Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Commentary

Rethinking the role of COVID-19 convalescent plasma in the critically ill

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An axiom of antibody therapy for infectious diseases that dates to the early 20th century is that efficacy requires treatment early in the course of disease with preparations that contain sufficient quantities of specific immunoglobulins to mediate a biological effect [1]. This principle was validated during the COVID-19 pandemic with COVID-19 convalescent plasma (CCP) and monoclonal antibodies to SARS-CoV-2, which were found to be more effective in ambulatory patients [2,3] than inpatients [4]. Hence, the report of Chowdhry et al. [5], which suggests that some patients in intensive care units may benefit from CCP, runs counter to considerable evidence that CCP is not effective in critically ill patients. However, before going further, we must note that the Chowdhry et. al., report is an observational study in which all patients received CCP, some of which was low quality, and the data were not adjusted for other medications (e.g., corticosteroids) or patient factors. Nonetheless, the possibility that CCP could be beneficial in some critically ill patients is intriguing, because it challenges current dogma that CCP efficacy is limited to the early phase of COVID-19, and hypothesis generating, because the therapeutic armamentarium for such patients remains limited. With these caveats in mind, we consider mechanisms by which CCP could be beneficial in critically ill patients.

COVID-19 pathogenesis is characterized by an early virologic phase that results from viral infection with replication in multiple tissues, including the lungs, followed by an inflammatory phase during which the immune response to the virus can damage tissues and impair function, e.g., pulmonary inflammation that interferes with gas exchange. CCP contains antibodies to SARS-CoV-2, which are responsible for its biological activity. Its ability to neutralize SARS-CoV-2 has been known since early in the pandemic when multiple studies showed a reduction in the viral loads of patients treated with CCP, even critically ill patients in whom it did not improve outcomes or affect survival. The ability of CCP to improve patient outcomes was firmly established when knowledge of COVID-19 pathogenesis was used to select patients with short symptom durations as a proxy for the viral phase for therapy [2,3]. Antiviral effects of CCP are observed in patients with and without their own antibody responses [6] and its clinical efficacy has been demonstrated in patients who do not produce their own SARS-CoV-2 antibodies, such as those with hematological malignancy [7]. However, the benefit of CCP may not be limited to antibody neutralization as it also contains non-neutralizing antibodies and cytokines and exosomes that can mediate immunomodulatory properties [8]. Thus, it is not surprising that CCP therapy also associates with a reduction in serum markers of inflammation [9] and anti-inflammatory signatures [10] in critically ill patients. Hence, based on its ability to exert antiviral as well as anti-inflammatory activity [11], CCP could conceivably improve patient outcomes by neutralizing residual virus and reducing inflammation through a reduction in viral load and/or by dampening inflammation via anti-inflammatory cytokines or Fc-mediated antibody functional activity. While its neutralizing activity may be most prominent in the viral phase, CCP Fc-mediated antibody functions, which can dampen inflammation and enhance clearance of infected cells, could be beneficial in the viral as well as the inflammatory phase if virus is present.

A review of published clinical evidence supports the hypothesis that CCP can be beneficial in some critically ill patients with COVID-19. A propensity score-matched study that investigated CCP efficacy in patients who were treated before or after 6 days of hospital admission found a benefit of CCP in the early group, in which 40 % were mechanically ventilated [12]. In a subgroup analysis of a small (74 patient) randomized controlled (RCT) trial that used 4:1 randomization to CCP or standard plasma, there was a statistically significant reduction in mortality of patients treated with CCP who were intubated at baseline, although there were only 5 CCP- and 3 standard plasma-treated patients in this analysis [13]. Another RCT that showed an overall reduction in mortality for CCP-treated patients also included a large proportion of critically ill patients in the intensive care unit [14]. However, larger RCTs have shown no mortality benefit in mechanically ventilated or non-ventilated critically ill patients [15].

Given hints of efficacy in some studies of critically ill patients and evidence that CCP can have antiviral and anti-inflammatory effects, it is logical to posit that some patients may benefit from CCP even if they are outside the 'early' viral phase and have clinical manifestations of the inflammatory phase of COVID-19. In support of this hypothesis, a machine learning-based model (Treatment Benefit index (TBI)) that was designed to predict which patients might benefit from CCP based on their oxygen requirement and COVID-19 risk factors, identified profiles

Abbreviations: convalescent, convalescent; coronavirus, coronavirus; plasma, plasma; antibody, antibody.

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of critically ill patients in whom CCP may be beneficial [16]. Blood type, which was found to associate with CCP benefit in the Chowdhry study [5], is an optional component of the TBI. Patient heterogeneity and the many factors that affect the course of COVID-19 make the design of a prospective study of CCP in this population challenging. Nonetheless, given its excellent safety profile, such an endeavor may be worthy of consideration if disease courses like those observed at the onset of the pandemic occur again. We note that while the TBI suggests CCP may be detrimental in some critically ill patients [16], it could be used to select patients who are likely to benefit for a study.

The study of Chowdhry et al. [5] reminds us that we should not automatically dismiss the possible benefit of CCP in critically ill patients or neglect its likely anti-inflammatory activity. The latter is deserving of consideration given increasing evidence that corticosteroid therapy can be detrimental in some patients with COVID-19 [17]. The ample hints in the literature that some critically ill patients benefit from CCP, combined with biological plausibility that it mediates antiviral activity [6], including via Fc mediated functions [11,18], and dampens the inflammatory response [9], suggests that further studies of CCP in critically ill patients are warranted. However, we note that our understanding of the conditions in which CCP could be effective remains limited because our knowledge of SARS-CoV-2 pathogenesis is still evolving. Nonetheless, despite the tremendous therapeutic advances during the pandemic, the mortality of critically ill COVID-19 patients remains unacceptably high. Consequently, the identification of critically ill patients who could benefit from CCP would provide an opportunity to further reduce mortality with an agent that to date has a stellar safety profile. Although extensive real world data has identified the early phase of COVID-19 as a time when CCP is beneficial, data mining to identify patients who benefit despite being critically ill may provide clues to populations in which CCP could be formally tested in an RCT.

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