Effectiveness and controversy of convalescent plasma therapy for COVID-19 patients

Since December 2019, a pneumonia associated with sever acute respiratory syndrome corona virus 2 (SARS-CoV-2), named as corona virus disease 2019 (COVID-19) by World Health Organization (WHO), emerged in Wuhan, China. The virus spread worldwide with staggering rate was announced a global pandemic by the WHO in March 2020. SARS-CoV-2 continues to spread around the world, at the beginning of November, 2020, over 50 million people have been infected, causing over 1.2 million deaths (https://coronavirus.jhu.edu/) in more than 200 countries，and these numbers continue with high speed increase .

Till today, there are still no approved specific antiviral drugs and therapies for COVID-19. Despite the efforts of scientists around the world, only a few targeted therapeutics, such as remdesivir, favipiravir, chloroquine are available to help prevent or relieve this disease, the antiviral efficacy of these drugs is not yet known. It is an urgent need to look for an alternative strategy for COVID-19 treatment, especially among severe patients. Meanwhile convalescent plasma therapy, a century-old medical treatment is being recommended as a feasible and immediate option for alleviating the suffering of this disease. Serum (plasma minus clotting factors) therapy was widely used to treat a range of infectious diseases such as scarlet fever and pneumococcal pneumonia over one hundred years. Plasma is used to treat a variety of diseases (such as hepatitis, mumps, polio, measles, rabies) and other infectious diseases (such as influenza, Argentine haemorrhagic fever, Middle East Respiratory Syndrome, Zaire ebolavirus. Most relevant and encouraging is the use of convalescent plasma during 2 previous coronavirus epidemics: severe acute respiratory syndrome (SARS) in 2003, and Middle East respiratory syndrome (MERS) in 2012. Theoretically speaking, virus specific neutralizing antibody, which could accelerate virus clearance and prevent entry into target cells, additionally alleviates hypercytokinemia. The high degree of success in achieving satisfactory clinical effects during these coronaviruses outbreaks establishes a compelling precedent and supports the notion that convalescent plasma could be a viable option for treatment of COVID-19 patients, particularly upon early administration. On account of this novel Beta coronavirus in 2019 is similar to SARS-CoV and MERS-CoV, based on its genetic proximity. There are some reasons to suppose convalescent plasma is a promising remedy for COVID-19.

The effectiveness of the convalescent plasma in COVID-19:

The convalescent plasma treatment is based on the principle of passive antibody therapy, a short-term strategy whereby antibodies from someone who recovered from an infection can be administered to protect or treat other infected patients. Antibodies are immune proteins that mark the evolution of the host humoral immune response to infection. Antibodies can be measured in a sensitive and specific manner, providing an archive that reflects recent or previous infection. If maintained at sufficiently high levels, antibodies can rapidly block infection on reexposure, conferring longer protection. Therefore, for COVID-19 patients, the expedited approach could prove lifesaving, such as improving the clinical symptoms, increasing the neutralizing antibody, decreasing the viral load even to negative, reducing the death rate, with safety and without seriously ADE. An Open-label, Expanded Access Program (EAP) initiated by Michael J and his colleagues, the results supposed that the convalescent plasma treatment induced mortality in 7 days and 30 days in patients included a high proportion of critically-ill patients. Meanwhile, the relationships between reduced mortality and both earlier time to transfusion and higher antibody levels provide signatures of efficacy for convalescent plasma in the treatment of hospitalized COVID-19 patients. In a preliminary uncontrolled case series of 5 critically-ill patients with COVID-19 and Acute Respiratory Distress Syndrome (ARDS), administration of convalescent plasma containing neutralizing antibody was followed by improvement in their clinical status. Following plasma transfusion, body temperature normalized, the sequential organ failure assessment (SOFA) score decreased, and PAO2/FIO2 increased at different times. Viral loads also decreased and became negative and neutralizing antibody titers corresponding increased following the transfusion. A similar and promising result was found in another program. A retrospective, propensity score-matched case-control study assessed the effectiveness of convalescent plasma therapy in 39 patients with severe or life-threatening COVID-19 at The Mount Sinai Hospital in New York City. Oxygen requirements on day 14 after transfusion worsened in 17.9% of plasma recipients versus 28.2% of controls who were hospitalized with COVID-19, further more survival also improved in plasma recipients. More than that no significant transfusion-related morbidity or mortality was observed in this convalescent plasma-recipient cohort, nor in a much larger national, multicenter cohort, however, potential harms are associated with plasma transfusion. Allergic reactions to plasma are typically mild and self-limited, but anaphylaxis, while rare, can occur.

The accessibility of the convalescent plasma in COVID-19:

Despite the high rate of SARS-CoV-2 infection, the relatively low

mortality rate（the mortality rate fluctuated between 0.3% and 0.66%）, high recovery rate, provides a rich pool of donors. However, potential COVID-19 donors must meet several eligibility criteria that ensure the donor has antibodies against SARS-CoV-2 and lacks the presence of other types of infections. Additionally, only plasma with high anti-SARS-CoV-2 titers of immunoglobulins G and M(IgG and IgM) are used, as determined by ELISA. The other concern is that the donors worry about antibodies in plasma be drawn and not be able to deal with re-infection. On the one hand, the level of specific neutralizing antibody decreases naturally since the half-life of antibodies. Cao and his colleagues showed that the 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. A paper about patients with the MERS-CoV and workers exposed the healthcare showed that the prevalence of MERS-CoV IgG seroreactivity was very low (2.7%), and the antibodies titers decreased sharply within 3 months. On the other hand, unlike previous studies, an Icelandic study suggested stability of SARS-CoV-2 humoral immunity. It is well known that infections and vaccines generate two waves of antibodies: the first wave is generated by early short-lived plasma cells, poised to populate the systemic circulation, but this wave subsides rapidly after resolution of acute infection. Most crucially, the second wave is generated by a smaller number of longer lived memory cells that provide long-lived immunity. So there is no need to worry too much about the decline of antibody concentration.

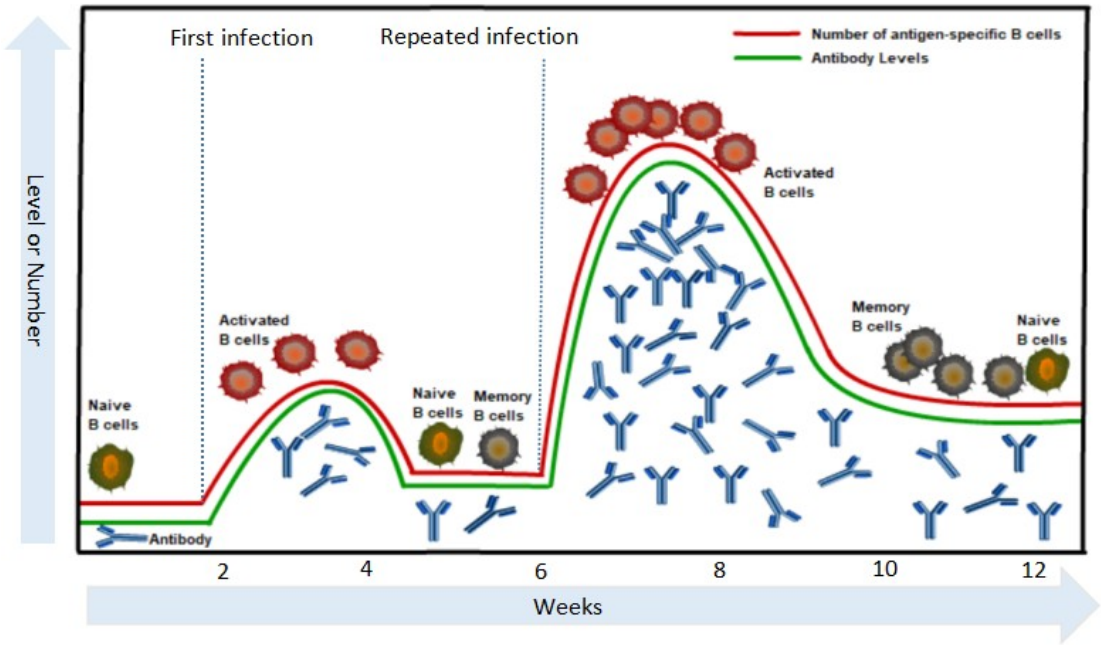

Figure1 :The number of B cells and level of antibody in first and repeated infection.

The first wave is primary immune response, naive B cell become activated, and differentiate into antibody-secreting cells that produce antibodies specific for the antigen from corona virus. Long-lived memory B cells are generated during the primary response. The second immune response is elicited when the same antigen stimulates these memory B cells, leading to rapid proliferation and differentiation and production of greater quantities of specific antibody than are produced in the primary response.

The potential deficiencies and counter measures of the convalescent plasma in COVID-19:

In the present study, even though no severe adverse effects were observed in convalescent plasma therapy, there are some potential risks and deficiencies. One theoretical complication that may arise is antibody-dependent enhancement(ADE), an antibody mediated proinflammatory disease enhancement. These antibodies from donors may aberrantly activate fragment crystallizable(Fc) or complement receptors, increasing recruitment of proinflammatory cytokines and chemokines to the site of infection and causing severe tissue damage. More than that, the presence of non-neutralizing antibodies may exacerbate viral endocytosis or phagocytosis into host cells, potentializing viral replication. However, it is clear that this phenomenon is well known with Dengue and other viral diseases, but there have not been any reported ADE cases with the use of convalescent plasma for SARS, MERS, or COVID-19. As mentioned above, the second shortcoming is that immunization with passive antibody therapy as typically of shorter-term protection, in part because of the half-life of antibodies in circulation. In spite of the convalescent plasma treatment protect patients with COVID-19 for a little time, clinically the short-term therapy may protect severe patients from critical situations by disappearance of viremia, and improved clinical symptom, and keep them out of danger. And this shortcoming may be resolved by multiple transfusions which can provide longer protection.

The third key factor associated with efficacy is the transfusion time point. A better treatment outcome was observed among SARS patients who were given convalescent plasma before day 14, highlighting the importance of timely rescue therapy. The mean time from onset of illness to convalescent plasma transfusion was day 16.5. Consistent with previous research, patients receiving plasma transfusion given before day 14 in the study showed a rapid improvement of lymphocyte counts, CRP, and remarkable absorption of lung lesions in CT. But these studies are small scale and non-randomized, the optimal transfusion time point needs further research to determine in the future. Also, for different types of patients, the dosage of transfusion should be taken into account.

Figure 2: Effectiveness, potential deficiencies and counter measures of convalescent plasma therapy.

Convalescent plasma therapy		
Effectiveness	**Potential Deficiencies**	**Counter Measures**
Improving the clinical symptoms	**Antibody-dependent enhancement**	**Transfusion timing, dosage, frequency**
Increasing the neutralizing antibody	**Antibody mediated Proinflammatory disease**	**Standard procedure for collection, preservation, transport, to transfusion.**
Decreasing the viral load	**Severe tissue damage**	
Reducing the death rate	**Potentializing viral replication**	
Normalize temperature	**Shorter-term protection**	
Decrease SOFA		
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Conclusion Facing with the seriousness and uncertainty of COVID-19 epidemic, it is pressing to pursue a more effective and systematic approach for treatment. Especially to develop convalescent plasma therapy into a more viable (albeit short-term) and more standardized treatment option for the severe even critically ill.
Meanwhile, it is urgent to perform large sample randomized controlled trials to confirm the transfusion timing, dosage, frequency and actively prevent adverse outcomes that may occur, establishing a standard procedure for treatment from convalescent plasma collection, preservation, transport, to transfusion.

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References:

1. Zhou, P., et al., *A pneumonia outbreak associated with a new coronavirus of probable bat origin*. Nature, 2020. **579**(7798): p. 270-273.
2. Beigel, J.H., K.M. Tomashek, and L.E. Dodd, *Remdesivir for the Treatment of Covid-19 - Preliminary Report. Reply.* N Engl J Med, 2020. **383**(10): p. 994.

3. Lu, H., *Drug treatment options for the 2019-new coronavirus (2019-nCoV)*. Biosci Trends, 2020. **14**(1): p. 69-71.
4. Gao, J., Z. Tian, and X. Yang, *Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies*. Biosci Trends, 2020. **14**(1): p. 72-73.
5. Casadevall, A. and L.A. Pirofski, *The convalescent sera option for containing COVID-19*. J Clin Invest, 2020. **130**(4): p. 1545-1548.
6. Montelongo-Jauregui, D., et al., *Convalescent serum therapy for COVID-19: A 19th century remedy for a 21st century disease*. PLoS Pathog, 2020. **16**(8): p. e1008735.
7. Shen, C., et al., *Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma*. JAMA, 2020. **323**(16): p. 1582-1589.
8. Luke, T.C., et al., *Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment?* Ann Intern Med, 2006. **145**(8): p. 599-609.
9. Casadevall, A., E. Dadachova, and L.A. Pirofski, *Passive antibody therapy for infectious diseases*. Nat Rev Microbiol, 2004. **2**(9): p. 695-703.
10. Hung, I.F., et al., *Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection*. Clin Infect Dis, 2011. **52**(4): p. 447-56.
11. Sahr, F., et al., *Evaluation of convalescent whole blood for treating Ebola Virus Disease in Freetown, Sierra Leone*. J Infect, 2017. **74**(3): p. 302-309.
12. Bloch, E.M., et al., *Deployment of convalescent plasma for the prevention and treatment of COVID-19*. J Clin Invest, 2020. **130**(6): p. 2757-2765.
13. de Jong, M.D., et al., *Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia*. Nat Med, 2006. **12**(10): p. 1203-7.
14. Wang, C., et al., *A human monoclonal antibody blocking SARS-CoV-2 infection*. Nat Commun, 2020. **11**(1): p. 2251.
15. Shen, C., et al., *An IgM antibody targeting the receptor binding site of influenza B blocks viral infection with great breadth and potency*. Theranostics, 2019. **9**(1): p. 210-231.
16. Lu, C.L., et al., *Enhanced clearance of HIV-1-infected cells by broadly neutralizing antibodies against HIV-1 in vivo*. Science, 2016. **352**(6288): p. 1001-4.
17. Zhu, N., et al., *A Novel Coronavirus from Patients with Pneumonia in China, 2019*. N Engl J Med, 2020. **382**(8): p. 727-733.
18. Alter, G. and R. Seder, *The Power of Antibody-Based Surveillance*. N Engl J Med, 2020. **383**(18): p. 1782-1784.
19. Joyner, M.J., et al., *Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience*. medRxiv, 2020.
20. Duan, K., et al., *Effectiveness of convalescent plasma therapy in severe COVID-19 patients*. Proc Natl Acad Sci U S A, 2020. **117**(17): p. 9490-9496.
21. Joyner, M.J., et al., *Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients*. Mayo Clin Proc, 2020. **95**(9): p. 1888-1897.
22. Joyner, M., et al., *Early Safety Indicators of COVID-19 Convalescent Plasma in 5,000 Patients*. medRxiv, 2020.
23. Liu, S.T.H., et al., *Convalescent plasma treatment of severe COVID-19: a propensity score-matched control study*. Nat Med, 2020.
24. Gudbjartsson, D.F., et al., *Humoral Immune Response to SARS-CoV-2 in Iceland*. N Engl J Med,

2020. **383**(18): p. 1724-1734.
25. Verity, R., et al., *Estimates of the severity of coronavirus disease 2019: a model-based analysis*. Lancet Infect Dis, 2020. **20**(6): p. 669-677.
26. Lai, C.C., et al., *Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges.* Int J Antimicrob Agents, 2020. **55**(3): p. 105924.
27. Epstein, J. and T. Burnouf, *Points to consider in the preparation and transfusion of COVID-19 convalescent plasma*. Vox Sang, 2020. **115**(6): p. 485-487.
28. Cao, W.C., et al., *Disappearance of antibodies to SARS-associated coronavirus after recovery.* N Engl J Med, 2007. **357**(11): p. 1162-3.
29. Arabi, Y.M., et al., *Feasibility of Using Convalescent Plasma Immunotherapy for MERS-CoV Infection, Saudi Arabia*. Emerg Infect Dis, 2016. **22**(9): p. 1554-61.
30. Cao, X., *COVID-19: immunopathology and its implications for therapy.* Nat Rev Immunol, 2020. **20**(5): p. 269-270.
31. de Alwis, R., et al., *Impact of immune enhancement on Covid-19 polyclonal hyperimmune globulin therapy and vaccine development*. EBioMedicine, 2020. **55**: p. 102768.
32. Lutz, H.U., *How immune complexes from certain IgG NAbs and any F(ab')$_2$ can mediate excessive complement activation.* Adv Exp Med Biol, 2012. **750**: p. 186-96.
33. Yip, M.S., et al., *Antibody-dependent enhancement of SARS coronavirus infection and its role in the pathogenesis of SARS.* Hong Kong Med J, 2016. **22**(3 Suppl 4): p. 25-31.
34. Tetro, J.A., *Is COVID-19 receiving ADE from other coronaviruses?* Microbes Infect, 2020. **22**(2): p. 72-73.
35. Chames, P., et al., *Therapeutic antibodies: successes, limitations and hopes for the future.* Br J Pharmacol, 2009. **157**(2): p. 220-33.
36. Cheng, Y., et al., *Use of convalescent plasma therapy in SARS patients in Hong Kong.* Eur J Clin Microbiol Infect Dis, 2005. **24**(1): p. 44-6.