

# Treatment of COVID-19 Patients with Two Units of Convalescent Plasma in a Resource-Constrained State

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**Abbreviations:** CCP, COVID-19 convalescent plasma; FDA, (US) Food and Drug Administration; eIND, emergency Investigational New Drug; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; AICP, Arkansas Initiative for Convalescent Plasma; S/Co, signal to cutoff; UAMS, University of Arkansas for Medical Sciences; CPH, Cox proportional hazards; ICU, intensive care unit; RCT, randomized controlled study; WHO, World Health Organization; EUA, Emergency Use Authorization.

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**Objective:** Many therapies are used to treat COVID-19, the disease caused by the virus SARS-CoV-2, including convalescent plasma. The clinical utility of using 2 units of convalescent plasma for COVID-19 hospitalized patients is not fully understood. Our study aims to determine the safety and efficacy of treating hospitalized COVID-19 patients with 2 units of COVID-19 convalescent plasma (CCP).

**Method:** This was a retrospective study of Arkansas patients treated with CCP using the (US) Food and Drug Administration (FDA) emergency Investigational New Drug (eIND) mechanism from April 9, 2020, through August 9, 2020. It was a multicenter, statewide study in a low-resource setting, which are areas that lack funding for healthcare cost coverage on various levels including individual, family, or social. Adult patients (n = 165, volunteer sample) in Arkansas who were hospitalized with severe or life-threatening acute COVID-19 disease as defined by the FDA criteria were transfused with 2 units of CCP (250 mL/unit) using the FDA eIND mechanism. The primary outcome was 7- and 30-day mortality after the second unit of CCP.

**Results:** Unadjusted mortality was 12.1% at 7 days and 23.0% at 30 days. The unadjusted mortality was reduced to 7.7% if the first CCP unit was transfused on the date of diagnosis, 8.7% if transfused within 3 days of diagnosis, and 32.0% if transfused at or after 4 or more days of diagnosis. The risk of death was higher in patients that received low, negative, or missing titer CCP units in comparison to those that received higher titer units.

**Conclusion:** The provision of 2 units of CCP was associated with a reduction in mortality in patients treated with high titer units within 3 days of COVID-19 diagnosis. Given the results, CCP is a viable, low-cost therapy in resource-constrained states and countries.

## ABSTRACT

**Importance:** Many therapies are used to treat COVID-19, the disease caused by the virus SARS-CoV-2, including convalescent plasma. The clinical utility of using 2 units of convalescent plasma for COVID-19 hospitalized patients is not fully understood.

Coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in Arkansas on March 11, 2020.<sup>1</sup> The Arkansas Initiative for Convalescent Plasma (AICP) was a statewide effort to provide COVID-19 convalescent plasma (CCP) to every patient in Arkansas diagnosed with

COVID-19 disease. This collaborative effort by several hospitals in the state and the Arkansas Department of Health was initiated because Arkansans experience many barriers to accessing healthcare, including potentially life-saving therapies.

Convalescent plasma is a passive antibody therapy that has been used successfully to treat respiratory illnesses during previous epidemics.<sup>2,3</sup> Given early reports of mortality secondary to COVID-19 in the United States during the early phases of the pandemic and the lack of effective treatment to combat the disease, patients in Arkansas were treated with CCP via the Food and Drug Administration (FDA) emergency Investigational New Drug (eIND) mechanism. Patients began receiving 2 units of CCP starting in April 2020. The AICP provided oversight and coordination for providing 2 units of CCP for adult patients with severe or life-threatening COVID-19 in many hospitals in the state. We performed exploratory analyses on the efficacy and safety of CCP and present here the first large multicenter study on this treatment for this patient population in the United States.

## Methods

### Population

A retrospective medical chart review was conducted of 165 patients treated for COVID-19 with 2 units of CCP at 5 hospitals in Arkansas utilizing the FDA eIND mechanism. Two units of CCP were provided in accordance with an interinstitutional protocol established by the participating hospitals in Arkansas. We previously described the process for providing CCP in Arkansas through the AICP program.<sup>1</sup> Eligible patients were adults 18 years or older meeting the following FDA criteria: laboratory-confirmed COVID-19 and severe or immediately life-threatening COVID-19 disease.<sup>4</sup> Severe disease was defined as having 1 or more of the following: shortness of breath (dyspnea), respiratory frequency >30/min, blood oxygen saturation <93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300, and lung infiltrates >50% determined radiographically by computed tomography within 24 to 48 hours.<sup>5</sup> Immediately life-threatening disease was defined as having 1 or more of the following: respiratory failure, septic shock, and multiple organ dysfunction or failure.<sup>5</sup> Informed consent was obtained from either the patient or a healthcare proxy before CCP was transfused.

Compatible or low-titer isohemagglutinin, anti-A and/or anti-B, CCP was administered according to the transfusion policies and practices at the 5 participating institutions. Some of these institutions had satellite facilities that participated in this study. Two units of CCP (approximately 250 mL each) were transfused to each patient. The second unit was transfused approximately 24 hours after the first unit, according to an interinstitutional protocol.

### Convalescent Plasma

CCP was obtained from a registered and licensed blood collector. It was donated by individuals who had recovered from COVID-19 and met the following FDA criteria: (1) evidence of COVID-19 documented by a diagnostic test (eg, nasopharyngeal swab) at the time of illness; (2) complete resolution of symptoms at least 14 days before the donation; (3) male donors, female donors who had never been pregnant, or female donors who had tested negative for HLA antibodies since their most recent pregnancy; and (4) negative diagnostic results for COVID-19 if donating

after 14 days or before 28 days postsymptom resolution.<sup>4</sup> Antibody titer and neutralizing antibody testing were not performed at the time of CCP donation. However, the blood center collected retention serum samples from each convalescent plasma donation in Arkansas. A total of 500 of these serum samples were randomly tested for antibody titers. Antibody titer testing was performed using an immunometric/sandwich ELISA-based assay which detects IgG antibodies to the spike protein of SARS-CoV-2 (Ortho Vitros anti-SARS-CoV-2 IgG; Ortho Clinical Diagnostics). The signal to cutoff (S/Co) ratio of the SARS-CoV-2 IgG immunoassay was defined as follows in the study: >12 (high titer), <11.99 to 1 (low titer), and <0.99 (negative).

### Data Collection

The University of Arkansas for Medical Sciences (UAMS) served as the academic research institution coordinating the collection of this exploratory data. After an institutional review board protocol was issued, a data use agreement was obtained from the 5 hospitals included in this study. A form was provided to the hospitals for the collection of laboratory and clinical parameters, including CCP administration and transfusion reaction reporting. Patient information was collected concurrently with their hospital admission and treatment with CCP. The clinical data were abstracted retrospectively from 165 patients' charts using a standardized data collection form by healthcare providers at each institution and then reviewed by a second physician at UAMS. The data were transferred for analysis into an Excel file.

### Statistical Analysis

Patients who were transfused with 2 units of CCP between April 9, 2020, and August 9, 2020, were included in our analyses. This allowed for a 7- and 30-day follow-up after the transfusions. Demographic and baseline medical characteristics were summarized using counts and percentages. Our primary outcome was 7- and 30-day mortality after transfusion with the second unit of CCP. Unadjusted mortality estimates and corresponding 95% confidence intervals were calculated. Crude mortality for various demographic and treatment categories was also estimated. A Cox proportional hazards (CPH) model was used to compare the survival distributions between the titer groups. Titer results were available for 54 (33%) patients in the study. For the CPH model, patients for whom titer testing was not performed were classified as "missing."

## Results

### Patient Demographics and Characteristics

A total of 165 patients who were transfused with 2 units of CCP using the FDA eIND between April 9 and August 9, 2020, were included in the analyses. Five hospitals provided the data. These hospitals were representative of the 5 metropolitan regions in the state. Demographic and medical characteristics are presented in **TABLE 1**. The male to female ratio was 1.7:1. White (n = 77, 46.67%) and Black (n = 62, 37.58%) patients made up the majority of COVID-19 cases in our sample, and most patients (n = 127, 76.97%) received CCP within the first 3 days of diagnosis. A large percentage of patients were in the intensive care unit (ICU) and progressing to respiratory failure but were not on a ventilator at the time of CCP transfusion (n = 124, 75.15%). The majority of patients had at least 1 or more comorbidities (n = 149, 90.30%), with 29.70% (n = 82) having 1 to 2, and 40.61% (n = 67) having 3 or more comorbidities. The

**TABLE 1. Summary of Demographic, Medical, and Outcome Characteristics of the Patients (n = 165) Included in This Study**

Variable	No. (%)
Age, y	
18–39	9 (5.45)
40–59	58 (35.15)
60–69	46 (27.88)
70–79	38 (23.03)
80+	14 (8.48)
Sex	
Female	62 (37.58)
Male	103 (62.42)
Race	
White	77 (46.67)
Black	62 (37.58)
Hispanic	15 (9.09)
Other	11 (6.67)
Time to first CCP transfusion, d	
0	13 (7.88)
1–3	127 (76.97)
4+	25 (15.15)
On ventilator prior to CCP transfusion?	
Yes	41 (24.85)
No	124 (75.15)
In ICU prior to CCP transfusion?	
Yes	89 (53.94)
No	76 (46.06)
No. of comorbidities	
0	16 (9.70)
1–2	82 (49.70)
3+	67 (40.61)
Medications	
Remdesivir	105 (63.64)
Hydroxychloroquine	8 (4.85)
Mortality	
7-day	20 (12.12)
30-day	38 (23.03)

CCP, COVID-19 convalescent plasma; ICU, intensive care unit.

most common comorbidities were hypertension (n = 114, 69.1%), diabetes mellitus (n = 76, 46.1%), obesity (n = 59, 35.8%), hypercholesterolemia (n = 49, 29.7%), pulmonary disease (n = 29, 17.6%), and renal disease (n = 26, 15.8%). Many patients (n = 105, 63.64%) received remdesivir before receiving the 2 units of CCP.

### Efficacy of CCP in COVID-19

The unadjusted mortality was 12.1% (n = 20; 95% CI, 7.6%-18.1%) at 7 days and 23.0% (n = 38; 95% CI, 16.8%-30.2%) at 30 days for the patients who received 2 units of CCP. The unadjusted mortality was reduced to 7.7% (n = 13; 95% CI, 0.2%-36.0%) if the first unit of CCP was transfused on the day of diagnosis. It was 8.7% (n = 127; 95% CI,

4.4%-15.0%) if CCP was transfused within 3 days of diagnosis and 32.0% (n = 25; 95% CI, 14.9%-53.5%) if CCP was transfused 4 or more days after diagnosis. The 30-day unadjusted mortality was 23.1%, 17.3%, and 52.0%, respectively, for the 3 CCP specified intervals. Additional risk modifiers such as age, sex, and race were analyzed (TABLE 2). The mortality rate at 7 days after CCP transfusion was 35.7% for patients who were >80 years, 14.5% for females, 10.7% for men, 14.3% for Whites, and 12.9% for Blacks. Patients on a ventilator had a 7-day mortality rate of 26.8% compared to 7.3% for patients not on a ventilator. Similarly, the mortality rate for patients in the ICU was 3.4 times higher than that of patients not in the ICU (18.0% for ICU patients vs 5.3% for non-ICU patients).

The competing risk analysis graph (FIGURE 1) shows the proportion of patients in various categories over time. The categories or states include in-hospital, discharged, and death. The time-to-event outcomes of death and discharge are competing risks in the context of this CCP analysis. This means that when estimating the time-to-death distribution, we must also account for patients who are discharged and vice versa. Initially, during multistate modeling, all patients are “in-hospital” immediately after receiving their first CCP treatment. And patients transition to either the discharged or the death state. The death state is a terminal, absorbing state.

Over time, most patients were discharged from hospitals within 30 days of follow-up. On average, the patient spent 11.7 days in the initial in-hospital state, 13.5 in the discharged state, and 4.9 days in the death state. Patients who received CCP treatment 4 or more days after diagnosis experienced more deaths and fewer discharges compared to the other 2 strata, that is, those who received CCP on the date of diagnosis or within 2–3 days of diagnosis. The strata, that is, in-hospital and discharged, were significantly different with respect to death distribution (P = .0029). However, the differences between in-hospital strata to discharge distribution were not significant.

The CPH model indicated that the overall effect of titer level (low, high, negative) on survival was not statistically significant (P = .1625) (TABLE 3). However, the model suggests that the risk of death may be higher in the low, negative, and missing categories as compared to the high titer category since the risk ratio is greater than 1 in all cases.

### Safety of CCP in COVID-19

There were no reports of transfusion reactions among the 165 patients who received 2 units of CCP in this study.

### Discussion

Analysis of the data from the 165 adult patients in Arkansas who were treated with 2 units of CCP demonstrated that CCP was safe and associated with lower rates of 7-day and 30-day mortality. Mortality was lower in patients treated within 3 days of diagnosis compared to patients treated 4 or more days after diagnosis (8.7% [95% CI, 5.7%-23.9%] vs 32% [95% CI, 14.9%-53.5%], respectively). This effect was also shown using a competing risk analysis graph, in which patients that received CCP on the day or within 2 to 3 days of diagnosis experienced less death and more discharges than patients who received their CCP treatment 4 or more days after diagnosis. Our mortality data were similar to data reported for the Mayo Clinic Expanded Access program (8.7% [95% CI, 8.3%-9.2%]).<sup>6</sup> Patients in Arkansas had reduced unadjusted 7-day and 30-day mortality rates, similar to their study. In terms of age groups, our study also shared similarities with the

**TABLE 2. Mortality Estimates for Various Demographic and Treatment Categories**

Variable	No.	7-Day Mortality		30-Day Mortality	
		No. (%)	95% CI	No. (%)	95% CI
Unadjusted	165	20 (12.1)	7.6–18.1	38 (23.0)	16.8–30.2
Age, y					
18–39	9	0 (0.0)	0.0–33.6	1 (11.1)	0.3–48.2
40–59	58	5 (8.6)	2.9–19.0	10 (17.2)	8.6–29.4
60–69	46	7 (15.2)	6.3–28.9	14 (30.4)	17.7–45.8
70–79	38	3 (7.9)	1.7–21.4	8 (21.1)	9.6–37.3
80+	14	5 (35.7)	12.8–64.9	5 (35.7)	12.8–64.9
Sex					
Female	62	9 (14.5)	6.9–25.8	15 (24.2)	14.2–36.7
Male	103	11 (10.7)	5.5–18.3	23 (22.3)	14.7–31.6
Race					
White	77	11 (14.3)	7.4–24.1	21 (27.3)	17.7–38.6
Black	62	8 (12.9)	5.7–23.9	13 (21.0)	11.7–33.2
Hispanic	15	0 (0.0)	0.0–21.8	2 (13.3)	1.7–40.5
Other	11	1 (9.1)	0.2–41.3	2 (18.2)	2.3–51.8
Time to first CCP, d					
0	13	1 (7.7)	0.2–36.0	3 (23.1)	5.0–53.8
1–3	127	11 (8.7)	4.4–15.0	22 (17.3)	11.2–25.0
4+	25	8 (32.0)	14.9–53.5	13 (52.0)	31.3–72.2
On ventilator prior to first CCP transfusion?					
Yes	41	11 (26.8)	14.2–42.9	21 (51.2)	35.1–67.1
No	124	9 (7.3)	3.4–13.3	17 (13.7)	8.2–21.0
ICU prior to first CCP transfusion?					
Yes	89	16 (18.0)	10.6–27.5	31 (34.8)	25.0–45.7
No	76	4 (5.3)	1.5–12.9	7 (9.2)	3.8–18.1
No. of comorbidities					
0	16	1 (6.2)	0.2–30.2	3 (18.8)	4.0–45.6
1–2	82	13 (15.9)	8.7–25.6	18 (22.0)	13.6–32.5
3+	67	6 (9.0)	3.4–18.5	17 (25.4)	15.5–37.5

CCP, COVID-19 convalescent plasma; CI, confidence interval; ICU, intensive care unit.

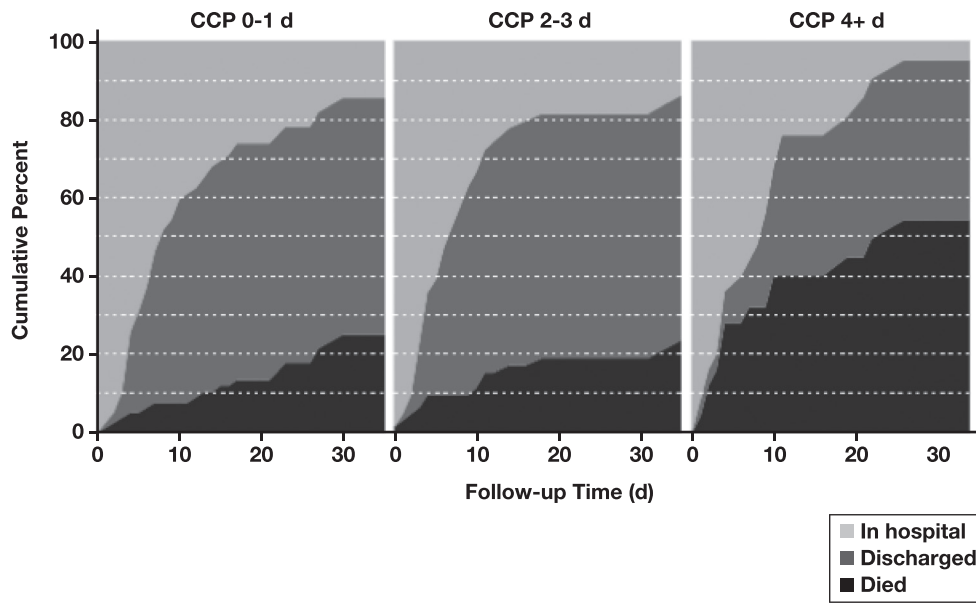
largest expanded access program in that patients between 40 and 59 years of age in our study were most affected.<sup>6</sup> Similarly, men were predominantly affected by COVID-19, but we found that women were more likely than men to die from COVID-19. Whites were most likely to die after contracting COVID-19 (14.3% [95% CI, 7.4%–24.1%]) at 7 days after receiving CCP. Blacks were the predominant minority group affected (37.58%), and these patients had a 12.9% (95% CI, 5.7%–23.9%) mortality rate at 7 days. The mortality rate increased if the patient was on a ventilator in the ICU before receiving CCP, and patients with more comorbidities were more likely to die from COVID-19.

There are 3 studies that reviewed the clinical benefit of 2 units of CCP: the PLACID study, the REMAP-CAP study, and the Stony Brook Medicine COVID Plasma Trial Group study.<sup>7–9</sup> The PLACID study, which was a randomized controlled study (RCT) conducted in India, did not demonstrate a significant benefit with 2 units of CCP transfusion. The limitations of this study included low participant enrollment and low titers of the administered CCP units.<sup>7</sup> REMAP-CAP, an open-label RCT, enrolled patients from 4 countries including the United States.<sup>8</sup> This study also did not find significant benefits in primary or secondary outcomes, such as hospital survival and

organ support-free days. However, in immunodeficient subjects, a trend toward benefit was observed. The limitations included the study design in which the physicians and patients knew the treatment administered and the lack of patient recruitment from the United States. The study conducted at Stony Brook hospital randomized 74 patients in a 4:1 ratio to either 2 units of CCP or standard plasma. A total of 59 patients were randomized to receive CCP units. This study found that while CCP increased antibodies to SARS-CoV-2, it did not show significant differences in ventilator-free days, death, or World Health Organization (WHO) ordinal scale.<sup>9</sup> Our large, multicenter observational study demonstrated that the risk of death was higher in patients who received low or negative titer CCP units. While the overall effect was not statistically significant, given the number of missing titer results, there was a trend toward reduced mortality in patients who were administered high titer CCP. This is in contrast to the PLACID and the Stony Brook Medicine COVID Plasma Trial Group study, which did not observe a difference between patients who received 2 units of CCP compared to standard of care.<sup>7</sup>

Although there were several limitations to this study, no studies in the United States have investigated the safety and efficacy of

**FIGURE 1.** Cumulative discharge and death rates stratified by time from diagnosis to COVID-19 convalescent plasma (CCP) treatment.



**TABLE 3.** Results of Cox Proportional Hazard Model Assessing the Effect of Titer Level on the Risk of Death for Patients Treated with COVID-19 Convalescent Plasma Therapy<sup>a</sup>

Titer Level	Referent	RR	95% CI	P Value
Low	High	1.13	0.23–5.67	.8804
Negative	High	3.02	0.95–9.67	.0620
Missing	High	2.22	0.89–5.52	.0854
Likelihood ratio test: 5.13 (3 degrees of freedom)				.1625

<sup>a</sup>Survival time was calculated from when the first dose was administered until death. Survival times were censored at the time of discharge for those patients who were discharged alive. Risk ratio (RR) and 95% confidence interval (CI) are presented for each level. A high titer level was used as the referent class for these calculations.

providing 2 units of convalescent plasma to treat COVID-19. One limitation was the predominant retrospective design of our study. We attempted to minimize the bias by collecting data concurrently with the treatment of the patient. In addition, Arkansas is a resource-constrained state, and the delivery of CCP in the state was to ensure access to life-saving therapy. In this setting, we formalized the delivery and transfusion of CCP through educational sessions with physicians at hospitals and blood collectors. Another is the potential small sample size of our study, which may have underestimated the mortality rate reduction and the ability to detect clinically significant differences. There is a potential for confounding by the heterogeneity that could not be adjusted for in the study. Furthermore, some patients in this study received other treatments in addition to CCP, which may confound the therapeutic benefit of this treatment.

Convalescent plasma can be a life-saving therapy that should be considered for COVID-19 given the demonstrated benefits in our study. Furthermore, given that it is relatively inexpensive in comparison to medications used to treat COVID-19, CCP may be utilized in resource-limited settings, including developing countries that have difficulty accessing expensive medications or lack the infrastructure to participate in research studies. In comparison to CCP, another passive immune therapy, monoclonal antibodies, have shown clinical benefit in the outpatient setting only. Studies on bamlanivimab plus etesevimab,

casirivirumab/imdevimab, and sotrovimab have not demonstrated benefit in the hospitalized patient population.<sup>10-12</sup> Therefore, the FDA has authorized the use of these medications for nonhospitalized patients only. This therapy is also expensive compared to CCP. Hyperimmune globulin, which is purified immunoglobulin G products, did not show disease progression risk reduction against COVID-19 in hospitalized patients.<sup>13</sup>

Presently, the FDA revised the Emergency Use Authorization (EUA) of CCP to immunocompromised patients in either the inpatient or outpatient settings based on recent studies showing benefits in this population. FDA-approved medications for COVID-19 hospitalized patients are limited. Remdesivir, an effective antiviral therapy did not demonstrate clinical benefits in studies on immunocompromised patients.<sup>14,15</sup> Therefore, immunocompromised patients in outpatient settings are unable to benefit from this treatment. Tixagevimab plus cilgivimab, which were shown to be efficacious against the Omicron variant, is EUA authorized but is expensive and difficult to obtain in low-resource states.<sup>16,17</sup>

In comparison to alternate therapies, the FDA should consider revising its CCP authorization because CCP is readily available and can be provided quickly, which may be beneficial in the setting of newly emerging variants. Furthermore, the risk of adverse events with the use of CCP appears negligible. It is also an inexpensive option.

## Conclusion

In conclusion, given that there is 1 FDA-approved treatment for hospitalized COVID-19 patients, high titer CCP should be considered a therapeutic option, especially in constrained settings such as Arkansas.

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## Disclosure

Dr Ipe is a consultant for Terumo Blood and Cell Technologies and Alexion Pharmaceuticals.

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