Should convalescent plasma therapy be used in the treatment of critically ill patients with COVID-19?

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This rapid review summarizes the available evidence on the efficacy and safety of convalesvent plasma therapy in treating patients with COVID-19. This may change as new evidence emerges.

KEY FINDINGS

- There is insufficient evidence to support the routine use and efficacy of convalescent plasma on critically-ill patients with COVID-19 at this time.

- **Passive antibody therapy, through administration of antibodies against a specific antigen, has been previously used to provide immediate immunity to susceptible individuals against pandemic viruses such as SARS, MERS, A(H1N1) influenza, and Ebola.**
- **Based on 2 case studies and a prospective cohort with historical controls, for a total of 19 critically ill patients, there is a potential clinical improvement and with good tolerability on the use of convalescent plasma that may warrant its use in clinical trials.**
- **However, there are no studies on its long term safety profile among these patients who received the CP.**
- **Nonetheless, at present, there is insufficient evidence to support the routine use of convalescent plasma for critically-iill patients with COVID-19.**
- **Currently, there are five ongoing clinical trials on the use of convalescent plasma infusion for the treatment of COVID-19 patients**
- **The Surviving Sepsis Campaign Guidelines on the management of critically ill patients with COVID-19 recommend against the routine use of CP until more evidence is available.**

RESULTS

The two clinical series included in this review had a total of nine patients and looked into the improvement of patient outcomes with the use of CP therapy in COVID-19 patients.

In the study of Shen *et al* that looked into the clinical outcomes of five critically ill patients with severe acute respiratory distress syndrome (ARDS) after receiving CP, clinical and laboratory improvements were noted and viral loads became negative within 2 weeks after transfusion. Of the 5 patients, 3 have been discharged (LOS: 53, 51, 55 days) and 2 are in stable condition but were still on mechanical ventilation at 37 days after transfusion. The authors did not report any transfusion related adverse event [8].

In the study by Zhang et al on critically ill patients with COVID-19, all four patients showed clinical improvement and viral clearance ranging from 3 to 22 days from time of transfusion of CP. Three patients were eventually discharged from the hospital. No serious adverse reactions were noted with transfusion of CP [9].

In a prospective cohort study done by Duan *et al* that included 10 patients receiving CP compared to 10 patients as historic controls, it showed that all patients in the treatment group were either discharged or had improved clinical status, while only 1 had clinical status improvement in the historic control group ($p<0.001$). Also, in the historic control group, three patients died while six patients had stabilized status. There were no recorded serious adverse reactions or safety events after CP transfusion [6].

For the first two studies in this review, although use of CP in a critically ill patients (n = 9) with COVID-19 infection showed improvement, CP therapy was not evaluated in a randomized controlled trial and there was a lack of a control group. It was not possible to determine whether the clinical and laboratory improvements observed was indeed due to the effect of CP. All the patients were also receiving antiviral therapy and steroids at the same time, which would make it hard to tell which of the therapies actually worked [8,10]. It is also important to note that level of neutralizing antibodies in donor CP were not determined in one of the case series [9]. However, in the study by Duan et al, it had a control group but made used of historic controls with a small sample size which made the comparison of the treatment to control group likely to be biased due to lack of randomization and to the differences in the background therapy of the patients included [6].

Convalescent plasma therapy has been used and studied in previous respiratory infection outbreaks including the 2003 SARS-CoV-1 epidemic, the 2009-2010 H1N1 influenza virus pandemic, 2012 MERS-CoV epidemic and the 2014 Ebola Virus Disease. Several studies specifically prospective cohort studies and case reports on the use of CP therapy in previous outbreaks reported improved patient, clinical and laboratory outcomes [11-16]. The use of CP therapy in related viral infections showed outcomes such as early discharge (i.e. <22 days from onset of illness) in 30 patients who had 2003 SARS infection and significant reduction in mortality in the treatment group compared to the non-treatment group (20.0% vs. 54.8%, respectively; p.01) among patients with H1N1 infection. However, there were no randomized controlled trials that looked into the efficacy and safety of CP therapy in these related viral infections.

CONCLUSION

There is limited evidence regarding the efficacy and safety of convalescent plasma infusion in the treatment of COVID-19. Several clinical trials are still underway.

Declaration of Conflict of Interest

No conflict of interest

REFERENCES

1. Marano G, Vaglio S, Pupella S, et al. Convalescent plasma: new evidence for an old therapeutic tool. Blood Transfus. 2016;14(2):152-157.
2. Casadevall A, Scharff MD. Return to the past: the case for antibody-based therapies in infectious diseases. Clin Infect Dis. 1995;21(1):150-161.
3. Zhang J, Chen J, Liu Y, Zhang Z, Gao H, Liu Y et al. A serological survey on neutralizing antibody titer of SARS convalescent sera. Journal of Medical Virology. 2005;77(2):147-150.
4. Marano G, Vaglio S, Pupella S, Facco G, Catalano L, Liumbruno GM, et al. Convalescent plasma: new evidence for an old therapeutic tool? Blood Transfus 2016;14:152–7. 10.2450/2015.0131-15.
5. Garraud O, Heshmati F, Pozzetto B et al. . Plasma therapy against infectious pathogens, as of yesterday, today and tomorrow. *Transfus Clin Biol* 2016; 23:39–44.
6. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J et al. The feasibility of convalescent plasma therapy in severe COVID-19 patients: a pilot study. 2020 (unpublished).
7. Sullivan N. Antibody-Mediated Enhancement of Viral Disease. Current Topics in Microbiology and Immunology. 2001;:145-169.
8. Shen C, Wang Z, Zaho F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA. 2020 Mar 27. doi:10.1001/jama/2020/4783
9. Zhang B, L. S. (2020). Treatment with convalescent plasma for critically ill patients with SARS-CoV-2 infection. CHEST. doi:10.1016/j.chest.2020.03.039
10. Roback J, Guarner J. Convalescent Plasma to Treat COVID-19. JAMA. 27 March 2020. doi:10.1001/jama.2020.4940
11. Cheng Y, Wong R, Soo Y, Wong W, Lee C, Ng M et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. European Journal of Clinical Microbiology & Infectious Diseases. 2004;24(1):44-46.
12. Hung I, To K, Lee C, Lee K, Chan K, Yan W et al. Convalescent Plasma Treatment Reduced Mortality in Patients With Severe Pandemic Influenza A (H1N1) 2009 Virus Infection. Clinical Infectious Diseases. 2011;52(4):447-456.
13. Ko J, Seok H, Cho S, Eun Ha Y, Baek J, Kim S et al. Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single centre experience. Antiviral Therapy. 2018;23(7):617-622.
14. van Griensven J, Edwards T, de Lamballerie X, Semple M, Gallian P, Baize S et al. Evaluation of Convalescent Plasma for Ebola Virus Disease in Guinea. New England Journal of Medicine. 2016;374(1):33-42.
15. Florescu D, Kalil A, Hewlett A, Schuh A, Stroher U, Uyeki T et al. Administration of Brincidofovir and Convalescent Plasma in a Patient With Ebola Virus Disease. Clinical Infectious Diseases. 2015;61(6):969-973.
16. Mora-Rillo M, Arsuaga M, Ramírez-Olivencia G, de la Calle F, Borobia A, Sánchez-Seco P et al. Acute respiratory distress syndrome after convalescent plasma use: treatment of a patient with Ebola virus disease contracted in Madrid, Spain. 2020.
17. Alhazzani W, Møller M, Arabi Y, Loeb M, Gong M, Fan E et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Medicine. 2020;.
18. Tanne J. Covid-19: FDA approves use of convalescent plasma to treat critically ill patients. BMJ. 2020;:m1256.

Appendix 1. Characteristics of included studies

Table 1. Characteristics of Included Studies

Author, Year	Patients (n)	Intervention	Comparator	Outcomes	Study Design
Shen, 2020	Critically ill COVID-19 positive patients with ARDS (n=5)	convalescent plasma with a SARS-CoV-2–specific antibody (IgG) binding titer greater than 1:1000 and a neutralization titer greater than 40 (end point dilution titer)	None	body temperature normalized within 3 days in 4 of 5 patients, the SOFA score decreased, and PAO2/FIO2 increased within 12 days Viral loads also decreased and became negative within 12 days after the transfusion	Case series
Duan et al. 2020	Critically ill COVID-19 patients (n=10)	200 mL inactivated CP with neutralization activity >1:640 was transfused into the patients within 4 hours	Historic controls from a cohort treated in the same hospitals and matched by age, gender and severity of the diseases	level of neutralizing antibody increased up to 1:640 in five cases, while that of the other four cases maintained at a high level (1:640) no serious adverse events 0 vs 3 deaths in CP vs control group	Prospective cohort study with historical controls
Zhang et al. 2020	Critically ill SARS-CoV-2-infected patients (n = 4)	treated with supportive care and convalescent plasma.	None	Disease course of patients given convalescent plasma, no adverse events	Case series

Appendix 2. Characteristics of ongoing clinical trials

There are five ongoing clinical trials that looked into the use of convalescent plasma infusion for the treatment of COVID-19 patients (Appendix 2).

Table 2. Ongoing clinical trials for Convalescent Plasma

Clinical Trial Identifier (Location)	Official Title	Methodology	Groups	Estimated Date of Completion
NCT04321421	Plasma From Donors Recovered From New Coronavirus 2019 As Therapy For Critical Patients with COVID-19	Open label Single group Assignment Longitudinal assessment of COVID-19 patients treated with hyperimmune plasma	Experimental: treated with hyperimmune plasma	May 31, 2020
NCT04323800	Convalescent Plasma to Stem Coronavirus: A Randomized, Blinded Phase 2 Study Comparing the Efficacy and Safety Human Coronavirus Immune Plasma (HCIP) vs. Control (SARS-CoV-2) Non-immune Plasma) Among Adults Exposed to COVID-19	Randomized, double blind	Experimental: Anti SARS-CoV-2 Plasma Active Comparator: SARS-CoV-2 non-immune plasma	December 31, 2022
NCT04264858	An Exploratory Clinical Study on the Treatment of Acute Severe 2019-nCOV Pneumonia With Immunoglobulin From Cured 2019-nCOVPneumonia Patients	Non-Randomized, Open Label	Experimental: Immunoglobulin of cured patients Placebo Comparator: γ-Globulin	April 30, 2020

NCT04325672	Convalescent Plasma to Limit Coronavirus Associated Complications: An Open Label, Phase 2A Study of High-Titer Anti-SARS-COV-2 Plasma in Hospitalized Patients With COVID-19	Single Group Assignment Open Label	Experimental: Anti-SARS-CoV-2 convalescent plasma obtained from patients identified as having recovered from COVID-19 with neutralizing antibody titers >1:64	December 21, 2022
NCT04292340	The Efficacy and Safety of Anti- SARS-CoV-2 Inactivated Convalescent Plasma in the Treatment of Novel Coronavirus Pneumonia Patient (COVID-19) : An Observational Study	Observational Case only Prospective	anti-2019-nCoV inactivated convalescent plasma	July 31, 2020

Appendix 3. Search strategy and literature search

A comprehensive systematic search of related literature from two electronic databases (Medline, CENTRAL) were done. The following clinical trial registries were also searched: ISRCTN registry and ClinicalTrial.gov. Freehand search using Google was done to check for other sources of information including society guidelines and country/international health authority recommendations. UpToDate was also searched for recent information on the use of convalescent plasma infusion in the treatment of COVID-19. Table 3 summarizes the search strategy used.

Table 3. Search strategy

Database	Search strategy	Date Searched	Studies Found
Medline	(((((((((novel coronavirus[Text Word]) OR coronavirus disease 19[Text Word]) OR coronavirus disease 2019[Text Word]) OR COVID[Text Word]) OR Wuhan coronavirus[Text Word]) OR ncov[Text Word]) OR 2019-ncov[Text Word]) OR sars cov2[Text Word]) OR sars cov19[Text Word]) OR sars cov 2019[Text Word]	March 29, 2020	26 studies found for COVID-19 2 studies eligible
Medline	(((((severe acute respiratory syndrome[Text Word]) OR SARS[Text Word]) OR SARS COV1[Text Word]) OR SARS COV[Text Word])) AND ((((((passive immunotherapy[Text Word]) OR passive antibody[Text Word]) OR (((convalescen*[Text Word] AND plasma[Text Word]))))) OR (((convalescen*[Text Word] AND blood[Text Word])))) OR (((convalescen*[Text Word] AND sera[Text Word])))) OR (((convalescen*[Text Word] AND serum[Text Word]))))	March 29, 2020	174 studies found for SARS-CoV-1 1 study eligible
Medline	(((((Ebolavirus[Text Word]) OR EHF[Text Word]) OR EVD[Text Word]) OR Ebola[Text Word])) AND ((((((passive immunotherapy[Text Word]) OR passive antibody[Text Word]) OR (((convalescen*[Text Word] AND plasma[Text Word]))))) OR (((convalescen*[Text Word] AND blood[Text Word])))) OR (((convalescen*[Text Word] AND sera[Text Word])))) OR (((convalescen*[Text Word] AND serum[Text Word]))))	March 29, 2020	108 studies found for Ebola 3 studies eligible
Medline	(((((Middle East respiratory syndrome[Text Word]) OR MERS[Text Word]) OR MERS COV[Text Word]) OR camel flu[Text Word])) AND ((((((passive immunotherapy[Text Word]) OR passive antibody[Text Word]) OR (((convalescen*[Text Word] AND plasma[Text Word]))))) OR (((convalescen*[Text Word] AND blood[Text Word])))) OR (((convalescen*[Text Word] AND sera[Text Word])))) OR (((convalescen*[Text Word] AND serum[Text Word]))))	March 29, 2020	34 studies found MERS 1 study eligible
Medline	(((((((((2009 influenza[Text Word]) OR 2009 flu[Text Word]) OR ((H1N1/09 virus[Text Word]) OR H1N1/09[Text Word])) OR H1N1/09 virus[Text Word]) OR H1N1/09[Text Word]) OR A/H1N1[Text Word]) OR H1N1[Text Word]) OR swine flu[Text Word])) AND ((((((passive immunotherapy[Text Word]) OR passive antibody[Text Word]) OR (((convalescen*[Text Word] AND plasma[Text Word]))))) OR (((convalescen*[Text Word] AND blood[Text Word])))) OR (((convalescen*[Text Word] AND sera[Text Word])))) OR (((convalescen*[Text Word] AND serum[Text Word]))))	March 30, 2020	82 studies found A/H1N1 1 studies eligible

ClinicalTrial.gov	Convalescent plasma OR immunoglobulin, COVID-19	March 29, 2020	5 ongoing studies found
ISRCTN registry	Convalescent plasma OR immunoglobulin, COVID-19	March 29, 2020	0 studies found

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