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## Perspective

## The Assessment of Convalescent Plasma Efficacy against COVID-19

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## SUMMARY

Antibody-based therapy for infectious diseases predates modern antibiotics and, in the absence of other therapeutic options, was deployed early in the SARS-CoV-2 pandemic through COVID-19 convalescent plasma (CCP) administration. Although most studies have demonstrated signals of efficacy for CCP, definitive assessment has proved difficult under pandemic conditions, with rapid changes in disease incidence and the knowledge base complicating the design and implementation of randomized controlled trials. Nevertheless, evidence from a variety of studies demonstrates that CCP is as safe as ordinary plasma and strongly suggests that it can reduce mortality if given early and with sufficient antibody content.

The coronavirus disease 2019 (COVID-19) pandemic in 2020, a catastrophic event in human history, led to rapid mobilization of the biomedical research establishment to find both preventive and therapeutic options. The causative agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), posed a major challenge because, as a new virus, it had no specific preexisting therapy. Consequently, early responses focused on optimizing respiratory care, managing thrombotic and inflammatory complications with anticoagulation and corticosteroids, and repurposing existing antiviral therapies, which, with the exception of remdesivir,<sup>1</sup> proved ineffective. Another approach, in the desperate early days of the pandemic, was the revival of convalescent plasma (CP), an old therapy dating back to the early 20th century. CP was used with apparent success in numerous epidemics and outbreaks, including the 1918 influenza pandemic,<sup>2,3</sup> and was proposed as a strategy for new pandemics a decade ago.<sup>4</sup> The premise for this therapeutic approach is that CP transfers specific antibodies made by individuals who have recovered from COVID-19 to people at risk for, or suffering from, this disease.<sup>5</sup>

First used against SARS-CoV-2 in China<sup>6,7</sup> and Italy,<sup>8</sup> COVID-19 CP (CCP) was rapidly deployed in many countries, including the United States, where more than 85,000 patients had been treated with CP as of late August 2020. The extensive use of CCP in the United States occurred after the U.S. Food and Drug Administration (FDA) allowed plasma administration to COVID-19 patients under three successive regulatory mechanisms. The first, issued in late March 2020, authorized case-by-case compassionate use upon physician request. Shortly thereafter, in early April, an expanded access program (EAP) permitted physicians to treat patients who were, or were at risk for becoming, critically ill with COVID-19 under the condition that they register their patients in a Biomedical Advanced Research and Development Authority (BARDA)-funded single-arm national observational study administered by the Mayo Clinic. The third step took place on August 23, when the FDA reviewed the safety and efficacy data generated by the EAP and authorized

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treatment of hospitalized patients with CCP as long as a national state of emergency existed, a step called an emergency use authorization (EUA). CCP and remdesivir are currently the only two treatments for COVID-19 patients that have received FDA EUA. Remdesivir received FDA approval on October 22, 2020.

Although sometimes seen as a bridge to other antibody-based therapies such as monoclonal antibodies (mAbs) and hyperimmune globulins, CCP established a definite presence in the therapeutic arsenal against COVID-19 early in the pandemic. In the months that followed the FDA's EAP issuance, CCP use increased beyond expectations, leading to criticism that this modality was being deployed clinically without sufficiently rigorous efficacy trials.<sup>9</sup> In this perspective, we review how CCP emerged as a leading COVID-19 therapy and consider the issues encountered in establishing its efficacy, with particular emphasis on the unique complexities involved in conducting randomized clinical trials with a heterogeneous product during a pandemic with limited information on the conditions for ideal use.

### A SHORT HISTORY OF ANTIBODY THERAPIES

The discovery that antibody administration was therapeutic against certain infectious diseases dates to the 1890s and led to awarding of the first Nobel Prize in Medicine to Emil von Behring in 1901 for the development of diphtheria antitoxin.<sup>10</sup> In the early decades of the 20th century, the use of antibody therapies blossomed, with increasing use of antitoxins in the form of serum therapy, which were effective against many infectious diseases.<sup>11,12</sup> However, the efficacy of antibody therapies varied greatly with the infectious disease targeted. For diphtheria, tetanus, and pneumococcal pneumonia, efficacy was widely accepted, but for tuberculosis the evidence was less clear, and serum therapy was not widely used.<sup>13,14</sup> In general, it was easier to make effective serum therapy for simple antigens such as diphtheria toxin than for whole microbes such as the pneumococcus, which targeted the capsular polysaccharide, of which there were multiple antigenically distinct types. Nevertheless, successful antibacterial antibody therapies were developed by the late 1930s,<sup>13</sup> and the concentrated research effort in this area in the first half of the 20th century catalyzed fundamental advances in microbiology and immunology. The search for ways to make serum therapy more effective led to further advances, particularly in relation to the pneumococcus.<sup>15</sup> A major lesson from the serum therapy era was that this modality was most effective when given early in the course of disease.<sup>11,16,17</sup>

By the 1940s, antibiotic development, inadvertent hepatitis transmission by CP, and complications such as serum sickness<sup>18</sup> led to the abandonment of antibody therapies for infectious diseases, except in niche areas such as rabies and tetanus. However, the option of using CP in infectious disease emergencies has remained in the medical arsenal, and it has emerged episodically for viral outbreaks such as Argentine hemorrhagic fever,<sup>19</sup> SARS-CoV-1,<sup>20</sup> Ebola virus,<sup>21</sup> and H1N1 influenza.<sup>22</sup>

In contrast, mAb development, a product of the late 20th century,<sup>23</sup> has been directed primarily toward cancer and inflammatory conditions, with just three licensed products for infectious diseases: palivizumab, for respiratory syncytial virus disease in high-risk infants; raxibacumab, for post-exposure management of anthrax; and bezlotoxumab for *Clostridioides difficile* colitis. In addition, mAbs have shown promise in the therapy of Ebola virus disease.<sup>24</sup> mAbs differ from the other preparations in that they are single molecules produced in the laboratory that can be used as single agents (monotherapy) or as a cocktail of multiple mAbs.

Antibody therapies thus come in many forms, including immune sera or plasma, concentrated IgG preparations (hyperimmune globulins), mAbs, and even antibody fragments, which can come from human or animal sources. Although these products differ in their formulation, the active agent in each is immunoglobulin specific to the microbe, a microbial component or a microbial product important for pathogenesis, such as a toxin. But a notable difference among these preparations is that all antibody strategies other than CP require many months of laboratory preparation, making them impossible to use in the early stages of an epidemic. Another notable difference is that only CP contains other isotypes apart from IgG, such as IgM and IgA, which could affect efficacy, as IgM has important antiviral properties.<sup>25</sup> In the past, gamma globulin preparations were occasionally associated with hemolytic adverse effects by virtue of having antibodies to ABO blood group antigens, but this concern is minimized by screening of lots for this activity.<sup>26</sup>

Historically serum, the liquid that remains after the blood has clotted, was the vehicle for much antibody therapy. Today, plasma, the liquid that remains when clotting is prevented with the addition of an anticoagulant, is the preferred modality. The presence of fibrinogen and other clotting factors in plasma, and their absence from serum, makes plasma the preferred agent for many applications in medicine other than antibody transfer. Plasma is obtained by centrifugation of whole blood or by plasmapheresis from the donor, a procedure that returns cellular components back to the donor, allowing more frequent donation.

On the basis of historical data demonstrating effectiveness and the absence of specific therapies, CCP was proposed for COVID-19 early in the epidemic.<sup>5</sup> To date, CCP is the most commonly used antibody-based therapy for COVID-19, with hyperimmune globulins, mAbs, and immune equine serum currently under development. Eight months into the pandemic in the United States, and 11 months globally, CCP efficacy can be examined in a variety of study designs ranging from randomized controlled trials (RCTs) to observational studies to mechanistic analysis of antibody action against SARS-CoV-2.

### RCTs AS THE GOLD STANDARD

RCTs are the best study design available for obtaining definitive information on the efficacy of preventive and therapeutic approaches in medicine. Well-designed RCTs are superior to observational studies because the latter do not contain untreated control groups and are vulnerable to biases and confounding factors that can influence results and conclusions. Although several studies in the 1890s suggested that administration of antitoxin lowered mortality from diphtheria, it was not clear whether this effect was due to the antibody preparation itself or to other factors such as reductions in poverty and changes in bacterial virulence.<sup>27</sup> The Danish physician Johannes Fibiger designed a study in which patients received either serum therapy or routine therapy depending on the day of the week, while standardizing the diagnosis, thus creating an early version of the RCT<sup>28</sup> in 1898. Using this method, Fibiger showed that serum therapy for diphtheria reduced mortality relative to standard therapy. Studies of serum therapy for pneumococcus also involved a quasi-experimental strategy whereby patients on certain wards received serum whereas those on others did not.<sup>29</sup>

In recent decades, RCT methodology has advanced to include placebos; disguising of interventions; masking of patients, health care providers, and data analysts to reduce bias; power calculations to enhance the likelihood of statistically significant

results; pre-planned outcomes; stratification to minimize the effect of confounders; and planned, statistically guided interim analyses. However, the level of organization and planning needed to deliver high-quality information in RCTs can make their deployment difficult amid an epidemic, with rapid fluctuations in the number of cases, stressed medical systems, concurrent application of unproven therapies, and rapidly changing knowledge. These conditions were evident in surge cities during early days of the COVID-19 pandemic in 2020, when hospitals in New York City and Detroit became overwhelmed with an influx of cases, whose incidence then rapidly declined.

The situation in March and April 2020 was not unprecedented. Historically, convalescent serum therapy was also taken up during pandemic crises that precluded the design and implementation of RCTs, and few RCTs of CP were conducted during most of the 20th century. Our understanding of the effectiveness of CP in reducing mortality during the 1918 influenza pandemic is based not on trials done at the time but on a retrospective meta-analysis of those experiences.<sup>2</sup> A notable exception is the very successful 1979 RCT of plasma therapy for Argentine hemorrhagic fever, documenting that CP reduced mortality by 90%.<sup>19</sup> The trial was feasible because the agent, Junin virus, was endemic, allowing the necessary planning and stability needed for conducting RCTs.

Adding to the difficulties of conducting RCTs of CP in epidemic conditions are factors specific to this type of therapy. The use of CP requires a supply of recovered donors to donate their plasma, which, depending on the disease involved, introduces necessary delays between epidemic recognition, identification of suitable donors, and trial initiation. The donor must also have cleared the infection before donating plasma to preclude transmitting the disease to health care personnel and must be qualified to donate blood. Given that antibody responses are highly variable among recovered individuals, ideal RCT design requires the availability of serological tests to measure the amount of antibody to therapeutically relevant antigens in CP donors. This in turn requires the availability of proper diagnostic facilities and immunological knowledge about the causative agent, which may not be immediately available during epidemic conditions. In fact, a trial of plasma therapy for Ebola virus disease carried out in epidemic conditions in an under-resourced area reported a reduction in mortality that was not significant when adjusted for confounders.<sup>30</sup> However, the trial physicians had no information of antibody content in CP units and a subsequent analysis showed that many units lacked antibodies.<sup>31</sup>

These problems are magnified when dealing with a new viral pathogen such as SARS-CoV-2, as the serological and virological tests needed are generally not available at the beginning of an epidemic. Compounding these difficulties for COVID-19 was the rate at which new information accrued during the pandemic, which can invalidate assumptions made when the trials are first designed or introduce new knowledge (e.g., expected mortality, the course or stages of illness, and, importantly, the amount of antibody in CP units necessary to confer a benefit).

RCTs initiated at the beginning of an epidemic run the risk of becoming obsolete as new information used in the initial design may be incorrect. This was the case for COVID-19, when mortality dropped rapidly during the first months of the epidemic as physicians learned to treat the disease, invalidating original estimates of effect size for power calculations. Trials needed more participants just as the epidemic began to wane and new participants became harder to find. In much of the United States, where the epidemic continued, most patients did not have access to clinical

**Table 1. Summary of the First Five RCTs for CCP in COVID-19 as of October 2020**

Study	Location	Mortality <sup>a</sup>	Other Benefits	Status	Comment
Li et al. <sup>35</sup>	China	26% → 16% (NS)	↓ viral load ↓ O <sub>2</sub> demand ↓ recovery time	premature termination	late use; efficacy in less critically ill patients
Gharbharan et al. <sup>36</sup>	the Netherlands	24% → 14% (NS)		premature termination	late use
Avendano-Sola et al. <sup>33</sup>	Spain	9% → 0 (p = 0.06)	↓ progression to ICU	premature termination	early use
Agarwal et al. <sup>34</sup>	India	13.6% → 14.7% (NS)	↓ viral load ↓ FiO <sub>2</sub> ↓ fever	completed	a large proportion of units had low or no specific antibody
Rashid et al. <sup>32</sup>	Iraq	40% → 5% (p < 0.05)	↓ recovery time	completed	small, not blinded, quirky randomization

FiO<sub>2</sub>, fraction of inspired oxygen; ICU, intensive care unit; NS, not significant.

<sup>a</sup>Mortality change from non-treated to plasma treated.

trials at the sites where they sought care, and many who did were reluctant to participate in placebo-controlled trials. Moreover, because the concentration of the antibody in plasma was neither uniform nor known at the time of treatment, assumptions for power calculations at the onset of a trial may not have been met by the time enrollment was ended. Interpretation of such trial results can be challenging for a medical culture adept at reviewing data from studies of well characterized molecules. The very strengths of RCTs that make them powerful epistemic instruments also make them unwieldy in epidemic conditions. Going forward, preparedness for future pandemics should include the availability of ready-to-deploy RCTs design that incorporates the lessons from the COVID-19 epidemic.

### RCTs OF CCP EFFICACY

At the time of this writing, the results of five RCTs of CP for COVID-19 are available (Table 1), and several more are ongoing. Although design features, including mechanism for randomization and outcomes of interest, vary across the five trials, each of the five reported some beneficial effect of CCP administration, and four of the five showed an association of CCP with lower mortality, which achieved statistical significance in the study of Rasheed et al.<sup>32</sup> and barely missed it in that of Avendano-Sola et al.<sup>33</sup> A study by Agarwal et al.,<sup>34</sup> hampered by using relatively low antibody plasma, is the only trial of the five that showed no association of CP treatment with mortality, although it reported reductions in tissue SARS-CoV-2 viral load and patient oxygen requirements.

Overall, the data from RCTs for COVID-19 showed that CCP administration was safe and associated with favorable trends. However, none of the five trials can be considered conclusive. The studies by Li et al.,<sup>35</sup> Gharbharan et al.,<sup>36</sup> and Avendano-Sola et al.<sup>33</sup> all terminated prematurely and thus lacked the power to provide a definitive answer as to whether plasma reduced mortality. The study by Agarwal et al.<sup>34</sup> went to completion but used many plasma units with low-antibody titer late in disease, making any conclusion about efficacy difficult, if not impossible. The study by Rasheed et al.<sup>32</sup> achieved a statistically significant reduction in mortality but was unblinded and involved a relatively small number of patients, raising concerns about vulnerability of the conclusions to the occurrence of a few events in either arm.

These five RCTs exemplify many of the difficulties RCTs face when conducted under epidemic conditions. The studies by Li et al.<sup>35</sup> and Avendano-Sola et al.<sup>33</sup>

terminated because the epidemic was controlled in their locales and they had no more patients to enroll, showing how a rapidly evolving epidemic can undermine RCT completion. The study by Gharbharan et al.<sup>36</sup> was terminated prematurely when the investigators determined that the intended CCP recipients already had their own antibody responses, raising questions of the value of additional antibody administration. However, that decision does not appear to have taken into account the possibility that CCP can function as an antiviral even in ill patients with endogenous antibody response, possibly because of superior quality of convalescent antibody or other constituents of CP.<sup>37</sup> The termination of the study by Gharbharan et al.<sup>36</sup> was unfortunate, as even with half the intended enrollment, the trend toward lower mortality in the treatment arm closely approximated the effect size predicted by the investigators used to estimate power.

### OBSERVATIONAL STUDIES OF CCP EFFICACY

In contrast to RCTs, observational studies are easier to conduct under epidemic conditions because they can be conducted as part of routine care. The analysis of observational studies of CCP mainly involves retrospective comparisons of CPP recipients with controls not treated with CCP identified by chart review. The level of sophistication of observational studies varies, ranging from simple comparisons of treated and untreated cohorts to various strategies to match for specific factors or with propensity scores, sometimes adding multivariate survival models. The feasibility of such approaches depends on the availability of untreated patients who are similar enough to the treated group to serve appropriately as controls. Importantly, despite best efforts, observational studies are vulnerable to conscious and unconscious investigator bias and uncontrolled confounders in the groups compared. Nonetheless, one should keep in mind that despite these limitations, observational studies have informed many lifesaving therapies in modern medicine, including widely accepted practices such as cardiopulmonary resuscitation, the Heimlich maneuver, many if not most surgical treatments, and large-scale multidimensional treatments such as newborn intensive care units and coronary care units.

More than a dozen observational studies of CCP efficacy are now available (summarized by Joyner et al.<sup>38</sup>). Like the aforementioned RCTs, nearly all of these studies report that administration of CCP is associated with lower mortality. A major contribution of the observational studies was the emergence of signals of efficacy when it was used early in the course of disease.<sup>39,40</sup> An observational trial with matched controls identified the first 44 h of hospitalization as a critical time for the effective administration of CCP.<sup>40</sup> The capacity to compare the effects of different times of administration is generally not easy to do in RCTs but may be performed in observational research.

### OTHER SIGNALS OF CCP EFFICACY

Although marked quantitative and qualitative variations in SARS-CoV-2 antibodies in CCP greatly complicated interpretations of its efficacy in RCTs, particularly in the trial by Agarwal et al.,<sup>34</sup> these variations provided a unique opportunity to evaluate efficacy in retrospective studies. Because CCP collection began before standardized serologic tests were available, high- and low-titer CCP was administered in a fashion that was masked to both provider and recipient. Using retrospectively analyzed plasma donor specimens for antibody titer, two published analyses took advantage of this masking and the virtual, if not formal, randomized nature of the assignment of antibody levels to patients to compare outcomes in recipients of high- and low-titer plasma. This approach offers many of the advantages as RCTs

and may be useful in future epidemic settings in which favorable antibody characteristics are unknown or are not initially accessible by an approved assay.

The first of these studies was connected to the issuance by the FDA of its EAP authorization in early April, which led to the administration of CCP to some 85,000 COVID-19 patients. Analysis of the EAP database shows a correlation of higher antibody titer in transfused CCP with lower mortality, a signal that was limited to patients who did not require mechanical ventilation at the time of transfusion. In these patients, a dose-response effect emerged, such that mortality was lowest in patients treated with CCP containing the top 20th percentile of antibody titers, highest in patients receiving plasma with the lowest 20th percentile, and intermediate in the remaining patients. Patients not requiring mechanical ventilation with the highest antibody levels in plasma had 31% lower mortality at 30 days than those treated with low titer CCP. No relationship of antibody level to mortality was found in mechanically ventilated patients. The restriction of efficacy to non-mechanically ventilated patients is consistent with the experience of more than 100 years of antibody therapy that administration of CP early in the course of disease before complications arise is needed for efficacy and is apparent in studies of CCP for COVID-19.<sup>39,40</sup> The dose-response finding directly implicates the active agent in CCP, specific antibody, or another substance that positively correlates with antibody, and provides strong evidence for causality in associating antibody with reduced mortality. In a second study, a comparison of mortality among Israeli patients receiving high- versus low-titer plasma also revealed a notable dose-response relationship.<sup>41</sup> The FDA subsequently re-analyzed a larger cohort of samples using a viral neutralization assay and confirmed the dose-response result ([https://www.fda.gov/media/142386/download#:~:text=Four%20lines%20of%20evidence%20continue,3\)%20data%20that%20continues%20to](https://www.fda.gov/media/142386/download#:~:text=Four%20lines%20of%20evidence%20continue,3)%20data%20that%20continues%20to)).

The wide variation in patients who received CCP through the FDA EAP also enabled the detection of additional efficacy signals from so-called experiments of nature. If CCP had been restricted entirely to trial patients, this information would not have become available. In the case of COVID-19, the natural experiment involves individuals with genetic or acquired immune deficiencies who develop COVID-19 and are treated with CCP. Of particular interest are individuals with humoral deficiencies who lack endogenous immunoglobulins. In these patients, recovery has been shown to be associated with restoring antibody immunity through CCP administration. Such scenarios provide strong evidence for a causal effect of CCP. The largest study of individuals with antibody deficits reported on 17 patients with B cell defects and chronic symptoms of COVID-19 who experienced rapid recovery upon CCP administration.<sup>42</sup> Recovery from COVID-19 with CCP has also been described in patients with X-linked agammaglobulinemia.<sup>43,44</sup>

## MECHANISM AND EFFICACY

In inferring causal relationships, an important criterion is the existence of a mechanism that establishes a plausible cause-and-effect relationship. Plasma treatment rests on a strong mechanistic foundation, as the function of antibodies is well understood in immunology.<sup>45</sup> Specific neutralizing antibody to SARS-CoV-2 interferes with viral replication by preventing attachment to its cellular receptor.<sup>46</sup> Several human trials of CCP efficacy have shown that it functions as an antiviral agent by clearing SARS-CoV-2. CCP administration protected mice and Syrian hamsters against SARS-CoV-2, providing additional evidence for its antiviral efficacy.<sup>47,48</sup> The combination of *in vitro* efficacy, animal model protection, and human evidence



for viral clearance suggest a mechanism for CCP efficacy whereby specific SARS-CoV-2 antibodies mediate a therapeutic effect by interfering with viral replication. This helps the host by removing or reducing the stimulus for viral damage, allowing host repair.

At least two mechanisms of action have been identified for the therapeutic effects of CCP against COVID-19. First, CCP administration has been shown to mediate viral clearance, which presumably reflects direct antiviral effects by antibodies binding SARS-CoV-2. Second, inflammatory markers such as C-reactive protein decline after CCP administration,<sup>49</sup> which could reflect its antiviral activity and/or anti-inflammatory effects of IgG.<sup>50</sup> Overall, the encouraging results with CCP are consistent with the historical experience of using plasma.

### CCP IS AS SAFE AS STANDARD PLASMA

One concern about CCP was whether the administration of specific antibody to individuals with COVID-19 could make the disease worse through the phenomenon of antibody-mediated enhancement (ADE) or by triggering cytokine storms through excessive immune stimulation. This concern was driven by laboratory observations with other coronaviruses whereby vaccines eliciting antibody responses, or the administration of virus-specific antibody, was associated with worsening outcomes. In the early days of the pandemic several publications warned about this possibility with respect to CCP use.<sup>51,52</sup> Fortunately, analysis of the first 5,000 patients treated with CCP in the United States revealed a safety profile comparable with conventional plasma used for transfusion,<sup>53</sup> a finding that was maintained when the treatment cohort reached 20,000 patients.<sup>54</sup> Although these studies did not include control groups, they reported very low rates of adverse effects relative to historical rates of complications due to plasma, confirming that CCP was at least as safe as plasma. This finding of safety in a very large sample of patients is one of the major contributions of the EAP. It reduced concern about ADE with neutralizing antibody responses against SARS-CoV-2 and has thus eased the way for the development of other antibody-based therapies such as mAbs and vaccines.<sup>55</sup>

### THE STATE OF KNOWLEDGE FOR CCP EFFICACY

As of the time of this writing, October 2020, our conclusion from the available data is that CCP used to treat COVID-19 is probably effective, and its safety is comparable with that of conventional plasma transfusions, but it is likely that certain patient groups will benefit more from CCP than others. CCP consistently reduces viral burden and functions as antiviral therapy.<sup>6</sup> As a general rule, plasma given early enough in the course of the illness and with a high enough anti-SARS-CoV-2 antibody concentration is more likely to have an impact than plasma that is given late or with low antibody concentration. Knowledge will of course continue to evolve as to optimal timing for the initiation of therapy, types of patients most likely to respond, and best methods to assess the quality of donated plasma in terms of its protective antibody concentration before it is transfused. But we do know that most studies associate CCP administration with reduced mortality when given early in the course of hospitalization before patients worsen and require mechanical ventilation.

In the 8 months since CCP was first deployed against COVID-19, it has been shown to be reasonably safe, and efficacy has been associated with early use of high-titer plasma. Perhaps the current state of CCP for COVID-19 can be summed up as operating within the precautionary principle, whereby its continued use is warranted by

substantial information suggesting low risk and high reward. At the same time, its continued testing is warranted by the absence of truly definitive evidence of effectiveness.

As plasma units vary in the amount of all antibody components, including IgG, IgM, and IgA,<sup>56</sup> testing of transfused plasma prior to infusion is advisable, and the FDA now requires labeling of units as high titer only when having a signal-to-cutoff value of 12 or greater by the Ortho VITROS SARS-CoV-2 IgG.<sup>57</sup> Although this labeling requirement relies on IgG, there are reports that IgM also contributes to the neutralizing activity of CCP.<sup>58</sup> IgM plays an important role in resistance to influenza and West Nile virus infection.<sup>25</sup> Clearly, much has yet to be learned about the most effective antibody response to SARS-CoV-2, and even CP with high titer of neutralizing antibody is a very heterogeneous product with regard to IgM and IgA content.<sup>56</sup> Yet it is remarkable that despite uncertainties as to the timing, composition, and antibody amount required for effective treatment, strong signals of efficacy have emerged in observational studies, RCTs, and the EAP analysis. This in turn suggests that if the correlates of efficacy are better understood, the effectiveness of CCP can be significantly enhanced in the future through optimal deployment.

### THE FUTURE OF CCP FOR COVID-19

Despite the many favorable reports of CCP efficacy, its future will be shaped largely by the results of several large ongoing RCTs, which promise to provide more conclusive and persuasive information on the big questions of if, when, and how CCP works, as well as evidence of efficacy emerging from studies of other antibody-based therapies. CCP has widely been assumed to be a stopgap therapy between a time when no specific therapies are available and the time when mAbs and hyperimmune globulins can be manufactured, proved safe and effective, and made available. However, interpretation of the CCP RCT results will need to be tempered by the risk profiles and disease severity of the participants, when in the course of illness CCP recipients were transfused, and the quality and quantity of CCP administered.

When the COVID-19 Convalescent Plasma Project ([ccpp19.org](http://ccpp19.org)) was launched in March 2020, the expectation was that the newer standardized antibody reagents would be available by the summer of 2020 or at the latest by the fall. However, these modalities remain in experimental studies as of this writing. At least two companies, Eli Lilly and Regeneron, have mAbs in advanced clinical trials, but as of October 2020 CCP remains the only widely available therapy in much of the world. Given that plasma is a locally produced product that is available in under-resourced areas that may not be able to afford more expensive therapies such as mAbs, it is likely that CCP will continue to be used as front-line therapy in many parts of the world for some time to come.

The experience with CCP against COVID-19 supports CP use in future pandemics.<sup>4</sup> CP deployment can begin within weeks of the onset of a pandemic. In the United States, for COVID-19, this was facilitated by a blood-banking industry that produces millions of plasma units each year.<sup>59</sup> This made it possible to rapidly redirect some of its tremendous capacity to provide an adequate supply of CCP for COVID-19 therapy. Although COVID-19 mortality has thus far been insufficient to disrupt industrial output, a localized outbreak of a pandemic with higher mortality in locales where industrial gamma globulin and mAb production are developed or produced could severely restrict the supply of those modalities if work is disrupted. In contrast, the geographically dispersed blood banking industry with its capacity to collect and

distribute CP nationwide is more nimble and less vulnerable to the disruptive effects of severe epidemics affecting specific regions. The intrinsically distributed nature of CP production, which relies on local donors and resources, is likely to be much less vulnerable to pandemic disruption.

Unlike many COVID-19 therapeutics, CCP in the United States lacked a pharmaceutical or government sponsor and was thus mobilized through physician and community self-organization. Medical need, a lack of proven options, and historical precedent drove engagement with highly developed transfusion medicine resources to produce CCP in the regulatory framework of the EAP. The argument that this precluded RCTs is false. RCTs began in numerous locations concurrently with the EAP but were delayed by the issues noted above, while there was substantial CCP use in institutions without access to clinical trials. Under these circumstances, CCP use under the EAP produced critical safety data and important signals of efficacy. EAP use also did not affect RCTs in the outpatient space, which aimed to determine the efficacy of CPP for prophylaxis and for ambulatory therapy.

At the time of this writing, CP is the only therapeutic intervention associated with reduced mortality in people hospitalized with COVID-19, apart from the use of dexamethasone in critically ill patients. Apart from direct benefits to those treated, perhaps the most long-lasting legacy of the CCP use against COVID-19 could be the return of antibody therapies for infectious diseases. After largely abandoning antibody therapies in the 1940s, the field of infectious disease has yet to re-embrace the potential of this class of biologics. Today, 45 years after their invention,<sup>23</sup> mAb therapies are commonplace in oncology and rheumatology. but only three mAbs have been licensed for infectious diseases, and these are niche-use therapies, as is the unlicensed use of mAbs in Ebola virus disease.<sup>24</sup> The use of CCP for COVID-19 may prove to be one of the largest applications of CP therapy in history against a specific infectious disease. With several mAbs to SARS-CoV-2 in advanced clinical development and a hyperimmune globulin trial now in process, antibody therapies have regained a place in the physician's armamentarium.

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## AUTHOR CONTRIBUTIONS

The seven authors constitute the leadership team of the COVID-19 Convalescent Plasma Project ([ccpp19.org](http://ccpp19.org)), and each contributed intellectually to the content and to the writing of this paper.

## DECLARATION OF INTERESTS

B.J.G. is a member of the FDA Blood Products Advisory Committee. Any views or opinions expressed in this manuscript are the author's, based on her own scientific expertise and professional judgment; they do not necessarily represent either the views of the Blood Products Advisory Committee or the formal position of FDA,

and they also do not bind or otherwise obligate or commit either the Blood Products Advisory Committee or the FDA to the views expressed.

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