of the composite primary endpoint of disease progression (i.e., hospital admission, death without hospitalization, or urgent or emergency care within 15 days after randomization) between the patients in the convalescent plasma arm and the placebo arm (30% vs. 32%; risk difference 1.9%; 95% CI, -6.0 to 9.8). There were no differences between the arms in any secondary endpoints, including the worst severity of illness based on an 8-point ordinal scale and hospital-free days after randomization. Five patients in the convalescent plasma arm and 1 patient in the placebo arm died. Infusion-related reactions,
which occurred more often in the convalescent plasma arm, included 3 serious reactions.

Results from additional, adequately powered, well-designed, and well-conducted randomized clinical trials are needed to provide more specific, evidence-based guidance on the role of COVID-19 convalescent plasma in the treatment of nonhospitalized patients with COVID-19.

The FDA has issued EUAs for several anti-SARS-CoV-2 monoclonal antibody products for the treatment of nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progression to severe disease (see Anti-SARS-CoV-2 Monoclonal Antibodies). The Panel recommends using these products for the population specified in the EUAs.

**For Hospitalized or Nonhospitalized Patients With Impaired Humoral Immunity**

People who are immunocompromised are more likely to become severely ill from COVID-19, experience prolonged SARS-CoV-2 infection and shedding, and require hospitalization for breakthrough SARS-CoV-2 infection despite COVID-19 vaccination. 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 reduced antibody responses to SARS-CoV-2 infection and vaccination. An analysis from the RECOVERY trial suggests that SARS-CoV-2 seronegative patients are more likely to benefit from convalescent plasma than seropositive patients. Therefore, convalescent plasma may be effective in SARS-CoV-2 seronegative patients even though no benefit was observed in the overall population of patients enrolled in the RECOVERY trial.

The REMAP-CAP investigators performed a prespecified subgroup analysis of 126 patients with immunodeficiencies who were critically ill. Immunodeficiency was defined as recent chemotherapy or radiation, high-dose or long-term steroid use, or presence of immunocompromising diseases. Although not statistically significant, results of this analysis suggest that, compared to placebo, convalescent plasma offers a potential benefit of improved survival and/or more organ support-free days in this subgroup of immunocompromised patients (OR 1.51; 95% CI, 0.80–2.92).

Severely immunocompromised individuals may experience prolonged SARS-CoV-2 infection with persistent viral replication over several months, as described in the case report of a patient with lymphoma who had received chimeric antigen receptor T cell therapy and who subsequently recovered following repeat transfusions of high-dose convalescent plasma. Data from case reports, case series, and a retrospective case-control study also suggest a potential benefit of convalescent plasma 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.

Although there is physiologic rationale for the value of convalescent plasma in immunocompromised people and some reports suggesting benefit, there are no definitive data to support the use of convalescent plasma in this patient population. Therefore, there is insufficient evidence for the Panel to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19 in hospitalized or nonhospitalized patients who have impaired humoral immunity. Adequately powered, well-designed, and well-conducted randomized clinical trials are needed to provide more specific, evidence-based guidance on the role of convalescent plasma in the treatment of patients with COVID-19 who have impaired humoral immunity.

**Clinical Data to Date**

*Table 3b* includes a summary of key studies of convalescent plasma for the treatment of COVID-19.
Considerations in Pregnancy

The safety and efficacy of using COVID-19 convalescent plasma 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. 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. If otherwise indicated, pregnancy is not a reason to withhold convalescent plasma.

Considerations in Children

The safety and efficacy of COVID-19 convalescent plasma have not been systematically evaluated in pediatric patients. Published literature on its use in children is limited to case reports and case series, as well as a systematic review of these reports. A few clinical trials of COVID-19 convalescent plasma in children are ongoing. The use of convalescent plasma may be considered on a case-by-case basis for hospitalized children with impaired immunity who meet the EUA criteria for its use. Convalescent plasma is not authorized by the FDA for use in nonhospitalized patients with COVID-19.

Several anti-SARS-CoV-2 monoclonal antibody products have received EUAs for treatment of nonhospitalized patients aged ≥12 years with mild to moderate COVID-19 who are at high risk of progression to severe disease. Use of these products may be considered on a case-by-case basis for children who meet the EUA criteria (see Anti-SARS-CoV-2 Monoclonal Antibodies).

Adverse Effects

Available data suggest that serious adverse reactions following the administration of COVID-19 convalescent plasma 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.

Additional risks of COVID-19 convalescent plasma 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 the use of convalescent plasma with nonfunctional anti-SARS-CoV-2 antibodies may be harmful. Subgroup analysis in the REMAP-CAP trial showed potential harm in convalescent plasma transfused >7 days into hospitalization.

When considering convalescent plasma for patients with a history of severe allergic or anaphylactic transfusion reactions, consultation with a transfusion medicine specialist is advised.

Clinical Trials

Randomized clinical trials evaluating convalescent plasma for the treatment of COVID-19 are underway. Please see ClinicalTrials.gov for the latest information.

References


