

Updated Evidence to Support the Emergency Use of COVID-19 Convalescent Plasma – as of 9/23/2020

On August 23, 2020, the U.S. Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for COVID-19 Convalescent Plasma for the treatment of hospitalized patients with COVID-19 (1). The issuance of this authorization followed the agency’s evaluation of the totality of the available evidence regarding the safety and the efficacy of the product and the agency’s finding that the product met the criteria for issuance of an EUA. Under the Federal Food, Drug, and Cosmetic Act (FD&C Act), the issuance of an EUA during a declared public health emergency does not require the same evidentiary standard as required for approval or licensure of a drug or biological product.” Instead, the FD&C Act requires that the product “may be effective” for its intended use, and that the “potential benefits outweigh the known and potential risks.”

FDA will continue to review the circumstances and appropriateness of the EUA. Four lines of evidence continue to support the emergency use of COVID-19 Convalescent Plasma at this time one month after initial issuance of the EUA: 1) historical data regarding prior experience with the use of convalescent plasma in other outbreak settings, 2) data from animal studies, 3) data that continues to emerge in the published literature from clinical studies performed during the current outbreak, and 4) results obtained from a large expanded access treatment protocol (National Expanded Program).

Experience with Convalescent Plasma Prior to the COVID-19 Pandemic

People who get certain viral infections develop antibodies in their blood that clear the virus from the body. The antibodies also protect them for some amount of time against reinfection by the same virus. Plasma is the liquid portion of the blood that contains these antibodies. In some other diseases previously studied, giving people plasma obtained from the blood of those who have recovered from the virus that causes the disease in question appears to have led to better clinical outcomes. For example, specific data are available for influenza and SARS-CoV-1, as well as some other viral infections (2). Among the most compelling data supporting the efficacy of convalescent plasma are those for the treatment of Argentine hemorrhagic fever. A randomized controlled trial in 188 individuals documented a case-fatality rate of 16.5% in patients treated with normal plasma versus 1.1% in those treated with immune plasma (3).

Data from Animal Studies

There are several animal models in which COVID-19 infection can be studied. These include the Syrian hamster and a genetically altered mouse that carries the human angiotensin converting enzyme 2 (ACE2) receptor. The SARS-CoV-2 virus uses the ACE2 receptor to enter cells to cause COVID-19. In these animal models the administration of convalescent plasma can protect the animals against infection with SARS-CoV-2 (4, 5). Though the situation of preventing a viral infection is not the same as treating an established infection, this protection against infection by through the transfer of plasma shows that antibodies are able to recognize the virus and lead to its clearance by the immune system.

Data in the Literature

Several articles now have been published regarding the use of COVID-19 Convalescent Plasma, and additional manuscripts have been posted as online pre-prints. None of the clinical trials that have appeared to date provide the level of evidence that would be needed to meet the effectiveness standard that FDA uses for drug and biological product approvals. Generally, these publications note that the administration of COVID-19 Convalescent Plasma appears to be safe. Regarding efficacy, although some

clinical trials have not shown any effect of COVID-19 Convalescent Plasma, others have indicated that it may be effective, particularly in certain settings (6).

The studies of COVID-19 Convalescent Plasma have generally fallen into the following categories: 1) randomized controlled trials (RCTs), 2) controlled trials based on availability of plasma but not truly randomized, 3) retrospective matched cohorts, and 4) case series. Notably, the two RCTs published in the literature were stopped prior to full enrollment, in one case because there were not enough patients available, and in the other because it was determined that those treated already had high antibody levels.

To provide an example from one of the larger published matched cohort studies, Salazar and colleagues evaluated 136 individuals with COVID-19 who received convalescent plasma and who had data available for 28-day outcomes. These individuals were well-matched to 251 non-transfused control COVID-19 patients. The analysis that these investigators performed indicated that there was a statistically significant reduction in mortality at 28 days that was most notable in the 112 patients transfused within 72 hours of admission with plasma having a high anti-spike protein receptor binding domain titer of $\geq 1:1350$ (7). Other clinical reports have tended to indicate a modest benefit of convalescent plasma, particularly when plasma containing similarly high levels of antibodies was used early in the disease course.

Results of an Expanded Access Treatment Protocol

In late March 2020, as the pandemic markedly worsened in large cities like New York, FDA began to receive many requests for emergency single patient Investigational New Drug applications (INDs) following reports from China that convalescent plasma could be beneficial in the treatment of patients with COVID-19. At the same time, FDA was also expediting the review of requests for the conduct of clinical trials to study COVID-19 Convalescent Plasma.

The National Expanded Access Program (EAP) for convalescent plasma was initiated in early April 2020 to fill an urgent need to provide patient expanded access to a therapy of possible benefit. The Mayo Clinic sponsored the IND and administered the EAP with funding from the Biomedical Advanced Research and Development Authority (BARDA). The primary objective of the EAP was to provide access for hospitalized patients to convalescent plasma and the secondary objective was to further assess the safety of doing so. The evaluation of efficacy was considered an exploratory objective of this program. Prior to the start of the EAP, it was recognized that it would not be possible to determine in advance the amount of antibody (known as the antibody titer) capable of neutralizing the virus in the units of plasma donated by people who had been documented to have COVID-19. Because of this limitation at the time, samples were retained for making this determination later, after the plasma had been transfused. The rationale for the titer determinations was that since the neutralizing activity of antibodies in convalescent plasma is thought to be the primary mechanism of action for its potential efficacy, demonstration of a dose-response relationship between neutralizing antibody titers and clinical outcomes could provide early evidence of the efficacy of convalescent plasma.

Enrollment into the EAP was possible in every state and the District of Columbia and over 100,000 patients were ultimately enrolled at over 2,700 sites across the United States. Enrolled patients mirrored the population of individuals with COVID-19 requiring hospitalization in the United States: 60% of the first 20,000 patients enrolled were over 60 years of age, about 20% were black and about 34% reported Latino or Hispanic heritage. In terms of the safety analysis performed, no concerns specific to COVID-19 Convalescent Plasma were identified. An analysis of the first 20,000 patients who were treated as part of

the EAP revealed that the rate of serious side effects was similar between the transfusion of COVID-19 Convalescent Plasma and the conventional plasma that is commonly administered in severely ill patients who do not have COVID-19 (9).

Several different assay methods were used to evaluate the levels of antibodies in the plasma in order to correlate antibody levels with outcomes. An assay performed by the Broad Institute in Cambridge, Massachusetts was found to be very reliable in the evaluation of these antibody levels. The Broad Institute assay looks at the ability of the samples derived from donors' blood to neutralize live virus and is conducted in a laboratory with a high biosafety level (a BSL-3 laboratory).

This viral neutralization assay was used to determine the antibody levels of convalescent plasma administered to 4,330 hospitalized people in the EAP. These levels were then correlated to the number of deaths that occurred at Day 7 and Day 28 in several different segments of the population including: (1) the overall population of hospitalized patients; (2) those who were not intubated (on mechanical ventilation) when they received the plasma; and (3) those who were not intubated who were 80 years of age or less, and who were treated within 72 hours of diagnosis. The analysis of the overall population and hospitalized patients who were not intubated was pre-planned, but the subset analysis of patients who were not intubated, were 80 years of age or less and were treated within 72 hours of diagnosis was not pre-specified. This subset analysis was conducted after the data were analyzed according to original analysis plan.

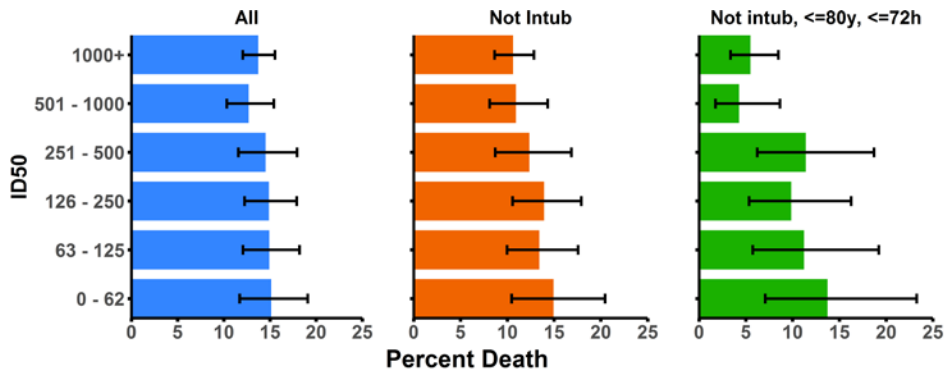
When comparing the 7-day and 28-day survival of hospitalized patients receiving convalescent plasma with lower levels of antibodies (lower titer, ID50 < 250) to those receiving higher levels of antibodies (higher titer, ID50 ≥ 250), there was no significant difference in survival in the overall population of hospitalized patients at Day 7 following the administration of COVID-19 Convalescent Plasma or in those hospitalized patients who were intubated. However, there were statistically significant improvements in survival at Day 7 in both those who were not intubated as well as those who were not intubated, 80 years of age or less, and who were treated within ≤ 72 hours of diagnosis (Table 1). In the overall population of 4,330 patients for whom 7-day data were available there was no effect of the administration of COVID-19 Convalescent Plasma across the range of titers administered (Figure 1). However, in the 2,488 patients who were not intubated, as well as in the 932 patients who were not intubated, up to 80 years of age, who were treated within 72 hours of diagnosis, there was a dose response of convalescent plasma evident, with higher antibody levels associated with better outcomes (fewer deaths). A similar dose response pattern was observed in the 2,817 patients who remained hospitalized at Day 28. For reference, note that evidence of a dose response relationship from a drug or biological product in a non-randomized clinical trial can provide evidence of the activity of that agent (10).

In summary, taking the totality of evidence into account, including prior experience with convalescent plasma in other outbreak settings, data from animal studies, data in the published literature from clinical studies performed during the current outbreak, and the results obtained from the hospitalized patients evaluated in the EAP, FDA continues to find that COVID-19 Convalescent Plasma has met the “may be effective” standard for an EUA. However, because the efficacy analysis of the EAP did not include an untreated group of patients for comparison who did not receive convalescent plasma, FDA strongly encourages the continuation of randomized controlled clinical trials to more definitively evaluate the potential benefits of this therapy.

Table 1. 7- and 28-Day Deaths in Patients Treated with COVID-19 Convalescent Plasma

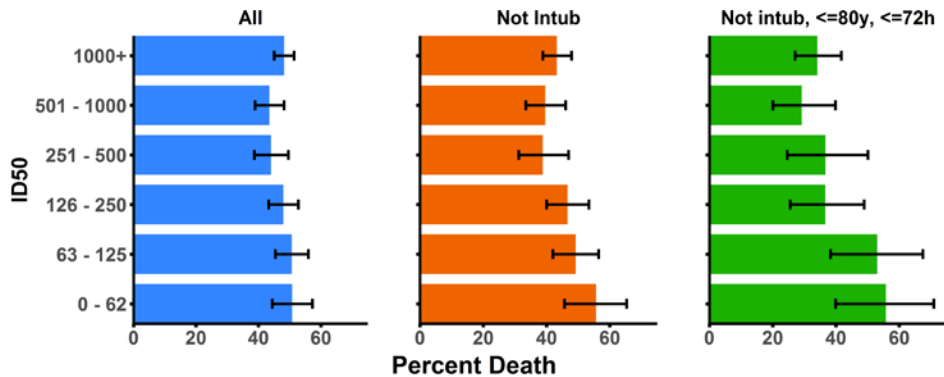
	7-day			28-day		
	Overall (N=4330)	Not Intub (N=2488)	Not intub, ≤80 y, ≤72 h (N=932)	Overall (N=2817)	Not Intub (N=1238)	Not intub, ≤80 y, ≤72 h (N=485)
Deaths Lower Titer	14.97%	13.99%	11.29%	49.57%	49.43%	46.63%
Deaths Higher Titer	13.61%	11.00%	6.27%	46.21%	41.48%	33.23%
Absolute Improvement	1.36%	2.99%	5.02%	3.36%	7.95%	13.40%
Relative Improvement	9%	21%	44%	7%	16%	29%
Statistical Significance	Not significant	Significant p=0.03	Significant p=0.008	Not significant	Significant p=0.004	Significant p=0.004

Figure 1 – Percentage Death in Hospitalized Patients by Day 7



Lowest titers are at the bottom of the graphs, and the titers increase moving up (along the y-axis). Reduction in the percentage death at higher titers is noted in the not intubated and in the subset analysis of patients who were not intubated (Not Intub), were 80 years of age or less and were treated within 72 (Not intub <=80y, <=72h) hours of diagnosis.

Figure 2 – Percentage Death in Hospitalized Patients by Day 28



Lowest titers are at the bottom of the graphs, and the titers increase moving up (along the y-axis). Reduction in the percentage death at higher titers is noted in the not intubated and in the subset analysis of patients who were not intubated (Not Intub), were 80 years of age or less and were treated within 72 (Not intub <=80y, <=72h) hours of diagnosis.

References

1. Emergency Use Authorization: Emergency Use Authorization (EUA) information, and list of all current EUAs. <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs>, last accessed 9/4/2020.
2. Mair-Jenkins J, Saavedra-Campos M, Kenney Baillie J, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: A systematic review and exploratory meta-analysis. *J Infect Dis.* 2015 Jan 1; 211(1): 80–90.
3. Maiztegui J.I., Fernández N.J., de Dalmazo A.J. Efficacy of immune plasma in treatment of Argentine hemorrhagic fever and association between treatment and a late neurological syndrome. *Lancet.* 1979;2(8154):1216–1217.
4. Imai, M, Iwatsuki-Horimoto K, Hatta M, et al. Syrian hamsters as a small animal model for SARS-CoV-2 infection and countermeasure development. *Proc Natl Acad Sci.* 2020; 117(28): 16587–16595.
5. Sun J, Zhuang Z, Zheng J, et al. Generation of a broadly useful model for COVID-19 pathogenesis, vaccination, and treatment. *Cell.* 2020, <https://doi.org/10.1016/j.cell.2020.06.010>.
6. Sharun K, Tiwari R, Iqbal Yattoo M, et al. Antibody-based immunotherapeutics and use of convalescent plasma to counter COVID-19: advances and prospects. *Expert Opin Biol Ther.* 2020; 20(9):1033-1046.
7. Salazar E, Christensen PA, Graviss EA, et al. Treatment of COVID-19 Patients with Convalescent Plasma Reveals a Signal of Significantly Decreased Mortality. *Am J Pathol.* 2020 Aug 11;S0002-9440(20)30370-9. doi: 10.1016/j.ajpath.2020.08.001. Online ahead of print.
8. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA.* 2020; 323(16):1582-1589.
9. Joyner MJ, Bruno KA, Klassen SA, et al. Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients
10. Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products>, last accessed 9/13/20.