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## Convalescent plasma – this is no time for competition

As of May 30, 2020, a randomized trial for the use of remdesivir in patients with severe coronavirus disease 2019 (COVID-19) has provided the only first-level evidence of efficacy in this infection, albeit with modest results.[1] The other therapeutic modality reported to affect mortality in patients suffering from infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the transfusion of plasma collected from donors who have recovered from the infection (convalescent plasma [CP]). Small observational studies in China[2-4]; larger studies in the United States,[5,6] including a study employing matched controls;[7] and a proof-of-concept study in Italy[8] have delivered promising results, while randomized trials have been proposed[9] or are under way.[10,11]

In tandem with the collection of CP for therapeutic use,[12] efforts are under way to collect plasma for manufacture into an immunoglobulin preparation rich in antibodies to SARS-CoV-2 (hyperimmune immunoglobulin [IG]), similar to other IGs used for prophylaxis against infections such as tetanus, hepatitis B, and other pathogens.[13] These efforts by the companies of the plasma therapeutics industry, most of whom have formed an umbrella "Plasma Alliance" to maximize plasma collection and the development of an IG.[14]

While several hyperimmune IGs are effective in prophylaxis against infectious agents, the use of these products for the treatment of infections is less well established. In recent years, only plasma-derived polyclonal IG against respiratory syncytial virus has been used therapeutically,[15] until replaced by a monoclonal antibody product.[16] Reservations exist regarding the evidence base for the efficacy of both of these therapies.[17] The efficacy of manufactured IG may be influenced by changes induced in the immunoglobulin G (IgG) subclass composition of these products by the plasma fractionation process. Changes of this kind have been reported for other IGs, and IgG3 has been shown to be particularly susceptible to depletion during fractionation.[18,19] IgG3 shows selectively enhanced potency against certain pathogens in polyclonal IGs,[20] as well as forming a substantial proportion of the neutralizing antibodies to SARS-CoV-2 generated during the infection.[21] Hence, extensive preclinical and clinical development of any anti–SARS-CoV-2 IG will be required to ensure therapeutic efficacy and equivalence to the antibody profile and clinical properties of CP.

We are therefore concerned by media reports of evolving competition for plasma donors between the two sectors collecting CP as outlined above.[22] We apprehend that potential CP donors who may approach the community blood sector for altruistic reasons may be deflected to the commercial sector through the high remuneration offered.[22] This may be accentuated during this period as the traditionally low-resource population of paid plasma donors[23] may be further augmented through the difficult economic situation, as occurred in previous economic crises.[24,25]

We propose that during the current phase of the epidemic, when 1000 of patients may benefit from CP transfusion, such a development may be detrimental to the public health. Given the previous history of hyperimmune IG, anti–SARS-CoV-2 IG may be limited to prophylaxis of groups at high risk of infection, rather than effective for treatment of patients with COVID-19 at different stages of clinical disease progression. Such a product should also be stocked in preparation for subsequent waves of the infection, particularly in the event that an efficacious prophylactic vaccine may not be widely available.

The best way forward, it seems, would be that national healthcare systems implement a structured and transparent policy that ensures continued collection and availability of therapeutic CP, coupled with a measured and regulated pace in the collection of plasma hyperimmune IG manufacturers require to validate their processes and fully characterize their products.

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## CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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