# Should convalescent plasma be used for COVID-19?

*This write-up summarises a rapid evidence review of convalescent plasma in patients with COVID-19. The information may be revised as new evidence emerges.*

## Background

Convalescent plasma is blood plasma from a person who has recovered from an infection. It contains antibodies against the infection such as SARS-CoV-2. Recovered patients with high titres of neutralising antibodies can donate plasma for administration to those at-risk to prevent infection (prophylaxis) or to those with confirmed disease to reduce symptoms and mortality.[1] This is known as passive antibody therapy or passive immunotherapy.

Convalescent plasma can be fractionated to immunoglobulin for intravenous use (IVIG), which contains concentrated globulin from pooled human plasma with the benefit that it can be given in a smaller volume and is a more uniform product compared with plasma. Hyperimmune immunoglobulin (H-IVIG) is IVIG chosen for its high titre of specific antibodies.[2]

Published articles have suggested convalescent plasma as a potential treatment option for COVID-19 citing its use and perceived efficacy in SARS, Ebola virus, H1N1, and MERS outbreaks[1,3] and international news coverage has reported that it has been used in China against COVID-19.[4-6]

The Food and Drug Administration (FDA) in the USA has listed COVID-19 convalescent plasma as an emergency Investigational New Drug (eIND) for patients who are critically ill with COVID-19.[7] This allows its use for the treatment of an individual patient upon FDA authorisation. Eligible patients must have confirmed COVID-19 with severe or immediately life-threatening disease and give informed consent. In addition, the FDA, National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) have developed guidance to coordinate collection and use of COVID-19 plasma.[8]

## Clinical evidence

The published evidence for convalescent plasma in the treatment of patients with COVID-19 is currently limited to case reports and uncontrolled studies; therefore, and as noted in a rapid Cochrane review,[9] definitive conclusions on relative efficacy and safety cannot be drawn:

- The outcomes of 26 patients who received convalescent plasma for severe or critical COVID-19 (24 in China and 2 in Korea) are documented in six articles, two of which are pre-print and non-peer reviewed.[10-15] The majority saw positive clinical improvement and were considered successful and without serious adverse events (AEs) although all patients received a variety of therapies in addition to plasma. One patient experienced serious anaphylactic shock and the transfusion was considered a failure.[13]
- Ten patients in China with severe COVID-19 received convalescent plasma along with antivirals and maximal supportive care in a single arm study. No severe AEs were observed, and secondary endpoints showed clinical improvement with undetectable viral load in seven patients with prior viremia. Better outcomes were seen in patients receiving plasma earlier.[16]
- Six patients with respiratory failure due to COVID-19 were administered convalescent plasma in China at a median of 21.5 days after first detection of viral shedding. Three days after infusion, all patients tested negative for SARS-CoV-2; however, five of the six patients died. The authors concluded that convalescent plasma therapy may inhibit viral shedding but not reduce mortality in patients with end-stage COVID-19 and that treatment should be initiated earlier.[17]
- A single arm safety study of 25 patients with COVID-19 conducted in the US, which is in preprint, stated that no AEs were observed as a result of plasma transfusion.[18]



ACE agency for care effectiveness
MINISTRY OF HEALTH SINGAPORE

- A preprint publication reviewing the safety of convalescent plasma in 5000 hospitalised patients with COVID-19 reported an incidence of serious AEs of less than 1% leading the authors to conclude in favour of its safety.[19]

Published evidence for convalescent plasma in other viral diseases show conflicting results. In SARS and severe influenza, a systematic review of low-quality, mainly uncontrolled studies of convalescent plasma showed a mortality reduction[20] and a study of H-IVIG fractionated from convalescent plasma compared with ordinary IVIG reported improvement in viral load and potential mortality benefit.[21] However, three randomised controlled trials were unable to find a benefit for H-IVIG or anti-influenza plasma over standard of care.[22-24] In Ebola virus, a case series indicated positive results[25] but a more recent study found no significant survival benefit.[26, 27]

Table 1 lists interventional trials for convalescent plasma in patients with COVID-19 which are listed on the US National Library of Medicine's register or the Chinese Clinical Trial Registry.

**Table 1: Registered studies for convalescent plasma in patients with COVID-19**

| Study identifier | Study Design | Intervention | Comparator(s) | Date of primary completion |
|---|---|---|---|---|
| NCT04292340[28] | SC,[†] observational | Anti-SARS-CoV-2 inactivated convalescent plasma | - | July 2020 |
| NCT04264858[29] | SC,[†] OL, clinical trial | Immunoglobulin of cured patients | ɣ-globulin | April 2020 |
| NCT04321421[30] | SC,[‡] OL, longitudinal assessment | Hyperimmune plasma | - | May 2020 |
| NCT04323800[31] | DB, SC,* phII, RCT | Anti-SARS-CoV-2 plasma | Non-SARS-CoV-2 immune plasma | December 2022 |
| NCT04327349[32] | OL, SC,** single arm | convalescent plasma | - | May 2020 |
| NCT04325672[33] [Withdrawn] | OL, SC,* phII, single arm | Anti-SARS-CoV-2 convalescent plasma | - | December 2022 |
| NCT04345289[34] | MC, DB, phIII, RCT (6 arms) | Convalescent plasma, sarilumab, hydroxychloroquine, baricitinib, | Injective placebo, oral placebo | June 2021 |
| NCT04345679[35] | OL, phI, SC,[H] single arm | Convalescent plasma | - | June 2020 |
| NCT04332380[36] | OL, SC,[C] phII, single arm | Convalescent plasma | - | August 2020 |
| NCT04332835[37] | OL, SC,[C] phII/III, RCT | Convalescent plasma, hydroxychloroquine, azithromycin | Hydroxychloroquine, Azithromycin | August 2020 |
| NCT04345991[38] | OL, SC,[F] phII, RCT | Convalescent plasma | Standard of care | May 2020 |
| NCT04343755[39] | OL, SC,* phII, single arm | Convalescent plasma | - | April 2021 |
| NCT04347681[40] | OL, phII, non-RCT | Convalescent plasma | - | December 2020 |
| NCT04345523[41] | MC, OL, phII, RCT | Convalescent plasma | Standard of care | July 2020 |
| NCT04340050[42] | OL, SC,* phI, single arm | Anti SARS-CoV-2 plasma | - | December 2020 |
| NCT04333355[43] | OL, phI, SC,[M] single arm | Convalescent plasma | - | December 2020 |
| NCT04342182[44] | single blind, MC,[N] phII/III, RCT | Convalescent plasma | Standard of care | July 2020 |
| NCT04343261[45] | OL, SC,* phII, single arm | Convalescent plasma | - | December 2020 |
| NCT04346589[46] | OL, SC,[‡] single arm | Anti-coronavirus antibodies (immunoglobulins) | - | July 2020 |
| NCT04344535[47] | OL, SC,* phI/II, RCT | Convalescent plasma | Standard plasma | April 2021 |
| NCT04346446[48] | OL, SC,[I] phII, RCT | Convalescent plasma | Supportive care | June 2020 |
| NCT04333251[49] | OL, phI, RCT | High-titre anti SARS-CoV-2 plasma | Best supportive care (oxygen therapy) | December 2022 |
| NCT04355897[50] | OL, SC, phI, single arm | Convalescent plasma | - | August 2020 |
| NCT04365439[51] | OL, SC, single arm | Convalescent plasma | - | May 2020 |
| NCT04372979[52] | DB, MC, phIII, RCT | Convalescent plasma | Standard plasma | October 2020 |
| NCT04353206[53] | OL, SC, phI, single arm | Convalescent plasma | - | May 2021 |
| NCT04356534[54] | OL, SC, RCT | Convalescent plasma | Standard of care | May 2020 |
| NCT04385043[55] | OL, MC, phII/III, RCT | Hyperimmune plasma | Standard therapy | October 2020 |
| NCT04374487[56] | OL, SC, phII, RCT | Convalescent plasma | Standard of care | May 2021 |

| Study identifier | Study Design | Intervention | Comparator(s) | Date of primary completion |
|---|---|---|---|---|
| NCT04390178[57] | OL, phI/II, single arm | Convalescent plasma | - | June 2020 |
| NCT04388410[58] | DB, MC, phII/III, RCT | Convalescent plasma | Placebo | October 2020 |
| NCT04384497[59] | OL, phI/II, single arm | Convalescent plasma | - | June 2020 |
| NCT04390503[60] | DB, phII, RCT | Convalescent plasma | Albumin | April 2021 |
| NCT04348656[61] | OL, MC, phIII, RCT | Convalescent plasma | Standard of care | October 2020 |
| NCT04348877[62] | OL, single arm | Convalescent plasma | - | October 2020 |
| NCT04384588[63] | OL, MC, phII/III, | Convalescent plasma | Convalescent plasma | April 2021 |
| NCT04389710[64] | OL, SC, phII, single arm | Convalescent plasma | - | April 2021 |
| NCT04354831[65] | OL, SC, phII, | Convalescent plasma | Convalescent plasma | May 2022 |
| NCT04383548[66] | OL, SC, single arm | Hyperimmunoglobulins | - | December 2020 |
| NCT04389944[67] | OL, SC, single arm | Convalescent plasma | - | June 2020 |
| NCT04380935[68] | OL, MC, phII/III, RCT | Convalescent plasma | Standard of care | August 2020 |
| NCT04373460[69] | DB, MC, phII, RCT | Convalescent plasma | Standard plasma | December 2022 |
| NCT04388527[70] | OL, phI, single arm | Convalescent plasma | - | August 2020 |
| NCT04355767[71] | DB, phII, RCT | Convalescent plasma | Standard plasma | December 2022 |
| NCT04352751[72] | OL, SC, single arm | Convalescent plasma | - | April 2021 |
| NCT04385199[73] | OL, SC, phII, RCT | Convalescent plasma | Standard therapy | August 2020 |
| NCT04375098[74] | OL, SC, phII, RCT | Convalescent plasma | Convalescent plasma | December 2020 |
| NCT04377568[75] | OL, MC, phII, RCT | Convalescent plasma | Standard of care | December 2021 |
| NCT04383535[76] | DB, MC, RCT | Convalescent plasma | Placebo | July 2020 |
| NCT04374526[77] | OL, phII/III, RCT | Convalescent plasma | Standard therapy | September 2020 |
| NCT04376788[78] | OL, SC, phII, RCT | Standard blood transfusion, Convalescent plasma, | Standard blood transfusion + convalescent plasma, | June 2020 |
| NCT04381858[79] | DB, phIII, RCT | Convalescent plasma | Human immunoglobulin | August 2020 |
| NCT04362176[80] | DB, phIII, RCT | Convalescent plasma | Ringer's solution with multivitamins | April 2021 |
| NCT04361253[81] | DB, phIII, RCT | Convalescent plasma | Standard plasma | June 2021 |
| NCT04356482[82] | OL, MC, phI/II, single arm | Convalescent plasma | - | November 2020 |
| NCT04366245[83] | OL, MC, phI/II, RCT | Hyperimmune plasma | Hydroxychloroquine + azithromycin or lopinavir/ritonavir + interferon β + hydroxychloroquine | December 2021 |
| NCT04363737[84] | DB, MC, phII, RCT | Convalescent plasma | Ringer's solution or saline | January 2023 |
| NCT04374565[85] | OL, phII, single arm | High-titre anti-SARS-CoV-2 plasma | - | April 2021 |
| NCT04357106[86] | OL, phII, single arm | Convalescent plasma | - | July 2020 |
| NCT04359810[87] | DB, phII, RCT | Convalescent plasma | Standard plasma | December 2020 |
| NCT04385186[88] | SB, MC, phII, RCT | Inactivated convalescent plasma | Support treatment | September 2020 |
| NCT04376034[89] | OL, phIII, non-randomised | Convalescent plasma | Standard of care ± convalescent plasma | March 2021 |
| NCT04377672[90] | OL, phI, single arm | Convalescent plasma | - | May 2021 |
| NCT04358783[91] | DB, phII, RCT | Convalescent plasma | Best available therapy | February 2021 |
| ChiCTR2000031501[92] | OL, SC,† non-RCT | Convalescent plasma | Routine treatment | July 2020 |
| ChiCTR2000030929[93] | DB, SC,† RCT | Convalescent plasma | Ordinary plasma | June 2020 |
| ChiCTR2000030702[94] | OL, MC,† RCT | Convalescent plasma and conventional treatment | Conventional treatment | August 2020 |
| ChiCTR2000030627[95] | SC,† RCT | Convalescent plasma and conventional treatment | Conventional treatment | May 2020 |
| ChiCTR2000030179[96] | SC,† RCT | Routine treatment plus plasma | Routine treatment | April 2020 |
| ChiCTR2000030039[97] | MC,† non-RCT | Convalescent plasma | Conventional therapy | Not stated |
| ChiCTR2000030010[98] | DB, SC,† RCT | Anti-SARS-CoV-2 inactivated convalescent plasma | Ordinary plasma | May 2020 |

| Study identifier | Study Design | Intervention | Comparator(s) | Date of primary completion |
|---|---|---|---|---|
| ChiCTR2000029850[99] | SC,† non-RCT | Convalescent plasma plus standardised comprehensive treatment | Standardised comprehensive treatment | Not stated |
| ChiCTR2000029757[100] | OL, MC,† RCT | Convalescent plasma and conventional treatment | Conventional treatment | February 2021 |
| ChiCTR2000030046[101] | OL, MC, single arm | Convalescent plasma | - | April 2020 |

Abbreviations: DB, double-blind or better; OL, open label, phI-III, phase I-III; RCT, randomised controlled trial; SARS, severe acute respiratory syndrome; SB, single blind
* USA ** Iran † China ‡ Italy F France C Colombia H Hungary I India M Mexico N Netherlands

## Recommendations from professional bodies

The World Health Organization (WHO) makes no official mention of convalescent plasma or related products specifically for COVID-19 and it does not appear in the interim clinical guidance.[102] However, Dr Mike Ryan (head of WHO health emergencies program) notes “hyperimmune globulin… has been proven “effective and life-saving” against other infectious diseases. It is a very important area to pursue [although] it has to be carefully timed and it’s not always successful.” [5]

In Singapore, the National Centre for Infectious Diseases (NCID) has issued interim treatment guidelines for COVID-19, which recommend that either hydroxychloroquine or convalescent plasma therapy be considered if contraindications exist to participation in a remdesivir trial, or to the use of lopinavir/ritonavir or interferon.[103]

The National Institutes of Health COVID-19 Treatment Guidelines (US) state there are insufficient data to recommend for or against the use of convalescent plasma or SARS-CoV-2 immune globulins for the treatment of COVID-19.[104]

The Johns Hopkins Coronavirus COVID-19 guide (US) proposes convalescent plasma as a useful treatment noting that RCTs are in progress. The guide also identifies risks including pathogen transmission, allergic reactions, transfusion-associated circulatory overload and transfusion-related lung injury.[105]

The China National Health Commission (NHC) has issued a seventh edition of guidance for COVID-19 diagnosis and treatment in which it refers to the use of recovered patients’ plasma therapy as suitable for severe and critically severe patients with rapid disease progression.[106]

COVID-19 operational recommendations from the Peking Union Medical College Hospital list early intravenous infusion of human immunoglobulin for critically ill patients based on their clinical condition.[107]

## Conclusion

There is currently limited published evidence on the use of convalescent plasma for treating COVID-19 infection although results of uncontrolled observations are promising. A range of studies are underway with data expected later this year. The best evidence to date for convalescent plasma (including H-IVIG) is for the treatment of other viral infections, however, results are variable. Positive survival benefit is based mainly on small, low-quality studies and case reports, while three RCTs in severe influenza and one in Ebola do not show any significant clinical benefit.

## References


1. Casadevall A, Pirofski L, (2020) The convalescent sera option for containing COVID-19. *J Clin Invest* 2020 Viewpoint
2. Hui DS, Lee N, Chan PK et al., (2018) The role of adjuvant immunomodulatory agents for treatment of severe influenza. *Antiviral Res* 2018 Feb; 150: 202-216
3. Chen L, Xiong J, Bao L et al., (2020) Convalescent plasma as a potential therapy for COVID-19. *Lancet Infect Dis.* 2020 Feb 27
4. Channel New Asia. (2020) Chinese doctors 'using plasma therapy' on COVID-19 patients. 2020 Feb 18. Accessed 21 March 2020 at: https://www.channelnewsasia.com/news/asia/chinese-doctors-using-plasma-therapy-on-covid-19-patients-12444244
5. Reuters (2020) Chinese doctors using plasma therapy on coronavirus, WHO says 'very valid' approach. Feb 19. Accessed 21 March 2020 at: https://www.medscape.com/viewarticle/925340
6. Nature (2020) How blood from coronavirus survivors might save lives. 24 March 2020. Accessed 25 March 2020 at: https://www.nature.com/articles/d41586-020-00895-8
7. Food and Drug Administration (FDA), USA. (2020) Investigational COVID-19 convalescent plasma – emergency INDs. Accessed 24 March 2020 at: https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds#foot
8. Food and Drug Administration (FDA), USA. (2020) Investigational COVID-19 Convalescent Plasma: Guidance for Industry. Accessed April 17 at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-covid-19-convalescent-plasma
9. Valk SJ, Piechotta V, Chai KL, et al., (2020) Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a rapid review. *Cochrane Database of Systematic Reviews* 2020, Issue 5. Art. No.: CD013600.
10. Shen C, Wang Z, Zhao F, et al., (2020) Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA*. 2020 Mar 27
11. Ahn JY, Sohn Y, Lee SH, et al., (2020) Use of Convalescent Plasma Therapy in Two COVID-19 Patients with Acute Respiratory Distress Syndrome in Korea *J Korean Med Sci*. 2020 Apr 13;35(14)
12. Zhang B, Liu S, Tan T, et al., (2020) Treatment With Convalescent Plasma for Critically Ill Patients With SARS-CoV-2 Infection *Chest* April 14
13. Pei S, Yuan X, Zhang Z, et al., (2020) PREPRINT Convalescent Plasma to Treat COVID-19: Chinese Strategy and Experiences *MedRxiv* April 16
14. Xu Y, Xu Z, Liu X, et al., (2020) PREPRINT Clinical findings in critically ill patients infected with SARS-CoV-2 in Guangdong Province, China: a multi-center, retrospective, observational study *MedRxiv* April 16
15. Ye M, Fu D, Ren Y et al., (2020) Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. *J Med Virol* Apr 15 epub
16. Duan K, Liu B, Li C, et al., (2020) Effectiveness of convalescent plasma therapy in severe COVID-19 patients *Proc Natl Acad Sci USA* 2020 April 6
17. Zeng QL, Yu ZJ, Gou JJ et al., (2020) Effect of Convalescent Plasma Therapy on Viral Shedding and Survival in COVID-19 Patients. *J Infect Dis*. April 29 epub
18. Salazar E, Peres KK, Ashraf M, et al., (2020) PREPRINT Treatment of COVID-19 Patients with Convalescent Plasma in Houston, Texas. *MedRxiv* May 13
19. Joyner M, Wright RS, Fairweather D, et al., (2020) PREPRINT Early Safety Indicators of COVID-19 Convalescent Plasma in 5,000 Patients *MedRxiv* May 14
20. Mair-Jenkins J, Saavedra-Campos M, Baillie JK et al., (2015) The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis.* 2015 Jan 1;211(1):80-90.
21. Hung IFN, To KKW, Lee CK, et al., (2013) The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *Chest*. 2013 Aug;144(2):464-473
22. Davey RT Jr, Fernández-Cruz E, Markowitz N (2019) Anti-influenza hyperimmune intravenous immunoglobulin for adults with influenza A or B infection (FLU-IVIG): a double-blind, randomised, placebo-controlled trial. *Lancet Respir Med.* Nov;7(11): 951-963.
23. Beigel JH, Tebas P, Elie-Turenne MC et al., (2017) Immune plasma for the treatment of severe influenza: an open-label, multicentre, phase 2 randomised study. *Lancet Respir Med.* 2017 Jun;5(6): 500-511.
24. Beigel JH, Aga E, Elie-Turenne MC et al., (2019) Anti-influenza immune plasma for the treatment of patients with severe influenza A: a randomised, double-blind, phase 3 trial. *Lancet Respir Med.* 2019 Nov;7(11):941-950.
25. Mupapa K, Massamba M, Kibadi K et al., (1999) Treatment of Ebola hemorrhagic fever with blood transfusions from convalescent patients. *The Journal of Infectious Diseases* 1999; 179, Suppl 1:S18-23
26. van Griensven J, Edwards T, de Lamballerie X, et al., (2016) Evaluation of Convalescent Plasma for Ebola Virus Disease in Guinea. *N Engl J Med.* 2016 Jan 7;374(1):33-42
27. van Griensven J, Edwards T, Baize S; et al., (2016) Efficacy of Convalescent Plasma in Relation to Dose of Ebola Virus Antibodies. *N Engl J Med.* 2016 Dec 8;375(23):2307-2309
28. Clinicaltrials.gov 24 March 2020 at: https://clinicaltrials.gov/ct2/show/study/NCT04292340?term=convalescent+plasma&draw=2&rank=5
29. Clinicaltrials.gov 24 March 2020 at: https://clinicaltrials.gov/ct2/show/record/NCT04264858?term=covid-19&draw=4&rank=77
30. Clinicaltrials.gov 27 March 2020 at: https://clinicaltrials.gov/ct2/show/NCT04321421?term=covid-19&draw=2&rank=26
31. Clinicaltrials.gov 1 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04323800?term=nct04323800&draw=2&rank=1
32. Clinicaltrials.gov 1 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04327349?term=nct04327349&draw=2&rank=1
33. Clinicaltrials.gov 1 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04325672?term=nct04325672&draw=2&rank=1
34. Clinicaltrials.gov 16 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04345289
35. Clinicaltrials.gov 16 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04345679?term=covid-19&draw=2
36. Clinicaltrials.gov 16 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04332380?term=covid-19&draw=2&rank=9
37. Clinicaltrials.gov 16 April 2020 at: https://clinicaltrials.gov/ct2/show/study/NCT04332835?term=covid-19&draw=2
38. Clinicaltrials.gov 16 April 2020 at: https://clinicaltrials.gov/ct2/show/record/NCT04345991?term=covid-19&draw=2
39. Clinicaltrials.gov 16 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04343755?term=covid-19&draw=2&rank=25
40. Clinicaltrials.gov 16 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04347681?term=covid-19&draw=2&rank=36
41. Clinicaltrials.gov 16 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04345523?term=covid-19&draw=2
42. Clinicaltrials.gov 16 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04340050?term=nct04340050&draw=2&rank=1
43. Clinicaltrials.gov 16 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04333355?term=covid-19&draw=2&rank=57
44. Clinicaltrials.gov 16 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04342182?term=nct04342182&draw=2&rank=1
45. Clinicaltrials.gov 16 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04343261?term=nct04343261&draw=2&rank=1
46. Clinicaltrials.gov 16 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04346589?term=nct04346589&draw=2&rank=1
47. Clinicaltrials.gov 16 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04344535?term=covid-19&draw=5&rank=362
48. Clinicaltrials.gov 16 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04346446?term=covid-19&draw=6&rank=448
49. Clinicaltrials.gov 16 April 2020 at: https://clinicaltrials.gov/ct2/show/NCT04333251?term=covid-19&draw=7&rank=539#contacts
50. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04355897?term=plasma&cond=COVID&draw=2&rank=2
51. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04365439?term=plasma&cond=COVID&draw=2&rank=8
52. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04372979?term=plasma&cond=COVID&draw=2&rank=9
53. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04353206?term=plasma&cond=COVID&draw=2&rank=12

54. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04356534?term=plasma&cond=COVID&draw=2&rank=13
55. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04385043?term=plasma&cond=COVID&draw=2&rank=15
56. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04374487?term=plasma&cond=COVID&draw=2&rank=16
57. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04390178?term=plasma&cond=COVID&draw=2&rank=17
58. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04388410?term=plasma&cond=COVID&draw=2&rank=19
59. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04384497?term=plasma&cond=COVID&draw=2&rank=20
60. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04390503?term=plasma&cond=COVID&draw=2&rank=21
61. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04348656?term=plasma&cond=COVID&draw=2&rank=23
62. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04348877?term=plasma&cond=COVID&draw=2&rank=24
63. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04384588?term=plasma&cond=COVID&draw=2&rank=25
64. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04389710?term=plasma&cond=COVID&draw=2&rank=26
65. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04354831?term=plasma&cond=COVID&draw=2&rank=28
66. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04383548?term=plasma&cond=COVID&draw=4&rank=29
67. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04389944?term=plasma&cond=COVID&draw=4&rank=31
68. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04380935?term=plasma&cond=COVID&draw=4&rank=32
69. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04373460?term=plasma&cond=COVID&draw=4&rank=33
70. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04388527?term=plasma&cond=COVID&draw=4&rank=34
71. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04355767?term=plasma&cond=COVID&draw=4&rank=36
72. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04352751?term=plasma&cond=COVID&draw=4&rank=39
73. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04385199?term=plasma&cond=COVID&draw=4&rank=40
74. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04375098?term=plasma&cond=COVID&draw=4&rank=41
75. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04377568?term=plasma&cond=COVID&draw=4&rank=44
76. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04383535?term=plasma&cond=COVID&draw=4&rank=46
77. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04374526?term=plasma&cond=COVID&draw=4&rank=47
78. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04376788?term=plasma&cond=COVID&draw=4&rank=48
79. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04381858?term=plasma&cond=COVID&draw=4&rank=49
80. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04362176?term=plasma&cond=COVID&draw=4&rank=50
81. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04361253?term=plasma&cond=COVID&draw=4&rank=51
82. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04356482?term=plasma&cond=COVID&draw=4&rank=53
83. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04366245?term=plasma&cond=COVID&draw=4&rank=54
84. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04364737?term=plasma&cond=COVID&draw=4&rank=56
85. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04374565?term=plasma&cond=COVID&draw=4&rank=58
86. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04357106?term=plasma&cond=COVID&draw=4&rank=59
87. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04359810?term=plasma&cond=COVID&draw=4&rank=61
88. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04385186?term=plasma&cond=COVID&draw=4&rank=63
89. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04376034?term=plasma&cond=COVID&draw=4&rank=66
90. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04377672?term=plasma&cond=COVID&draw=4&rank=68
91. Clinicaltrials.gov 17 May 2020 at: https://clinicaltrials.gov/ct2/show/NCT04358783?term=plasma&cond=COVID&draw=4&rank=69
92. Chinese Clinical Trial Registry 16 April 2020 at: http://www.chictr.org.cn/showprojen.aspx?proj=50254
93. Chinese Clinical Trial Registry 16 April 2020 at: http://www.chictr.org.cn/showprojen.aspx?proj=50696
94. Chinese Clinical Trial Registry 16 April 2020 at: http://www.chictr.org.cn/showprojen.aspx?proj=50537
95. Chinese Clinical Trial Registry 16 April 2020 at: http://www.chictr.org.cn/showprojen.aspx?proj=50727
96. Chinese Clinical Trial Registry 16 April 2020 at: http://www.chictr.org.cn/showprojen.aspx?proj=50059
97. Chinese Clinical Trial Registry 16 April 2020 at: http://www.chictr.org.cn/showprojen.aspx?proj=49544
98. Chinese Clinical Trial Registry 16 April 2020 at: http://www.chictr.org.cn/showprojen.aspx?proj=49777
99. Chinese Clinical Trial Registry 16 April 2020 at: http://www.chictr.org.cn/showprojen.aspx?proj=49533
100. Chinese Clinical Trial Registry 16 April 2020 at: http://www.chictr.org.cn/showprojen.aspx?proj=49081
101. Chinese Clinical Trial Registry 17 May 2020 at: http://www.chictr.org.cn/showprojen.aspx?proj=49861
102. World Health Organization (WHO) Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Interim Guidance. Accessed 23 March 2020 at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/patient-management
103. Interim Treatment Guidelines for COVID-19 (Version 1.0, 2 April 2020): National Centre for Infectious Diseases. Accessed 17 April 2020 at: https://www.ncid.sg/Health-Professionals/Diseases-and-Conditions/Documents/Treatment%20Guidelines%20for%20COVID-19%20%282%20Apr%202020%29%20-final.pdf
104. National Institutes of Health (NIH). COVID-19 Treatment Guidelines. Accessed 17 May 2020 at: https://www.covid19treatmentguidelines.nih.gov/introduction/
105. Auwaerter PG (2020). Johns Hopkins ABX Guide: Coronavirus COVID-19 (SARS-CoV-2). Accessed 17 April 2020 at: https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540747/all/Coronavirus_COVID_19__SARS_CoV_2_#4.3
106. Chinese National Health Commission (NHC) Chinese clinical Guidance for COVID-19 Pneumonia diagnosis and Treatment. Accessed 23 March 2020 at: https://www.acc.org/latest-in-cardiology/articles/2020/03/17/11/22/chinese-clinical-guidance-for-covid-19-pneumonia-diagnosis-and-treatment
107. Taisheng Li (2020) Diagnosis and clinical management of severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection: an operational recommendation of Peking Union Medical College Hospital (V2.0), Emerging Microbes & Infections, 9:1, 582-585