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Commentary

COVID-19 convalescent plasma therapy through the lens of the third year of the pandemic

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Therapeutic use of serum obtained from recovered patients (convalescent serum/plasma) dates to the late 19th century when serum therapy became the inaugural form of antimicrobial therapy [1]. The first Nobel Prize in medicine was awarded to Emil von Behring for the development of serum therapy, which was used throughout the first third of the 20th century to treat a myriad of infectious diseases, including diphtheria, pneumococcal pneumonia, meningococcal meningitis, scarlet fever, influenza, measles, mumps, and polio. However, serum therapy was discontinued when antibiotics were introduced. As a consequence, clinicians are no longer familiar with the use of antibody therapy.

The efficacy of convalescent plasma is governed by the following principles: (a) it must contain microbe-specific antibodies, its active ingredient; (b) in a sufficient amount to mediate a biological effect, and (c) be administered early in the course of disease [2]. As knowledge of COVID-19 pathogenesis unfolded, it became clear that it had an initial viral phase followed by an inflammatory phase with tissue damage driven by the immune response [3]. COVID-19 convalescent plasma (CCP) contains SARS-CoV-2 spike-protein–binding antibodies that neutralize the virus along with a broad array of antibodies, other SARS-CoV-2 specificities, and functional activities [4]. Although the neutralizing antibodies exert their effect during the viral phase of COVID-19, virus may also be present in the inflammatory phase and non-neutralizing antibodies may clear virus and/or dampen the inflammatory response via Fc-mediated functions [4]. The endogenous spike-protein–antibody response limits COVID-19 progression and severity, as evidenced by the stunning success of spike-protein-based vaccines [5,6]. Because CCP can neutralize virus in the presence of endogenous antibodies, it is likely to have greater antibody breadth and functional activity than early endogenous antibodies [7,8]. Moreover, recently collected CCP contains antibodies to circulating variants and is unlikely to promote and/or develop resistance to escape variants, because it is polyclonal and contains antibodies with a multitude of SARS-CoV-2 specificities, including a diverse array of spike protein determinants [9]. This is underscored by the ability of plasma from persons with hybrid (vaccination and infection) immunity to neutralize ancestral and emergent viral variants [10].

Early in the pandemic, CCP was readily available from recovered patients and rapidly deployed as an antiviral agent for a deadly new disease with no validated therapy. Most studies conducted early in the pandemic enrolled critically ill hospitalized patients with COVID-19 and most were negative [11]. Additionally, meta-analyses were influenced by large trials that enrolled critically ill patients and/or did not administer sufficient antibody, although a real time meta-analysis of randomized trials using patient level data had a more nuanced conclusion [12,13]. A large open label study, also conducted early in the pandemic, found a dose response whereby mortality was lower in non-intubated patients who received high versus low-titre CCP, and multiple studies found consistent signals of efficacy in patients treated early in disease with well-qualified CCP [11,14]. In most early studies, CCP was administered too late in disease and/or did not contain sufficient antibody. This was a lesson learned. When COVID-19 swept the globe as an entirely new disease of humans, it was not known that pneumonia and supplemental oxygen requirement were markers of the inflammatory phase during which an antiviral agent may not be effective. Additionally, there were no universally agreed upon titre and/or...
neutralization thresholds to qualify CCP and a variety of criteria were used [11].

In this issue, Gharbharan et al. [15] report the results of their randomized-controlled trial (RCT) B of CCP versus non-convalvescent fresh frozen plasma (CP) conducted in ambulatory patients in the Netherlands from November 2020 to July 2021. Participants were enrolled within 8 days of symptom onset; median age was 60 years, 90% were spike-protein antibody seronegative and <3% were vaccinated at enrolment. The CP used had a neutralizing titre >1:160. Although the primary endpoint, clinical improvement on day 28, was not met, the study was discontinued with only 416 of 690 planned enrolments when vaccine uptake in the Netherlands reached 80%. Notably, the primary endpoint may have been affected by the presence of more participants with severe immunodeficiency in the CP (4.8%) than in CCP (2.4%) arm because for this population CCP was beneficial [16]. Nonetheless, the odds ratio for clinical improvement (0.58) was low, as were hospital admissions for CCP recipients treated <5 days after symptom onset. This parallels the findings of the RCT by Sullivan et al. [17] in which CCP was also beneficial in ambulatory participants treated <5 days after symptom onset. Notably, in a subset of Gharbharan et al. [15], participants, post-treatment spike-protein antibody levels were higher in the CCP than CP arm on day 3 and (by extrapolation) day 5, but not day 7. Although the study was not designed to link antibody levels to clinical outcome, this observation suggests a biologically plausible explanation for CCP benefit in those with <5 days of symptoms.

The results of Gharbharan et al. [15] as well as Sullivan et al. [17] reinforce the principle that antibody must be administered early in disease to be beneficial in (largely) immunocompetent patients. The most robust RCT evidence of CCP efficacy in ambulatory patients was found in an older (aged >65 years with 50%–75 years) cohort treated <40 hours after symptom onset, in which high-titre CCP was more effective than low-titre CCP [18]. Therefore, in the study by Gharbharan et al. [15], participants may have required more antibody, given that patients who are older, immunosuppressed, and/or cannot generate an endogenous SARS-CoV-2 antibody response may need more antibody [18] and/or multiple CCP doses to alleviate symptoms and eliminate virus [19,20]. With the ongoing evolution of the pandemic, which continues to disable and affect the lives of millions across the globe, large scale randomized trials to assess CCP timing, dosing and/or efficacy in various clinical settings are not clinically feasible or possible, given the lack of infrastructure and resources for such studies. Nonetheless, registries and/or well-designed studies that leverage electronic data can provide high-quality evidence to guide CCP use and identify questions amenable to testing in trials, particularly in defined populations, such as immunosuppressed patients.

Nearly all participants in the studies by Sullivan et al. [17] and Gharbharan et al. [15], were unvaccinated. Although there is a knowledge gap regarding CCP efficacy in vaccinated persons, the original idea behind CCP treatment for COVID-19 was that it would be a stopgap measure until other therapies and vaccines were available [1]. Although vaccines and other therapies are now available for most immunocompetent patients, this is not the case for immunosuppressed patients, who do not reliably respond to COVID-19 vaccines and in whom antiviral drugs may be contraindicated. It is in this population that CCP has found a critically important niche. Evidence of benefit in such patients led the United States Food and Drug Administration to limit its CCP authorization [21] to immunosuppressed patients and those on immunosuppressants, irrespective of symptom duration and/or setting (inpatient or outpatient). CCP is now recommended for immunosuppressed persons by the Infectious Diseases Society of America, the Advancement of Blood and Biotherapies, and the National Comprehensive Cancer Network.

Currently, three years into the pandemic, COVID-19 management was complicated by viral evolution. These Omicron variants are highly transmissible and the original mRNA vaccines are less effective against these than prior variants [22], which prompted development of bivalent vaccines that include an Omicron and the original spike-protein antigen. Because plasma from vaccinated and boosted persons and/or those with breakthrough Omicron infection neutralizes Omicron and prior variants [10,23], recently collected CCP is likely to neutralize circulating variants. Given that nearly all SARS-CoV-2 monoclonal antibodies in clinical use have lost or are expected to lose activity against emerging Omicron variants [24], CCP will soon be the only reliable antibody therapy for COVID-19. CCP is likely to retain activity, even as the virus continues to evolve, because of its polyclonal assortment of antibodies with a myriad of viral specificities [9]. Nonetheless, despite the effectiveness of well-qualified CCP [11,16,25], a better understanding of dosing, and the quantity, specificity, and functional activity of the most effective CCP is needed. Investment in both science and infrastructure needed to close this knowledge gap is an essential piece of pandemic preparedness that is necessary to keep up with the virus now and make it possible to rapidly deploy effective antibody therapies in the future. This is well worth the investment. No other therapeutic modality can adapt to microbial evolution or be as rapidly available.

Transparency declaration

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