The efficacy of CCP was uncertain early in the pandemic, whereby the data that supported its use were largely gleaned from observational studies of variable quality, prompting calls for clinical trials to guide practice [12]. Multiple
trials and meta-analyses have since been reported, attesting to the survival benefit of early administration (ie, relative to symptom onset) of high-titer units to patients with COVID-19 [13, 14]. By contrast, transfusion of CCP in late-stage disease has shown little benefit compared with placebo or control (eg, standard of care alone) [15, 16]. It is important to continue the ongoing randomized trials in order to fully understand the efficacy of CCP across different patient populations and settings.

Donor qualification and optimal selection of donors to ensure high-titer units of CCP remain a challenge. Certain factors have already been established, such as the association between male sex, severe disease requiring hospitalization, and advanced age with higher titers of neutralizing antibodies [17]. Neutralizing activity may be the best surrogate of functional effect, but its assessment is not amenable to high-throughput donation testing, thus forcing reliance on clinical assays. Pertinent to the current study, Girardin and colleagues [1] offer insight into the correlation with one clinical assay, the Ortho Vitros SARS-CoV-2 IgG assay, which has been used to benchmark CCP under the EUA. They also provide data on the durability of neutralizing effect.

One challenge—as acknowledged by the authors—is the neutralization assay itself, which suffers from inherent variability, limiting comparability of neutralization findings across laboratories. Similarly, the performance characteristics of the clinical assays vary [18], explaining, in part, the seemingly disparate findings across studies. For example, one group reported a decline in antibodies 3–4 months after resolution of infection [19], while another indicated that neutralizing effect remained robust at 5 months [20].

Another challenge, as highlighted by Girardin and colleagues [1], is how to meet the growing demand for CCP, while optimizing functionality within a narrow window when donor antibody titers against SARS-CoV-2 are highest. These authors suggest that there is a 6-week window (approximately 3–9 weeks after symptom onset) when recruitment would be ideal to assure collection of high-titer CCP. Unfortunately, fewer than half of donors in the study demonstrated adequate neutralizing effect approximately 3 months after initial donation. In short, it is difficult to operationalize a policy with such narrow parameters. For one, the findings suggest that repeated donation, which is foundational to safety and sustainability of the blood supply, would be time limited.

Compounding this situation, the availability of CCP will likely continue to decline as SARS-CoV-2 vaccination gains traction. Some have proposed that CCP should be collected among recently vaccinated individuals. However, questions remain unaddressed surrounding the efficacy of CCP that is collected from individuals after a vaccine-induced response and how this compares with that following natural infection. The logistics of segregating inventories accordingly are not trivial.

As Girardin and colleagues have demonstrated in the current study [1], studying CCP continues to provide invaluable insight into the immunopathogenesis of SARS-CoV-2 [21, 22]. While their findings suggest potential modification of CCP donation, refined practice may be impractical. Despite early support for CCP, collections have been comparatively static relative to demand, thus affecting reserves of CCP [10]. With evolution of policy pertaining to CCP, there have been progressively more restrictive requirements in an effort to standardize this investigational product. At the outset, many—if not most—units of CCP were transfused without determination of titers before transfusion.

With waning inventories of CCP, as would be expected, higher Ortho Vitros IgG ratios may be correlated with higher NTs, but there are insufficient donors to sustain an inventory of high-titer units alone. Clinical trials evaluating the use of CCP as postexposure prophylaxis and early outpatient treatment are currently underway. Should these show favorable effects on morbidity and mortality rates, demand for CCP could increase dramatically. It will be important for US government regulators to work with the transfusion medicine, infectious disease, and blood donor communities to ensure a sustainable model for CCP supply through the end of the pandemic.

**Notes**

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