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Reply to 'Use of convalescent plasma in the treatment of COVID-19'

We appreciate the comments by Joyner and colleagues on our Review (Murakami, N. et al. Therapeutic advances in COVID-19. *Nat. Rev. Nephrol.* **19**, 38–52; 2023)[1] and the use of COVID-19 convalescent plasma (CCP) (Joyner, M. J. et al. Use of convalescent plasma in the treatment of COVID-19. *Nat. Rev. Nephrol.* https://doi.org/10.1038/s41581-023-00690-4; 2023)[2]. Although not seen in all trials of hospitalized patients, which failed to show a benefit overall with CCP, we agree that some trials included hypothesis-generating subgroup analyses that suggested a potential benefit from CCP among those with shorter duration of symptoms, those not receiving supplementary oxygen and those with negative SARS-CoV-2 serology at baseline[3,4]. However, subgroup analyses also suggested a trend towards harm in those receiving invasive mechanical ventilation on enrollment[3] and those who received CCP more than 7 days after hospitalization[4]. Nonetheless, although data among outpatients are conflicting, it remains possible that CCP provides a small benefit to unvaccinated patients who present early in their disease course, albeit with a magnitude of benefit that appears far smaller than that observed in trials of recombinant neutralizing monoclonal antibodies. These findings are not unexpected, as the latter have much higher titres of antibodies. A key challenge with CCP is that its neutralizing activity is highly variable depending on its source, and CCP is probably most useful if obtained from contemporaneous patients infected with current variants. Moreover, the magnitude of potential benefit from CCP as a treatment for early or mild disease is unclear in a period where most people, at least in high-income regions, already have immunity from vaccination or natural infection.

We agree that there is a stronger biologic rationale for use of CCP in immunocompromised patients than in the general population because they might be less able to generate a native antibody response to vaccination or infection. However, as noted in our Review[1] and by others[5], data on the use of CCP among immunocompromised patients are unfortunately sparse. Although observational studies[6,7] and limited data from subgroup analyses of trials suggest some benefit[8], high-quality data are lacking.

In summary, we agree with the NIH treatment guidelines[9] regarding use of CCP for COVID-19, which recommend against the use of CCP collected before emergence of the Omicron variant, and also among hospitalized, immunocompetent patients. These guidelines further conclude that evidence to recommend either for or against the use of CCP collected after the emergence of Omicron for immunocompromised patients and for non-hospitalized, immunocompetent patients is insufficient. Contrary to the claim by Joyner et al. that CCP has been endorsed by the IDSA, their guidelines[10] are quite similar to those of the NIH, although the IDSA acknowledges (with low certainty of evidence) a potential role for CCP in ambulatory patients at high risk for progression to severe disease but only if there are no other treatment options available. We have come a long way from the early widespread use of CCP, outside of trials and in the absence of evidence; current data suggest that most patients do not benefit from it, but potential benefits in specific subgroups warrant further study in well-designed clinical trials.

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Competing interests

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