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.

patients treated with COVID-19 convalescent plasma (CCP) and patients treated with placebo.[1]

Self et al[1] hypothesized that prior trials in hospitalized patients failed to show a benefit because of the wide variability in the neutralizing activity of CCP and the inclusion of patients with established immune responses to SARS-CoV-2. PassITON used plasma that has been shown to neutralize SARS-CoV-2 and did not benefit the 30% of participants who tested seronegative at baseline. Even under these ideal conditions (neutralizing plasma; seronegative patients), no evidence of CCP benefit emerged.

But the authors also noted that the premise of CCP is that it should be used in patients who are "in the early stages of infection." Although PassITON strove to enroll and treat early, random assignment took place at a median of 8 days after symptom onset, and up to 24 hours could pass before treatment was initiated. Additionally, at baseline, 13% of participants were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 22% of participants were receiving oxygen therapy or noninvasive ventilation, and 91% of participants were receiving oxygen. Thus, despite a strong motivation to do so, PassITON was unable to reach patients early enough during the disease course for the optimal use of CCP. The findings of PassITON are also consistent with the results of the Expanded Access Program, in which the dose-response benefit of high-antibody CCP in hospitalized patients who were found in the first 3 days of illness and in unventilated patients was not found in patients who were treated later in the disease course.[2]

CCP provides its greatest benefit in outpatients, as shown by the randomized controlled trials of Libster et al[3] and Sullivan et al[4] and in subsets of hospitalized patients with lower baseline World Health Organization scores.[5] An exception to this early treatment rule likely occurs among the patients who are immunocompromised, for whom evidence of CCP utility is found even late in disease.[6]

The dependence of the value of CCP on the use-case, which has been documented in all trials reported to date, indicate the critical need for a careful planning process to guide the deployment of convalescent plasma and other forms of antibody therapy in response to the inevitable outbreaks of novel infectious diseases of the future.

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COVID-19 Convalescent Plasma and Concomitant Therapies in PassITON

To the Editor:

The Passive Immunity Trial for Our Nation (PassITON) investigators concluded in this issue of *CHEST* that treatment with COVID-19 convalescent plasma (CCP) did not improve clinical outcomes.[1] However, this conclusion, which implies that CCP is ineffective, is

potentially in error because it does not consider that approximately 80% of patients in both arms were receiving remdesivir, another antiviral therapy. Antibodies active against SARS-CoV-2 in CCP function as antivirals,[2] which means that, for most patients in PassITON, CCP was assessed as an add-on combination therapy with another antiviral agent. Hence, the absence of a favorable effect for CCP in PassITON may simply reflect an non-significant incremental effect of combination therapy rather than a shortcoming for this antibody therapy. Indeed, the Convalescent Plasma to Limit COVID-19 Complications in Hospitalized Patients (CONTAIN COVID-19)[3] and O'Donnell et al[4] trials published in 2021 demonstrated CCP efficacy in the reduction of mortality rates for patients who were hospitalized early in the pandemic before remdesivir became part of standard clinical practice. It is notable that an analogous negative result for antibody-drug combination therapy was also observed in the early antibiotic era when physicians added sulfonamides to convalescent serum to try to improve the outcome of pneumococcal pneumonia.[5] Because serum or sulfonamide monotherapy were each effective against pneumococcal pneumonia, there was likely no opportunity for improvement when they were combined.

We recognize that this trial was conducted at a time when therapeutic approaches were changing rapidly and remdesivir and corticosteroids were introduced as standard of care; investigators could not have controlled for these shifting variables while providing optimal patient care. Nevertheless, the results should be interpreted in the context of known biologic effects and published clinical experience. Given the concerns about concurrent remdesivir use, the current PassITON analyses on CCP efficacy are inconclusive.

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Response

To the Editor:

We appreciate the dialogue about the Passive Immunity Trial for Our Nation (PassITON) stimulated by letters to the editor from Casadevall and Henderson, Shoham and Focosi, and Senefeld et al. PassITON was a multicenter, blinded, placebo-controlled randomized clinical trial that evaluated the efficacy of COVID-19 convalescent plasma added to usual care among 960 adults who were hospitalized with COVID-19 at 25 hospitals in the United States.[1] Key findings from PassITON included null results for convalescent plasma compared with placebo for clinical status (illness severity on an ordinal scale) 14 days after randomization (adjusted OR, 1.04; 1/7 support interval, 0.82-1.33) and for 28-day mortality rates (adjusted OR, 1.04; 1/7 support interval, 0.69-1.58).

Casadevall and Henderson note that convalescent plasma vs placebo in PassITON was added to usual care therapies for COVID-19; thus, the trial did not provide insight into the efficacy of convalescent plasma alone in the absence of other COVID-19 treatments. In PassITON, participants were not treated with concomitant passive antibody therapies (such as anti-SARS-CoV-2 monoclonal antibodies, hyperimmunoglobulin, or open label convalescent plasma). However, PassITON participants were permitted to receive non-immunologic COVID-19