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Review Article

Convalescent Plasma Therapy for Coronavirus in Critically ill Patients

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***ABSTRACT*:**
Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease (COVID-19), has spurred a global health crisis. To date, there are no proven options for prophylaxis for those who have been exposed to SARS-CoV-2, nor therapy for those who develop COVID-19. Immune (i.e. "convalescent") plasma refers to plasma that is collected from individuals, following resolution of infection and development of antibodies. Passive antibody administration through transfusion of convalescent plasma may offer the only short-term strategy to confer immediate immunity to susceptible individuals. Convalescent plasma has also been used in the COVID-19 pandemic; limited data from China suggest clinical benefit, including radiological resolution, reduction in viral loads and improved survival. Globally, blood centers have robust infrastructure to undertake collections and construct inventories of convalescent plasma to meet the growing demand. Nonetheless, there are nuanced challenges, both regulatory and logistical, spanning donor eligibility, donor recruitment, collections and transfusion itself.
Keywords Coronavirus, Convalescent plasma therapy, neutralizing antibodies.

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INTRODUCTION

Convalescent blood product therapy has been introduced since early 1900s to treat emerging infectious disease based on the evidence that polyclonal neutralizing antibodies can reduce duration of viremia. Recent large outbreaks of viral diseases for whom effective antivirals or vaccines are still lacking has revamped the interest in convalescent plasma as life-saving treatments. Recent viruses with pandemic potential include flaviviruses (e.g. West Nile virus, dengue virus, Zika virus), chikungunya virus, influenza viruses A, e.g. H1N1, H5N1, Ebola virus, and respiratory beta coronaviruses (SARS-CoV, MERS-CoV, and SARS-CoV2). Transfusion of convalescent blood products (CBP), especially convalescent plasma (CP), are useful against emerging infectious agents if the latter induces neutralizing antibodies.[1]

Since December 2019, a pneumonia associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), named as coronavirus disease 2019 (COVID-19) by World Health Organization (WHO), emerged in Wuhan, China.[2] The epidemic spread rapidly worldwide within 3 months and was characterized as a pandemic by WHO on March 11, 2020. As of April 16th, 2020, a total of 20,83,913 confirmed cases and 1,34,658 deaths had been reported worldwide and the count is still up as each day passes on. Currently, there are no approved specific antiviral agents targeting the novel virus, while some drugs are still under investigation, including Remdesivir and Lopinavir/Ritonavir.[3] Moreover, the corticosteroid treatment for COVID-19 lung injury remains controversial, due to delayed clearance of viral infection and complications.[4] Since the effective vaccine and specific antiviral medicines are unavailable, it is an urgent need to look for an alternative strategy for COVID-19 treatment, especially among severe patients.[5]

A meta-analysis from 32 studies of SARS coronavirus infection and severe influenza showed a statistically significant reduction in the pooled odds of mortality following CP therapy, compared with placebo or no therapy (odds ratio, 0.25; 95% confidence interval, 0.14–0.45).[6] However, the CP therapy was unable to significantly improve the survival in the Ebola virus disease, probably due to the absence of data of neutralizing antibody titration for stratified analysis.[7] Since the virological and clinical characteristics share similarity among SARS, Middle East Respiratory Syndrome (MERS), and COVID-19,[8] CP therapy might be a promising treatment option for COVID-19 rescue.[9] Patients who have recovered from COVID-19 with a high neutralizing antibody titer may be a valuable donor source of CP.[5]

Ideally in plasma therapy, the donors will donate plasma by plasmapheresis, but where that is not possible, whole blood can also be collected, with plasma separation in the blood establishment. Plasma obtained by plasmapheresis should be split before freezing into 2-3 separate units (e.g. 3x200 ml). Final products should be specifically labeled as COVID-19 Convalescent Plasma/Blood and stored in a dedicated location. Any serious adverse reactions in the donor should be notified to the competent authority without delay. It is strongly recommended that defined SARS-CoV-2 neutralizing antibody titers be measured in the donated plasma. It is suggested that neutralizing antibody titers should optimally be greater than 1:320, but lower thresholds might also be effective. Clinical symptoms and laboratory parameters– according to the disease progression scale by WHO (**Table 1**) should be noted especially during transfusion, after 5 days and after discharge from the hospital.[10]

Table 1: WHO Progression scale

OMS progression scale	**Descriptor**	**Score**
Uninfected	Uninfected, No Viral RNA detected	0
Ambulatory	Asymptomatic, Viral RNA detected	1
Ambulatory	Symptomatic, Independent	2
Ambulatory	Symptomatic Assistance needed	3
Hospitalized: Mild disease	Hospitalized; no oxygen therapy	4
Hospitalized: Mild disease	Hospitalized; Oxygen by mask or nasal prongs	5
Hospitalized: Severe disease	Hospitalized; Oxygen by NIV or High flow	6
Hospitalized: Severe disease	Intubation and Mechanical Ventilation	7
Hospitalized: Severe disease	Mechanical Ventilation (conditional use of vasopressors like norepinephrine)	8
Hospitalized: Severe disease	Mechanical Ventilation+ vasopressors or Dialysis or ECMO	9
Death	Dead	10

NIV-Non-Invasive Ventilation, ECMO-Extracorporeal membrane oxygenation

DISCUSSION

Severe pneumonia caused by human coronavirus was characterized by rapid viral replication, massive inflammatory cell infiltration, and elevated proinflammatory cytokines or even cytokine storm in alveoli of lungs, resulting in acute pulmonary injury and acute respiratory distress syndrome (ARDS).[11] Recent studies on COVID-19 demonstrated that the lymphocyte counts in the peripheral blood were remarkably decreased and the levels of cytokines in the plasma from patients requiring intensive care unit (ICU) support, including IL-6, IL-10, TNF-α, and granulocyte-macrophage colony-stimulating factor, were significantly higher than in those who did not require ICU conditions.[12] CP, obtained from recovered COVID-19 patients who had established humoral immunity against the virus, contains a large quantity of neutralizing antibodies capable of neutralizing SARS-CoV-2 and eradicating the pathogen from blood circulation and pulmonary tissues.[13]

The key factors associated with CP therapy is the neutralizing antibody titer as well as efficacy. A small sample study in MERS-CoV infection showed that the neutralizing antibody titer should exceed 1:80 to achieve effective CP therapy.[14] To find eligible donors who have high levels of neutralizing antibody is a prerequisite. Cao et al. showed that the level of specific neutralizing antibody to SARS-CoV decreased gradually 4 months after the disease process, reaching undetectable levels in 25.6% (IgG) and 16.1% (neutralizing antibodies) of patients at 36 months after disease status.[15] A study from the MERS-CoV−infected patients and the exposed healthcare workers showed that the prevalence of MERS-CoV IgG sero-reactivity was very low (2.7%), and the antibodies titer decreased rapidly within 3 months.[16] These studies suggested that the neutralizing antibodies represented short lasting humoral immune response, and plasma from recently recovered patients should be more effective.[5]

Studies have shown that viral loads are highly correlated with disease severity and progression.[17] Fatal outcome of human influenza A(H5N1) has been associated with high viral load and hypercytokinemia.[18] Apart from antiviral treatment, virus specific neutralizing antibody, which could accelerate virus clearance and prevent entry into target cells, serves as the main mechanism for the restriction and clearance of the viruses by the host.[19]

Notably, a small retrospective case-comparison study (19 vs 21 patients) showed a case fatality rate reduction after convalescent plasma treatment of 23% (95% CI: 6%-42%, p=0,049)16. Each patient received 200 to 400 ml of plasma. Also, a case series including 80 treated patients reported an overall mortality rate of 12,5% in severe deteriorating SARS-CoV - infected patients while the overall SARS-related mortality rate in Hong-Kong was 17% during the SARS epidemic in 2003.[20] The mean volume of plasma infused was 279 + 127 ml (range 160-640 ml). Interestingly, a subgroup analysis found that those treated with a PCR positive but seronegative for SARS-CoV-1 has a significantly better outcome (i.e. discharge by day 22 vs after day 22 or death) than those who were seropositive at the time of plasma infusion (61% vs 21%, $p<0.001$). Similarly, those receiving convalescent plasma before (versus after) 14 days after onset of symptoms were found to have a better outcome. In multivariate analysis, the time of convalescent plasma was reported to stay significant.[21]

In a convalescent plasma trial for Ebola disease we contributed to in 2015, no serious adverse events were reported in 99 patients (minor adverse events were observed 8% of patients, mostly an increase in temperature (5%) and/or itching or skin rash (4%)). Notably, 2 case reports of possible transfusion-related acute lung injury (TRALI) following convalescent plasma have been reported in a patient with Ebola disease19 and patient with MERS-CoV20. In both cases, transfused plasma were found free of anti-HLA or anti-HNA Ab. [21]

Peak in viral load in SARS patients has been reported to coincide with the first appearance of an Ab response. In vitro, higher concentration of Ab collected from SARS-CoV(1) -infected patients (i.e. non-convalescent) facilitated SARS-CoV(1) infection and induced higher levels of virus-induced apoptosis.[22] Importantly, this phenomenon occurred via anti-spike (S) Ab that mediated ADE, but not via anti-nucleocapsid (N) Ab21,28. A possibly relevant observation is that temporal changes in S-specific and N-specific neutralizing Ab responses may differ significantly in patients who have either recovered from or succumbed to SARS-CoV(1) infection. In comparison to patients who subsequently died, recovered patients had a delayed but sustained increase in (serum) neutralizing Ab titers with an increasing contribution of anti N Ab (not observed in patients that subsequently died). Increasing Ab affinity is most probably occurring as well. Lastly, long-term persistence of robust Ab (and cytotoxic T cell responses) has been reported in patients infected with SARS CoV-1. Interestingly, very recent data in COVID-19 patients indicates seroconversion occurring after 6-12 days, but not followed by rapid decline in viral load. This later finding is compatible with a suboptimal endogenous early Ab response with regard to SARS-CoV-2 replication.[21]

CONCLUSION

COVID-19 requires urgent development of successful curative treatment modalities. Convalescent plasma may be one of them. Making such plasma available and rigorous clinical evaluation of such an approach is a priority in a number of jurisdictions.

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