In the commentary[1] accompanying the Sullivan *et al.* COVID-19 convalescent plasma (CCP) trial[2], the authors assert that antibodies to human common cold coronaviruses (hCCCoV) in control plasma could have harmed control group subjects. They cite a study suggesting that hCCCoV infection biases subsequent SARS-CoV-2 responses toward non-neutralizing SARS-CoV-2 antibodies[3]. This is, however, a B cell activation phenomenon that is not applicable to passive immunization such as plasma administration. In fact, a separate patient study found lower ICU admission rates and higher survival in patients with hCCCoV infection history[4]. Based on these studies, it is instead quite possible that control plasma tends to prevent, not cause, severe COVID-19, leading Sullivan *et al.* to underestimate the beneficial effect of CCP therapy.

Given that plasma and other blood products are transfused daily in every hospital, the suggestion that normal human plasma *worsens* COVID-19 should not be made lightly. The totality of evidence from studies with and without plasma control groups is most consistent with an absolute benefit from FDA-qualified CCP, given early in disease, or to immunosuppressed patients.

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1) Estcourt L, Callum J: Convalescent Plasma for Covid-19 — Making Sense of the Inconsistencies. New Engl J Med 2022; 386;18.
2) Sullivan DJ *et al.* Early outpatient treatment for Covid-19 with convalescent plasma. N Engl J Med 2022; 386: 1700-11.
3) Lin C-Y *et al.* Pre-existing humoral immunity to human common cold coronaviruses negatively impacts the protective SARS-CoV-2 antibody response. Cell Host Microbe 2022; 30(1): 83-96.e4.
4) Sagar M *et al.* Recent endemic coronavirus infection is associated with less-severe COVID-19. J. Clin. Invest. 2021; 131(1):e143380.