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VIEWPOINTS

Guidance on the Use of Convalescent Plasma to Treat Immunocompromised Patients With Coronavirus Disease 2019

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Coronavirus disease 2019 (COVID-19) convalescent plasma (CCP) is a safe and effective treatment for COVID-19 in immunocompromised (IC) patients. IC patients have a higher risk of persistent infection, severe disease, and death from COVID-19. Despite the continued clinical use of CCP to treat IC patients, the optimal dose, frequency/schedule, and duration of CCP treatment has yet to be determined, and related best practices guidelines are lacking. A group of individuals with expertise spanning infectious diseases, virology and transfusion medicine was assembled to render an expert opinion statement pertaining to the use of CCP for IC patients. For optimal effect, CCP should be recently and locally collected to match circulating variant. CCP should be considered for the treatment of IC patients with acute and protracted COVID-19; dosage depends on clinical setting (acute vs protracted COVID-19). CCP containing high-titer severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies, retains activity against circulating SARS-CoV-2 variants, which have otherwise rendered monoclonal antibodies ineffective.

Keywords. passive immunization; plasma; antibodies; immunocompromised host.

Coronavirus disease 2019 (COVID-19) convalescent plasma (CCP) refers to plasma that has been collected from individuals who have recovered from natural severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (with or without SARS-CoV-2 vaccination) [1]. CCP has been shown to be a safe [2] and an effective treatment for COVID-19, when it contains high titers of antibodies against SARS-CoV-2 and is optimally administered early following onset of infection [3–5]. CCP played a significant role in the early public health response to COVID-19. CCP usage diminished following the advent of monoclonal antibodies (mAbs), small molecule antivirals, and—most importantly—preventive strategies (ie, effective vaccines) against COVID-19.

CCP still remains an important therapy for immunocompromised (IC) patients with COVID-19. Although IC patients are a minority (eg, comprising 2.7% of the US population [6]), they are disproportionately affected by COVID-19 [7], with a higher risk of persistent infection and an inability to clear the virus, severe disease and death, despite treatment with small molecule antivirals and/or mAbs [8]. Furthermore, successive waves of viral variants have rendered mAbs ineffective [9]. In contrast, high-titer CCP—by virtue of its polyclonal composition— retains activity against circulating SARS-CoV-2 variants [10]. In acute COVID-19, CCP may be used either in combination with antivirals or alone when alternative options are contraindicated or not readily available. CCP may also be used to treat IC patients with protracted COVID-19 [11–13].

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Despite the continued clinical use of CCP to treat IC patients with COVID-19, the optimal timing of its administration, dose, frequency/schedule, and duration of treatment has yet to be determined in IC patients, and related best practices guidelines are lacking.

A General Overview of CCP and Mechanism of Action

Early trials of CCP were disproportionately focused on hospitalized patients with advanced COVID-19, such as those with respiratory distress, hypoxemia, and/or those requiring mechanical ventilation. The findings show that CCP use in "moderate to severe disease does not reduce mortality and has little to no impact on measures of clinical improvement" [14]. By contrast, the early administration of CCP relative to symptom onset or diagnosis of COVID-19 was shown to prevent hospitalization and progression of respiratory disease in the case of outpatient use, as well as improve survival when used early relative to hospital admission [3–5]. Of note, these studies were conducted in largely immunocompetent, unvaccinated subjects with pre-alpha or alpha variant SARS-CoV-2 infection, using plasma that had been collected from donors who had recovered from COVID-19 with pre-Alpha or Alpha variant SARS-CoV-2 [3, 4, 15].

The postulated mechanisms of action of CCP include direct antiviral effects (eg, viral neutralization), viral clearance via immunoglobulin (Ig) M and IgA-mediated neutralization, non-neutralizing IgG Fc-mediated functions (eg, antibody-dependent cellular cytotoxicity, phagocytosis and complement activation) [16], and immunomodulation [17]. CCP is polyclonal, containing thousands of Spike protein-specific antibodies that not only interfere at the receptor binding domain (RBD) but also mediate virus neutralization in non-RBD regions of the Spike protein. This imparts greater durability of CCP to withstand viral evolution [10]. By contrast, mAbs are highly targeted, rendering them vulnerable to mutation: multiple mutations in variants of concern (VOC) have rendered most mAbs ineffective [18]. This risk of viral escape extends to any future mAbs unless the target(s) cannot be mutated or shielded.

Evidence of CCP Use in Immunocompromised Patients With COVID-19

IC patients are at higher risk for poor outcomes after acute COVID-19 as well as protracted COVID-19 symptoms and/or viral persistence (eg, "smoldering" COVID-19), sometimes lasting for months [8, 19].

A systematic review of CCP use in patients with innate or acquired immunosuppression [9] included three randomized clinical trials (collectively representing 214 participants), 5 matched cohort studies (n = 1560 participants) and 138 case reports or case series (n = 623 individuals). These studies were analyzed using a standard fixed effects model that compared the observed deaths among patients transfused with CCP with the expected deaths if all patients were equally at risk [9]. This meta-analysis showed an association between CCP use and a mortality benefit in hospitalized IC patients with COVID-19, and there was a high level of concordance between individual studies. Limitations of this study include its lack of individual patient data, restriction to a single outcome (ie, mortality), differences in the volume and titer of CCP used, and how IC was defined. Nonetheless, the findings from this analysis suggests that CCP is safe and may be beneficial in IC patients with COVID-19.

Numerous case series and case reports also suggest that the effect of CCP in IC patients with COVID-19 is rapid, often achieving viral clearance, improved clinical outcomes and survival [9, 20, 21]. Nonetheless, limitations of these studies (eg, the absence of randomization, a lack of controls, and susceptibility to bias) preclude their use in making a definitive recommendation for CCP.

Evaluation of CCP treatment in IC patients with protracted COVID-19 is limited to 2 case series and 1 case report [11–13]. Clinical improvement was observed in 43 of 49 patients who received CCP. All were treated with other COVID-19-specific therapies; therefore, evaluating the effect of CCP alone is impossible. Of note, 5 of the 49 patients required invasive mechanical ventilation, 4 of whom died despite transfusion of CCP. This is consistent with collective experience that there is limited—if any—clinical benefit of CCP in patients who require invasive mechanical ventilation [14].

Guidelines From Professional Societies and Regulatory Bodies

The US Food and Drug Administration (FDA) authorizes the use of CCP "for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment in either the outpatient or inpatient setting" [22]. Additionally, multiple professional societies provide guidance on CCP in IC patients. AABB (Association of Advancement of Blood and Biotherapies) "suggests CCP transfusion in addition to the usual standard of care for hospitalized patients with COVID-19 and preexisting immunosuppression" yet grades the recommendation as weak with low-certainty evidence [23]. The European conference of infections in leukemia (ECIL-9) and the National Comprehensive Cancer Network (NCCN) also recommend CCP for selected patients, notably for SARS-CoV-2 seronegative hematological patients [24]. The Infectious Diseases Society of America (IDSA) also includes high-titer CCP as a treatment option for outpatients when other options are not possible [25]. The National Institutes of Health (NIH) neither recommends for or against CCP in IC patients [26].

Definition of Immunocompromise

Immunocompromise is a broad term that encompasses a variety of clinical states in which immunity is impaired, including non-modifiable conditions, (eg, advanced age, genetic immunodeficiencies), treatable comorbidities (eg, human

immunodeficiency virus [HIV], diabetes, cancer), and iatrogenic states (eg, immunosuppressive and myeloablative therapies). The terms IC, immunosuppression, and immunodeficiency are often used interchangeably. The nature of immunocompromise is often not defined among enrolled participants in CCP trials. Further study is needed to identify which IC patients are most likely to benefit from CCP.

It is biologically plausible that IC individuals who fail to produce an appropriate antibody response to COVID-19 and/or SARS-CoV-2 vaccination are likely to benefit from the SARS-CoV-2 antibodies provided by CCP. Established high risk groups that would qualify for CCP based on this definition include—but are not limited to—organ transplant recipients, patients with auto-immune diseases treated by B-cell depleting agents, and patients with cancer diagnoses, especially those with B-cell deficiency or depletion that may be primary (eg, due to malignancy) or acquired (eg, due to treatment with B-cell depleting agents such as Rituximab) [27, 28]. Practically, these patients are likely to have a minimal or absent response to SARS-CoV-2 vaccination. Testing for the presence of SARS-CoV-2 antibodies could be used to identify suitable candidates for CCP, but there are caveats to this approach: antibody levels may wane with time, be difficult to interpret in patients who have had Evusheld prophylaxis, and may not correlate with CCP functional activity. At present, antibody testing has not been prioritized, impeding its use in clinical decision making. Despite these shortcomings, antibody levels are an objective measure of an individual's ability to mount an immune response and —in the setting of IC—are currently the best biomarker of candidacy for CCP therapy.

DOSAGE, TIMING, AND DURATION DEPEND ON THE INDICATION (Table 1)

Timing of Administration

There are 2 settings when CCP therapy should be considered for IC patients with SARS-CoV-2 infection: (1) acute symptomatic SARS-CoV-2 infection (COVID-19) when there is concern that viral clearance is unlikely (given underlying disease/immune compromise), particularly where there are contraindications to antivirals and limited or no access to effective mAbs; (2) viral persistence in the absence of acute disease (ie, protracted COVID-19), which nevertheless delays return to normal life and/or resumption of full-dose immunosuppression or chemotherapy [29]. Protracted COVID-19 is distinct from "long COVID-19" or post-COVID-19 condition.

CCP Alone or in Combination With Other Therapies

Currently, there is a paucity of data on when or how to administer CCP in concert with other therapies (ie, antiviral therapy) or to comment upon the utility of combination therapy versus CCP alone. Although optimal regimens have yet to be determined, a combination of a direct-acting antiviral plus passive antibody-based therapy (eg, CCP) may be considered for patients with persistent SARS-CoV-2 infection. These patients may not be eligible for nirmatrelvir/ritonavir and molnupiravir (ie, based on duration of symptoms) according to the criteria for emergency use authorization (EUA) in the United States. Therefore, 1 approach for consideration for inpatients with persistent SARS-CoV2 positivity and symptoms is remdesivir plus CCP (eg, 1 unit of CCP every other day × 3 units total if available), again acknowledging that the optimal regimen is unknown.

Dosage and Duration of Treatment

One to 2 units of CCP should be used to treat acute COVID-19 with continued dosing based on clinical response thereafter. In the case of persistent SARS-CoV-2 infection with very high viral loads, multiple doses should be considered at defined intervals until viral clearance is achieved. The group's recommendation acknowledges that the ideal dosage and duration of CCP treatment remains uncertain. The timing and dosage (single vs multiple units) of CCP, should depend on the

Table 1. Clinical Recommendations

Target population	• Immunocompromised patients who are expected to have delayed or inadequate immune responses to SARS-CoV-2 infection and in whom other effective options are contraindicated or are not readily available • Patient type examples: Hematologic malignancy (especially chronic lymphocytic leukemia), solid organ transplant recipients, treatment with rituximab or other anti-CD20 therapy, treatment with mycophenolate or other antimetabolite therapy, individuals who have failed to seroconvert following infection and/or vaccination
Product qualification	• Needs to contain high-titer anti-Spike antibodies against SARS-CoV-2 • Plasma obtained from individuals who have recovered from COVID-19 and also been vaccinated ("Vax-Plasma" or hybrid plasma) may be preferable to standard CCP but is not yet an approved product, at least not in the US
Initial dose	• Optimal dose is uncertain. Whenever feasible we suggest using 1–2 units so as to ensure delivery of high levels of neutralizing antibodies during a time of high viral burden • Higher doses (400–600 mL) have been employed in Europe with reported favorable outcomes [29]
Treatment duration	• Variable: Driving by clinical response and viral load measurements (eg, PCR cycle threshold)
Frequency	• The optimal frequency is unknown: Based on antibody half-life, we recommend consideration of re-dosing at 7 d as dictated by clinical and virologic response.

Abbreviations: CCP, convalescent plasma; COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

clinical situation (ie, acute symptomatic vs persistent [infection with few or no symptoms]) and response to previous treatment (eg, failure to clear the virus following treatment with mAbs and/or small molecule antivirals).

Most studies—independent of immune status—pertain to acute COVID-19 in which a dose of 1–2 units of CCP (200–300 mL per unit) has been used; that dose was based on experience with convalescent plasma prior to the COVID-19 pandemic [1]. Two units are more likely to result in detectable antibodies in the recipient than 1 unit alone [30].

Specific to the IC patient population, there is no consensus regarding optimal dosing either in the number of units or dosing frequency. In a systematic review of reported use of CCP in IC patients, the median dose was 2 units (range 1–11 units) [9]. Several cases reports have used multiple units and repeated dosing in IC patients, but there are limited data to support this practice. In the case of dosing multiple units, the risk of transfusion-associated circulatory overload should be considered if administered over short periods, given that IC patients may have concomitant comorbid disease (eg, cardiorespiratory disease and/or renal impairment); however, most patients are likely to tolerate dosages higher than 200 mL [31]. In the case of viral persistence, there is more variability in practice whereby multiple and repeat doses may be administered at different intervals, in an attempt to achieve viral clearance [29, 32].

Determination of Efficacy and Monitoring Outcomes

Monitoring of outcomes should include clinical, laboratory and imaging data; decisions to re-dose should involve an infectious diseases specialist and review of all available data.

Clinical measures include the work of breathing, respiratory rate and oxygen saturation. The radiological response is ascertained by evidence of radiological improvement such as resolution of infiltrates. Although formal laboratory assays of SARS-CoV-2 viral load are preferable when available, sequential cycle threshold (Ct) values can reveal whether CCP treatment had an effect on viral load and in so doing guide recommendations for additional CCP and/or other therapies. Although Ct values are a semi-quantitative measure of viral load and CCP effect, not all laboratories routinely report Ct values, and Ct values are not a standard (ie, approved) clinical test. Some institutions utilize Ct values in decision making; however, different platforms and lack of consistent correlation with viral loads impair interpretation and therefore professional societies have recommended against their use until more data are available. When Ct values are used, the same laboratory/platform is advisable to facilitate interpretation of the results, given the variability between polymerase chain reaction (PCR) platforms. At present, the optimal timing and frequency of Ct determination following CCP transfusion is not known, but in generally 5–7 days seems a reasonable approach for stable patients.

Research and Future Directions

Research is needed to address the knowledge gaps in each of the cited elements governing CCP use, for example, dose, frequency, duration, and monitoring, as well as the interplay between CCP, viral evolution, and the host immune responses. As a first step, we recommend that a registry of immunocompromised CCP recipients be established to obtain high quality observational data.

The US FDA has defined acceptable CCP antibody thresholds for qualification of CCP for clinical use, based on various Spike protein antibody assays [22]. At present, the FDA authorization requires a history of SARS-CoV-2 infection, with a maximum time allowed since that infection, to be eligible to donate CCP. Individuals are not eligible to donate CCP based on a history of SARS-CoV-2 vaccination alone. We recommend that the current algorithm for donor selection be revised given ample evidence that most blood donors are both convalescent and vaccinated [33]. Routine donor-based laboratory screening for SARS-CoV-2 Spike antibodies would simplify workflow considerably.

The CCP collected from individuals who have been vaccinated and recovered from natural COVID-19 [so called "VaxPlasma" or "hybrid plasma"] has 10-times greater titers of antibodies (potentially delivering more antibody neutralization with similar or less volume) against SARS-CoV-2 than standard high-titer CCP [30, 34, 35], upon which initial authorizations of CCP were granted. Moreover, "VaxPlasma" is highly effective against Omicron variants, unlike most mAbs, which have been shown to be ineffective [35–37]. Nonetheless, "VaxPlasma" or hybrid plasma is not yet an approved product and qualification requirements still need to be defined.

A fundamental challenge is the inherent variability in the composition of CCP, whereby it remains uncertain as to whether any two units are of similar dose and efficacy, even when both are collected from the same donor. This may be a contributing factor for negative findings in studies of CCP [38]. Approaches that merit investigation include pooling multiple ABO-identical units to create a more uniform (ie, refined) version of CCP, or transfusing units from different donors.

Logistical Considerations and Challenges

CCP is not being actively collected by most blood services, thus forcing reliance on old stocks of CCP, introducing several challenges. First, CCP that is in use is not temporally or geographically matched to circulating variants and, therefore, may have diminished efficacy [39]. Second, dosing is subject to the availability of CCP and any recommendation to transfuse high doses of CCP to IC patients requires the confidence that multiple units will be available. Similarly, the waning supply with a notable low representation of Group B and AB plasma could restrict CCP to A and O recipients; even if multiple doses were to be prescribed, there may not be sufficient units available.

Despite a lack of consensus on whether out-of-group plasma should be allowed, examples of how transfusion with ABO incompatible plasma could be undertaken safely, have been described [40].

CCP is optimally effective when transfused early relative to onset of symptoms or diagnosis [3, 4]. This highlights the need for rapid diagnostics, timely referral for treatment, and —ideally—capacity for outpatient transfusion (CCP is mainly being administered in an inpatient setting). There are challenges of outpatient or home administration CCP [41]. However, with at-home testing, mAbs have been administered in patients' homes to prevent hospitalization. Outpatient facilities that have been used to infuse mAbs could be repurposed for CCP transfusions, in collaboration with the local transfusion services [41]. Of note, IC patients are still at risk of disease progression despite early intervention, whereby later administration of CCP may still be beneficial, contrary to the recommendations for those who are immunocompetent.

There are inherent challenges that are especially pertinent to IC patients. These include the inability to conduct traditional randomized controlled trials in this patient population. Although formal evidence-based clinical guidelines are needed to address the oversight and approval of CCP, it is impractical to conduct new trials of CCP each time a novel variant or new CCP collection workflow arises. Instead, it is reasonable to apply in vitro data, as has occurred with the mAbs.

CONCLUSION

In summary, there is a growing body of evidence for the role of CCP in the treatment of IC patients with COVID-19. Our view is consistent with and supported by recommendations of other learned groups such as AABB, NCCN, and ECIL-9 [23, 24]. Despite knowledge gaps, our panel recommends that CCP be considered for treatment of IC patients as follows: dosing (number of units and frequency) should be tailored to the indication, for example, acute symptomatic COVID-19, protracted COVID-19 (persistent SARS-CoV-2 positivity). For IC patients with acute COVID, CCP should be considered but the role of combination therapy (ie, with antivirals) is not yet known. For patients with persistent infection, transfusion of CCP should occur at regularly scheduled intervals along with antivirals. Clinical outcomes, for example, improvement in symptoms for patients with acute and/or protracted disease, should be used to guide treatment along with Ct values when available. Finally, there are regulatory and logistical barriers to the use of CCP. Given that data show that the majority of donors are now vaccinated and/or have a history of natural SARS-CoV-2 infection, there is a case to revisit the regulatory requirements for donation and qualification of CCP, which would simplify procurement, thus improving its availability.

Notes

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