

Immunoglobulins or convalescent plasma to tackle COVID-19: buying time to save lives – current situation and perspectives

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Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), appeared in December 2019 in Wuhan, China and is now a global challenge since its rapid spread worldwide. As of 28 April 2020, there are globally 2,883,603 laboratory-confirmed cases, 198,842 confirmed deaths, and 213 countries, areas or territories with cases. The global mortality appears to be around 6.84% [1]. Published data indicate a rate of admission to an intensive care unit (ICU) of hospitalised patients for SARS-CoV-2 pneumonia of 25.9%. Moreover, 20.1% of patients developed acute respiratory distress syndrome (ARDS) [2].

At the moment, there is no effective antiviral therapy against COVID-19 for critically ill patients, nor a specific vaccine. Several pharmaceutical companies are developing vaccines, but it is estimated that it will take months to years before they are available for sale. Additionally, there are currently no approved treatments for any coronavirus disease, including COVID-19. However, several drugs are used off-label.

The mainstay of management of patients with COVID-19 is based on supportive care, i.e., antipyretics, oxygen therapy, ventilation and fluid management. Combination treatment with low-dose systematic corticosteroids and off-label therapies such as antivirals and chloroquine have been encouraged as part of the management of critical COVID-19 cases [3].

The antibody-mediated humoral response is an important tool for preventing or treating viral infections. In past epidemics, passive immunisation has been successfully employed to treat infections, in particular in clinically compromised patients. Some subsets of antibodies reduce the viral load by binding to the epitopes of the external surface of the viral particles, thus blocking the entry of the virus into the cells and viral replication. For this reason, these antibodies are defined neutralising antibodies (NAbs) [4]. These have been proved useful in several viral infections, such as Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS), and Chikungunya, Ebola and Zika virus infections [5, 6]. On the other hand, in bacterial infections antibiotics have stolen the show.

In a meta-analysis and systematic review, Mair-Jenkins J et al. demonstrated a significant reduction in viral load and mortality with use of convalescent plasma in patients with severe acute respiratory infections of viral aetiology, including those caused by coronaviruses (SARS-CoV and MERS-CoV) [7]. No evidence of serious adverse events or complications due to therapy were found, and there was limited evidence of a reduction in the use of critical care resources and the length of hospital stay. A significantly better outcome was obtained with earlier transfusion (before day 14). Moreover, during the pandemic of influenza H1N1, in Hong Kong there was evidence of the beneficial effect of convalescent plasma or hyperimmune intravenous immunoglobulin (H-IVIG) on lower respiratory tract viral load and mortality [8, 9]. During the current pandemic, Shen et al. [10] have presented a case series of five patients admitted to the ICU with COVID-19 and ARDS, in whom the infusion of convalescent plasma resulted in clinical improvement. This result gives some evidence to support the use of passive immunisation to treat COVID-19, even though trials of plasma against placebo would be certainly of help to clarify the overall effect.

To date, there are currently 935,205 patients who have recovered from COVID-19. They could represent an important resource of convalescent plasma or H-IVIG.

The use of sera from patients recovered from SARS-CoV could provide a certain degree of protection against SARS-CoV-2 infection. In fact, SARS-CoV-2 shares 74.5% genome identity with SARS-CoV, and SARS-CoV test assays have been shown to detect the presence of SARS-CoV-2 in 85% of patients about 1 week after the onset of symptoms [11]. Although the cross-neutralisation activity between these two viruses has been reported in pre-clinical studies, further studies are warranted [12–14].

Nevertheless, inherent in such a therapeutic strategy are problems and unsolved questions (table 1). First of all, there is quite a hurdle in the form of convalescent plasma collection, production and use. Several logistic difficulties have to be overcome as outlined by Roback and Guarner [15]. Protection of donors' welfare, blood safety and quality are important and must not be compromised. Secondly, treatment with human immunoglobulin during the SARS-

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Table 1: Advantages and disadvantages of the use of immunoglobulins or convalescent plasma to treat COVID-19.

PROs	CONS
High-titre specific antibodies to bind to SARS-CoV-2 and neutralise the viral particles	High costs
Possible application in critically ill patients	Burdensome logistics
Few significant secondary effects	Lack of high-quality studies, i.e., randomised controlled trials
Proved efficacy in past viral outbreaks	Lack of knowledge of the basic biology of SARS-CoV-2, including virus variability and mutations
Large pool of plasma donors due to the large number of patients recovered from COVID-19	Passive immunisation, thus a short duration of the effect

CoV-2 pandemic has been associated with a significantly increased risk of same-day thrombotic events (from 0.04 to 14.9%) [13]. Thirdly, due to the lack of full knowledge of the biology of SARS-CoV-2, including virus variability and mutations, plasma collected locally may better reflect the circulating virus in the population. Finally, the lack of high-quality studies and the need for adequate selection of donors with high neutralising antibody titres can be considered another issue.

In conclusion, during the SARS-CoV-2 pandemic different treatments are being explored and tested, in the absence of official management protocols. Some show initial promise, many have been tried out without sound biological bases. As of 28 April 2020 there have not been any published conclusive results for a specific effective agent. Before a vaccine becomes available, observational studies, pre-clinical and clinical research are warranted to shed some light on COVID-19 characteristics and possible therapies. Plasma and H-IVIG of recovered patients are a tried and tested approach that could prove helpful in the short term.

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