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Narrative review

Treatment of COVID-19 with convalescent plasma: lessons from past coronavirus outbreaks

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Abstract

Background: There is currently no treatment known to alter the course of coronavirus disease 2019 (COVID-19). Convalescent plasma has been used to treat a number of infections during pandemics, including severe acute respiratory syndrome coronavirus (SARS-CoV), Middle Eastern respiratory syndrome coronavirus (MERS-CoV) and now severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).

Objectives: To summarize the existing literature and registered clinical trials on the efficacy and safety of convalescent plasma for treating coronaviruses, and discuss issues of feasibility, and donor and patient selection.

Sources: A review of articles published in PubMed was performed on 13 July 2020 to summarize the currently available evidence in human studies for convalescent plasma as a treatment for coronaviruses. The World Health Organization International Clinical Trials Registry and clinicaltrials.gov were searched to summarize the currently registered randomized clinical trials for convalescent plasma in COVID-19.

Content: There were sixteen COVID-19, four MERS and five SARS reports describing convalescent plasma use in humans. There were two randomized control trials, both of which were for COVID-19 and were terminated early. Most COVID-19 reports described a potential benefit of convalescent plasma on clinical outcomes in severe or critically ill patients with few immediate adverse events. However, there were a number of limitations, including the concurrent use of antivirals, steroids and other treatments, small sample sizes, lack of randomization or control groups, and short follow-up time. Data from SARS and COVID-19 suggest that earlier administration probably yields better outcomes. The ideal candidates for recipients and donors are not known. Still, experience with previous coronaviruses tells us that antibodies in convalescent patients are probably short-lived. Patients who had more severe disease and who are earlier in their course of recovery may be more likely to have adequate titres. Finally, a number of practical challenges were identified.

Implications: There is currently no effective treatment for COVID-19, and preliminary trials for convalescent plasma suggest that there may be some benefits. However, research to date is at high risk of bias, and randomized control trials are desperately needed to determine the efficacy and safety of this therapeutic option.

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Introduction

On 24 March 2020, the United States Food and Drug Administration (FDA) announced the approval of convalescent plasma therapy for critically ill individuals with coronavirus disease 2019 (COVID-19) as an emergency investigational new drug [1]. At the time of writing on 13 July 2020, there are no therapies known to alter the course of COVID-19, which has now reached over 12,700,000 confirmed cases and over 566,000 deaths globally [2]. Although remdesivir, an adenosine analogue antiviral agent, had promising effects against coronaviruses in vitro [3,4] and in animal models [4–6], an initial randomised control trial from China published in April found no significant effect of the drug on viral load or time to clinical improvement in humans [7]. Similarly, hydroxychloroquine had promising initial results in non-randomized

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studies, but more recent reports highlighted less benefit and even possible harm [8–10]. As vaccines and effective therapies for COVID-19 are not yet available, it is clear that additional clinical trials and global action are required [11].

Convalescent plasma has been used for decades to prevent and treat infectious diseases where no specific treatment is available [12]. The use of convalescent plasma involves transfusing plasma collected from patients who have already recovered from an illness, in an attempt to transfer neutralizing antibodies and confer passive immunity [13]. The potential efficacy of convalescent plasma was first described during the Spanish influenza pandemic of the early 1900s [14]. Since then, convalescent plasma has been used to attempt to treat a wide range of viral infections, including measles, parvovirus B19, H1N1, Ebola and some coronaviruses [12,15,16]. Among the many coronaviruses that are only mildly pathogenic to humans, there are three that have caused notably severe clinical manifestations and have been treated with convalescent plasma: severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and the 2019 novel coronavirus (SARS-CoV-2) that causes COVID-19 disease (Table 1) [15,17–19].

Other than two trials that were published after being terminated early [20,21], there is a lack of randomized control trials investigating convalescent plasma as a therapy for coronaviruses, though observational studies have reported some promising benefits [15,20–35]. Therefore, the purpose of this review is to summarize the literature and identify areas for future focus regarding the use of convalescent plasma to treat coronaviruses (SARS-CoV, MERS-CoV and, in particular, SARS-CoV-2). A PubMed search was conducted on 13 July 2020, to examine the literature published in English with no date limitations. Search terms included ‘coronavirus convalescent patients’, ‘MERS-CoV convalescent plasma’, ‘SARS-CoV convalescent plasma’, and ‘COVID-19 convalescent plasma’. Studies describing the use of convalescent plasma as a treatment for one of these three coronaviruses in humans were included in the primary literature described in Table 2. Primary articles that were not returned in the initial search, but which were cited by reviews or meta-analyses from the initial search, are also included. Additional searches were conducted to add to the discussion of topics explored herein: efficacy, risks, patient selection, donor selection and feasibility.

In addition, searches were performed on clinicaltrials.gov and on the WHO International Clinical Trials Registry platform on 13 July 2020, to summarize the currently registered randomized clinical trials for convalescent plasma in COVID-19. The following search terms were used with no date limitations for clinical-trials.gov: Condition = COVID-19, other terms = ‘convalescent plasma’ randomized, study type = ‘interventional studies’. This search returned 59 results, of which 56 were randomized controlled trials for convalescent plasma and are included herein. In addition, the WHO platform was searched using the following terms: ‘COVID-19’ and ‘randomized’ and ‘convalescent plasma’, which returned 51 results, of which 15 were not registered on clinicaltrials.gov, and of which 13 were randomized clinical trials for convalescent plasma. These trials are summarized in Table 3 in order of the primary completion date.

Reports of efficacy and safety of convalescent plasma for treatment of prior coronaviruses

A summary of the primary literature describing the use of convalescent plasma is found in Table 2 [15,20–42]. Sixteen reports of convalescent plasma in COVID-19 (n = 5353 treated), four in MERS-CoV (n = 13 treated), and five in SARS-CoV (n = 125 treated) were identified. There were two randomized control trials [20,21], and there was a comparator group in seven COVID-19 studies, and in two SARS-CoV studies. Most of the identified studies reported a benefit of convalescent plasma therapy, manifested as clinical improvement, reduced mortality, longer survival time, earlier discharge, increased viral clearance or increased virus-specific IgG or IgM following treatment [15,20,22–35]. Before COVID-19, the two largest studies were reported, retrospectively, from the same group in Hong Kong during the SARS-CoV outbreak of 2003 [24,25]. Of 40 SARS patients who were refractory to antiviral and steroid treatment, the 19 patients who received steroid and convalescent plasma were more likely to be discharged early (73% versus 19%), and have lower mortality (0% versus 24%), than the 21 patients treated with a steroid alone [25]. Similarly, patients who received convalescent plasma sooner (before day 14 of symptom onset) were significantly more likely to be discharged before day 22 (58% versus 16%) and trended toward lower mortality (6.3% versus 21.9%, p 0.08) than those who received treatment after day 14 [24]. Although there were many limitations, these data identified convalescent plasma therapy as a potential avenue for coronavirus treatment during an outbreak. A meta-analysis that included SARS-CoV as well as non-coronaviruses (H1N1pdm09, H5N1 and H1N1) identified a 75% reduction in the odds of mortality among patients treated with convalescent plasma or serum with no serious adverse events or complications, though these studies were deemed to be at moderate-to-high risk of bias [43].

Reports of efficacy and safety of convalescent plasma for treatment of COVID-19

In the first COVID-19 study, by Shen et al., all five patients who were treated in China with convalescent plasma between days 10 and 22 of admission improved clinically after receiving treatment [15]. All five patients had severe pneumonia with rapid progression, low PaO2/FiO2, and were receiving mechanical ventilation and various steroids and antivirals. Approximately 1 week after infusion, patients exhibited normalized body temperature, and improved PaO2/FiO2 and Sequential Organ Failure Assessment (SOFA) scores. However, at the time the study was completed, two patients remained hospitalized, and although their SOFA scores were markedly improved, their ultimate clinical course was not followed up. This was the first study to report a promising outcome of convalescent plasma for treating COVID-19, but similar to most observational studies described herein, there was no control group, and it is unclear whether patients would have improved without the transfusion, or if their improvement was more related to one of the other therapeutic agents they received.

Another early report studied six convalescent plasma-treated COVID-19 patients in China, and described a benefit in terms of viral clearance and longer survival times, but this did not translate to a mortality benefit compared with those not receiving
| Virus | Reference | RCT | Comparator | Treated population | Timing and dose | Donor details | Prior or concurrent treatments | Outcomes | Adverse events |
|-------|-----------|-----|------------|-------------------|----------------|---------------|-------------------|----------|----------------|
| COVID-19 | Joyner, M.J., et al., 2020 [31] | No | None | n = 5000 adults with, or at high risk of, severe life-threatening disease | Timing not specified, 200–500 mL | Recovered without symptoms ≥14 days, ABO compatible with no minimum neutralizing Ab titre | Not specified | Safety trial. 14.9% 7-day mortality after CP. Adverse events in the first 4 h: 0.08% mortality, 0.14% TACO, 0.22% TRALI, 0.06% severe allergic transfusion reaction. | Overall <1% rate of serious adverse events |
| COVID-19 | Enzmann, M.O. et al., 2020 [44] | No | n = 1430 Standard treatment | n = 138 Severe or critical | Median day 45 of illness, 200–1200 mL | ABO-compatible donor | Not specified | Reduced mortality and % patients with shortness of breath in CP versus standard treatment. Clinical improvement following CP in severe patients but not critical patients. No effect of CP on primary outcome of time to clinical improvement. Significant effect of CP on time to improvement in severe patients (91% versus 68% receiving standard treatment), but no effect in critical patients. No effect of CP on mortality, disease severity or time to discharge. | n = 3 minor allergic, no immediate severe |
| COVID-19 | Li, L. et al., 2020 [20] | Yes | n = 52 Standard treatment | n = 51 Severe or life-threatening disease | Median day 27 of illness, 4–13 mL/kg recipient BW | Recovered without symptoms ≥14 days, ABO compatible, plaque reduction neutralization test titre ≥1:80 | Varied, includes antibiotics, antivirals, steroids, human immunoglobulin, Chinese herbal medicines, others national | Improved survival in CP versus no CP in non-intubated patients but not intubated patients. | No immediate |
| COVID-19 | Gharbharan, A., et al., 2020 [21] | Yes | n = 43 Standard treatment | n = 43 Not on mechanical ventilation for >96 h | Median day 9 of illness, 300 mL | Recovered without symptoms ≥14 days, ABO compatible, plaque reduction neutralization test titre ≥1:80 | Varied, includes chloroquine, azithromycin, antivirals, tocilizumab, anakinra, others national | No effect of CP on laboratory values (CBC, ferritin, LDH, liver enzymes, CRP etc.). n = 20 survivors, n = 6 deceased | No immediate |
| COVID-19 | Liu, S. T.H., et al., 2020 [32] | No | n = 39 Retrospective matched controls | n = 39 Severe or life-threatening disease | Median day 4 of admission, ≥500 mL | Recovered without symptoms ≥14 days, ABO compatible with ≥1:320 Ab titre | Varied, includes antibiotics, antivirals, hydroxychloroquine, anticoagulants, corticosteroids, stem cells, IL-1 and IL-6 inhibitors | No significant effect of CP on laboratory values (CBC, ferritin, LDH, liver enzymes, CRP etc.). n = 20 survivors, n = 6 deceased | No immediate |
| COVID-19 | Erkurt, M.A., et al., 2020 [30] | No | None | n = 26 Severe, ICU admitted | Mean day 14 of admission, one session, 200 mL | Recovered for ≥14 days from mild-moderate disease | Varied, includes azithromycin, hydroxychloroquine, multiple combinations | Similar proportion CP and control patients discharged. Lower case fatality rate in CP versus controls at 7 and 14 days. No deaths when CP was given before 7 days of hospitalization versus 10% deaths when CP was given after 7 days of hospitalization. Significant improvement in clinical symptoms within 1–3 days, improved O₂ saturation, reduced ventilatory support requirements. | No immediate |
| COVID-19 | Hegerova L., et al., 2020 [33] | No | n = 20 Retrospective matched controls | n = 20 Severe or life-threatening disease | Median day 2 of admission, 1 unit | Recovered without symptoms ≥28 days, none were hospitalized during illness | Varied, includes azithromycin, hydroxychloroquine, multiple combinations | Improved survival in CP versus no CP in non-intubated patients but not intubated patients. | No immediate |
| COVID-19 | Duan, K., et al., 2020 [37] | No | Historic control group | n = 10 Severe | Median day 16.5 of illness, 200 mL | Recovered, neutralizing Ab titre ≥1:640 | Varied, includes maximal supportive care, antivirals, antibiotics, antifungals, steroids national | No effect of CP on laboratory values (CBC, ferritin, LDH, liver enzymes, CRP etc.). n = 20 survivors, n = 6 deceased | No immediate |
| Virus       | Reference                  | RCT | Comparator | Treated population          | Timing and dose | Donor details | Prior or concurrent treatments | Outcomes                                                                 | Adverse events |
|------------|-----------------------------|-----|------------|-----------------------------|-----------------|---------------|-------------------------------|---------------------------------------------------------------------------|----------------|
| COVID-19   | Shen, C., et al., 2020 [15]  | No  | None       | n = 5                       | Days 10–22 of admission, 400 mL | Asymptomatic 10 days, serum SARS-CoV-2 titre >1:1000, neutralizing Ab titre >40 | Steroids, antivirals, mechanical ventilation +/– ECMO | Superior clinical improvement in CP versus historical controls. Improved body temperature, SOFA score, PaO₂/FiO₂, viral load, and SARS-CoV-2-specific neutralizing antibody titres. All patients discharged (n = 3) or stable (n = 2) at 37 days. No change in mortality for CP (5/6) versus non-CP (14/15). Significantly greater viral clearance in deceased CP (5/5) versus deceased non-CP (3/14). Significantly longer survival in CP versus non-CP. | Not specified |
| COVID-19   | Zeng, Q-L., et al., 2020 [36]| No  | n = 11, no CP | n = 5                       | Median day 21.5 of illness, 300 mL | 1–2 weeks recovered, negative SARS-CoV-2 RNA and IgM, positive IgG | Includes mechanical ventilation, ECMO, antibiotics, antivirals, steroids, IGV, traditional Chinese medicine, and continuous renal replacement therapy | No immediate |
| COVID-19   | Ye, M., et al., 2020 [38]    | No  | None       | n = 6                       | >4 weeks after symptom onset, ≥200 mL | Recovered (afebrile 3 days, no respiratory symptoms, negative SARS-CoV-2 nucleic acid), ≥3 weeks after disease onset, seropositive for anti-SARS-CoV-2 | Varied, includes antivirals | Varied, includes O2 saturation, radiologic findings, elimination of SARS-CoV-2 on throat swab, reduced respiratory symptoms. | No immediate |
| COVID-19   | Zhang, B., et al., 2020 [39] | No  | None       | n = 4                       | Day 16–19 of illness, 200–2400 mL | Not specified | Varied, includes ECMO, antivirals, interferon-, IFN-, IgG, antibiotics, antifungals, steroids, continuous renal replacement therapy Varied, includes systemic steroids, hydroxychloroquine, antivirals, antibiotics, steroids, antifungals, traditional Chinese medicine, and continuous renal replacement therapy | Varied, includes O2 saturation, radiologic findings, reduced viral load, reduced ventilatory support needs. Reduced O₂ demand, decreased CRP and IL-6, increased PaO₂/FiO₂, improved radiologic findings, negative SARS-CoV-2. | No immediate |
| COVID-19   | Ahn, J.Y., et al., 2020 [40] | No  | None       | n = 2                       | Day 6 or day 11 of admission, 500 mL | Donor 1: recovered for 21 days, asymptomatic, IgG OD ratio 0.586 | Varied, includes mechanical ventilation, ECMO, antibiotics, antivirals, steroids, continuous renal replacement therapy | Varied, includes O2 saturation, radiologic findings, reduced viral load, reduced ventilatory support needs. Reduced O₂ demand, decreased CRP and IL-6, increased PaO₂/FiO₂, improved radiologic findings, negative SARS-CoV-2. | No immediate |
| COVID-19   | Abdullah H.M., et al., 2020 [29] | No  | None       | n = 2                       | Day 9 or day 11 of illness, 200 mL | Recovered from moderate COVID-19 | Hydroxychloroquine, azithromycin, meropenem, antivirals, enoxaparin | Patient 1: clinical improvement 4d after infusion (dyspnoea, O₂ saturation, CXR), discharged 16 days after admission. Patient 2: clinical improvement 70 h after infusion (fever, dyspnoea, lymphocyte counts), discharged 21 days after admission. Improvement in respiratory distress symptoms for 3 days after transfusion, improved PaO₂/FiO₂. | No immediate |
| COVID-19   | Im, J.H., et al., 2020 [35]  | No  | None       | n = 1                       | Day 9 of admission, 500 mL | ABO non-compatible donor | Hydroxychloroquine, .antivirals | Subacute worsening, eventual recovery | Subacute worsening, eventual recovery | No immediate |

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convalescent plasma [36]. Also, Duan et al. described ten individuals with severe COVID-19 in China who were treated earlier in their disease course, at a median time of 16.5 days after onset, describing marked improvement in symptoms within 1–3 days of convalescent plasma treatment and generally reduced ventilatory support requirements [37]. In addition, all ten patients were discharged or had much improved clinical status, in comparison with a historical control group which included three deaths, six stabilized patients and one patient with improved clinical status [37].
| Trial number (acronym) | Status | Primary outcome(s) | Phase | Enrolment | Start | Primary completion | Completion | Country |
|-----------------------|--------|--------------------|-------|-----------|-------|-------------------|------------|---------|
| NCT04345991 (CORIPLASM) | Recruiting | Survival without ventilator and clinical improvement | Phase 2 | 120 | Apr, 2020 | May, 2020 | Jun, 2020 | France |
| NCT04346446 | Completed | Mechanical ventilation requirement | Phase 2 | 29 | Apr, 2020 | May, 2020 | May, 2020 | India |
| NCT04441424 | Completed | Mortality | Phase 2 | 49 | Apr, 2020 | Jun, 2020 | Jun, 2020 | Iraq |
| NCT04405310 (CPC-SARS) | Recruiting | Laboratory parameters | Phase 2 | 60 | May, 2020 | Jun, 2020 | Jun, 2020 | Turkey |
| NCT04356534 | Recruiting | Mechanical ventilation requirement | Phase 2 | 80 | May, 2020 | Jun, 2020 | Jul, 2020 | Mexico |
| NCT04345523 (ConPlas-19) | Recruiting | Mortality | Phase 2 | 40 | Apr, 2020 | Jun, 2020 | Jun, 2020 | Bahrain |
| NCT04342182 (ConCoVid-19) | Recruiting | Mechanical ventilation requirement | Phase 2 | 278 | Apr, 2020 | Jul, 2020 | Jul, 2020 | Spain |
| NCT04346446 | Completed | Mechanical ventilation requirement | Phase 2 | 29 | Apr, 2020 | May, 2020 | May, 2020 | India |
| NCT04346446 | Completed | Mechanical ventilation requirement | Phase 2 | 29 | Apr, 2020 | May, 2020 | May, 2020 | India |
| NCT04346446 | Completed | Mechanical ventilation requirement | Phase 2 | 29 | Apr, 2020 | May, 2020 | May, 2020 | India |
| NCT04346446 | Completed | Mechanical ventilation requirement | Phase 2 | 29 | Apr, 2020 | May, 2020 | May, 2020 | India |
There are a number of early studies documenting the effects of convalescent plasma therapy in small sample sizes. One descriptive study of COVID-19 patients from China included six participants who were treated later in their disease course (generally >4 weeks after onset), following any other treatments they received at their initial hospital site [38]. All six patients had clinical improvement and did not require admission to the intensive care unit following treatment. Zhang et al. described four complex cases of critically ill COVID-19 patients in China who underwent extensive therapy including convalescent plasma, and showed potential therapeutic

| Trial number (acronym) | Status | Primary outcome(s) | Phase | Enrolment | Start | Primary completion | Completion | Country |
|-----------------------|--------|--------------------|-------|-----------|-------|-------------------|-----------|---------|
| NCT04438694 (CP IN COVID19) | Recruiting | Hospitalization time | Phase 1/2 | 60 | Jun, 2020 | May, 2021 | Dec, 2021 | Egypt |
| NCT04418518 (CONCOR-1) | Recruiting | Intubation or death in hospital | Phase 3 | 1200 | Jun, 2020 | Jun, 2021 | Dec, 2021 | USA |
| NCT04391101 | Not yet recruiting | Mortality in hospital | Phase 3 | 231 | Jun, 2020 | Jun, 2021 | Dec, 2021 | Colombia |
| NCT04361253 (ESCAPE) | Recruiting | Clinical improvement | Phase 3 | 220 | Apr, 2020 | Jun, 2021 | Dec, 2021 | USA |
| NCT04428021 (PLACO-COVID) | Not yet recruiting | Survival | Phase 2 | 180 | Jun, 2020 | Jun, 2021 | Dec, 2021 | Italy |
| NCT04345289 (CCAP) | Recruiting | Mechanical ventilation requirement and mortality | Phase 3 | 1500 | May, 2020 | Jun, 2021 | Jun, 2021 | Denmark |
| NCT04468009 | Recruiting | Mortality | Phase 2 | 36 | Jun, 2020 | Jun, 2021 | Jul, 2021 | Argentina |
| NCT04456413 | Not yet recruiting | Hospitalization rate | Phase 2 | 306 | Jul, 2020 | Jul, 2021 | Jul, 2021 | USA |
| NCT04438057 | Not yet recruiting | Time to symptom resolution and serious adverse events | Phase 2 | 150 | Jul, 2020 | Jul, 2021 | Jul, 2021 | USA |
| NCT04467151 | Not yet recruiting | Disease progression | Phase 2 | 96 | Aug, 2020 | Oct, 2021 | Dec, 2021 | USA |
| NCT04429854 (DAWN-Plasma) | Recruiting | Mechanical ventilation requirement and mortality | Phase 2 | 483 | May, 2020 | Nov, 2021 | Nov, 2021 | Belgium |
| NCT04377568 (CONCOR-KIDS) | Not yet recruiting | Clinical recovery | Phase 2 | 100 | Jul, 2020 | Dec, 2021 | May, 2022 | Canada |
| NCT04381936 (RECOVERY) (COOPCOVID-19) | Recruiting | Mortality | Phase 2/3 | 15000 | Mar, 2020 | Dec, 2021 | Apr, 2021 | UK |
| NCT04355767 (C3PO) | Not yet recruiting | Time to clinical improvement or discharge | Phase 3 | 600 | Jul, 2020 | Dec, 2022 | Dec, 2022 | USA |
| NCT04373460 (CSSC-004) | Recruiting | Mortality, hospitalization, adverse events | Phase 2 | 1344 | Jun, 2020 | Dec, 2022 | Jun, 2023 | USA |
| NCT04323800 (CSSC-001) | Recruiting | Clinical improvement | Phase 2 | 487 | Jun, 2020 | Dec, 2022 | Dec, 2022 | USA |
| NCT04333251 | Recruiting | Mechanical ventilation and oxygen requirement | Phase 1 | 115 | Apr, 2020 | Jan, 2023 | Dec, 2022 | USA |
| NCT04364737 (ChiCTR2000029757) | Recruiting | Clinical improvement | Phase 2 | 300 | Apr, 2020 | Jan, 2023 | Apr, 2023 | USA |
| ChiCTR2000030702 | Recruiting | Time to clinical recovery | Phase 0 | 50 | Mar, 2020 | — | — | China |
| ChiCTR2000030381 | Pending | N/A | N/A | 40 | Feb, 2020 | — | — | China |
| IRCTN85216856 (IRCT20200404046948N1) | Recruiting | Mortality | Phase 2/3 | 200 | May, 2020 | — | Dec, 2020 | Ecuador |
| IRCT20200413047056N1 | Recruiting | Clinical improvement Imaging and laboratory values, hospital length of stay, mechanical ventilation | Phase 3 | 60 | Apr, 2020 | — | — | Iran |
| CTRI/2020/04/024775 | Not Recruiting | ARDS and mortality | Phase 2 | 452 | Apr, 2020 | — | — | India |
| CTRI/2020/04/024706 | Not Recruiting | Mechanical ventilation requirement | Phase 2 | 40 | Apr, 2020 | — | — | India |
| CTRI/2020/04/024915 | Not Recruiting | ARDS and mortality | Phase 2 | 100 | May, 2020 | — | — | India |
| CTRI/2020/05/025803 | Recruiting | Time to clinical improvement | Phase 3 | 400 | Jun, 2020 | — | — | India |
| IRCTN50189673 (CTRI/2020/05/025346) | Recruiting | Mortality | Phase 2/3 | 15000 | Mar, 2020 | — | — | UK |
| NLB633 | Recruiting | Mortality, mechanical ventilation, ICU admission and length of hospital stay | Phase 2/3 | 430 | May, 2020 | May, 2021 | — | Netherlands |

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; ICU, intensive care unit.
benefit and no serious adverse reactions, although the relative role of convalescent plasma treatment in patient outcomes could not be determined [39]. Ahn et al. describe two individuals with severe COVID-19 in Korea with acute respiratory distress syndrome who were treated with convalescent plasma on day 10 and day 6 of admission, respectively (day 22 and day 7 of symptom onset) [40]. Both patients eventually tested negative for SARS-CoV-2 RNA, improved in clinical, biochemical and radiological findings and were discharged home [40]. Finally, Figlerowicz et al. reported successful use of convalescent plasma in a paediatric patient, aged 6 years, who had severe COVID-19 leading to aplastic anaemia that was refractory to the first 5 weeks of treatment in hospital [34]. Convalescent plasma successfully eliminated SARS-CoV-2 from her nasopharyngeal swabs, which were previously positive for 5 weeks, but it did not improve her haematological parameters [34].

Promisingly, larger studies of COVID-19 have now emerged from the USA, describing the safety and efficacy of convalescent plasma therapy in the early stages of the expanded access programme. For example, 39 individuals with severe or immediately life-threatening disease who were treated with convalescent plasma were found to be more likely than retrospectively matched controls to have improvements in supplementary oxygen requirements, and improved survival [32]. Of note, there was improved survival in non-intubated patients but not in intubated patients, which may provide insight into patient selection [32]. Another larger study of 138 convalescent plasma-treated patients who were compared with 1430 patients receiving standard therapy showed promising benefits such as reduced mortality and reduced proportion of patients exhibiting shortness of breath [44].

Despite the above studies reporting positive outcomes, their limitations make it impossible to conclude whether this therapeutic option is safe and efficacious. These observational studies have a high risk of bias, owing to many factors including non-randomization, confounders, description of predictors, patient selection, small sample size, and treatment dose and duration [45].

Finally, there have been two randomized clinical trials so far, both of which were terminated early. The first was conducted in Wuhan, China, between February and April 2020. It was halted due to lack of enrolment, as the outbreak was beginning to be contained in Wuhan, leading to an enrolment of only about half the intended sample size (n = 103 versus n = 200) [20]. Ultimately, there was no significant effect of convalescent plasma on the primary outcome of time to clinical improvement within 28 days [20]. However, an editorial carefully points out hopeful signals that can be gleaned from what was likely an underpowered study [46]. Although it was not the primary end point, there was a significant effect of treatment after patients were stratified into subgroups, leading those with severe disease to have a significantly shorter time to clinical improvement with convalescent plasma (nearly 5 days), whereas those with the life-threatening disease did not [20]. This is similar to the study in a cohort of 138 treated patients, convalescent plasma benefited those with severe but not critical illness [44], which is in alignment with the general principle that convalescent plasma is more effective when administered early in the disease course [47]. In addition, while findings did not reach statistical significance, the trend for a modest improvement in mortality (24% versus 16%) is useful for informing power calculations in upcoming randomized control trials [46].

The second randomized trial, conducted in the Netherlands, was halted after 86 patients were enrolled because the vast majority of patients were found to have baseline neutralizing antibody titres that were comparable to donor levels [21]. Hence, somewhat unsurprisingly, there was no effect of treatment on mortality, hospital length of stay or disease severity [21]. The important lessons from this study are that hospitalized patients may not benefit if they already have high baseline neutralizing titres, and future studies should consider investigating patient populations that are less likely to have high titres and who could benefit from additional treatment, such as certain outpatients who are at high risk of disease progression. In addition, testing potential recipients for existing antibody titres before treatment is not in the current protocol for most trials but is an important consideration [21].

**Risks of convalescent plasma therapy**

There are a number of known and theoretical risks of convalescent plasma. Known risks include risks associated with any blood product, such as transmission of infectious diseases including the potential pathogen being treated, and reactions to serum including serum sickness [37,48,49]. With modern screening of donor plasma for blood-borne pathogens and blood type, these risks are low [48]. Nonetheless, transfusion-related acute lung injury is a life-threatening complication and this issue of potential toxicity must be considered, especially in those at increased risk due to significant lung injury causing critical illness [50,51]. Theoretical risks include antibody-dependent enhancement of infection, and vulnerability to re-infection due to attenuated immune responses. In antibody-dependent enhancement, it is proposed that the presence of antibodies elicited by one coronavirus strain would cross-react with, but fail to neutralize, another coronavirus [49]. Although in vitro data lend theoretical support to this concept [52], there are few epidemiological data to suggest this as a concern in humans in the context of coronaviruses [43,50]. In addition, an initial safety assessment of 5000 patients who received convalescent plasma therapy in the USA demonstrated a <1% rate of serious adverse events immediately following treatment, indicating that the risks of convalescent plasma therapy are likely not excessive relative to the risks of severe COVID-19 [31]. Though convalescent therapy seems to be a safe treatment option both in general and with regards to COVID-19, this should continue to be assessed in future trials [53].

**Patient selection**

Convalescent plasma for treating coronaviruses has demonstrated potential benefit in patients with severe illness, who continued to deteriorate even after the administration of other available therapies such as steroids and/or antivirals [15,20,24,26–34]. However, the age, clinical status and comorbidities of the patients described in the studies to date are highly variable and a description of the optimal recipient cannot be easily concluded from this literature.

A clear theme, supported both theoretically and by clinical studies in previous coronaviruses, is that earlier administration is probably better. As described above, SARS-CoV patients with better outcomes were treated earlier (mean day 11.7 versus 16) [24], and those who received treatment after day 16 had a poor clinical response [25]. This, and the fact that viral load in COVID-19 appears to peak within the first 2 weeks of illness, suggests that there may be a window of opportunity early in the disease course [54]. Similarly, Zeng et al. speculate that the lack of mortality benefit observed in their study, despite convalescent plasma successfully achieving viral clearance, may have been due to treatment being administered too late in the disease course, at a median time of 21.5 days, whereas the one patient who received treatment earlier (day 11) survived [36]. In a cohort of 20 COVID-19–treated patients who were compared to retrospectively matched controls, there was a 0% mortality rate in those who were treated before day 7 of hospitalization, compared with a 10% rate in those treated later in the course of their disease [33]. Nonetheless, in COVID-19, most...
studies generally showed some potential benefit of treatment, even though the treatment date ranged from a few days up to >4 weeks after symptom onset [38,40].

**Donor selection**

Aside from general safety measures for blood product donation such as ABO and RhD grouping, screening tests for human immunodeficiency virus, hepatitis B virus, hepatitis C virus, syphilis, or other locally transmitted infections, and screening for clearance of the virus of concern, previous attempts to use convalescent plasma for coronaviruses identified obtaining an adequate antibody titre as a specific, important consideration in donor selection [22,55,56]. Donor plasma can be tested for antibody titres of specific IgG antibodies using simple, widely available laboratory assays, such as ELISA, or ideally, plasma can be functionally screened for a neutralizing antibody titre. For example, a commonly employed laboratory assay is a plaque-reduction neutralization test, which entails incubating serial dilutions of donor plasma with viral plaques to determine the highest plasma dilution at which viral plaques are reduced by a cut-off amount [90%, for example] [57]. While employing widespread neutralizing tests during MERS-CoV proved to be challenging, as biosafety level 3 laboratories were required [22], SARS-CoV-2 is encouragingly approved for biosafety level 2 containment, which may facilitate broader availability of neutralization testing [58].

One study of three recipients and four donors for MERS-CoV convalescent plasma found that a meaningful serological response was only achieved when the neutralizing antibody titre was at least 1 : 80 [22]. In the same study, neutralization activity could be predicted with 95%–100% specificity by ELISA IgG, providing a possible alternative test for donor selection when a neutralization assay cannot be performed [22]. A larger-scale feasibility study for MERS-CoV identified that only approximately 2% of 443 potential donors had a reactive ELISA with adequately high neutralization titre, such that large-scale screening may be required to identify donors with sufficient antibody levels [55]. Possible reasons identified for inadequate titres included low antibody responses following mild disease, and decreasing antibody titres within months of illness onset.

A kinetics study for MERS-CoV described the highest titres of neutralizing antibodies in the first 50 days after symptom onset, particularly in individuals who had recovered from severe disease, followed by substantial wane within the first 6 months [59]. This same study also showed that MERS-CoV S1 IgG ELISA correlated with neutralizing antibody titres, which may be a suitable alternative screening test when neutralizing titres could not be obtained [59]. For SARS-CoV, neutralizing antibodies appear to be relatively short-lived, peaking at 4 months and diminishing in many patients by 12–36 months and appears to be higher in those with more severe illness [55,60,61]. The kinetics of antibody responses for COVID-19 are still under early investigation, but one report describes the median duration of IgM and IgA anti-SARS-CoV-2 ribonucleoproteins of 5 days, and detection of IgG antibodies 14 days after symptom onset, though time course and host factors probably contribute to variable humoral responses [62].

Convalescent plasma used in two initial trials for COVID-19 had a SARS-CoV-2-specific IgG titre >1 : 1000 and neutralizing titre >40, and >1 : 640 respectively [15,37]. The US FDA currently suggests an optimal neutralizing antibody titre >1 : 160, though 1 : 80 may be considered acceptable if an alternative is not available [63]. Although the optimal titre is not known, studies above indicate that testing for an adequate titre is likely to be important (ideally, by testing neutralizing antibodies, though IgG may be an alternative option), and may be more commonly achieved in a subset of patients who are recently recovered and/or had severe illness.

**Feasibility**

Employing convalescent plasma as a treatment option is accompanied by a number of practical challenges. Currently, the US FDA has issued three pathways for convalescent plasma use in COVID-19: (a) Clinical trials, (b) expanded access (a US nationwide programme to centralize collection and administration of convalescent plasma at participating centres), and (c) single patient emergency investigational new drug pathway (available upon approval, for those patients who do not have access to the first two pathways for various reasons) [63]. Successfully employing this therapy involves a number of carefully orchestrated steps, each with its own challenges and variables that are not yet optimized, including defining optimal donor eligibility requirements, recruiting donors, screening potential donors, testing potential donor plasma for antibody titres, collecting donations, distributing plasma equitably, optimizing dosing and transfusion protocols, and selecting appropriate recipients [49].

Despite the practical challenges, there are currently a number of registered randomized clinical trials from around the globe preparing to tackle this problem (Table 3) [64]. Overall, initial studies of convalescent plasma for COVID-19 and previous coronavirus outbreaks are promising, but it is clear that high-quality, randomized control trials are desperately needed to assess whether this option can effectively treat COVID-19.

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**Author’s contributions**

HB conceptualized, reviewed and edited the manuscript, and procured financing acquisition. DJW investigated, wrote, reviewed and edited the manuscript.

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