www.CCPP19.org August 9, 2022

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Dear NIH COVID – 19 Guidelines Committee,

We read with interest the recently updated (Aug 8, 2022) inpatient(1) outpatient (2) and immunocompromised(3) treatment guidelines for COVID-19 but were disappointed to see that the NIH committee declined to issue a recommendation on COVID-19 convalescent plasma (CCP) therapy in the immunocompromised population. We remain concerned that the committee is overlooking key data on CCP efficacy, and worse, applying a double standard in light of the criteria used to recommend bebtelovimab.

Current FDA-approved CCP resumed collection in 2022 after the widespread availability of SARS-CoV-2 vaccines and the emergence of Omicron. CCP from vaccinated and convalescent donors has extremely high titers and neutralizes multiple Omicron variants of concern (4,5,6). Unlike monoclonal antibody preparations, the polyclonal antibody response in recently collected CCP effectively adapts in real time to new variants and is readily sourced given the high community prevalence of SARS-CoV-2 infections (7). Notably, these current CCP units have markedly higher SARS-CoV-2 antibody titers than the CCP units used in many of the randomized clinical trials (RCT) and observational data published over the last two years. These kinds of data – *in vitro* binding and viral neutralization – were deemed sufficient for the committee's recommendation of Bebtelovimab in the outpatient setting, even in the absence of RCT data on this product. In contrast, two well-conducted outpatient CCP RCTs (8,9) have demonstrated CCP efficacy. In view of this, it appears to us that different evidentiary standards were used to consider these two antibody-based therapies.

Data supporting CCP use in immunosuppressed - particularly B-cell depleted - patients, in inpatient and ambulatory settings, continues to emerge and have been recently summarized in a meta-analysis (10).We further note that three major societies, the IDSA, (11) the AABB, (12) and the European Conference on Infections in Leukemia (13) each recommend CCP use in immunosuppressed patients. The FDA EUA (14) explicitly endorses the use of CCP in immunosuppressed patients and patients on immunosuppressive therapy.

Relative to the threshold set for the committee's bebtelovimab recommendation, we believe there is more than sufficient evidence for the NIH to support CCP use in immunocompromised

patients and other high risk groups in accordance with the FDA authorization. In a letter from our group dated May 9. 2022 signed by dozens of prominent physicians (15) we asked the NIH to fully update and revise its CCP recommendations. Three months later, this has not happened.

Finally, beyond the rationale above, shrinking bebtelovimab supplies from the US Government (which may be exhausted by the end of August), rapid escape of mAbs by new variants, (16) non-durable responses to antivirals, and the smoldering cases (17) now seen in the immune suppressed, mean that CCP may become the only accessible antibody therapy in the near future. We ask again that the committee revisit the utility of CCP in multiple use cases and extend an offer to present the case for CCP to the committee via Zoom. The time to act is now.

Sincerely,

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www.CCPP19.org August 9, 2022

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www.CCPP19.org August 9, 2022

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www.CCPP19.org August 9, 2022

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