

COVID-19 convalescent plasma; time for “goal directed therapy”?

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In the field of transfusion medicine, laboratory results are commonly used to identify patients most likely to benefit from transfusion. While the primary purpose of transfusions is to reduce mortality/morbidity, laboratory values are commonly used as surrogates to help guide transfusion therapy. Common examples include measuring hemoglobin or hematocrit to determine who will benefit from red blood cells and platelet count to determine who will benefit from platelet transfusion. Similarly, fibrinogen level or INR are commonly used to determine whether a patient might benefit from cryoprecipitate or plasma. The short-term “goal” of these transfusions is to correct or partially correct the abnormal laboratory values that had been identified prior to transfusion. Providers commonly use this paradigm when ordering many if not most transfusions.

Since March of 2020, the US and many other countries sought to establish procedures for the collection and transfusion of COVID-19 Convalescent plasma (CCP) to treat patients with COVID-19. The efficacy of CCP remains to be clearly proven with several studies and even meta-analysis suggesting this may be a promising therapy.^{1–3} Other trials have failed to show benefit of CCP in hospitalized patients including the REMAP-CAP trial (NCT02735707) and the RECOVERY trial (NCT04381936) which were halted due to futility. Recently, a randomized control trial of CCP given early (within 72 h of symptom onset) reduced the progression to severe disease by nearly half.⁴ Despite these mixed results, CCP continues to be widely used in the US and other countries. As with all transfusions, the objective of this therapy is to reduce morbidity and mortality in these patients. Since CCP was first utilized, a great deal of effort has been put into identifying donors/units that are believed to provide the maximum benefit to patients.^{5–7} While there are many potential mechanisms by which CCP may benefit

patients, neutralizing antibodies found in CCP are likely important mediators of protection.⁸ Recent studies have demonstrated that CCP with high levels of antibody may be more effective than CCP with low level of antibody.⁹ Therefore, many efforts are made to identify donors with high levels of antibodies able to inhibit or neutralize viral growth. Neutralization assays are not readily amenable to routine laboratory use so antibody binding assays (ELISAs) are commonly used as a surrogate test for neutralizing antibodies and have been shown to correlate to some degree with Neutralizing antibodies.^{10–12} In the US, current FDA recommendations involve testing donors using a variety of binding assays to qualify products as CCP and to label them as either high- or low-titer CCP.

In contrast to efforts to improve the quality of CCP, little has been done to identify recipients most likely to benefit from CCP. In the US, many patients were initially enrolled as part of a nationwide expanded access program (EAP) (NCT04338360) and are currently being treated under the emergency use authorization (EUA) that the FDA granted for CCP on August 23, 2020. The EUA is very broad regarding patient eligibility for CCP and simply requires patients have confirmed COVID-19 and be hospitalized. Some have suggested patients be treated early within 10 days of symptom onset or be treated within 3 days of hospitalization.⁹ One recent study found that CCP treatment within 72 h of symptom onset significantly reduced the onset of severe respiratory disease.⁴ Both studies seem to support the concept that CCP likely works best in seronegative donors by increasing SARS-COV2 antibody levels and patients later in disease are more likely to be antibody positive and thus less likely to benefit from CCP. Multiple studies demonstrate that CCP is being used in antibody-positive patients.¹³ A randomized controlled study in the Netherlands was halted due to antibody positivity rates near 80% in subjects in this

study.¹⁴ In another randomized control trial based out of Argentina, over 50% of the subjects in the study were antibody positive prior to receiving treatment.¹⁵ This study showed no beneficial effect of CCP and the authors recommend that CCP not be used in patients with severe pneumonia. Based on these results and the increasing availability of SARS-CoV-2 antibody assay, we propose that antibody testing be performed in patients prior to the use of CCP.

Multiple tests for SARS-CoV-2 antibodies have been granted EUA with the primary purpose to determine if patients have previously been infected with COVID-19. Studies have demonstrated that most patients infected with COVID-19 develop antibodies within 1 to 2 weeks after they are infected.¹⁶ We believe that antibody tests have the potential to assist in identifying patients most likely to benefit from CCP and advocate that providers use antibody testing prior to considering the use of CCP. Patients who are seronegative are the best candidates for CCP and the goal of therapy should be to seroconvert them from negative to positive. Experience at our facility has shown that antibody-negative patients treated with 1 or 2 units of “high titer” CCP is enough to seroconvert these patients (data not shown). Others have also shown increases in antibody level following CCP treatment.¹³ While patients early in the course of disease are almost certainly more likely to be seronegative, we propose it is time to replace these surrogate measures for identifying seronegative patients with direct testing of antibodies whenever feasible. At our facility, antibody testing is performed in a high throughput instrument (Roche) and if negative is generally reported within 2 h of receipt. If positive, reporting is delayed by several hours as a second confirmatory assay is performed. The two ELISAs results are concordant in greater than 90% of patients (data not shown).

There are many unknowns regarding the use of CCP starting with the patients most likely to benefit from this therapy. Assuming CCP is beneficial to some patients, the optimal transfusion “trigger” is unknown and current assays for SARS-Cov2 antibodies are only FDA approved for qualitative results. Given the current limitations of this testing, the only transfusion trigger that can currently be used in patient care is a negative result. Understanding these limitations, we have advocated with our providers that antibody testing be performed prior to CCP use and if positive then CCP not be given. We understand that patients with “low positive” antibody levels may or may not benefit from CCP and that this approach would preclude these patients from this treatment. However, CCP is not a proven therapy in any patients and under the EUA, the FDA requires all patients be informed that this is an investigational therapy. Investigational therapies such as CCP should focus

on patients most likely to benefit from the therapy and in our view seronegative patients are most likely to benefit from this therapy. We also advocate that clinical trials of CCP incorporate antibody screening into their design whenever possible.

In summary, we advocate that providers utilize antibody testing in COVID-19 patients to help identify seronegative patients. Assuring patients are antibody negative prior to using CCP would help conserve the inventory of CCP as past studies have demonstrated that many transfused subjects have been antibody positive prior to CCP infusion. Our own experience is consistent with these results as we have found that even patients hospitalized within 3 days of treatment are seropositive. This approach would increase the inventory of CCP and allow for more restrictive antibody criteria for CCP donation. In our hospital-based donor center, a spike protein ELISA (DiaSorin) is used to qualify CCP donors and the cutoff value is set such that only about 20% of potential donors have antibody levels high enough for donation. Using these stringent criteria, our inventory of CCP has been sufficient to support our patients. We understand that not all collection facilities currently have the luxury of using such a high threshold for donation but as cases and utilization are reduced by the vaccine, this will allow for more selective use of CCP with higher antibody levels.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest relevant to this manuscript submitted to TRANSFUSION.

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