# Convalescent Plasma: What the Data Shows for this Promising Potential COVID-19 Treatment

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In the midst of the COVID-19 pandemic, the entire healthcare industry is working tirelessly to develop the innovative diagnostic and therapeutic tools needed to save lives and end this global crisis. Convalescent plasma therapy is one approach that may provide effective prophylactic and therapeutic benefit to COVID-19 patients. Serological testing plays a key role in identifying qualified donors for convalescent plasma therapy.

To understand the role convalescent plasma may play in ending this global pandemic, we will discuss:

1. A brief history of convalescent plasma use, including the mechanism of action, pros and cons of convalescent plasma treatment, and potential applications for COVID-19 patients.
2. A review of outcomes and available clinical publications, the current status of the use of COVID-19 convalescent plasma, and the data supporting the FDA's Emergency Use Authorization—including data from the Expanded Access Program (EAP) led by the Mayo Clinic.

## WHAT IS CONVALESCENT PLASMA? HOW HAS IT BEEN USED TO TREAT INFECTIOUS DISEASES?

COVID-19 convalescent plasma (CCP) is the liquid portion of the blood obtained from a donor who has recently recovered from a SARS-CoV-2 infection. The plasma contains neutralizing antibodies to the pathogen. When transfused to a patient with COVID-19 disease, the specific antibodies can help clear the pathogen and control the infection.[1]

The use of convalescent plasma (CP) to prevent or treat infectious diseases is not new. In fact, CP has been used for a range of human infectious diseases for more than 100 years.[2]

**Recent History of CP**

**2003: SARS**
Several studies reported observing shorter hospital stays and lower mortality rates in patients treated with CP. A meta-analysis showed reduced mortality with no adverse events or complications after the treatment.[2]

**2009: H1N1**
A prospective cohort study showed a significant reduction in the relative risk of mortality in patients treated with CP for H1N1 influenza, with significantly lower viral load and no adverse events.[2]

**2014: Ebola**
The WHO recommended CP as an empirical treatment for Ebola.[2]

**2015: MERS**
Protocols were established for the use of CP to treat MERS.[2]

All these observations suggest the therapeutic potential of CP therapy for the treatment of infectious diseases. However, the clinical efficacies of CP therapies in different disease settings were rather anecdotal. There is a lack of high-quality, large-scale, randomized, and placebo-controlled clinical trials necessary to provide definitive evidence.[1, 2]

## HOW DOES CP THERAPY WORK? WHAT IS THE MECHANISM OF ACTION?

Several mechanisms of action have been described:[3]

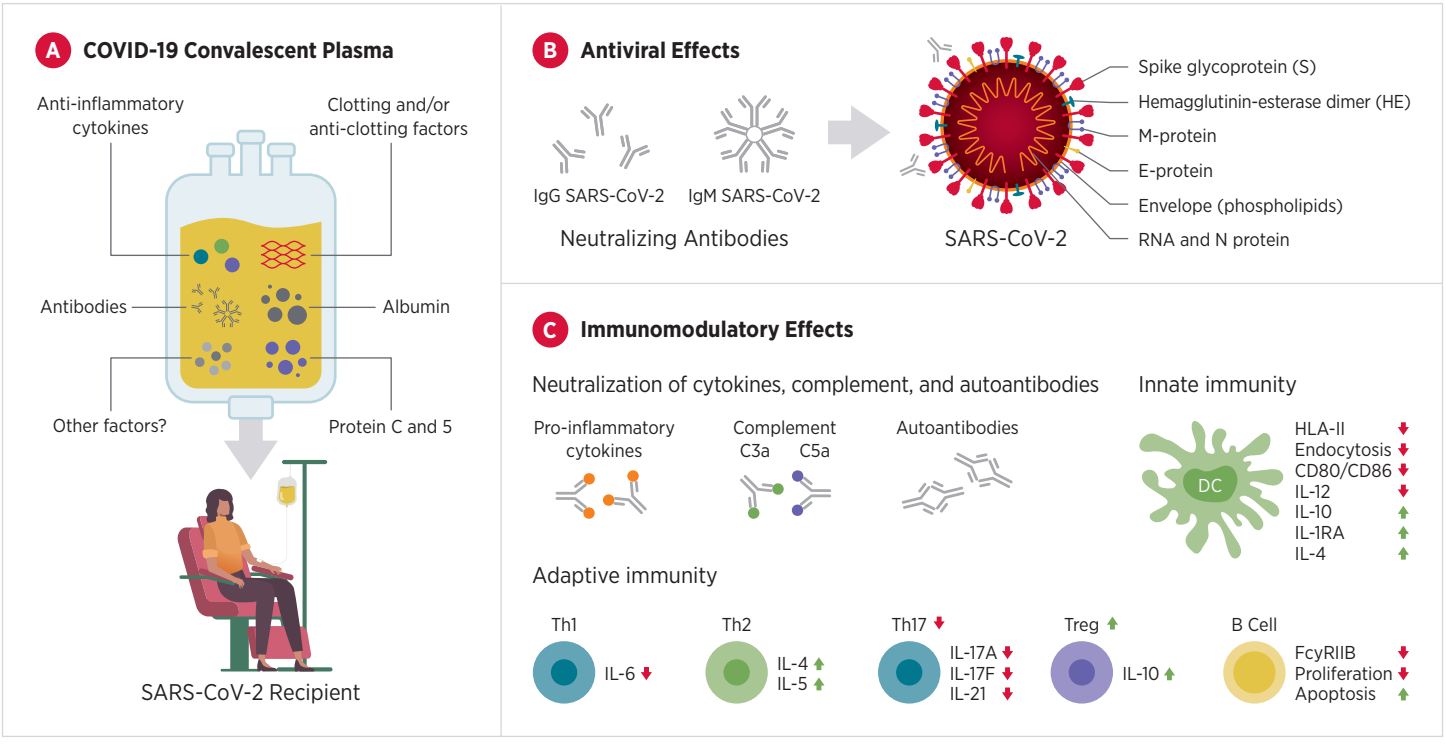
1. Antiviral[3]
2. Immunomodulation[3]
3. Dendritic cells[3]
4. B cells[3]
5. T cells[3]
6. Other immune cells[3]

The main mechanism of action of convalescent plasma therapy is the neutralizing antibodies that inhibit viral replication.[3] These neutralizing antibodies not only clear viruses and block new infection, but also accelerate the clearance of infected cells. In addition, other plasma components may also offer beneficial effects, for example, replenishing coagulation factors when transfused to patients with hemorrhagic fevers such as Ebola.[1, 3]

## ARE THERE PROS AND CONS TO ADMINISTERING CP THERAPY?

Although the efficacy of convalescent plasma varied with the virus and the study, there was consensus that this intervention was useful, and thus, CP was used in numerous outbreaks. Especially for those infectious diseases without specific treatment or effective vaccine, convalescent plasma provides a passive immunization to achieve immediate protection for patients.[2]

**Figure 1:** Schematic representation of convalescent plasma components and its mechanism of action




Adapted from Convalescent plasma in Covid-19: Possible mechanisms of action. Rojas M, et al. Autoimmun Rev. 2020;19(7):102554. doi:10.1016/j.autrev.2020.102554

*Especially for those infectious diseases without specific treatment or effective vaccine, convalescent plasma provides a passive immunization to achieve immediate protection for patients.*[2]

**Potential benefits of CP therapy and collection**

There are multiple advantages of convalescent plasma therapy: for example, large volumes of plasma can be collected from donors, so one collection may be used to treat multiple patients. Plasma has a long shelf life and can be frozen and stored for later use. As plasma donation has a minimal impact on the donor's hemoglobin level is negligible, convalescent plasma can potentially be collected frequently. In addition, the recruitment of local donors can offer antibodies specific to the local strain of the pathogen.[1]

**Potential risks of CP therapy**

However, the use of convalescent plasma as a therapeutic agent is not without risks. Like any blood product, plasma may contain blood borne pathogens. Transfusion with a large volume of plasma may cause transfusion-related acute lung injury (TRALI) or other complications. In addition, although hypothetical, convalescent plasma may potentially induce antibody-dependent enhancement of infection (ADE). As ADE is less likely with high neutralizing antibody (NAb) titers, it is important to select high titer plasma.[1] The FDA and European Commission have guidelines regarding recommended titer thresholds.[4, 5]

**Guidelines for CCP titer levels and testing**

FDA:

- When measurement of neutralizing antibody titers is available, the recommended titers is at least 1:160.[4]
- A titer of 1:80 may be considered acceptable if an alternative matched unit is not available.[4]
- When measurement of neutralizing antibody titers is not available, consider storing a retention sample from the convalescent plasma donation for determining antibody titers at a later date.[4]
- It is important to note that as of August 22, 2020, NAb titer is not included in the FDA issued Emergency Use Authorization (EUA).[6]

European Commission:

- It is suggested that NAb titers should optimally be greater than 1:320, but lower thresholds may also be effective.[5]
- When the measured neutralizing activity in the collected plasma is considered to be too low, the plasma should be made available for other use (ideally fractionation). In the absence of neutralizing antibody testing, a test for the presence of anti-SARS-CoV-2 antibody should ideally be performed prior to release.[5]
- In emergency cases, where plasma is released for transfusion without antibody testing, archived samples should be tested at a later date once testing is available.[5]

## WHAT ARE THE POTENTIAL APPLICATIONS OF COVID-19 CONVALESCENT PLASMA (CCP) FOR COVID-19 PATIENTS?

While the clinical trial data for the antiviral medication Remdesivir is encouraging, there is still a huge unmet need for both specific treatment for COVID-19 and effective vaccines for SARS-CoV-2. Currently, the main treatment approach for COVID-19 patients is supportive care, such as supplemental oxygen.[7] Convalescent plasma as a passive immune therapy can potentially offer immediate protection from or control of SARS-CoV-2 infection via viral neutralization. Convalescent plasma may be more effective if used prophylactically or during the early stages of infection.[7] The hope is that convalescent plasma may prophylactically protect those in high risk populations from infection or may shorten the duration of illness, prevent disease progression, and reduce morbidity for COVID-19 patients.[7]

## HAS CONVALESCENT PLASMA THERAPY DEMONSTRATED THERAPEUTIC OUTCOMES IN COVID-19 PATIENTS?

The clinical efficacy of CCP for the treatment of COVID-19 patients has not been proven by large-scale, randomized, placebo-controlled clinical studies.[7] However, in the midst of the COVID-19 pandemic, CCP is currently in use in many countries, including the U.S., in exploratory or investigational settings.

The published clinical outcomes are anecdotal reports from small, uncontrolled case series or observational studies. Several of these papers are summarized in the table below.

**Table 1:** Assessing efficacy of CCP in severe to critically ill patients

| Publication & Design | Patients | Results & Conclusion |
|---|---|---|
| **Shen et al., *JAMA*, March 2020**[8]<br>Efficacy of CCP measured by clinical status of patient | 5 | *Results:* Suggest improved clinical status<br>*Conclusion:* Administration of convalescent plasma was followed by improvement in patient condition, but the study was not definitive, due to limited sample size and study design |
| **Duan et al., *MedRxiv,* March 2020**[9]<br>*Primary endpoint:* Safety pf transfusion<br>*Secondary endpoints:* (1) Clinical improvement (2) Laboratory parameters within 3 days after CP transfusion | 10 | *Results:* Clinical improvement<br>*Conclusion:* CP therapy was well tolerated and could potentially show clinical improvement clinical outcome through neutralizing viremia |
| **Zhang et al., *Chest Journal*, July 2020**[10]<br>Case report of disease course in patients | 4 | *Results:* All patients recovered<br>*Conclusion:* Convalescent plasma may be a potential therapy for critically ill patients |
| **Zeng et al., *Journal of Infectious Diseases*, June 2020**[11]<br>*Primary endpoint:* Death or recovery<br>*Secondary endpoint:* SARS-CoV-2 RNA clearance | 6 | *Results:* Improved survival<br>*Conclusion:* Patients were transfused 21.5 days after diagnosis; suggests use in earlier phase to obtain best effect |
| **Salazar et al., *The American Journal of Pathology*, May 2020**[12]<br>*Primary endpoint:* Safety<br>*Secondary endpoint:* Improvement in the modified six-point World Health Organization ordinal scale at day 14 | 25 | *Results:* No adverse events attributed to plasma transfusion<br>*Conclusion:* Administration of CCP is a safe treatment option for those with severe COVID-19 disease |

There are several controlled clinical trials ongoing and the results from these studies will be important to determine the clinical outcomes of CCP transfusion for COVID-19 patients. The analysis of the results demonstrated in studies performed for a new therapy to assess safety and/or efficacy can vary from positive, negative or neutral, and this can be influenced by several factors such as inclusion criteria, patient severity, strength of nABs, and timing of therapy (early vs. later in course of disease).

Below is a table summarizing two randomized, controlled clinical studies which were published or stopped. Details and more information about ongoing studies can be found on the official site clinicaltrials.gov.

**Table 2:** Assessing efficacy of CCP in severe to critically ill patients in randomized, controlled studies

| Publication & Design | Patients | Results & Conclusion |
|---|---|---|
| **Gharbharan et al., *MedRxiv*, July 2020**[13]<br>*Primary endpoint:* Day-60 mortality<br>*Secondary endpoints:* Hospital stay and WHO 8-point disease severity scale improvement on day 15 | 86 | *Results:* Suggested improved clinical status but showed no difference in mortality, hospital stay, or day-15 disease severity between plasma treated patients and patients on standard of care<br>*Conclusion:* Study was halted prematurely due to neutralizing Abs in 79% of the patients studied |
| **Li et al., *JAMA,* August 2020**[14]<br>*Primary endpoint:* Clinical improvement<br>*Secondary endpoints:* 28-day mortality, time to discharge, the rate of viral polymerase chain reaction (PCR) results turned from positive at baseline to negative at up to 72 hours | 103<br>(CCP: 52; Standard of care: 51) | *Results:* Trend toward improvement<br>*Conclusion:* No statistical difference |

Other multiple-center and randomized clinical trials should provide additional insight to outline the risks versus benefits and the safety and efficacy of CCP treatment.[15, 16]

## HAS CONVALESCENT PLASMA BEEN APPROVED FOR USE BY THE FDA?

On August 23, 2020, the FDA issued an Emergency Use Authorization (EUA) for CCP as a potential promising COVID–19 treatment, given that there is no adequate, approved, and available alternative to CCP for treating COVID-19.[6, 17]

This EUA was primarily based on data gathered during the FDA's Expanded Access Program (EAP) for CCP, run by the Mayo Clinic, but also included three additional lines of scientific evidence to support CCP as potentially effective in the treatment of hospitalized patients with COVID-19. The four lines of evidence are:[17]

1. Historical evidence regarding the use of convalescent plasma in prior outbreaks of respiratory viruses
2. Certain preclinical evidence
3. Results from small clinical trials and observational studies of convalescent plasma conducted during the current COVID-19 outbreak
4. Data obtained from the ongoing national Expanded Access Program (EAP) sponsored by the Mayo Clinic[18]

## WHAT DATA FROM THE EAP WAS USED TO SUPPORT THE REQUEST FOR AN EUA?

The EAP provided access to investigational convalescent plasma for patients in acute care facilities infected with SARS-CoV-2 who had severe or life-threatening COVID-19. At the time the EUA was issued by the FDA, more than 56,000 patients had been treated with CCP. Safety analysis was conducted in 20,000 patients and the analysis of the correlation between neutralizing antibody titers and observed clinical outcomes was conducted in 4,330 patients.[17, 18]

### Program goals

The goals of the program were to:

- Provide access to investigational convalescent plasma for patients who had severe or life-threatening COVID-19.[17]
- Gather the data needed to assess the safety and clinical outcomes of the treatment, based on 7- and 30-day survival.[18]
- Conduct a retrospective determination of neutralizing antibody titers in the CCP units and their correlation with clinical outcomes.[18]

### Antibody levels

Antibody level was measured by VITROS® Anti-SARS-CoV-2 IgG assay, a fully automated, HTP, Chemiluminecent IA targeting the S1 protein of SARS-CoV-2. Neutralizing titers were determined by a pseudovirus neutralization assay developed at the Mayo Clinic and the Broad Institute SARS-CoV-2 neutralization assay.[17]

The FDA defined high titer CCP as neutralizing antibody titer greater than an ID50 of 250 on the Broad assay, which corresponds to an S/C value of 12 on the Ortho VITROS IgG.[17]

### Safety and outcomes

Early data describing the safety and outcomes for the initial 5,000 subjects and then 20,000 subjects were shared by Joyner et al. and included *low overall rates of serious adverse events* and evidence that *CCP may be effective*.[17] The investigators also observed an *association between reductions in adjusted 7- and 30-day mortality rate and early transfusion and high antibodies levels*.[17]

Additional findings are outlined in the following study.

### STUDY OVERVIEW: Effect Of Convalescent Plasma On Mortality By The US EAP COVID-19 Plasma Consortium

The study showed that human convalescent plasma reduced mortality among hospitalized patients with COVID-19. Data from 35,322 patients hospitalized for COVID-19 at 2,807 acute care facilities across the U.S. were included in the analysis.

- Convalescent plasma with higher antibody levels significantly reduced 7- and 30-day mortality compared with convalescent plasma with lower antibody levels.
- The 7-day mortality rate was lower in patients transfused within 3 days of COVID-19 diagnosis compared with patients transfused 4 or more days after diagnosis.
- The investigators grouped the CCP into 3 categories, based on the VITROS test, to demonstrate the importance of using convalescent plasma with high antibody levels, leading to reduced mortality rate.

**Table 3:** IgG plasma classifications[18]

| Classification | Measure |
|---|---|
| High IgG plasma | CCP with S/Co > 18.45[18] |
| Medium IgG plasma | CCP with S/Co between 4.62 and 18.45 |
| Low IgG plasma | CCP with S/Co < 4.62[18] |

S/Co = signal cut-off ratio

### 7- and 30-Day Adjusted Mortality

Seven-day mortality for patients receiving high, medium, and low IgG plasma was 8.9%, 11.6%, and 13.7% respectively. Similar observation in 30-day mortality (p=0.021).

Compared with low IgG plasma units, high IgG plasma units reduced the 7-day risk of mortality by 35% (0.65 relative risk) and the 30-day risk of mortality by 23% (0.77 relative risk).

**Figure 2:** 7- and 30-day adjusted mortality rates for Ortho IgG groups


Adapted from Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: Initial three-month experience. Joyner MJ, et al, *MedRxiv*, published online August 12, 2020. https://doi.org/10.1101/2020.08.12.20169359

**Table 4:** Overview of study on the effect of CP on mortality by the US EAP COVID-19 Plasma Consortium[18]

| | |
|---|---|
| **Objective** | ■ Perform an exploratory analysis for potential signals of efficacy of the transfusion of convalescent plasma in COVID-19 patients.<br>■ Evaluate whether transfusion of human convalescent plasma reduces mortality among hospitalized COVID-19 patients. |
| **Study Design** | ■ Adult participants enrolled were hospitalized with (or at risk of) severe or life threatening acute COVID-19.<br>■ Antibody levels were measured using the sera of recently recovered COVID-19 survivors. Antibody levels were unknown at the time of transfusion.<br>■ At least one unit of human COVID-19 convalescent plasma was transfused during hospitalization.<br>■ Only plasma recipients of a single unit of plasma were included in the analysis. |
| **Setting** | ■ Multicenter analysis, including 2,807 acute care facilities in the US and territories.<br>■ 35,322 patients transfused with plasma donated by recently recovered COVID-19 survivors.<br>■ Approximately half of the patients were in the intensive care unit and 27.5% were receiving mechanical ventilation at the time of plasma transfusion.<br>■ Eligible patients were aged 18 years or older, hospitalized with a laboratory confirmed diagnosis of infection with SARS CoV-2 and had (or were judged to be at high risk of progression to) severe or life-threatening COVID-19. |
| **Measures** | The primary outcome was 7- and 30-day mortality, based on timing of delivery of convalescent plasma (within 3 days or 4 or more days after diagnosis) and the levels of IgG antibodies. |
| **Results** | Earlier use of convalescent plasma was associated with lower observed rates of 7-day and 30-day mortality.<br>■ The 7-day mortality rate was:<br>8.7% (95% confidence interval [CI] 8.3% to 9.2%) in patients transfused within 3 days of COVID-19 diagnosis, but 11.9% (11.4%-12.2%) in patients transfused 4 or more days after diagnosis (P < .001).<br>Findings were similar for 30-day mortality (21.6% vs. 26.7%, P < .0001).<br>Importantly, the higher the SARS-CoV-2 IgG antibody levels present in transfused plasma, the lower the mortality.<br>■ For high IgG plasma (>18.45 signal-to-cut-off [S/Co]), 7-day mortality was 8.9 % (6.8%, 11.7%)<br>■ For medium IgG plasma (4.62 to 18.45 S/Co) 7-day mortality was 11.6% (10.3%, 13.1%)<br>■ For low IgG plasma (<4.62 S/Co) 7-day mortality was 13.7% (11.1%, 16.8%)<br>- 7-day mortality for high vs. low, P = .048<br>- 30-day mortality for high vs. low, P = .021 |
| **Conclusions** | **The relationship between reduced mortality and both earlier time to transfusion and higher antibody levels suggest that convalescent plasma is a beneficial therapeutic approach in the treatment of hospitalized COVID-19 patients.** |

## HOW DOES THE FDA EUA DEFINE CONVALESCENT PLASMA FOR COVID-19?

CCP is human plasma collected by FDA-registered blood establishments from individuals whose plasma contains anti-SARS-CoV-2 antibodies, and who meet all donor eligibility requirements (21 CFR 630.10 and 21 CFR 630.15), and are qualified to donate.[17]

Manufacturing CCP includes testing for anti-SARS-CoV-2 antibodies as a step to determine titer levels before release. Units tested by the Ortho VITROS SARS-CoV-2 IgG test as part of manufacture and found to have a signal-to-cutoff ratio of 12 or greater qualify as high titer COVID-19 convalescent plasma. If a center is considering using an alternative test in manufacturing in order to qualify high titer CCP, they should contact CBER to determine acceptability of the proposed test, which, if accepted, would require an amendment to the EUA.[17]

*CCP includes testing for anti-SARS-CoV-2 antibodies as a step to determine titer levels before release. Units tested by the Ortho VITROS SARS-CoV-2 IgG test as part of manufacture and found to have a signal-to-cutoff (S/Co) ratio of 12 or greater qualify as high titer COVID-19 convalescent plasma.*

Units containing anti-SARS-CoV-2 antibodies but not qualified as high titer COVID-19 convalescent plasma by the test described above are considered low titer units and must be labeled as "COVID-19 Convalescent Plasma of Low Titer." These units are authorized for use. Health care providers can decide whether to use the units based on an individualized assessment of benefits and risks. The FDA will continue to evaluate this authorized use based on additional data that become available.[17]

**Latest clinical trials data**

Simonovich et al has recently published on the New England Journal of Medicine the results of a randomized controlled double-blind study conducted at 12 clinical sites in Argentina from May 28 to August 27, 2020. The primary outcome was clinical status 30 days post intervention. Eligible hospitalized patients with severe COVID-19 pneumonia were randomized to receive either convalescent plasma or placebo in a 2:1 ratio. SARS-CoV-2 IgG antibody titer was measured prior to transfusion with a total antibody titer goal of greater than 1:800.[19]

Secondary outcomes included clinical status based on the WHO clinical scale based on six categories: (1) death, (2) invasive ventilatory support, (3) hospitalized with supplemental oxygen required, (4) hospitalized without supplemental oxygen, (5) discharged without full return to baseline physical function, and (6) discharged with full recovery at days 7 and 14.[19]

A total of 333 patients were randomized to receive convalescent plasma (n=228) or placebo (n=105). The median time from symptom onset to enrollment was 8 days. Over 90% of patients were receiving oxygen or corticosteroid treatment at the time of enrollment. 46% of patients had no detectable anti–SARS-CoV-2 IgG antibody level at baseline and a median titer of 1:50 was found among 215 patients. For donor plasma, the total IgG antibody median value of all pools was 1:3200 (interquartile range, 1:800 to 1:3200).[19]

No significant difference in clinical status at day 30 was found between the groups. In terms of secondary outcomes, no significant differences in clinical status were found at day 7 or day 14. The 30-day mortality was 10.96% in the convalescent plasma group and 11.43% in the placebo group, for a risk difference of −0.46 percentage points (95% CI, −7.8 to 6.8).

No significant differences were found in terms of the time to death or the time to clinical improvement of at least two WHO clinical scale categories.[19]

In another open label phase II multicentre randomised controlled trial (PLACID Trial), Agarwal et al described the results from the study Convalescent plasma in the management of moderate COVID-19 in adults in India, which the primary outcome of the study was a composite of progression to severe disease (PaO2/FiO2 ratio < 100 mm Hg) any time within 28 days of enrolment or all cause mortality at 28 days.[20]

464 adults (≥ 18 years) admitted to hospital with confirmed moderate COVID-19 in which 235 were assigned to convalescent plasma with best standard of care (intervention arm) and 229 to best standard of care only (control arm). Progression to severe disease or all cause mortality at 28 days after enrolment occurred in 44 (19%) participants in the intervention arm and 41 (18%) in the control arm.[20]

One of the interesting approach is that the PLACID Trial was conducted to generate context specific evidence relevant to all stakeholders, including policymakers, healthcare providers, and patients.[20]

**Conclusion**

In one of the trials on of the inclusion criteria were all patients enrolled with severe pneumonia in which the authors acknowledge the limitations of the study.[19] In addition, the PLACID trial found no difference in 28 day mortality or progression to severe disease among patients with moderate COVID-19 treated with convalescent plasma along with best standard of care compared with best standard of care alone, nevertheless treatment with convalescent plasma was associated with a higher resolution of shortness of breath and fatigue on day 7.[20]

Areas of future research could include effectiveness of convalescent plasma among neutralizing antibody negative patients and the use of convalescent plasma with high neutralizing antibody titres. The challenge will be to find both suitable patients and suitable plasma donors.[20]

As such, no conclusion should be extrapolated to other clinical studies, no firm conclusion can be drawn regarding the potential efficacy of passive immune therapy earlier than the median time of entry to this trial or in patients with milder forms of the disease.

## CONCLUSION

Based on the data from the EAP as well as historical evidence regarding the use of convalescent plasma in prior outbreaks of respiratory viruses, certain pre-clinical evidence and results from small clinical trials and observational studies of convalescent plasma conducted during the current COVID-19 outbreak (see Table 2 and Table 3), the FDA concludes that COVID-19 convalescent plasma (CCP) meets the "may be effective" criterion for issuance of an EUA.[6, 17]

It is reasonable to conclude that the known and potential benefits of CCP outweigh the known and potential risks of CCP for the proposed EUA.[6, 17] *Current data suggest the largest clinical benefit is associated with high-titer units of CCP administered early in the course of disease.*[6, 17] Adequate and well-controlled randomized trials remain necessary for a definitive demonstration of CCP efficacy and to determine the optimal product attributes and appropriate patient populations for its use.[6, 17]

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