

# Has Convalescent Plasma Therapy Hesitancy Increased COVID-19 Mortality?

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## Abstract



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We bring to you our viewpoint and a snapshot of the journey of convalescent plasma therapy (CPT) in the management of ongoing coronavirus disease 2019 (COVID-19) pandemic. We also discuss how best to use the updated data on this important treatment option and maximize benefit for our patients, thereby saving lives, especially in resource constraint settings.

## Keywords

pandemic, SARS-CoV-2, antibodies, immunity, titer, donor

## Introduction

The fact that convalescent plasma therapy (CPT) has medicinal value is nothing new. Its use commenced more than 100 years ago.<sup>1</sup> The simple principle is that the blood of a previously infected individual (who has now recovered) has circulating antibodies which can be given to another individual (after precautions and testing) with the hope that the protective antibodies will be able to target the same infective agent, rescue from acute and fatal consequences, and hasten the recovery of the second patient.

The ongoing coronavirus disease 2019 (COVID-19) pandemic resulted in renewed interest in this form of therapy, but initial results were disappointing. The emergence of virulent mutated variations of COVID-19 and the second wave has forced us to relook at this treatment option.<sup>2</sup>

A simple online search using the terms “convalescent plasma therapy COVID-19” gives interesting results. There were 22,20,000 hits on google, 18,200 references on google scholar, and 820 articles on PubMed.<sup>3–5</sup> When we added the words “randomized trial” to the above search terms, we got 74 (for 2020) and 43 (for 2021) results on PubMed.<sup>5</sup>

## Negative Studies

The first study was reported in JANA in 2020 and included data from seven centers in Wuhan, China.<sup>6</sup> Patients were enrolled between February 14, 2020 and April 1<sup>st</sup>, 2020. All patients had severe or life threatening COVID. While the initial plan was to enroll 200 patients, only 103 could be included. They found no difference in day 28 mortality (15.7 vs. 24.0%;  $p = 0.30$ ) or time of discharge (51.0 vs. 36.0% discharged by day 28; hazard ratio, 1.61 [ $p = 0.12$ ]). The advantage they identified was a better rate of RT PCR negativity at 72 hours, i.e., 87.2% of the convalescent plasma group vs. 37.5% of the control group (OR, 11.39 [95% CI, 3.91–33.18];  $p < 0.001$ ).

Another negative study was reported by Ventura et al.<sup>7</sup> In their trial, 228 patients were assigned to receive convalescent plasma and 105 to receive placebo. The overall mortality was 10.96% in the convalescent plasma group and 11.43% in the placebo group (95% CI, -7.8 to 6.8;  $p = NS$ ).

Several other studies (in United States, Spain, United Kingdom, China, Netherlands) could not complete intended enrolment and had to close prematurely, including the C3PO NIH Trial (enrolled 511/900 patients).<sup>8</sup> The U.S. FDA sponsored program at Mayo Clinic enrolled more

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than 1,00,000 patients. Though many patients improved clinically, the exact role of CPT was clouded by confounding factors like simultaneous administration of other therapies (antivirals/corticosteroids). They did a retrospective analysis on the subset of 3,082 patients whose neutralizing antibody titer data was available. They concluded that the relative risk of mortality was lower in hospitalized nonventilated patients who received high titer CPT.<sup>8</sup>

An open label, parallel arm, phase II, multicenter, randomized controlled trial conducted in India showed that convalescent plasma was not associated with a reduction in progression to severe COVID-19 or all-cause mortality.<sup>9,10</sup> However it was noted that CPT was associated with earlier resolution of shortness of breath and fatigue and higher negative conversion of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA on day seven of enrolment. This finding opened discussion regarding the use of CPT earlier in disease course, possibly reducing progression to severe disease and acting as a bridge for recovering patients.

No wonder, guidelines could not recommend CPT because of several limitations. Yet, the common thread amongst these reports was that CPT was likely to benefit patients if instituted early when the patients' condition was still not severe.<sup>11</sup>

## Turning Point

On August 23, 2020, U.S. FDA permitted use of CPT for COVID-19 outside the clinical trial through emergency use authorization.<sup>12</sup>

Subsequently it was reported by Casadevall et al in 2021 that the number of CP units dispensed by American blood banks correlated with the number of COVID-19 patients in that country.<sup>13</sup>

## Positive Studies

Eric Salazar and colleagues published their cohort data wherein the Kaplan-Meier curves for mortality within 60 days (day 0 is day of receiving plasma with an antireceptor binding domain IgG titer  $\geq 1:1,350$ ) showed impressive benefit.<sup>14</sup> Unfortunately, such "ideal world" protective titers were seen in less than 5% of potential donors.

Jim et al also recently published data on the neutralizing antibody titer in their 250 consecutive patients.<sup>15</sup> They measured plasma titers at a median of 67 days after onset of symptoms, giving adequate time to the body to mount an appropriate immune response. Interestingly only 60% had neutralizing antibody titer of more than 1:80 in their publication whereas Ling et al detected almost all (93%) individuals had titers of more than 1:640.<sup>16</sup> Higher titers correlate with older age, male gender, and those who had fever and/or hospitalization at the time of having their COVID-19 infection. Their data also showed that the neutralizing antibody titers decline within approximately 90 to 100 days, suggesting the right time to utilize potential donors. This is the

reason the cut-off for acceptable CPT donors has been revised internationally.<sup>17</sup>

Very interesting is the manuscript by Anand et al, accepted for publication in Cell Reports Medicine.<sup>18</sup> It includes the study related to the humoral immunity response against COVID-19 spike protein over a period of more than 31 weeks (→ Fig. 1). This data will act as a backbone for future studies as well as the management strategies in overcoming the COVID-19 pandemic.

A four-center study from Kuwait was conducted between May 21st and June 30<sup>th</sup>, 2020.<sup>19</sup> This was a nonrandomized but prospective cohort study. The CPT arm had 135 cases and control arm (standard treatment for COVID-19 without CPT) included 233 patients. All the 368 patients had moderate to severe COVID-19 disease. Patients with severe COVID-19 had faster clinical improvement (7 days in CPT arm vs. 15.5 days in control group [ $p = 0.003$ ]). Moderate COVID-19 patients in study arm had significantly lower 30-day mortality rate. All patient treated with CPT had faster O<sub>2</sub> saturation improvement; faster lymphocyte count improvement; and faster C-reactive protein decline. There were no serious transfusion reactions.

Another randomized, double-blind, placebo-controlled trial was conducted of convalescent plasma with high IgG titers against SARS-CoV-2 in older adult patients.<sup>20</sup> Administration of CPT was within 72 hours of onset of mild COVID-19 symptoms. A total of 160 patients underwent randomization. In the intention-to-treat population, severe respiratory disease developed in 13 of 80 patients (16%) who received convalescent plasma and 25 of 80 patients (31%) who received placebo with a relative risk reduction of 48%.

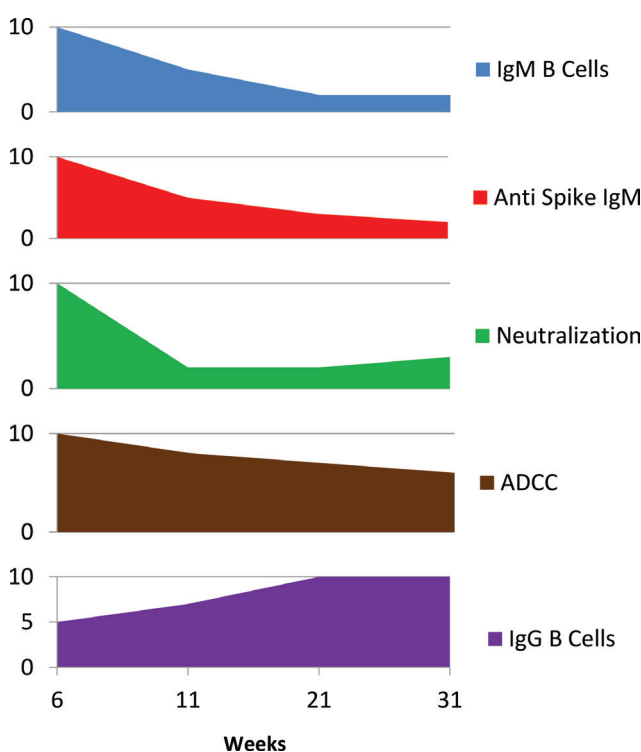


Fig. 1 Anti COVID-19 spike humoral responses.<sup>18</sup>

An observational study led by Budhiraja et al, evaluated 333 patients that received plasma therapy during COVID-19 treatment.<sup>21</sup> Among patients with COVID-19 admitted to ICU, mortality was significantly lower in plasma group (25.5 vs. 33.2%;  $p = 0.026$ ). The study concluded that the use of CPT reduced mortality in patients admitted to ICU who were older than 60 years, females, those with comorbidities, and especially those who required some form of ventilation.

## Indian Initiatives

Currently India is in the midst of a massive second wave of the COVID-19 pandemic.<sup>22</sup> All stake holders have ramped up their efforts to tackle the increasing load of sick patients who require significant treatment.<sup>23</sup>

Amberhealth.in is one such volunteer run nonprofit initiative based out of Bangalore set up by Dr. Tanvi Sood and Nikhil Joy.<sup>24</sup> Operational since the first wave in India, it was launched in mid-August around the same time as USFDA EUA approval for plasma therapy for COVID-19 management. It was started to provide a digital platform for COVID-19 plasma donation facilitation. It is operated by members with medical background and technical expertise to counsel potential donors, answer frequently asked questions, and build relations with existing plasma banks across hospitals in the country. It focuses on helping voluntary plasma donors get connected with licensed plasma donor centers for a safe and smooth plasma donation experience and also with recipient requests through verified channels in times of emergency.

The peak months of operation lasted till November 2020 after which donors reduced as active cases saw a dip in India. Amberhealth.in has received 63 registrations from willing potential donors till date of which 43 donors cleared the initial eligibility criteria (age 18–60 years, weight >50 kg, nullipara women, no comorbidities, 28 days post recovery from last symptom or 14 days post COVID RT PCR negative test). These 43 donors were personally facilitated to plasma banks for the elective donation process or connected directly to families looking for plasma urgently for patients. The donation process collects 2 units of 220 mL plasma per donor. The second level of eligibility is determined at the actual site of donation during which further six donors were deemed ineligible based on low antibody titer (<1:80) or low hemoglobin levels (<12.5 mg/dL). Of the 43 donors, 37 were eligible with high titer antibodies and their plasma collection was completed. Data was followed up through the families on the outcomes of the patients which were connected directly to donors facilitated through our initiative. Of the 26 recipients, 10 patients had moderate severity of the disease and the remaining 16 had severe disease. All the patients were receiving steroids and 21 patients were receiving Remdesivir. Seven patients succumbed to their disease (all of them belonged to the severe disease category, on NIV or ventilator). Plasma therapy has been used as an affordable treatment option for patients with steroid refractory hypoxia, possibly helping in reducing the recovery time and progression to invasive

ventilation. The resurgence of the second wave from March 2020 has seen an increasing demand for plasma. While availability of eligible donors lags behind its demand, involvement of well-known personalities like Bhoomi Pednekar leads to a quantum jump in awareness amongst the general public and thus a ramp up in donor availability is expected.<sup>25</sup>

## Take Home Messages

1. Convalescent plasma therapy (CPT) is not new—having been used by medical professionals since more than 100 years.
2. There are more than xxx publications in PubMed regarding CPT for coronavirus disease 2019 (COVID-19).
3. Earlier clinical trials were unsuccessful in delineate true benefit of CPT because we had limited knowledge about its application; They were used in patients at the time when COVID-19 had become serious; and results were confounded by other medications being given to the patients.
4. Several prospective clinical trials could not be completed because of insufficient enrolment—especially during the first wave of the pandemic.
5. U.S. FDA approval of CPT use outside a clinical trial setting as emergency use authorization was a watershed turning point in the application of CPT for COVID-19.
6. More recent clinical trials have shown most appropriate use of CPT.
7. Patients should be selected early in their phase of the COVID-19 infection—before they have significant reduction in  $\text{SiO}_2$  or require ICU care. For LMIC, CPT is a cheaper alternative that can save lives amongst patients who are not eligible for or cannot take more expensive antiviral, antibodies, etc.
8. With increasing population already being vaccinated, both the incidence and severity of COVID-19 is likely to fall. Having said that, if previously vaccinated patients are being considered for CPT, it would be prudent to check their neutralizing antibody titers first. CPT should be given only to those whose titers are not elevated.
9. Appropriate donor selection should be based on neutralizing antibody titers. Older male persons who have recovered from COVID-19 infection that was associated with fever for 3 days and/or required hospitalization can be used as clinical criteria to enrich eligible donor selection.
10. Several initiatives from India have pioneered the use of CPT to the benefit of thousands of COVID-19 patients. Amberhealth.in and Bhoomi Pednekar taking up this cause are only two such examples.
11. With more than 100,000 patients having received CPT in United States alone, we now have published data from more than 20,000 patients. Serious adverse events are seen in less than 1% of instances and most of them are found to be unrelated to CPT, reinforcing their safety.

**Conflict of Interest**

None declared.

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