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Commentary

# Towards characterized convalescent plasma for COVID-19: The dose matters

Hans P. Verkerke, Cheryl L. Maier*

*Department of Pathology and Laboratory Medicine, Center for Transfusion and Cellular Therapies, Emory University School of Medicine, 1364 Clifton Road NE, Atlanta, GA 30322, USA*

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of COVID-19, remains a global health crisis with limited treatment options. While randomized controlled trials have demonstrated some efficacy of the antiviral agent remdesivir and the corticosteroid dexamethasone in COVID-19 treatment, any beneficial role of convalescent plasma (CP) has been less clear [1,2]. Since the early 20th century convalescent blood products and their antibody derivatives have been used for the treatment and prevention of infectious diseases. The discovery of potent antibiotics has largely supplanted any role for CP in treating bacterial infections, yet CP remains an important tool in the early stages of outbreaks of emerging or re-emerging viral pathogens for which therapeutic options are limited. A historical meta-analysis by Luke et al. [3] on the 1918 H5N1 influenza pandemic found a significant reduction in mortality associated with CP use. This finding is consistent with reductions in both viral load and mortality with CP use among severely ill patients in the more recent 2009 H1N1 swine flu pandemic [4]. Evidence from other coronavirus outbreaks, including MERS and SARS-CoV-1, as well as the 2014 Ebola virus outbreak, is less conclusive [5–7], relying on limited patient cohorts and case series. These conflicting results are to be expected given the heterogeneous nature of CP, the common practice of transfusing CP prior to its characterization, and the clinical severity and diversity of recipients qualifying for its empirical use. The total antibody amount, class, subclass, specificity, neutralizing activity, and potential to induce antibody-dependent cell-mediated cytotoxicity are just some of the complex factors that may influence CP-associated outcomes.

A broad consensus among physicians and scientists has emerged in the current pandemic that characterization of the antibodies within CP units is essential for determining correlates of efficacy. In recent weeks, a multi-center study including 35,322 patients from 2807 acute care facilities by the US EAP COVID-19 Plasma Consortium reported significant reductions in 7 and 30 day mortality with early use of CP containing high levels of SARS-CoV-2 specific IgG antibodies in a subset of patients [8]. The results reported by Maor et al. [9] in EClinicalMedicine are consistent with those of the consortium and highlight the importance of considering SARS-CoV-2 specific antibody levels prior to transfusing CP. Maor et al. [9] report a significant association of SARS-CoV-2 specific IgG antibody levels, which they correlate with virus-neutralizing activity, in CP units used to treat 49 prospectively enrolled patients with the primary outcome of clinical improvement 14 days after CP use. Specifically, 61.2% of patients receiving CP containing high levels of virus-specific antibodies improved relative to only 36.7% of those receiving low-IgG CP. Consistent with reports from this and previous pandemics, the use of CP had a favorable safety profile with no adverse events reported among these patients.

The major limitation of the study by Maor et al. [9] relates to its observational design and limited patient cohort, and large-scale randomized controlled trials will be necessary to demonstrate the true efficacy of CP in COVID-19 treatment. Such trials must be carefully designed to provide equipoise, since evidence already exists supporting an association between CP and reduced morbidity and mortality in SARS-CoV-2 and other infections. Future studies would benefit from characterization of patient antibody levels prior to CP transfusion, as the therapy may involve complementing a patient's developing or, perhaps, inadequate immune response. Examination of the levels and functional significance of anti-viral IgA and IgM in both patient and donor plasma should also be considered, as all three antibody classes and their subclasses have different roles in naturally occurring immune responses [10].

Within the broader context of the pandemic the work of Maor et al. [9] and that of the consortium beg the question: how would COVID-19 outcomes improve if every patient received an optimally high dose of virus-specific antibody-containing plasma. In addition, what other antibody characteristics might contribute to variable CP efficacy and how might we deliver them in the appropriate clinical window? How might pre-existing antibody levels in patients alter the utility of CP? And finally, could the class or subclass of virus-specific antibodies further influence the therapeutic effect or half-life of donor plasma? After decades of methodical work developing analytical tools to study, understand, and combat pandemic influenza, HIV, Zika virus, SARS-CoV-1, MERS, and other viral threats to global

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* Corresponding author.
*E-mail address:* cheryl.maier@emory.edu (C.L. Maier).

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health, we as a scientific and clinical community are uniquely poised to determine the specific factors that mediate CP efficacy with the goal of standardizing and optimizing this long-standing approach in the treatment of infectious diseases.

## Declaration of Interests

The authors declare no conflicts of interest.

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