

Convalescent Plasma to Treat COVID-19 Possibilities and Challenges

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In this issue of JAMA, Shen et al report findings from a preliminary study of 5 severely ill patients with coronavirus disease 2019 (COVID-19) who were treated in the Shenzhen Third People's Hospital, China, using plasma from recovered



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individuals.¹ All patients had severe respiratory failure and were receiving mechanical ventilation; 1 needed extracorporeal membrane oxygenation (ECMO) and 2 had bacterial and/or fungal pneumonia. Four patients without coexisting diseases received convalescent plasma around hospital day 20, and a patient with hypertension and mitral valve insufficiency received the plasma transfusion at day 10. The donor plasma had demonstrable IgG and IgM anti-SARS-CoV-19 antibodies and neutralized the virus in *in vitro* cultures. Although these patients continued to receive antiviral treatment primarily with lopinavir/ritonavir and interferon, the use of convalescent plasma may have contributed to their recovery because the clinical status of all patients had improvement approximately 1 week after transfusion, as evidenced by normalization of body temperature as well as improvements in Sequential Organ Failure Assessment scores and PAO_2/FIO_2 ratio. In addition, the patients' neutralizing antibody titers increased and respiratory samples tested negative for SARS-CoV-2 between 1 and 12 days after transfusion.

Even though the cases in the report by Shen et al are compelling and well-studied, this investigation has important limitations that are characteristic of other "anecdotal" case series. The intervention, administration of convalescent plasma, was not evaluated in a randomized clinical trial, and the outcomes in the treatment group were not compared with outcomes in a control group of patients who did not receive the intervention. Therefore, it is not possible to determine the true clinical effect of this intervention or whether patients might have recovered without this therapy. In addition, patients received numerous other therapies (including antiviral agents and steroids), making it impossible to disentangle the specific contribution of convalescent plasma to the clinical course or outcomes. Moreover, convalescent plasma was administered up to 3 weeks after hospital admission, and it is unclear whether this timing is optimal or if earlier administration might have been associated with different clinical outcomes. Despite these limitations, the study does provide some evidence to support the possibility of evaluating this well-known therapy in more rigorous investigations involving patients with COVID-19 and severe illness.

The use of convalescent plasma is not new; it was used for severe acute respiratory syndrome (SARS), pandemic 2009 influenza A (H1N1), avian influenza A (H5N1), several hemorrhagic fevers such as Ebola, and other viral infections. For instance, in 2005, Cheng et al reported outcomes of patients who received convalescent plasma in Hong Kong during the 2003 SARS outbreak.² Although this investigation was not a randomized trial, of 1775 patients, the 80 who received convalescent plasma had a lower mortality rate (12.5%) compared with the overall SARS-related mortality for admitted patients ($n = 299$ [17%]). The antibody titers and plasma transfusion volumes varied and did not appear to correlate with clinical response; however, patients receiving transfusion within 14 days of symptom onset ($n = 33$) had better outcomes. No adverse events were reported among patients receiving convalescent plasma.

Despite the potential utility of passive antibody treatments, there have been few concerted efforts to use them as initial therapies against emerging and pandemic infectious threats. The absence of large trials certainly contributes to the hesitancy to employ this treatment. Also, the most effective formulations (convalescent plasma or hyperimmune globulin, H-Ig) are unknown. Convalescent plasma has the advantage that while its antibodies limit viral replication, other plasma components can also exert beneficial effects such as replenishing coagulation factors when given to patients with hemorrhagic fevers such as Ebola.³⁻⁵ On the other hand, individual convalescent plasma units demonstrate donor-dependent variability in antibody specificities and titers. H-Ig preparations, in contrast, contain standardized antibody doses, although fractionation removes IgM, which may be necessary against some viruses. Nonetheless, the construction of a strategic stockpile of frozen, pathogen-reduced plasma, collected from Ebola-convalescent patients with well-characterized viral neutralization activities, is one example of how to proceed despite existing unknowns.⁶

Deploying passive antibody therapies against the rapidly increasing number of COVID-19 cases provides an unprecedented opportunity to perform clinical studies of the efficacy of this treatment against a viral agent. If the results of rigorously conducted investigations, such as a large-scale randomized clinical trial, demonstrate efficacy, use of this therapy also could help change the course of this pandemic.⁴ Shen et al used apheresis products produced in the hospital.¹

How could this be scaled to meet increased demands? One approach would be to combine the use of convalescent plasma and H-Ig in a complementary way to treat infected patients in the current COVID-19 pandemic, and subsequent infectious

waves, perhaps with the following steps and considerations. First, blood centers could start collecting plasma from convalescent donors, preferably at the leading edge of the infectious wave; health care workers could encourage COVID-19-infected patients to donate after hospital discharge. Plasma would be tested, frozen, and distributed to hospitals; paired samples would be retained for concurrent investigations.

Second, within days of collection, clinicians could transfuse convalescent plasma to infected patients. This approach would be expected to be most effective in patients before they develop a humoral response to COVID-19; serology tests that detect COVID-19 neutralizing antibodies would be beneficial in identifying the best treatment candidates. Monitoring patient responses by clinical, laboratory, and imaging results could be compared against antibody titers, specificities, and neutralizing activities in paired plasma samples to develop better algorithms for identifying patient and donor factors that predict clinical efficacy.

Third, funding to expand plasma collection capabilities, as well as for academic, industry, and government research initiatives, could mobilize these efforts. However, despite potentially rapid availability, the deployment of convalescent plasma will have limited reach because transfusions are typically performed in hospital settings and may require large infusion volumes. In addition, plasma transfusions are also associated with adverse events ranging from mild fever and allergic reactions to life-threatening bronchospasm, transfusion-related acute lung injury, and circulatory overload in patients with cardiorespiratory disorders, which must be carefully tracked.³ There is also a small, but nonzero, risk of infectious disease transmission.

Fourth, dynamic modeling of COVID-19 infections and factors that are associated with clinical efficacy could be used to inform the distribution of convalescent plasma (and donors) between blood centers and the source plasma industry so the latter can manufacture concentrated COVID-19 H-Ig. Fifth, within several months, it could be possible for clinicians to begin using small volume H-Ig preparations in ambulatory settings and drive-through clinics, as well as in hospitals. Concentrated H-Ig

preparations are an injectable, time-tested treatment for viral (eg, hepatitis A and B) and bacterial (eg, tetanus, diphtheria) diseases. In principle, each dose delivers antibody preparations with accurately determined specificities, affinities, and titers against COVID-19 and is logistically simpler than plasma to distribute worldwide. As with convalescent plasma, it will be critical to identify factors that predict responses to COVID-19 H-Ig, and also to track adverse events.

While H-Ig (like plasma) can be stored for years,⁷ a similar pathway may need to be reactivated next season, especially as passive antibody efficacy wanes due to accumulated viral mutations. During each iteration, the investigations performed in parallel to clinical use will drive improvements, for example by guiding the relative amounts of convalescent plasma vs H-Ig that are prepared, or by identifying patients most likely to benefit from these treatments.

Both academic⁴ and industry groups are beginning to investigate the efficacy of passive antibody therapies for COVID-19 infection. If substantial, robust evidence from rigorously conducted clinical trials clearly establishes effectiveness, and if tests could identify patients who could benefit from passive immunity, the US and other countries could consider a national campaign to provide such treatment. Although a logistical challenge, this may be one approach to protect high-risk populations and could synergize with parallel efforts to develop vaccines and antiviral drugs. However, just as executive direction was critical for rapid implementation of COVID-19 tests, so it will be important to accelerate this effort. Specifically, guidance would be needed to direct blood centers and plasma fractionators to begin prioritizing collections from COVID-19-convalescent donors; expedite the availability of these products for therapeutic use; create a data collection, analysis, and regulatory infrastructure to identify factors that predict therapeutic efficacy and to inform the relative levels of convalescent plasma vs H-Ig production; and remove regulatory barriers that, for example, currently limit the use of pathogen reduction technology for convalescent plasma collections or that require several-month inventory holds on H-Ig pharmaceuticals.

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