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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Letter to the Editor

Current studies of convalescent plasma therapy for COVID-19 may underestimate risk of antibody-dependent enhancement

To the Editor,

As more and more patients recover from coronavirus disease 2019 (COVID-19) in the coming weeks, convalescent plasma will become increasingly accessible as a treatment option. The first case series describing the use of convalescent plasma to treat critically-ill patients with COVID-19 showed clinical improvement and a decline in viral load in all treated patients, serving as a proof-of-concept for this strategy [1]. However, evidence from animal models of severe acute respiratory syndrome coronavirus (SARS-CoV) suggests that the role of antibodies in the pathogenesis of highly-pathogenic coronaviruses is complex. Rhesus macaques immunized with vaccines containing SARS-CoV spike protein who developed high neutralizing anti-spike titers prior to inoculation with SARS-CoV developed more severe acute lung injury (ALI) than non-immunized controls, despite having lower viral loads [2]. One possible explanation for these findings is that antibodies help to shift the burden of infection into macrophages and other immune cells, a process which has been shown to occur *in vitro* [3]. SARS-CoV infection of macrophages may then lead to changes at the transcriptional level that potentiate the exuberant and dysregulated innate immune response that typifies ALI in SARS [4].

This shift may have a greater impact on disease severity if antibodies are present early in the course of infection. Retrospective studies of SARS patients found an association between early seroconversion and ICU admission and mortality [5]. SARS-CoV-infected macaques who developed anti-spike antibodies prior to clearing the virus from their lungs were found to have more severe ALI with recruitment of pro-inflammatory macrophages compared to macaques who developed antibodies after clearing the virus [2]. Early seroconversion may have reflected development of non-neutralizing antibodies, which are known to cause antibody-dependent enhancement (ADE) in other viral infections, although even neutralizing SARS-CoV antibodies at the ACE2 receptor site can contribute to ADE in immune cells [3].

Current studies of convalescent plasma are limited by lack of representation of patients in the early phase of infection, as well as confounding from multiple concurrent therapies and small patient numbers. It is possible that ADE could result in more severe disease only in a subset of patients who are genetically susceptible, therefore, studies of convalescent plasma with small numbers of patients may underestimate the risks of paradoxical worsening in selected populations [6]. While convalescent plasma has potential to benefit a large number of patients, its overall safety and the appropriate timing of administration need further study. In the interest of avoiding harms, convalescent plasma should undergo the same rigorous scientific approach as other experimental treatments.

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Andrew B. Fleming: Writing - original draft. **Vanessa Raabe:** Writing - review & editing.

Declaration of Competing Interest

None.

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Andrew B. Fleming*, Vanessa Raabe
New York University Langone Vaccine Center and Division of Infectious Diseases & Immunology, Department of Medicine, New York University Grossman School of Medicine, New York, NY, USA
E-mail address: Andrew.fleming@nyulangone.org (A.B. Fleming).

* Corresponding author.

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