

EDITORIAL



(A Little) Clarity on Convalescent Plasma for Covid-19

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Passive immunotherapy has been used since the late 19th century, and in 1901, the first Nobel Prize in Physiology or Medicine was awarded for serum therapy for patients with diphtheria. During the 1918 pandemic, serum from convalescent patients was used to treat influenza, with some apparent success.¹ Today, the use of immunoglobulins has been established for the prophylaxis and treatment of a variety of infections, including those with respiratory syncytial virus, cytomegalovirus, and hepatitis B or hepatitis A virus. More recently, passive immunotherapy has been evaluated for severe acute respiratory syndrome (SARS), Middle East respiratory syndrome, and Ebola virus disease. Intravenous human immunoglobulin has revolutionized the management of immunoglobulin deficiency states.

The use of convalescent plasma against SARS coronavirus 2 (SARS-CoV-2) is advocated for the treatment of patients with coronavirus disease 2019 (Covid-19). The experience with influenza A is relevant, and a meta-analysis suggested that early treatment, before critical illness develops, may be an important predictor of the efficacy of passive immunotherapy for that pathogen.¹ The authors of that meta-analysis acknowledged the low quality of the available evidence regarding early treatment. Another meta-analysis of studies of convalescent plasma and hyperimmune immunoglobulin in patients with influenza A and SARS suggested a mortality benefit “when convalescent plasma is administered early after symptom onset.”² However, in a randomized, controlled trial, high-titer convalescent plasma from patients who had recovered from H1N1 influenza was ineffective against severe influenza A infection in hospitalized children and adults.³

Initial randomized trials of convalescent plasma in patients with Covid-19 focused on hospitalized patients who were already moderately to severely ill, and these trials provided weak evidence of clinical efficacy.⁴⁻⁶ Some were underpowered when nonpharmaceutical interventions such as masking and social and physical distancing reduced the incidence of Covid-19 and enrollment was limited. Also, these trials were heterogeneous with respect to the characteristics of the convalescent plasma used (e.g., its antibody content and the stratification of the recipients according to their serologic status). No unexpected safety signals beyond the recognized risks of plasma transfusion (i.e., fluid overload, transfusion-associated acute lung injury, and allergy) have emerged, nor has there been evidence of antibody-dependent enhancement of Covid-19 severity. Accordingly, it is difficult to make actionable conclusions about the clinical value of convalescent plasma.

Observational studies have been more positive than randomized trials; some, but not all, of these studies have suggested modest clinical effects and measurable surrogate virologic outcomes.^{7,8} They have confirmed the safety profile of plasma transfusions but have some of the same issues as randomized trials, in addition to the potential biases and shortcomings inherent in observational studies.

The Food and Drug Administration (FDA) argued that a “totality of the evidence” suggested that the benefits of convalescent plasma would outweigh its risks, and given the lack of effective treatments, the FDA granted an Emergency Use Authorization (EUA) and provided guidance on the manufacture and use of convalescent plasma

in hospitalized patients with signs of progressive infection. By contrast, a National Institutes of Health guidelines panel stated that “the data are insufficient to recommend for or against” the use of convalescent plasma. The Infectious Diseases Society of America and the AABB (formerly known as the American Association of Blood Banks) recommend that the use of convalescent plasma be limited to clinical trials, that critically ill patients and those in the intensive care unit (ICU) are unlikely to benefit from transfusions of convalescent plasma, and that convalescent plasma should be used as early as possible in the course of infection (preferably within 3 days after diagnosis) in order to achieve the best outcomes.⁹

Considering the number of SARS-CoV-2 infections, the paucity of treatment options, and the enthusiasm for and controversy about convalescent plasma, a high-quality, multicenter, randomized, controlled trial is most welcome. Libster and colleagues now report in the *Journal*¹⁰ the results of a well-executed trial of early convalescent plasma in older adult patients in whom symptomatic SARS-CoV-2 infection was diagnosed with the use of a polymerase-chain-reaction assay. In this double-blind trial, 250 ml of convalescent plasma with an IgG titer greater than 1:1000 against SARS-CoV-2 spike (S) protein was compared with saline placebo in patients who were 65 to 74 years of age and had prespecified coexisting conditions and in patients who were 75 years of age or older with or without coexisting conditions.

The patients received convalescent plasma or placebo less than 72 hours after symptom onset. In the intention-to-treat population, a primary end-point event (progression to predefined severe disease during follow-up) occurred in 16% (13 of 80 patients) and 31% (25 of 80 patients) of the well-matched convalescent plasma and placebo groups, respectively. A dose-dependent effect relative to the antibody titers after infusion was observed, and this effect was larger after the exclusion of 6 patients who had a primary end-point event before infusion. The benefits of convalescent plasma with respect to the secondary end points were consistent with those associated with the primary end point. No serious adverse events were observed. The authors conclude that “early administration of high-titer convalescent plasma against SARS-CoV-2 to mildly ill infected older

adults reduced the progression of Covid-19.” Even before the current trial, the EUA emphasized the potential advantages of early therapy with high-titer convalescent plasma. Unfortunately, a direct comparison of antibody levels in the current trial with assays specified in the FDA EUA is not available. Antibody titers in the recipients at enrollment were not provided, so no comment can be made about the usefulness of seroreactivity in patients as a criterion for convalescent plasma use.

At this time, convalescent plasma should be reserved for patients in whom the duration, severity, and risk of progression of illness are similar to those in the patients in this trial. Younger high-risk patients (and certain immunodeficient patients) with these disease characteristics should be considered as well.

The supply of convalescent plasma has been tenuous during the marked increase in Covid-19 cases during the fall in the United States, although recent collections have improved. From September 28 through December 27, 2020, distributions of new and stockpiled units of convalescent plasma to hospitals in the United States exceeded collections by 7785 units (Block W: personal communication). If collections are restricted to the high-antibody titers and patient indications described in the article by Libster et al., the supply of convalescent plasma will be stressed. At my center, high-titer collections (as defined by the FDA) account for only 19.5% of seroreactive convalescent plasma donations. Shifting the pool of potential recipients away from those included in the EUA to the many infected outpatients whose risk of hospitalization and eventual need for advanced care cannot be precisely estimated should lead to the extension of convalescent plasma transfusions to prehospital venues (although this is not yet permitted in the EUA).

Uncontrolled compassionate use of convalescent plasma in patients other than those with an early infection that is likely to progress to more severe illness should be discouraged, even though clinicians recognize how difficult it can be to “just stand there” at the bedside of a patient in the ICU. Constraints on therapies for Covid-19 that are effective for limited patient populations are a powerful argument for continued consistent adherence to recommended nonpharmaceutical interventions and the rapid deployment and uptake of effective vaccines.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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1. Luke TC, Kilbane EM, Jackson JL, Hoffman SL. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? *Ann Intern Med* 2006;145:599-609.
2. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis* 2015;211:80-90.
3. Beigel JH, Aga E, Elie-Turenne M-C, et al. Anti-influenza immune plasma for the treatment of patients with severe influenza A: a randomised, double-blind, phase 3 trial. *Lancet Respir Med* 2019;7:941-50.
4. Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening covid-19 a randomized clinical trial. *JAMA* 2020;324:460-70.
5. Simonovich VA, Burgos Pratz LD, Scibona P, et al. A random-

ized trial of convalescent plasma in Covid-19 severe pneumonia. *N Engl J Med*. DOI: 10.1056/NEJMoa2031304.

6. Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P; PLACID Trial Collaborators. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). *BMJ* 2020;371:m3939.
7. Joyner MJ, Carter RE, Senefeld JW, et al. Convalescent plasma antibody levels and the risk of death from Covid-19. *N Engl J Med*. DOI: 10.1056/NEJMoa2031893.
8. Salazar E, Christensen PA, Graviss EA, et al. Treatment of COVID-19 patients with convalescent plasma reveals a signal of significantly decreased mortality. *Am J Pathol* 2020;190:2290-303.
9. Infectious Diseases Society of America. Clarifying the Emergency Use Authorization framework for COVID-19 convalescent plasma: considerations for clinicians prepared jointly by the Infectious Diseases Society of America and AABB. November 18, 2020 (<https://www.idsociety.org/globalassets/covid-19-real-time-learning-network/therapeutics-and-interventions/convalescent-plasma/aabb-idsa-convalescent-plasma-eua-final.pdf>).
10. Libster R, Pérez Marc G, Wappner D, et al. Early high-titer plasma therapy to prevent severe Covid-19 in older adults. *N Engl J Med*. DOI: 10.1056/NEJMoa2033700.

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