European Centre for Disease Prevention and Control

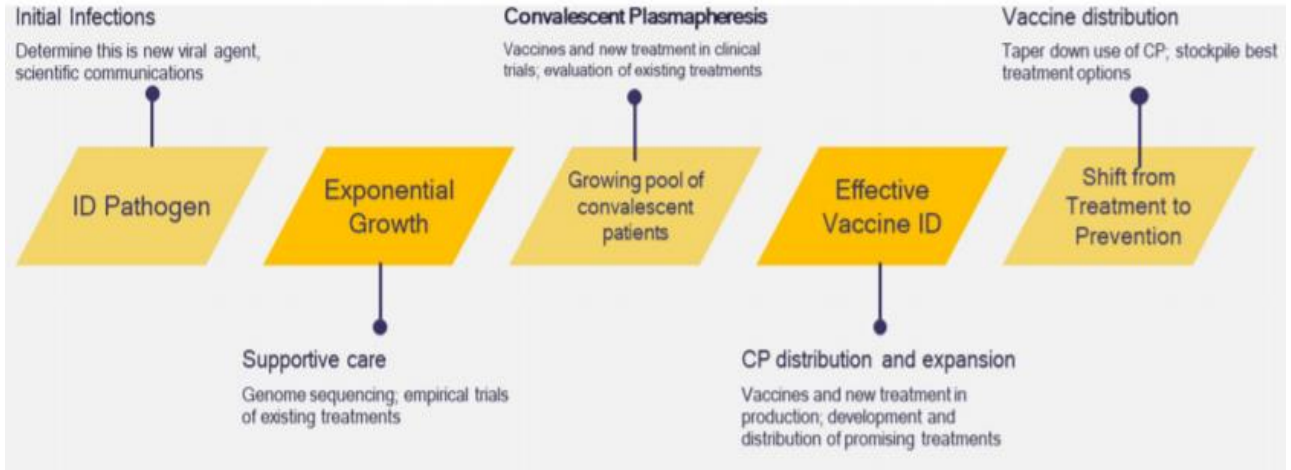
An overview of the available publications and evidence on therapeutic safety and effectiveness for COVID-19 convalescent plasma

Competent Authorities on Substances of Human Origin Expert Group (CASoHO E01718)
COVID-19 meeting of the Competent Authorities for Blood and Blood Components
17 September 2020, 13:30-18:00 Central European Time

Dragoslav Domanovic, MD, PhD,

Drivers influencing research of COVID-19 convalescent plasma therapy

- **Disease impact: pandemic spread, disease severity and mortality rate**
- **Lack of effective therapy or vaccination**
- **Historical experiences**
- **Immediate availability and growing pool of convalescent patients**
- **Promising outcomes of initial case series and animal studies**



History of convalescent plasma use for SARS and MERS

Disease	Location	Dose of CP	Titer	Summary finding
SARS1	Hong Kong, China	Mean volume 279.3 ± 127.1 mL (range, 160–640 mL)	Not performed	- Retrospective chart review of 80 patients who received CP - ~14 (range, 7–30 days) following the onset of symptoms - Good clinical outcome in 33 (41.3%) patients as defined by hospital discharge by day 22 - Improved outcome associated with early administration - No adverse events
SARS1	Taipei, Taiwan	500 mL	Serum antibody (IgG) titer was >640	- Uncontrolled case series of 3 severely ill patients - Improvement in clinical status of all 3 patients
SARS1	Hong Kong, China	200 mL	Not stated	- Case report of one patient - Improved clinical status - Other therapies also used - No adverse effect
SARS1	Shenzhen, China	2 units of 250 mL each (total 500 mL); transfused 12 hours apart	Not stated	- Letter to editor/case report of one patient - Improvement in clinical status
MERS	Seoul, South Korea	4 transfusions of CP to 3 patients; volumes not stated	PRNT negative (n = 2), 1:40 (n = 1) and 1:80 (n = 1)	- Uncertain benefit, although all 3 patients survived - ELISA IgG optical density of 1.9 predictive of PRNT titer ≥1:80 with 100% specificity
MERS	Riyadh, Saudi Arabia	2 units (250–350 mL/unit) proposed for phase 2	- Of 196 individuals with suspected or confirmed MERS-CoV: 8 (2.7%) reactive by ELISA; 6 of 8 reactive by MN. - Of 230 exposed healthcare workers: 4 (1.7%) reactive by ELISA; 3 of 4 reactive by MN.	- Feasibility study to assess proportion of convalescent donors that had antibodies against MERS-CoV - No transfusions of CP undertaken
MERS	Seoul, South Korea	250 mL	Not stated	- Case report (letter to editor) of 1 patient - Possible TRALI reported

J Clin Invest DOI: 10.1172/JCI138745

Animal model studies

SARS-CoV-1

Subbarao, K., et al., Prior infection and passive transfer of neutralizing antibody prevent replication of severe acute respiratory syndrome coronavirus in the respiratory tract of mice. J. Virol., 2004. 78(7): p. 3572-7.

- **The passive transfer of SARS-CoV-1 immune serum to naïve mice prevented virus replication in the lower respiratory tract following intranasal challenge**

SARS-CoV-2

Imai, M., et al., Syrian hamsters as a small animal model for SARS-CoV-2 infection and countermeasure development. Proc. Natl. Acad. Sci. U. S. A., 2020. 117(28): p. 1658716595.

Chan, J.F., et al., Simulation of the clinical and pathological manifestations of Coronavirus Disease 2019 (COVID-19) in golden Syrian hamster model: implications for disease pathogenesis and transmissibility. Clin. Infect. Dis., 2020.

Sun, J., et al., Generation of a Broadly Useful Model for COVID-19 Pathogenesis, Vaccination, and Treatment. Cell, 2020. 182(3): p. 734-743.e5.

- **The passive transfer of convalescent serum from infected animals could restrict viral replication in the respiratory tract of infected animals**

Desk review of the literature

- Accessed databases and search engines:
  - PubMed, Embase, medRxiv
- Observed period:
  - up to 10/09/2020
- Type of articles:
  - research articles and reviews
- Search terms:
  - COVID-19, convalescent plasma therapy, safety, effectiveness
- Language:
  - English

Published and pre-published safety and efficacy studies of COVID-19 convalescent plasma, as of 10/09/2020

Pub Med :	339 articles
Embase :	323 articles
medRxiv:	372 articles

Articles	Study type	Number
Clinical research articles	Randomized controlled study	4
	Controlled non-randomized study	4
	Retrospective matched cohort study	5
	Case series (Uncontrolled, single-arm study)	18
	Total	31
Review articles	Systematic review articles incl. meta analysis	9
	Review articles	53
	Total	62
All articles		93

Initial reports

Uncontrolled case series of COVID-19 convalescent plasma administration

- 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.
  - Beijing, China, 10 severe patients, 200 ml CCP, NTA 1:640
- Shen, C., et al., Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. JAMA, 2020. 323(16): p. 1582-1589.
  - Shenzhen, China, 5 critically ill patients, mechanical ventilation and ARDS, 2 consecutive transfusions of 200 to 250 mL NTA 1:40
- Zhang, B., et al., Treatment With Convalescent Plasma for Critically Ill Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Infection. Chest, 2020. 158(1): p. e9e13
  - Dongguan, Xiangtan, Zhongshan, China, 4 critically ill patients, 900/200/2400/300 ml CCP

Summary finding:

- **The absence of serious adverse reactions to plasma,**
- **The reduction of viral load,**
- **Improved clinical symptoms and radiographic findings**
- **CCP may be beneficial for COVID-19 patient treatment.**
- **findings limited by small size and lack of controls.**

Randomized controlled studies - summary

Author/ Country (reference)	Patients	Clinical status	Dose of CCP NTAb - titer	Summary finding
Li, L., et al. China, (1)	n=103; n=52 treatment n=51 control	Severe or critically ill	4 to 13 mL/kg	• Better clinical improvement only in the subgroup of severe CCP patients; • Higher clearance of viral load in all CCP patients; • No significant difference in the 28-day mortality; • Non severe allergic/febrile non-haemolytic reaction (n=1); • Possible severe transfusion-associated dyspnoea (n=1); • Early termination of the trial,(no cases for enrolment)- limited power
Gharbharan, A., et al. Netherlands (2)	n = 86 n = 43 treatment n = 43 control	Severe or critically ill	300 ml CCP 1:80	• The trial stopped early because they observed that antibody titers in the recipients were already high at the time of transfusion. • At the time of study stopping No difference in mortality, hospital stay or day-15 disease severity was observed although 14% of CCP patients had died and compared to 26% control that had died • The study may have been underpowered to detect statistically significant clinical benefit at study stopping.
Avendano-Sola, C., et al. Spain (3)	n = 81 n = 38 treatment n = 43 control	Severe	250-300 ml CCP >1:80,	• The trial was stopped after first interim analysis due to the fall in recruitment related to pandemic control. • No patients progressing to mechanical ventilation or death among CCP patients versus 6 out of 43(14%) control patients progressing. • Mortality rates were 0% vs 9.3% at days 15 and 29 for the active and control groups, respectively.
Agarwal A, et al. India (4)	n=464 n = 235 n = 229	Moderate	2x 200 mL of CCP, 24 hours apart, Median 1:40	• CCP was not associated with reduction in mortality or progression to severe COVID-19

Randomized controlled studies - references

1. Li, L., et al., Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial. JAMA, 2020.
2. Gharbharan, A., et al., Convalescent Plasma for COVID-19. A randomized clinical trial. medRxiv, 2020: p. 2020.07.01.20139857.
3. Avendano-Sola, C., et al. Convalescent Plasma for COVID-19: A multicenter, randomized clinical trial. medRxiv. 2020:2020.08.26.20182444.
4. Agarwal A, et al. Convalescent plasma in the management of moderate COVID-19 in India: An open-label parallel-arm phase II multicentre randomized controlled trial (PLACID Trial). medRxiv. 2020:2020.09.03.20187252.

Controlled non-randomized studies - summary

Author/ Country (reference)	Patients	Clinical status	Dose of CCP NTAb - titer	Summary finding
Rasheed, A.M., et al. **Iraq, (5)**	N=49 N= 21 treatment N=28 control	Critical	n.a. n.a.	• As compared to the control group, CCP arm showed a lower mortality, shorter length of hospital stay and better clinical improvement • Allergic reaction to plasma transfusion (n=1)
Abolghasemi, H., et al., **Iran, (6)**	N= 189 N = 115 treatment N = 74 control	Severe	500 ml repeated after 24 h n.a.	• Significantly lower mortality rate, improved clinical status, a shorter length of hospital stay, a higher proportion of discharged were observed in treatment group compared to control • Acute febrile non-haemolytic transfusion reaction (n = 1)
Xia X, et al. **China (7)**	N = 1568 N = 138 treatment N = 1430 control	Severe or critical	200 -1200 ml n.a.	• Treatment group showed significantly lower mortality, reduced viral load, better clinical and laboratory status • Better results with plasma containing a higher titres of antibodies • No serious adverse reactions to transfusion of plasma
Zeng, Q.-L., et al. **China, (8)**	N = 21 N = 6 treatment N = 15 control	Severe or critical	300 ml (200-600)	• CCP can discontinue the viral shedding and contribute longer survival duration in COVID-19 patients with respiratory failure, although it cannot reduce the mortality in critically end-stage patients. • No immediate and noticeable adverse effects were observed

Controlled non-randomized studies - references

5. Rasheed, A.M., et al., The therapeutic effectiveness of Convalescent plasma therapy on treating COVID-19 patients residing in respiratory care units in hospitals in Baghdad, Iraq. medRxiv, 2020: p. 2020.06.24.20121905.
6. Abolghasemi, H., et al., Clinical efficacy of convalescent plasma for treatment of COVID-19 infections: Results of a multicenter clinical study. Transfusion and apheresis science : official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis, 2020: p. 102875-102875.
7. Xia X, et al. Improved clinical symptoms and mortality among patients with severe or critical COVID-19 after convalescent plasma transfusion. Blood. 2020 Aug 6;136(6):755-9.
8. Zeng, Q.-L., et al., Effect of Convalescent Plasma Therapy on Viral Shedding and Survival in Patients With Coronavirus Disease 2019. The Journal of Infectious Diseases, 2020. 222(1): p. 38-43.

Retrospective matched cohort studies - summary

Author/ Country (reference)	Patients	Clinical status	Dose of CCP NTAb - titer	Summary finding
Perotti, C., et al. Italy (9)	N = 46	Moderate to severe	1-3 units 250-300 ml 1:160	• Lower mortality and improved clinical signs and laboratory parameters compared to expected data in standard care patients • Adverse reactions to plasma transfusion (n = 4) : acute febrile non-haemolytic reaction(1), allergic reaction (2), possible TRALI (1)
Liu, S.T.H., et al. USA, (10)	N = 39	Severe or critical	2 units ~ 250 ml ≥1:320	• improvements in supplemental oxygen requirements and improved survival (non-intubated patients) as compared to matched retrospectively identified control group • No adverse reactions to plasma transfusion
Hegerova, L., et al. USA, (11)	N = 20	Severe or critical	1 unit	• Improved survival if CCP given early in the course of disease • Although laboratory and respiratory parameters were improved in patients following CCP infusion, their status was similar to that of controls. • No adverse reactions to plasma transfusion
Salazar, E., et al., USA, (12)	N = 25	Severe or critical	300 ml, (2 x 300 ml one patient) 0 – 1: 1350	• Improvement in clinical status • No adverse reactions to plasma transfusion
Rogers R., et al. USA, (13)	N = 64	Severe or critical	1-2 units	• No significant difference in the risk of mortality or overall rate of hospital discharge • a subgroup of patients 65-years-old or greater who received CP demonstrated a significantly increased hospital discharge rate • A greater than expected frequency of transfusion reactions in the CP group (2.8% reaction rate observed per unit transfused).

Retrospective matched cohort studies - references

9. Perotti, C., et al., Mortality reduction in 46 severe Covid-19 patients treated with hyperimmune plasma. A proof of concept single arm multicenter interventional trial. medRxiv, 2020: p. 2020.05.26.20113373.
10. Liu, S.T.H., et al., Convalescent plasma treatment of severe COVID-19: A matched control study. medRxiv, 2020: p. 2020.05.20.20102236.
11. Hegerova, L., et al., Use of Convalescent Plasma in Hospitalized Patients with Covid-19 - Case Series. Blood, 2020.
12. Salazar, E., et al., Treatment of COVID-19 Patients with Convalescent Plasma Reveals a Signal of Significantly Decreased Mortality. Am. J. Pathol., 2020
13. Rogers R., et al. Convalescent plasma for patients with severe COVID-19: a matched cohort study. medRxiv. 2020:2020.08.18.20177402.

Case series (1) - summary

Author/ Country (reference)	Patients	Clinical status	Dose of CCP NTAb - titer	Summary finding
Hartman, W., et al. USA, (14)	N = 31	Sever to critical	n.a. n.a.	• CCP associated with clinical benefit in both the severe and life-threatening patient populations, but appears to be most beneficial when administered early in the course of disease when patients meet the criteria for severe illness. • No adverse effects of plasma transfusion
Martinez-Resendez, M.F., et al. Mexico (15)	N = 8	Critical	2 units (250 ml) n.a.	• CCP patients showed a decrease of inflammatory and cellular injury markers, pulmonary infiltrates have been significantly reduced, viral load progressively diminished over time. All patients were discharged home. • No adverse effects of plasma transfusion.
Joyner, M.J., et al.,USA, (16)	N = 5000	Sever to critical	n.a. n.a.	• The seven-day mortality rate was 14.9%. • The incidence of all serious adverse events in the first four hours after transfusion was <1% (SAE total =36; TACO =7, TRALI=11, allergic =3)
Joyner, M.J., et al.,USA, (17)	N = 20 000	Sever to critical	200 to 500 ml n.a.	• The seven-day mortality rate was 13%. • The incidence of all serious adverse events in the first four hours after transfusion was <1% (SAE total = 78, TACO =36 TRALI =21; allergic=21)
Ahn, J. Y. et al. South Korea (18)	N = 2	critical	2 units 250 ml n.a.	• Favourable outcome after the use of convalescent plasma in addition to systemic corticosteroid • No adverse effects of plasma transfusion.

Case series (1) - references

14. Hartman, W., et al. Hospitalized COVID-19 patients treated with Convalescent Plasma in a mid-size city in the midwest. medRxiv, 2020: p. 2020.06.19.20135830
15. Martinez-Resendez, M.F., et al., Initial experience in Mexico with convalescent plasma in COVID-19 patients with severe respiratory failure, a retrospective case series. medRxiv, 2020: p. 2020.07.14.20144469.
16. Joyner, M.J., et al., Early safety indicators of COVID-19 convalescent plasma in 5,000 patients. The Journal of Clinical Investigation, 2020.
17. Joyner, M.J., Bruno, K.A., Klassen, S.A., Kunze, K.L., Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients. Mayo Clin. Proc., 2020. In press.
18. Ahn, J. Y. *et al.* Use of convalescent plasma therapy in two COVID-19 patients with acute respiratory distress syndrome in Korea. *J. Korean Med. Sci.* 35, (2020).

Case series (2) - summary

Author/ Country (reference)	Patients	Clinical status	Dose of CCP NTAb - titer	Summary finding
Joyner MJ, et al. USA (19)	N = 35322	Severe or critical	1 unit	• Significantly lower mortality when plasma infused earlier in the course of disease and the gradient of mortality was related to the level of IgG antibody in the plasma
Olivares-Gazca, J. C. et al. Mexico, (20)	N = 10	Critical	n.a. n.a.	• Improved pulmonary function but not clinical status • No adverse effects of plasma transfusion.
Valentini R, et al. Argentina, (21)	N =87	Severe or critical	300-600 ml n.a.	• Improved 14 day clinical symptoms especially in severe patients • survival at 28 days after infusion was 80%; for patients who were infused with O2 support 91%, and for those treated with invasive mechanical ventilation 63% • 1 mild TACO and 1 mild allergic reaction
Jin C, et al. China, (22)	N = 6	Severe or critical	200 ml n.a.	• Improved clinical condition • No adverse effects of plasma transfusion.
Ibrahim D, et al. USA, (23)	N = 38	Severe or critical	2 x 200 ml 1:320	• CCP transfusion early in the disease course significantly lower hospital mortality 13% vs 55% ($p<0.02$) and shorten the mean hospital length of stay 15.4 vs 33 days ($p<0.01$). • One patient experienced a transient transfusion reaction.
Donato M, et al. USA, (24)	N = 47	Severe or critical	200 – 500 ml 1:500	• Significantly improved mortality, decreased viral load and improved clinical status • There was no difference in outcomes when neutralizing titres > 1:1000. • The only adverse event was a mild rash in one patient.

Case series (2) - references

19. Joyner MJ, et al. Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience. medRxiv. 2020:2020.08.12.20169359.
20. Olivares-Gazca, J. C. et al. Infusion of convalescent plasma is associated with clinical improvement in critically ill patients with COVID-19: a pilot study. Rev Invest Clin 72, 159–164 (2020).
21. Valentini R, et al. Convalescent plasma as potential therapy for severe COVID-19 pneumonia. medRxiv. 2020:2020.09.01.20184390.
22. Jin C, et al. Treatment of Six COVID-19 Patients with Convalescent Plasma. medRxiv. 2020:2020.05.21.20109512.
23. Ibrahim D, et al. Factors Associated with Good Patient Outcomes Following Convalescent Plasma in COVID-19: A Prospective Phase II Clinical Trial. medRxiv. 2020:2020.08.27.20183293 .
24. Donato M, et al. Clinical and laboratory evaluation of patients with SARS-CoV-2 pneumonia treated with high-titer convalescent plasma: a prospective study. medRxiv. 2020:2020.07.20.20156398.

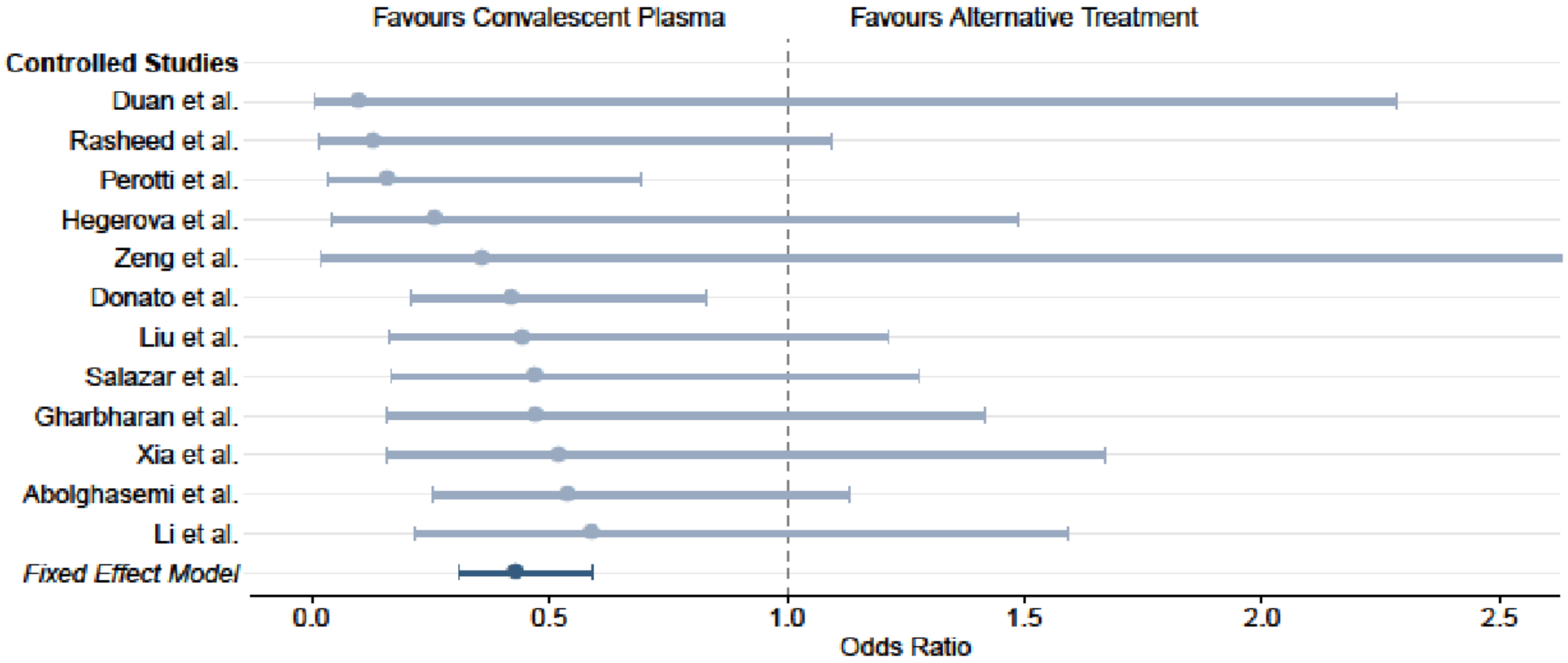
Case series (3) - summary

Author/ Country (reference)	Patients	Clinical status	Dose of CCP NTAb - titer	Summary finding
Bobek, I. et al. Hungary, (25)	N = 2	Critical	3 × 200 mL n.a.	• Oxygenation improved and inflammatory markers decreased in both individuals • No adverse effects of plasma transfusion.
Im, J. H et al. Rep. of Korea (26)	N = 1	Critical	2x 250 ml n.a.	• Clear but temporary improvement in respiratory distress and fever symptoms for 3 days after the plasma transfusion. • No adverse effects of plasma transfusion. (AB recipient and A donor)
Peng, H. et al. China, (27)	N = 1	Severe	2 x 200 ml n.a.	• The symptoms of dyspnoea improved, and the non-invasive ventilator weaned, • Possible synergistic therapeutic effect of CCP and mesenchymal cells • No adverse effects of plasma transfusion.
Xu, T., et al. China, (28)	N = 1	Critical	2 units n.a.	• No significant clinical improvement, • Effectiveness of combination therapy with CP and hydroxychloroquine may be non-optimal, • No adverse effects of plasma transfusion.
Duan, K., et al China (29)	N = 10	Severe	200 ml 1:640	• The reduction of viral load, • Improved clinical symptoms and radiographic findings • No adverse effects of plasma transfusion.
Shen, C., et al. China (30)	N = 5	Critical	2x (200 - 250 ml) 1:40	• The reduction of viral load, • Improved clinical symptoms and radiographic findings • No adverse effects of plasma transfusion.
Zhang, B., et al., China, (31)	N = 4	Critical	200 - 2400	• The reduction of viral load, • Improved clinical symptoms and radiographic findings • No adverse effects of plasma transfusion.

Case series (3) - references

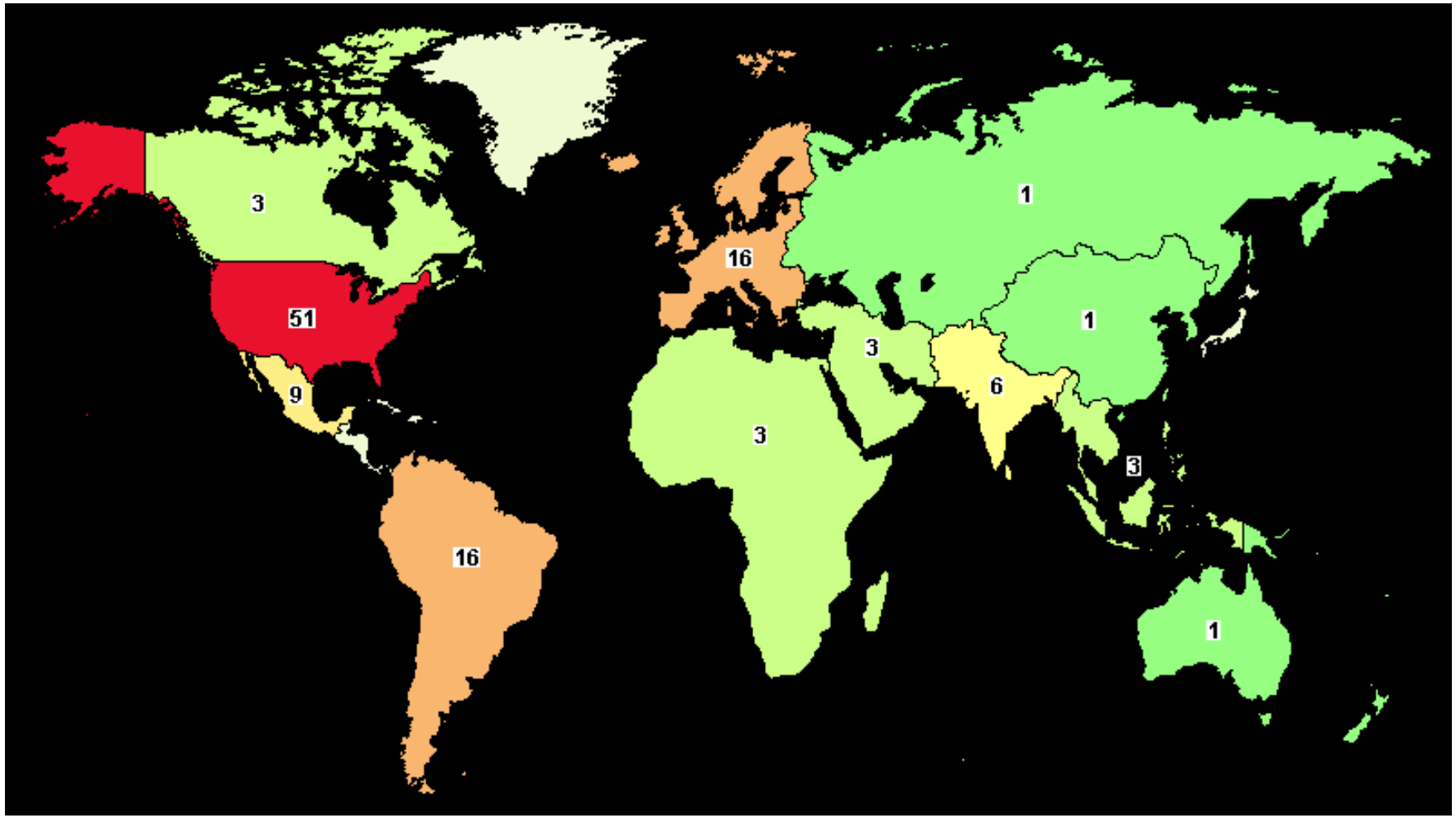
25. Bobek, I. *et al.* Successful administration of convalescent plasma in critically ill COVID-19 patients in Hungary: the first two cases. *Orv. Hetil.* 161, 1111–1121 (2020).
26. Im, J. H et al.. Convalescent plasma therapy in coronavirus disease 2019: a case report and suggestions to overcome obstacles. *J. Korean Med. Sci.* 35, (2020).
27. Peng, H. *et al.* A synergistic role of convalescent plasma and mesenchymal stem cells in the treatment of severely ill COVID-19 patients: a clinical case report. *Stem Cell Res. Ther.* 11, 1–6 (2020).
28. Xu, T., et al.. Non-optimal effectiveness of convalescent plasma transfusion and hydroxychloroquine in treating COVID-19: a case report. *Virol. J.* 17, 1–3 (2020).
29. 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.
30. Shen, C., et al., Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. JAMA, 2020. 323(16): p. 1582-1589.
31. Zhang, B., et al., Treatment With Convalescent Plasma for Critically Ill Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Infection. Chest, 2020. 158(1): p. e9e13

The effect of COVID-19 convalescent plasma on mortality – meta analysis



Joyner MJ, Klassen SA, Senefeld J, Johnson PW, Carter RE, Wiggins CC, et al. Evidence favouring the efficacy of convalescent plasma for COVID-19 therapy. medRxiv. 2020:2020.07.29.20162917.

Ongoing Registered Clinical Trials of Convalescent Plasma for COVID-19



Region Name	Number of Studies
World	121
Africa	3
East Asia	1
Europe	16
Middle East	3
North America	61
Canada	3
Mexico	9
United States	51
North Asia	1
Pacifica	1
South America	16
South Asia	6
Southeast Asia	3

Studies found for Covid-19 Convalescent plsma; Recruiting, Not yet recruiting, Available, Active, not recruiting, Enrolling by invitation, Approved for marketing - ClinicalTrials.gov

Conclusion

Results from various types of clinical trials and expanded emergency use showed no increase in the frequency of adverse effects after CCP treatment.

These studies also suggest that the transfusion of CCP containing a high titer of neutralizing antibodies is potentially effective in reducing the mortality of hospitalized patients having the moderate and severe illness, accelerating viral clearance, decreasing progression into the critical phase and shortening the hospital stay.

The evidence obtained in the randomized controlled trials is required to fully demonstrate the efficacy of CCP, and to determine the indication, dosing and optimal CCP product characteristics.