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EDITORIAL

The Fast and the Furious: Chasing a Clinical Niche for COVID-19 Convalescent Plasma

Convalescent plasma (CP) has been explored as therapy for a range of infectious diseases for over a century. Before the COVID-19 pandemic, Argentine hemorrhagic fever was the only condition for which it had proven value (1). From early in the pandemic, COVID-19 CP (CCP) has been available in the United States, initially through emergency investigational new drug applications, then an expanded access program in which nearly 100 000 patients received CCP (2), and then in August 2020 through emergency use authorization (EUA) from the U.S. Food and Drug Administration. Randomized controlled trials were eventually done, and these have provided inconsistent results. Given the rapidly changing landscape of SARS-CoV-2 variants, the variability of host immune responses due to prior infection and vaccination, and the growing availability of new antiviral therapies, including monoclonal antibodies, the clinical niche for CCP remains uncertain.

In an article by Estcourt and colleagues (3), the Association for the Advancement of Blood and Biotherapies (AABB) reports a thorough analysis of existing data and guidelines for the use of CCP for treatment and prophylaxis of COVID-19 using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria. Although the AABB provides a strong recommendation with high certainty against the use of CCP in unselected, hospitalized patients, recommendations in other settings are either weak or based on low-certainty evidence. We applaud the AABB for the rigorous evidence review, detailed interpretations, and proposed guidance on the potential use of CCP for treatment of COVID-19.

Passive immunotherapy is a strategy to augment the host immune response. It can be antibody-based or cell-based, and natural or genetically engineered. In the context of COVID-19, antibody strategies have included CCP, hyperimmune immunoglobulin, and monoclonal antibodies. Although CCP is collected from a single donor and was easily obtained early in the pandemic, its neutralizing potency is highly variable between units and plasma also includes non-Ig protein components that may have unintended effects (4). Hyperimmune immunoglobulin is purified IgG pooled from multiple donors, creating a more consistent polyclonal product with standardized high neutralizing titers. Plasma used for hyperimmune immunoglobulin or CCP may also be selected from donors with "hybrid immunity"—reflecting both vaccination and natural infection—for a strategy that substantially increases neutralizing titers. Finally, anti–SARS-CoV-2 monoclonal antibodies targeting a single epitope with very high potency have demonstrated clear benefit when given early among nonhospitalized patients (5–7), but this strategy remains highly vulnerable to immune escape from new variant lineages (8).

There has been strong advocacy for CCP. In the United States, the initial path was through emergency investigational new drug applications for single patients. When the demand for that process became overwhelming, an expanded access program was implemented with the Mayo Clinic. Then, in response to increasing demand and the sense that it was reasonable to believe the product was effective, the Food and Drug Administration issued an EUA in August 2020. At that time, the EUA limited CCP treatment to unselected, hospitalized patients. Ironically, although it seemed plausible at the time that CCP might be of value to hospitalized patients, the eventual trials showed otherwise. An important lesson for future responses to emerging infectious diseases is that although it is important to rapidly provide therapies that "may be effective," it is essential that those therapies are evaluated in robust trials as soon as possible. As additional data became available, the Food and Drug Administration modified the EUA for CCP in February 2021 to limit use to high-titer CCP units for patients who were early in the disease course or had impaired humoral immunity. In December 2021, the EUA further limited use to immunocompromised patients in either outpatient or inpatient settings **Table**).

Multiple organizations have developed guidelines on the treatment of patients with COVID-19. Recommendations have varied between guideline groups because of differences in membership, timing, scope, and approach—all factors that are important for clinicians to consider when evaluating and applying recommendations. At present, guidelines from the AABB, the Infectious Diseases Society of America, and the National Institutes of Health Treatment Guidelines Panel (of which both authors of this editorial are members) are fairly well aligned in the area of CCP, with all noting potential value in immunocompromised patients and recommending against CCP in unselected, hospitalized patients (**Table**). The main difference is that the AABB also "suggests" use of CCP in combination with other standard-of-care treatments for outpatients at high risk for disease progression, regardless of immune status. Of note, the currently available data for CCP in ambulatory patients have been from studies of nonimmunized participants who were not receiving any of the currently recommended outpatient treatments with direct-acting antiviral agents or anti–SARS-CoV-2 monoclonal antibodies (9).

The primary question facing clinicians today is, When should one consider CCP as a treatment for a patient with COVID-19? Passive antibody therapy has been shown to be of value for unvaccinated, otherwise untreated, ambulatory patients with early COVID-19 at risk for disease progression. In that setting, data are strongest for monoclonal antibodies when activity for the infecting variant is maintained, and some but not all studies have shown benefit for CCP. However, the precise niche for CCP and

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Table. Comparison of CCP Guidance and Authorization (August 2022)

Patients With COVID-19	AABB Guidelines	NIH COVID-19 Treatment Guidelines*	IDSA Guidelines*	FDA EUA for CCP Use in the United States
Immunocompromised	*Inpatients:* suggest use with standard of care (weak, low certainty) *Outpatients:* suggest use with standard of care, regardless of immune status (weak, moderate certainty)	Insufficient evidence to recommend for or against use; some clinicians consider use if patient is not responding to other therapies Recommend against use of CCP collected before emergence of Omicron (AIII)	No specific recommendation	*Authorized*, use of high-titer units only; outpatient or inpatient setting
Outpatient, immunocompetent but high risk for progression	Suggest use with standard of care, regardless of immune status (weak, moderate certainty)	Insufficient evidence to recommend for or against use†	Suggest use if no other options (conditional, low certainty)†‡	*Not authorized*, alternative treatments have demonstrated benefit
Inpatient, immunocompetent	Recommend against in unselected groups (strong, high certainty) Suggest use with standard of care, if no detectable SARS-CoV-2 antibodies (weak, low certainty)	Recommend against (AI)	Recommend against (strong, moderate certainty)	*Not authorized*, randomized trials suggest benefit unlikely

AABB = Association for the Advancement of Blood and Biotherapies; CCP = COVID-19 convalescent plasma; EUA = emergency use authorization; FDA = U.S. Food and Drug Administration; IDSA = Infectious Diseases Society of America; NIH = National Institutes of Health.
* These guidelines are living documents; latest updates are available online.
† FDA EUA authorizes CCP only for immunocompromised patients.
‡ Patient value factors should be considered, and in this context it may be reasonable to decline CCP.

other antibody therapies today remains unclear, in large part because most available evidence was generated in the absence of current standard strategies for prevention and care, such as vaccines and antiviral agents, including nirmatrelvir–ritonavir (Paxlovid [Pfizer]) (10). At this point in the pandemic, it seems that the patient most likely to benefit from passive antibody therapy is the immunocompromised host with COVID-19 who cannot mount their own antibody response to vaccine or prior infection. In that setting, and in the absence of other antiviral treatments or progression despite receipt of standard treatments, high-titer CCP from a recently recovered donor is a reasonable approach.

The experience with CCP during this pandemic provides at least 2 important lessons as we prepare for the next emerging infectious disease. First, despite how logical and available an intervention may appear, we cannot determine its benefit absent evidence from scientifically robust, ethically sound clinical trials. Second, it is incumbent on government, academia, and professional groups to ensure that, in our haste to provide treatments that *may be* of benefit, we make sure clinical evidence is generated as quickly as possible to determine whether they *are* of benefit.

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