Technoleg Iechyd Cymru
Health Technology Wales

Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

1. Determine the quantity and quality of evidence available for a technology of interest.
2. Identify any gaps in the evidence/ongoing evidence collection.
3. Inform decisions on topics that warrant fuller assessment by Health Technology Wales.

Topic:	Plasmapheresis of convalescent plasma to confer passive immunity.
Topic exploration report number:	TER203

Introduction and aims

Health Technology Wales researchers searched for evidence on the use of convalescent plasma (CP) to confer passive immunity by plasmapheresis or other methods. Evidence of the effectiveness of CP as an intervention specifically for COVID-19 patients was of particular interest.

CP from recovered COVID-19 patients contains antibodies against SARS-CoV-2 produced by their immune system. Collecting donations of CP from recovered COVID-19 patients and transfusing this into others could confer a degree of passive immunity. This may allow the recipient time for their own immune system to develop resistance to SARS-CoV-2.

Collection of CP during whole blood donation yields approximately 250ml and the donor is unable to donate again for three months. Plasmapheresis is an alternative which removes whole blood, collecting the plasma component whilst returning the remaining blood products to the donor. This approach typically yields over 500ml and can be repeated every 2 weeks as red and white cells are not depleted in the donor and they do not risk becoming anaemic.

Summary of evidence

We did not identify any evidence specifically about the effectiveness of plasmapheresis of convalescent plasma (CP) to confer passive immunity in patients with COVID-19, however, this may be due to lack of prominent reporting regarding the plasma collection method. Broadening the evidence search to the effectiveness of CP (collected by any method) as an intervention for COVID-19 offered a range of primary and secondary evidence as well as guideline positions.

We identified a Cochrane rapid review of CP or hyperimmune immunoglobulin for COVID-19 and a systematic review of CP for COVID-19 which included seven case series and a single-arm intervention study. The authors concluded that they were very uncertain whether CP is effective for people admitted to hospital with COVID-19 this was due to the inconsistency in

how results were reported and high risk of bias. Alongside the Cochrane review, we identified a systematic review of the effectiveness of CP for COVID-19 patients (Rajendran et al. 2020) which included five studies, all of which incorporated in the Cochrane rapid review. The authors concluded that CP could be an effective therapeutic option. In addition to these reviews there have been a number of primary reviews assessing the effectiveness, safety and practicality of using CP.

A number of studies have been published on the effectiveness of CP for other viral diseases: clinical outcomes were reported for SARS and severe influenza patients. Studies which compare CP to standard treatment in patients with SARS or severe influenza report inconsistent findings for overall mortality. However, studies suggest that CP may result in earlier discharge from hospital in SARS patients, particularly if given earlier on in treatment, and lower viral load in patients with severe influenza.

There are a number of protocols for systematic reviews and trials of CP for COVID-19 currently published. This suggests that the evidence base is likely to increase in future in this area.

Evidence for convalescent plasma to confer passive immunity to COVID-19 patients

Secondary evidence

An update search identified a Cochrane rapid review of the effectiveness of CP or hyperimmune immunoglobulin for COVID-19; a report on CP for COVID-19 published by the Canadian Agency for Drugs and Technologies in Health (CADTH); and a systematic review. The Cochrane review (Duan et al. 2020) found seven case series and one single-arm intervention study, all of which were identified by our searches and are included as primary evidence (see below). Overall, all outcomes were found to have very low certainty and the numerical data could not be summarised in a meaningful way. It was reported that all-cause mortality at hospital discharge, improvement of clinical symptoms, time to discharge from hospital, admission to ICU, and length of stay in ICU could all be related to the underlying natural history of the disease or other concomitant treatment, rather than CP. The authors were very uncertain whether or not CP affects the risk of moderate-to-severe, or serious, adverse events. There are plans to update the rapid review on a monthly basis.

The CADTH work identified a non-randomised study (Zeng et al. 2020) in addition to those highlighted by the Cochrane review. The CADTH review identified six case reports or series and four systematic reviews and 55 ongoing trials across 18 countries. No conclusions were drawn from the evidence.

A systematic review by Rajendran et al. (2020) included five of the studies identified by the Cochrane rapid review and CADTH work (Duan et al. 2020; Shen et al. 2020; Zhang et al. 2020a; Ye et al. 2020; Ahn et al. 2020). The authors summarised that all five studies found viral load to be significantly reduced and neutralising antibody levels to increase over time. Almost all patients showed improvement of symptoms and all studies reported that CP was well tolerated with zero mortality. They concluded that CP could be an effective therapeutic option with promising evidence on safety, improvement of clinical symptoms, and reduced mortality but that a definitive conclusion could not be drawn on optimal doses and treatment time point.

Zhang & Liu (2020) published the findings of a review of all treatment options relating to COVID-19 and reported that CP should be given to all COVID-19 patients if it is available. However, CP was only referred to in the abstract and conclusions, where reference was made

to the study by Arabi et al. (2015) in MERS patients, and the studies by Cheng et al. (2005) and Soo et al. (2004) in SARS patients (see below). No studies on CP were included in the results and the search methodology was not systematic in nature.

Primary evidence - effectiveness

Two non-randomised studies were identified (one initially and one in an update search). Duan et al. (2020) reports that of ten severe COVID-19 patients, symptoms had improved or disappeared 1-3 days after CP. Of those that were PCR-positive before CP was given, all were PCR-negative at 2-6 days. A historic control group of 10 recent patients was used and found to be significantly different in their clinical status (death, stable, improved or discharged). Zeng et al. (2020) compared six critically ill patients who received CP to 15 who did not. There was no significant difference in the duration of viral shedding between groups, however, significantly more patients had undetectable SARS-CoV-2 before death in the treatment group.

A clinical expert shared a retrospectively matched control study (Liu et al. 2020) of CP for hospitalised patients with severe to life-threatening COVID-19. Patients who received CP (n=39) were found to be significantly more likely to remain the same or have improvements in their supplementary oxygen requirements by post-transfusion day 14 in multivariate analysis (OR 0.86 95% CI 0.75 to 0.98; p=0.039).

The only other primary evidence identified which looked at CP for use in patients with COVID-19 were case reports or series, with patient numbers ranged from 1 to 10. Shen et al. (2020) found viral loads to be negative within 12 days of CP in five patients, three of whom were discharged and the remaining two stable at time of publication. Zhang et al. (2020a) reported all four patients to be PCR-negative 3-22 days after CP and all to have recovered (three discharged and one transferred to an unfenced ICU). Ahn et al. (2020) reported that two patients had improved symptoms after CP and were PCR-negative at days 24 and 26. It should be noted that without a comparator group it is not possible to say whether improvements were due to CP.

Since the initial search, Tan et al. (2020) reported use of CP in a non-severe patient with persistent viral shedding. The patient had negative oropharyngeal swabs within 1 day of receiving CP. Ye et al. (2020) reported on six COVID-19 patients receiving CP, they reported that no adverse reactions were observed in the 3 days following CP and all patients were considered cured. Zhang et al. (2020b) reported on the use of CP in one critically ill patient who no longer required mechanical ventilation at 11 days after receiving CP. Xi et al. (2020) report on three COVID-19 patients who were severely ill and received CP alongside methylprednisolone, immunoglobulin and thymalfascin. All three patients were eventually discharged. Anderson et al. (2020) report on a critically ill obstetric patient who received CP and remdesivir for COVID-19 who subsequently improved and was discharged.

Primary evidence – safety

Early safety findings of a multicentre, open-label expanded access programme of CP for 5,000 patients hospitalised with severe or life-threatening COVID-19 in the US have been reported (Joyner et al. 2020). The mortality rate was 0.3% (n=15) in the first 4 hours after transfusion and 14.9% (95% CI 13.8% to 16.0%; n=602) at 7 days. Of the 15 deaths within the first 4 hours, three were judged as 'possibly' related and one 'probably' related by the treating physician. The 7-day mortality rate among patients admitted to ICU (n=3,316) was 16.7% (95% CI 15.3% to 18.1%) and among hospitalised patients not admitted to ICU (n=1,682) was 11.2% (95% CI 9.5% to 12.9%). The authors compare this against case fatality rates reported in the literature of

around 4% among those diagnosed with COVID-19, around 15-20% among hospitalised patients, and 57% among patients admitted to ICU and did not consider it alarming.

The incidence of all serious adverse events was <1% (n=36) in the first 4 hours. This included seven (0.14%) reports of transfusion-associated circulatory overload (TACO), 11 (0.22%) reports of transfusion-related acute lung injury (TRALI), and three (0.06%) reports of severe allergic transfusion reaction. All were classed as related to the CP transfusion ('possibly'=9, 'probably'=7, and 'definitely'=2). The authors compare this to a reported incidence of TACO from around 0.01% in surveillance studies to 12% in higher risk populations in the literature, and a reported incidence of 0.01% to 8% for TRALI respectively.

Liu et al. (2020) found that survival was significantly improved in non-intubated patients who received CP compared to those who did not in multivariate analysis (HR 0.19 95% CI 0.05 to 0.72; p=0.015), but not for intubated patients.

In addition, Duan et al. (2020) reported no serious adverse reactions or safety events in 10 patients after transfusion. Zeng et al. (2020) found no significant difference in mortality between critically ill patients treated with CP and those who were not (a total of 19 out of 21 patients died). Patients in the treatment group had a significantly longer survival period.

Primary evidence – Other

Budhei et al. (2020) report on the practicalities of their experience creating a COVID-19 CP programme to support compassionate use through a national expanded access programme.

Published guidance

The U.S. Department of Health and Human Services: Food and Drug Administration (FDA) published Guidance for Industry on the use of investigational COVID-19 convalescent plasma in April 2020. This includes guidance on the pathway, patient eligibility, collection of CP (including donor eligibility), and record-keeping. In addition, the European Commission published guidance on collection, testing, processing, storage, distribution and monitored use of COVID-19 convalescent plasma in April 2020 with an aim of facilitating a common approach across EU Member States. The Italian Society for Transfusion Medicine and Immunohaematology (SIMTI) and the Italian Society for Haemapheresis and Cell Manipulation (SIdEM) published a position paper on preparation of immune plasma for treatment of patients with COVID-19. This makes recommendations on the biological characteristics of a plasma preparation.

Ongoing studies and protocols

Thirteen protocols for systematic reviews of COVID-19 treatments which specifically reference CP have been published.

Two ongoing trials of interest were identified, the REMAP-CAP study and the RECOVERY trial. The REMAP-CAP trial is a large randomised control trial taking place across 16 countries to assess the effectiveness of a range of treatments for community acquired pneumonia. The convalescent plasma arm of REMAP-CAP was added to the protocol on 19th April. Convalescent plasma is compared to no intervention for patients post 48 hours in ICU. The reported study completion is December 2023, however, preliminary results may be reported earlier in response to the current COVID-19 situation. Wales has multiple active sites and, at the date of writing, there is an ongoing collection of plasma through the full blood process. The RECOVERY trial focusses on therapies for the treatment of people hospitalised with COVID-19. RECOVERY trial is assessing a wide range of possible treatments, whilst it doesn't currently

include convalescent plasma there is the possibility there will be a convalescent plasma arm added to the study.

In addition to the two trials mentioned above, a CADTH review identified 55 ongoing trials across 18 countries. The CONCOR study in Canada of hospitalised patients (N = 1,200) is expected to complete in December 2020. There are three small (N <50) trials in China, Italy and Egypt which are expected to complete at the end of May 2020 alongside the CORIPLASM trial (N = 120) in France. A further four small trials (N <50) in Bahain, Italy and India are due to complete in June or July, alongside the ConPlas-19 trial in Spain (N = 278) and CONCOVID in The Netherlands (N = 426). Three further small trials will complete in August or September in Mexico, China and Iran, alongside a study in the USA (N = 100). A further three trials are expected to complete in December 2020 (N ≤100) in Mexico, Columbia and China. During 2021, a further 24 trials are expected to complete worldwide. The largest of these are one in Pakistan (N = 2,000, non-RCT) due to complete in April 2021, CCAP in Denmark (N = 1,500, RCT) due in June 2021, and an RCT in the USA (N = 1,344) due to complete in January 2023. Most studies are in patients with severe COVID-19, with a few looking at the use of CP as prophylaxis in those exposed.

Evidence for convalescent plasma to transfer immunity to non-COVID-19 patients

Secondary evidence

We identified some secondary evidence on the use of convalescent plasma to confer passive immunity in conditions other than COVID-19. Mair-Jenkins et al. (2015) undertook a systematic review and meta-analysis of the effectiveness of CP and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections (SARIs) of viral etiology. They identified 32 studies of SARS coronavirus and severe influenza which provided consistent evidence in the narratives of a reduction in mortality. Exploratory meta-analysis combining studies from a range of conditions found a statistically significant reduction in mortality compared to placebo or no therapy (OR 0.25 95% CI 0.14 to 0.45). However, this analysis used outcome data from non-randomised studies, many of which were assessed by the review authors as being at high risk of bias, and so should be interpreted with caution.

A recent systematic review and meta-analysis (Devasenapathy et al. 2020) of CP in severe respiratory viral infection did not identify any studies in COVID-19. However, authors were able to pool estimates from four RCTs on influenza (N = 572) and found no convincing effects on deaths, complete recovery, or length of stay.

Mo & Fisher (2016) undertook a literature review on treatment of MERS-CoV and SARS-CoV. In addition to the systematic review by Mair-Jenkins et al. (2015), they found two case reports and a study protocol for intravenous immunoglobulin to treat MERS-CoV and four studies of CP in SARS-affected patients. The latter demonstrated that use of CP led to earlier discharge, rapid decrease in viraemia, and survival benefits.

Stockman et al. (2006) undertook a systematic review of treatments for SARS. Amongst other treatments, they identified seven studies of CP or intravenous immunoglobulin of which the results were inconclusive.

A Cochrane review (CD010056) looked at post-exposure passive immunisation for preventing measles. This assessed intramuscular injection, or intravenous infusion of polyclonal

immunoglobulins derived from human sera of plasma to confer passive immunity. However, these were exposed, susceptible individuals and not patients hospitalised with infection. When given within seven days of exposure, convalescent serum was found to be effective at preventing measles.

Primary evidence

Multiple studies using convalescent plasma were identified across a range of disease areas. Hung et al. (2011) looked at the use of CP for patients with severe H1N1 2009 infection requiring intensive care, harvested by apheresis from recovering patients. They found lower mortality among the 20 patients receiving CP compared to controls who declined CP (OR 0.20 95% CI 0.06 to 0.69; p=0.011) and a lower viral load in patients receiving CP at day 3, 5 and 7 ($p<0.05$).

Wong et al. (2010) assessed the practicalities of collecting CP in pandemic preparation using plasmapheresis and reported on the potential limitations. They found that of around 9,100 recovered patients invited to be screened for donating plasma, 8.6% attended screening, and of these, 38.3% (3.3% of all invited) could donate by plasmapheresis. Reasons why patients could not donate included failure to meet donation criteria, failed laboratory tests, insufficient neutralisation antibody titres, and inability to make the appointment.

In addition to the studies by Hung et al. (2011) and Wong et al. 2010) using apheresis, three studies and one case report were identified which looked at the use of CP for severe influenza. Hung et al. (2013) undertook an RCT using CP fractionated to hyperimmune IV immunoglobulin compared to normal IV immunoglobulin in patients requiring intensive care (N=35). The intervention was associated with reduced mortality when given within 5 days of symptom onset (OR 0.14 95% CI 0.02 to 0.92; p=0.04) and a lower viral load in patients receiving CP at day 5 and 7 (p=0.04 and p=0.02 respectively). Davey et al. (2019) undertook a multi-country placebo-controlled RCT of patients hospitalised for influenza A or B (N=308). They found no statistically significant difference in the proportion (30%) which had a composite safety outcome of death, serious adverse event, or grade 3-4 adverse event at 28 days. Wu et al. (2011) presented a feasibility model of using CP for a population-wide passive immunotherapy programme during an influenza pandemic, using Hong Kong as a case study and based on the assumption of clinical effectiveness. Wu et al. (2015) reported that a patient who received CP on day 10 of their illness was discharged on day 24.

Two studies and one case series were identified which looked at CP for SARS. Cheng et al. (2005) found a higher day-22 discharge rate among SARS patients who received CP before day 14 of illness compared to those who received it later ($p<0.001$; N=80) and an overall mortality rate of 12.5% in patients given CP with no difference in mortality by the day at which the infusion was given. Soo et al. (2004) found no significant difference in mortality between patients receiving CP or further methylprednisolone after previous treatment with ribavirin and methylprednisolone. However, those who received CP had a shorter hospital stay ($p<0.001$) than those who received further methylprednisolone (N=40). Yeh et al. (2005) saw improvements in healthcare workers with SARS following CP. One case series was identified which found that two of three MERS patients showed neutralising activity after receiving CP (Ko et al. 2018).

Two studies and two case reports were identified which looked at CP for Ebola virus disease (EVD). Van Griensven (2018) published a protocol for a study comparing CP with supportive care to supportive care alone in Guinea. Another protocol compares CP to placebo in Sierra Leone. One study looked at CP for MERS-CoV - Arabi et al. (2016) undertook a survey of physicians in Saudi Arabia to assess whether an RCT of CP for MERS-CoV would be feasible.

One case report of a patient given Brincidofavir and CP at day 8 of illness was discharged on day 20, while the other found that the patient given CP on days 9, 10, 11 and 12 was discharged on day 34.

Ongoing studies and protocols

There are four protocols of systematic reviews of CP for SARS published. One is a review of CP for SARS or MERS resulting from coronavirus infection (with direct reference to COVID-19); one is a review of SARS resulting from viral infection with coronavirus or influenza; and two look at CP for SARS resulting from any viral infection.

Areas of uncertainty

It is not clear as to how transferable research on the effectiveness of CP from outside of COVID-19 is to our research question.

Conclusions

There is some evidence available on the effectiveness of CP to confer passive immunity for COVID-19 which is supported by research on other viral infections which may be useful. CP for COVID-19 currently lacks a mature evidence base, however, there are a high number of active trials. Research into related conditions may help inform the development of research and use of CP. The systematic review and meta-analysis of CP in SARS patients which was published in 2015 was identified as particularly useful.

Brief literature search results

Resource	Results
HTA organisations	
Healthcare Improvement Scotland	No relevant evidence identified
Health Technology Assessment Group	No relevant evidence identified
Health Information and Quality Authority	No relevant evidence identified
UK guidelines and guidance	
SIGN	No relevant evidence identified
NICE	No relevant evidence identified
International Guidance	
FDA	U.S. Department of Health and Human Services. Food and Drug Administration. April 2020. Investigational COVID-19 Convalescent Plasma: Guidance for Industry.
EC	European Commission. An EU programme of COVID-19 convalescent plasma collection and transfusion: Guidance on collection, testing, processing, storage, distribution and monitored use. April 2020.
Secondary literature and economic evaluations	
ECRI	No relevant evidence identified
EUnetHTA	No relevant evidence identified
Cochrane library	Valk_SJ, Piechotta_V, Chai_KL, Doree_C, Monsef_I, Wood_EM, Lamikanra_A, Kimber_C, McQuilten_Z, So-Osman_C, Estcourt_LJ, Skoetz_N. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a rapid review. *Cochrane Database of Systematic Reviews* 2020, Issue 5. Art. No.: CD013600. DOI: 10.1002/14651858.CD013600. Rajendran K, Krishnasamy N, Rangarajan J, Rathinam J, Natarajan M, Ramachandran A. Convalescent plasma transfusion for the treatment of COVID - 19: Systematic review. J Med Virol. 2020;1–9. https://doi.org/10.1002/jmv.25961 Convalescent plasma to confer passive immunity to measles: Young MK, Nimmo GR, Cripps AW, Jones MA. Post-exposure passive immunisation for preventing measles. Cochrane Database of Systematic Reviews 2014, Issue 4. Art. No.: CD010056. DOI: 10.1002/14651858.CD010056.pub2 https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010056.pub2/epdf/full Platelet rich plasmapheresis (blood is returned to the donor):

	Carless PA, Rubens FD, Anthony DM, O'Connell D, Henry DA. Platelet-rich-plasmapheresis for minimising peri-operative allogeneic blood transfusion. Cochrane Database of Systematic Reviews 2011, Issue 3. Art. No.: CD004172. DOI: 10.1002/14651858.CD004172.pub2 https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004172.pub2/epdf/full There are also Cochrane reviews which look at treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) (where the plasma is returned to the same patient); and given concomitantly with alkylating agents for Waldenstrom's macroglobulinaemia.
PubMed	Mair-Jenkins J et la. (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 211(1): 80-90. https://www.ncbi.nlm.nih.gov/pubmed/25030060 Zhang L & Liu Y (2020). Potential interventions for novel coronavirus in China: A systematic review. J Med Virol. 92(5): 479-490. https://www.ncbi.nlm.nih.gov/pubmed/32052466 Mo Y & Fisher D (2016). A review of treatment modalities for Middle East Respiratory Syndrome. J Antimicrob Chemother. 71(12): 3340-3350. https://www.ncbi.nlm.nih.gov/pubmed/27585965 Stockman LJ et al. (2006). SARS: systematic review of treatment effects. PLoS Med 3(9): e343. https://www.ncbi.nlm.nih.gov/pubmed/16968120 Accorsi P et al. (2020). Italian Society for Transfusion Medicine and Immunohaematology (SIMTI) and the Italian Society for Haemapheresis and Cell Manipulation (SIdEM). Position paper on the preparation of immune plasma to be used in the treatment of patients with COVID-19. Blood Transfus. 2020 May;18(3):163-166. doi: 10.2450/2020.0124-20 Devasenapathy et al. (2020). Efficacy and safety of convalescent plasma for severe COVID-19 based on evidence in other severe respiratory viral infections: a systematic review and meta-analysis. CMAJ. doi: 10.1503/cmaj.200642
Primary studies	
Cochrane library	CP by apheresis for severe influenza: Hung IFN et al. (2011). Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. Clinical infectious diseases 52(4): 447-456. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00891926/full?highlightAbstract=plasmaphaeresis%7Cplasmapheresi%7Cplasmaphaeresi%7Cplasmapheresis%7Cpandem%7Cpandemic CP for severe influenza: Hung IFN et al. (2013). Hyperimmune IV immunoglobulin treatment: a multicentre double-blind randomized controlled trial for patients with severe 2009 influenza A (H1N1) infection. Chest 144(2) 464-473 https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00965115/full?highlightAbstract=convalescent%7Cplasm%7Cpandem%7Cconvalesc%7Cplasma%7Cpandemic Davey et al. (2019). Anti-influenza hyperimmune intravenous immunoglobulin for adults with influenza A or B infection (FLU-IVIG): a double-blind randomised, placebo-controlled trial. The lancet respiratory medicine 7(11): 951-963. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02006066/full?highlightAbstract=convalescent%7Cplasm%7Cpandem%7Cconvalesc%7Cplasma%7Cpandemic

	CP for Ebola: Cochrane Central Register of Controlled Trials (CENTRAL). Convalescent plasma for early Ebola virus disease in Sierra Leone: an open-label, non-randomized, controlled clinical trial. CN-01811568. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01811568/full?highlightAbstract=convalescent%7Cconvalesc%7Cplasm%7Cplasma Van Griensven J (2015). Emergency evaluation of convalescent plasma for ebola virus disease (EVD) in guinea. American Journal of Tropical Medicine and Hygiene 93(4): 387. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01249874/full?highlightAbstract=convalescent%7Cconvalesc%7Cplasm%7Cplasma There are a wide array of trials for the use of plasmapheresis for other conditions e.g. Guillain-Barre syndrome; lupus nephritis; progressive MS; cardiac surgery; pemphigus; myasthenia gravis; rheumatoid vasculitits.
PubMed	CP for COVID-19 Duan K et al. (2020). Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U.S.A 117(17): 9490-9496 https://www.ncbi.nlm.nih.gov/pubmed/32253318 Zeng QL et al. (2020). Effect of Convalescent Plasma Therapy on Viral Shedding and Survival in COVID-19 Patients. J Infect Dis. 29: 29. PubMed: PM32348485 *Case reports or series:* Shen C et al. (2020). Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA doi: 10.1001/jama.2020.4783 [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/32219428 Zhang B et al. (2020). Treatment with convalescent plasma for critically ill patients with SARS-CoV-2 infection. Chest doi: 10.1016/j.chest.2020.03.039 [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/32243945 Ahn JY et al. (2020). Use of convalescent plasma therapy in two COVID-19 patients with acute respiratory distress syndrome in Korea. J Korean Med Sci 35(14): e149 https://www.ncbi.nlm.nih.gov/pubmed/32281317 Pei_S, Yuan_X, Zhimin_ZZ, Run_YR, Xie_Y, Minxue_SM, et al. Convalescent plasma to treat COVID-19: Chinese strategy and experiences. medRxiv 2020. [DOI: 10.1101/2020.04.07.20056440] Tan_L, Kang_X, Zhang_B, Zheng_S, Liu_B, Yu_T, et al. A special case of COVID-19 with long duration of viral shedding for 49 days. medRxiv 2020. [DOI: 10.1101/2020.03.22.20040071] Ye_M, Fu_D, Ren_Y, Wang_F, Wang_D, Zhang_F, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. Journal of Medical Virology 2020. [DOI: 10.1002/jmv.25882] Zhang_L, Pang_R, Xue_X, Bao_J, Ye_S, Dai_Y, et al. Anti-SARS-CoV-2 virus antibody levels in convalescent plasma of six donors who have recovered from COVID-19. Aging 2020 Apr 22 [Epub ahead of print]; 12. [DOI: 10.18632/aging.103102] Xi A et al. (2020). Epidemiological and Clinical Characteristics of Discharged Patients Infected With SARS-CoV-2 on the Qinghai Plateau. J Med Virol May 21. doi: 10.1002/jmv.26032. Anderson J et al. (2020). The Use of Convalescent Plasma Therapy and Remdesivir in the Successful Management of a Critically Ill Obstetric Patient With Novel Coronavirus 2019 Infection: A Case Report. doi: 10.1016/j.crwh.2020.e00221.

	Other: Budhai A et al. (2020). How did we rapidly implement a convalescent plasma program? [published online ahead of print] *Transfusion*. 2020;10.1111/trf.15910. doi:10.1111/trf.15910 CP for severe influenza: Wu JT et al. (2012). Logistical feasibility and potential benefits of a population-wide passive immunotherapy program during an influenza pandemic. Influenza Other Respi Viruses 5(Suppl 1): 226-229. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3357494/ Wong HK et al. (2010). Practical limitations of convalescent plasma collection: a case scenario in pandemic preparation for influenza A (H1N1) infection. Transfusion 50(9): 1967-71. https://www.ncbi.nlm.nih.gov/pubmed/20412524 CP for MERS-CoV: Arabi YM et al. (2016). Feasibility of a randomized controlled trial to assess treatment of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection in Saudi Arabia: a survey of physicians. BMC Anesthesiol. 16(1): 36. https://www.ncbi.nlm.nih.gov/pubmed/27405596 CP for SARS: Cheng Y et al. (2005). Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis 24(1): 44-46. https://www.ncbi.nlm.nih.gov/pubmed/15616839 Soo YO et al. (2004). Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. Clin Microbiol Infect 10(7): 676-8. https://www.ncbi.nlm.nih.gov/pubmed/15214887
Ongoing primary or secondary research	
PROSPERO database	Systematic review protocol for CP for COVID-19: Cao et al. The effectiveness of convalescent plasma for the treatment of Novel Corona Virus Disease 2019 (COVID-19): a systematic review and meta-analysis. PROSPERO 2020 CRD42020177511. https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=177511 Souza K et al. A rapid systematic review about the efficacy and safety of the use of convalescent plasma in the treatment of COVID-19. PROSPERO 2020 CRD42020188643 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020188643 Osvaldo D. et al. Pharmacological interventions for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): systematic review and network meta-analyses. PROSPERO 2020 CRD42020183143 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020183143 Chang Y et al. The safety of prescription-only medications for breastfeeding in women who took or were administered them for diagnosed or suspected COVID-19 infection: a living systematic review. PROSPERO 2020 CRD42020187101 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020187101 Qizilbash N et al. Real-time systematic review and meta-analysis of non-randomised comparative treatment studies for COVID-19. PROSPERO 2020 CRD42020184089 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020184089

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Cochrane library (CENTRAL)	CP for COVID-19: Efficacy and Safety of Novel Treatment Options for Adults With COVID-19 Pneumonia. https://clinicaltrials.gov/show/NCT04345289 Efficacy and Safety Human Coronavirus Immune Plasma (HCIP) vs. Control (SARS-CoV-2 Non-immune Plasma) Among Adults Exposed to COVID-19. https://clinicaltrials.gov/show/NCT04323800 Convalescent Plasma as Therapy for Covid-19 Severe SARS-CoV-2 Disease (CONCOVID Study). https://clinicaltrials.gov/show/NCT04342182 Convalescent Plasma for Patients With COVID-19: a Randomized, Open Label, Parallel, Controlled Clinical Study. https://clinicaltrials.gov/show/NCT04332835 Study Testing Convalescent Plasma vs Best Supportive Care. https://clinicaltrials.gov/show/NCT04333251 CONvalescent Plasma for Hospitalized Adults With COVID-19 Respiratory Illness (CONCOR-1). https://clinicaltrials.gov/show/NCT04348656 Convalescent Plasma vs. Standard Plasma for COVID-19. https://clinicaltrials.gov/show/NCT04344535 Efficacy of Convalescent Plasma Therapy in Severely Sick COVID-19 Patients. https://clinicaltrials.gov/show/NCT04346446 Convalescent Plasma Therapy vs. SOC for the Treatment of COVID19 in Hospitalized Patients. https://clinicaltrials.gov/show/NCT04345523
Clinicaltrials.gov	Plasmapheresis for COVID-19: A Pilot Study to Explore the Efficacy and Safety of Rescue Therapy With Antibodies From Convalescent Patients Obtained With Double -Filtration Plasmapheresis (DFPP) and Infused in Critically Ill Ventilated Patients With Coronavirus Disease 2019 (COVID-19). ClinicalTrials.gov Identifier: NCT04346589 https://clinicaltrials.gov/ct2/show/NCT04346589?term=plasmapheresis&draw=3&rank=62 Anti COVID-19 Convalescent Plasma Therapy. ClinicalTrials.gov Identifier: NCT04345679 https://clinicaltrials.gov/ct2/show/NCT04345679?term=plasmapheresis&draw=4&rank=152 REMAP-CAP clinical trial https://clinicaltrials.gov/ct2/show/NCT02735707 REMAP-CAP protocol summary https://static1.squarespace.com/static/5cde3c7d9a69340001d79ffe/t/5e82b60d225239559569ff77/1585624604501/REMAP-CAP+Protocol+Summary+V3+-+11+Sep+2019_WM.pdf Convalescent plasma arm of REMAP-CAP https://static1.squarespace.com/static/5cde3c7d9a69340001d79ffe/t/5ea3fddb1de102540e627663/1587805670273/REMAP-CAP+COVID-19+Immunoglobulin+Therapy+Domain-Specific+Appendix+V1-+19+April+2020_WM.pdf

	RECOVERY trial: https://www.recoverytrial.net/files/recovery-protocol-v5-0-2020-04-24.pdf CP for COVID-19: Phase IIa Study Exploring the Safety and Efficacy of Convalescent Plasma From Recovered COVID-19 Donors Collected by Plasmapheresis as Treatment for Hospitalized Subjects With COVID-19 Infection. ClinicalTrials.gov Identifier: NCT04343755 https://clinicaltrials.gov/ct2/show/NCT04343755?term=plasmapheresis&draw=4&rank=113
Other	
Clinical experts	Convalescent plasma to limit coronavirus associated complications: a randomized open label, phase 1 study comparing the efficacy and safety of high-titre anti-SARS-CoV-2 plasma vs. placebo in hospitalized patients with interstitial pneumonia due to COVID-19 (CSSC-002). Covid-19 convalescent plasma collection in the Netherlands. 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 (CSSC-001). A randomized, prospective, open label clinical trial of convalescent plasma compared to best supportive care for treatment of patients with severe COVID-19 infections (CAPSID). Plasma from donors cured of the disease caused by the novel coronavirus 2019 (COVID-19) as a treatment for critical patients suffering from COVID-19. Proof of concept study. Nested trial in corimmuno-19. Efficacy of hyperimmune plasma for patients with COVID-19. The COVIPLASM trial. Joyner et al. (2020). Early safety indicators of COVID-19 convalescent plasma in 5,000 patients. doi: https://doi.org/10.1101/2020.05.12.20099879 preprint Convalescent Plasma Therapy for the Treatment of COVID-19: Clinical Effectiveness. Ottawa: CADTH; 2020 May Liu S et al. (2020). Convalescent plasma treatment of severe COVID-19: a matched control study. preprint doi: https://doi.org/10.1101/2020.05.20.20102236

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Concepts used:	Convalescent plasma; plasmapheresis For primary evidence the additional terms were used to enhance specificity were helpful: pandemic; SARS; COVID; coronavirus