Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical Microbiology and Infection 26 (2020) 1436–1446

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Narrative review

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

Denise J. Wooding [1], Horacio Bach [2,*]

[1)] Department of Medicine, University of British Columbia, Vancouver, BC, Canada
[2)] Department of Medicine, Division of Infectious Diseases, University of British Columbia, Vancouver, BC, Canada

ARTICLE INFO

Article history:
Received 17 May 2020
Received in revised form
18 July 2020
Accepted 2 August 2020
Available online 11 August 2020

Editor: J. Rodriguez-Baño

Keywords:
Convalescent plasma
Coronavirus
COVID-19
MERS-CoV
SARS-CoV
SARS-CoV-2

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. **Denise J. Wooding, Clin Microbiol Infect 2020;26:1436**

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

DOIs of original article: https://doi.org/10.1016/j.cmi.2020.07.023, https://doi.org/10.1016/j.cmi.2018.07.006.
* Corresponding author: H. Bach, 2660 Oak Street, Vancouver, BC, V6H3Z6, Canada.
E-mail address: hbach@mail.ubc.ca (H. Bach).

https://doi.org/10.1016/j.cmi.2020.08.005

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 clinicaltrials.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.

Table 1
Clinical and molecular comparison of coronaviruses

	SARS-CoV	MERS-CoV	SARS-CoV-2
First cases	Nov, 2002 Guangdong, China	Jun, 2012 Jeddah, Saudi Arabia	Dec, 2019 Wuhan, China
Confirmed cases	8096	2494	>12 768 000[a]
Mortality rate	9%	34%	4.4%[a]
R0	1.4–4.4	<1	2–4[b]

Abbreviations: SARS-CoV, severe acute respiratory syndrome coronavirus; MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a] Data from WHO, 13 July 2020 situation report [2].
[b] Data from American Thoracic Society, 30 March 2020 [65]. Table adapted from Prompetchara et al. [66].

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 Pao_2/Fio_2, and were receiving mechanical ventilation and various steroids and antivirals. Approximately 1 week after infusion, patients exhibited normalized body temperature, and improved Pao_2/Fio_2 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

Table 2
Reports of convalescent plasma for treating coronaviruses

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.	$n = 3$ 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 with ≥1:640 S-RBD-specific IgG titre	Varied, includes antibiotics, antivirals, steroids, human immunoglobulin, Chinese herbal medicines, others	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.	$n = 2$ adverse events
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	No effect of CP on mortality, disease severity or time to discharge.	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	Improved survival in CP versus no CP in non-intubated patients but not intubated patients.	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	Hydroxychloroquine, azithromycin, antivirals	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	Hegerova L., et al., 2020 [33]	No	$n = 20$ Retrospective matched controls	$n = 20$	Median day 2 of admission, 1 unit	Recovered without symptoms ≥28 days, none were hospitalized during illness	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.	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	Significant improvement in clinical symptoms within 1–3 days, improved O_2 saturation, reduced ventilatory support requirements.	No immediate

Table 2 (*continued*)

Virus	Reference	RCT	Comparator	Treated population	Timing and dose	Donor details	Prior or concurrent treatments	Outcomes	Adverse events
								Superior clinical improvement in CP versus historical controls.	
COVID-19	Shen, C., et al., 2020 [15]	No	None	$n = 5$ Severe, critically ill	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	Improved body temperature, SOFA score, Pao_2/Fio_2, viral load, and SARS-CoV-2-specific neutralizing antibody titres. All patients discharged ($n = 3$) or stable ($n = 2$) at 37 days.	Not specified
COVID-19	Zeng, Q-L., et al., 2020 [36]	No	$n = 11$, no CP	$n = 5$ Severe, ICU admitted	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, IVIG, traditional Chinese medicine, and continuous renal replacement therapy	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.	No immediate
COVID-19	Ye, M., et al., 2020 [38]	No	None	$n = 6$ Deteriorated after standard treatment, critically ill	>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 improved radiological findings, elimination of SARS-CoV-2 on throat swab, reduced respiratory symptoms.	No immediate
COVID-19	Zhang, B., et al., 2020 [39]	No	None	$n = 4$ Critically ill	Day 16–19 of illness, 200-2400 mL	Not specified	Varied, includes ECMO, antivirals, interferon-, IVIGs, antibiotics, antifungals, steroids, continuous renal replacement therapy	Varied, includes improved O2 saturation, radiologic findings, reduced viral load, reduced ventilatory support needs.	No immediate
COVID-19	Ahn, J.Y., et al., 2020 [40]	No	None	$n = 2$ Severe, acute respiratory distress syndrome	Day 6 or day 11 of admission, 500 mL	Donor 1: recovered for 21 days, asymptomatic, IgG OD ratio 0.586 Donor 2: recovered for 18 days, IgG OD ratio 0.532	Varied, includes systemic steroids, hydroxychloroquine, antivirals, antibiotics	Reduced O_2 demand, decreased CRP and IL-6, increased Pao_2/Fio_2, improved radiologic findings, negative SARS-CoV-2 14–16 days after treatment.	No immediate
COVID-19	Abdullah H.M., et al., 2020 [29]	No	None	$n = 2$ Severe, refractory to supportive care and antivirals	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, O_2 saturation, CXR), discharged 16 days after admission. Patient 2: clinical improvement 70 h after infusion (fever, dyspnoea, lymphocyte counts), discharged 21 days after admission.	No immediate
COVID-19	Im, J.H., et al., 2020 [35]	No	None	$n = 1$ Deteriorated after standard treatment, severe	Day 9 of admission, 500 mL	ABO non-compatible donor	Hydroxychloroquine, antivirals	Improvement in respiratory distress symptoms for 3 days after transfusion, improved Pao_2/Fio_2	Subacute worsening, eventual recovery

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Table 2 (*continued*)

Virus	Reference	RCT	Comparator	Treated population	Timing and dose	Donor details	Prior or concurrent treatments	Outcomes	Adverse events
								and CXR on day 3, followed by acute worsening requiring 12 days of ECMO, at which point patient was discharged home.	
COVID-19	Figlerowicz, M., et al., 2020 [34]	No	None	$n = 1$ Age 6, severe, aplastic anaemia	~Day 35 of admission, 200ml	IgG titre 1:700	IVIG, azithromycin, antivirals, steroids, blood and platelet transfusions, antifungals	Nasopharyngeal SARS-CoV-2 RNA swab became negative for the 3 weeks following CP, after 5 weeks of positive swabs. Haematological parameters (pancytopenia) did not improve.	No immediate
MERS-CoV	Choi, W.S., et al., 2016 [23]	No	None	$n = 7$	Not specified	Not specified	Not specified	$n = 6$ survivors, $n = 1$ deceased	Not specified
MERS-CoV	Ko, J-H., et al., 2018 [22]	No	None	$n = 3$ Severe, respiratory failure	Day 8–14 of illness	Mild MERS-CoV, 2 consecutive negative sputum PCR tests and symptom resolution	Varied, includes mechanical ventilation and ECMO	$n = 1$ patient had meaningful Ab response $n = 2$ patients demonstrated neutralizing activity $n = 3$ patients discharged from hospital	Possible TRALI ($n = 1$)
MERS-CoV	Hong, K-H., et al., 2018 [41]	No	None	$n = 2$	Not specified	Not specified	Not specified	$n = 1$ survivor, $n = 1$ deceased	Not specified
MERS-CoV	Chun, S., et al., 2016 [42]	No	None	$n = 1$	Day 8 of illness	Not specified	Antivirals, interferon -2a	Not reported; adverse event	Possible TRALI ($n = 1$)
SARS-CoV	Cheng, Y., et al., 2005 [24]	No	Early CP versus late CP	$n = 80$ Deteriorated after steroids and antivirals	Day 7–30 of illness	7 days afebrile, 25% CXR improvement, no O_2 supplement, ≥14 days from symptom onset	Antibiotics, antivirals, steroids	Lower mortality in early (6.3%) versus late (21.9%) administration of CP. Lower mortality in CP (12.5%) versus overall Hong Kong (17%).	No immediate
SARS-CoV	Soo, Y.O.Y., et al., 2004 [25]	No	CP + steroid versus steroid	$n = 40$	Mean 11 −16 days of illness	Seropositive for SARS-CoV, titre 160–2560	Antivirals, steroids	Discharge by 22 days more likely in CP + steroid (73%) versus steroid only (19%).	No immediate
SARS-CoV	Yeh, K.-M., et al., 2005 [26]	No	None	$n = 3$	Day 10 or 11	Serum IgG titre >640, negative plasma SARS-CoV via PCR	Varied, includes antivirals, antibiotics, steroids	$n = 3$ survived and viral load dropped to 0 or 1 copy/mL 1 day after transfusion, anti-SARS-CoV IgM and IgG increased in time-dependent manner.	Not specified
SARS-CoV	Wong, V., et al., 2003 [27]	No	None	$n = 1$	Day 15 of admission	Not specified	Antibiotics, antivirals, steroids	Resolved fever, resolution of lung infiltrates on CXR, recovered	No immediate
SARS-CoV	Kong L., 2003 [28]	No	None	$n = 1$ Pregnant woman	Not specified	1 month post-recovery	Antivirals, steroids, respirator	Improved oxygen saturation, HR, no longer required respirator, improved CXR	No immediate

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV, severe acute respiratory syndrome coronavirus; RCT, randomized control trial; CP, convalescent plasma; Ab, antibody; CXR, chest X-ray; ECMO, extracorporeal membrane oxygenation; SOFA, sequential organ failure assessment; Pao_2/Fio_2, partial pressure of arterial oxygen/fraction of inspired oxygen; HR, heart rate; TRALI, transfusion-related acute lung injury.

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].

Table 3
Currently registered randomized clinical trials for convalescent plasma in COVID-19

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	N/A	49	Apr, 2020	Jun, 2020	Jun, 2020	Iraq
NCT04442958	Completed	Laboratory parameters	N/A	60	May, 2020	Jun, 2020	Jun, 2020	Turkey
NCT04405310 (CPC-SARS)	Recruiting	Mortality	Phase 2	80	May, 2020	Jun, 2020	Jul, 2020	Mexico
NCT04356534	Recruiting	Mechanical ventilation requirement	N/A	40	Apr, 2020	Jun, 2020	Jun, 2020	Bahrain
NCT04345523 (ConPlas-19)	Recruiting	Clinical improvement	Phase 2	278	Apr, 2020	Jul, 2020	Jul, 2020	Spain
NCT04342182 (ConCoVid-19)	Recruiting	Mortality	Phase 2/3	426	Apr, 2020	Jul, 2020	Jul, 2020	Netherlands
NCT04403477	Recruiting	Mortality in-hospital, time to death	Phase 2	20	May, 2020	Jul, 2020	Oct, 2020	Bangladesh
NCT04392414	Recruiting	Body temperature	Phase 2	60	May, 2020	Aug, 2020	Sep, 2020	Russia
NCT04385199	Recruiting	Clinical improvement	Phase 2	30	May, 2020	Aug, 2020	Aug, 2020	USA
NCT04383535 (PLASM-AR)	Recruiting	Clinical improvement	N/A	333	May, 2020	Aug, 2020	Sep, 2020	Argentina
NCT04381858	Recruiting	Hospitalization time, oxygenation, ARDS, time to death and ventilation time	Phase 3	500	May, 2020	Aug, 2020	Sep, 2020	Mexico
NCT04332835 (CP-COVID-19)	Not yet recruiting	Viral load, IgG and IgM titres	Phase 2/3	80	May, 2020	Aug, 2020	Dec, 2020	Colombia
NCT04380935	Not yet recruiting	Mortality	Phase 2/3	60	May, 2020	Aug, 2020	Aug, 2020	Indonesia
NCT04397757	Recruiting	Clinical improvement and serious adverse events	Phase 1	80	May, 2020	Sep, 2020	Nov, 2020	USA
NCT04393727 (TSUNAMI)	Recruiting	Mechanical ventilation requirement	Phase 2	126	May, 2020	Sep, 2020	Oct, 2020	Italy
NCT04374526 (LIFESAVER)	Recruiting	Rate of clinical progression	Phase 2/3	182	May, 2020	Sep, 2020	Jun, 2021	Italy
NCT04372979 (PLASCOSSA)	Not yet recruiting	Survival time without ventilator requirements	Phase 3	80	May, 2020	Oct, 2020	May, 2021	France
NCT04385043 (COV2-CP)	Recruiting	Mortality	Phase 2/3	400	May, 2020	Oct, 2020	May, 2021	Italy
NCT04388410 (EPCOvid-1)	Not yet recruiting	Severity, mortality, adverse events	Phase 2/3	250	Jun, 2020	Oct, 2020	Dec, 2020	Mexico
NCT04348656 (CONCOR-1)	Recruiting	Intubation or death in hospital	Phase 3	1200	May, 2020	Oct, 2020	Dec, 2020	USA
NCT04385186	Not yet recruiting	Mortality	Phase 2	60	Jun, 2020	Nov, 2020	Dec, 2020	Colombia
NCT04433910 (CAPSID)	Recruiting	Severity, mortality	Phase 2	106	Jun, 2020	Dec, 2020	Feb, 2021	Germany
NCT04395170	Not yet recruiting	ICU admission or mechanical ventilation	Phase 2/3	75	Sep, 2020	Dec, 2020	Jun, 2021	Colombia
NCT04375098	Recruiting	Mechanical ventilation requirement, longer hospitalization and mortality	Phase 2	58	May, 2020	Dec, 2020	Dec, 2021	Chile
NCT04359810	Recruiting	Time to clinical improvement	Phase 2	105	Apr, 2020	Dec, 2020	Apr, 2021	USA
NCT04425837	Not yet recruiting	Mortality, adverse events, ICU admission and mechanical ventilation	Phase 2/3	236	Jul, 2020	Feb, 2021	Feb, 2021	Colombia
NCT04358783 (COP-COVID-19)	Recruiting	Mortality	Phase 2	30	Apr, 2020	Feb, 2021	May, 2021	Mexico
NCT04452812 (PROMETEO)	Not yet recruiting	Mortality and side effects	Phase 1/2	15	Jul, 2020	Mar, 2021	Apr, 2021	Mexico
NCT04390503	Recruiting	Disease severity	Phase 2	200	May, 2020	Apr, 2021	Apr, 2021	USA
NCT04362176 (PassItOnII)	Recruiting	Clinical improvement	Phase 3	500	Apr, 2020	Apr, 2021	Apr, 2021	USA
NCT04421404 (CAPRI)	Recruiting	Severe hypoxaemic respiratory failure	Phase 2	30	Jun, 2020	Apr, 2021	Apr, 2021	USA
NCT04344535	Enrolling by invitation	Mechanical ventilation requirement	Phase 1/2	500	Apr, 2020	Apr, 2021	Aug, 2021	USA
NCT04442191	Recruiting	Oxygen requirement	Phase 2	50	May, 2020	May, 2021	May, 2021	USA
NCT04374487	Not yet recruiting	Progressive to severe ARDS and all-cause mortality	Phase 2	100	May, 2020	May, 2021	May, 2021	India
NCT04425915	Recruiting	Time to clinical improvement	Phase 3	400	Jun, 2020	May, 2021	May, 2021	India

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Table 3 (*continued*)

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	Jun, 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)	Recruiting	Mortality	Phase 2/3	15000	Mar, 2020	Dec, 2021	Dec, 2031	UK
NCT04415086 (COOPCOVID-19)	Recruiting	Time to clinical improvement or discharge	Phase 2	120	Jun, 2020	Apr, 2022	May, 2022	Brazil
NCT04355767 (C3PO)	Not yet recruiting	Disease progression within 15 days	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	Jan, 2023	USA
NCT04323800 (CSSC-001)	Recruiting	Clinical improvement	Phase 2	487	Jun, 2020	Dec, 2022	Jan, 2023	USA
NCT04333251	Not yet recruiting	Mechanical ventilation and oxygen requirement	Phase 1	115	Apr, 2020	Dec, 2022	Dec, 2022	USA
NCT04364737	Recruiting	Clinical improvement	Phase 2	300	Apr, 2020	Jan, 2023	Apr, 2023	USA
ChiCTR2000029757	Recruiting	Time to clinical improvement	Phase 0	200	Feb, 2020	—	—	China
ChiCTR2000030702	Recruiting	Time to clinical recovery	Phase 0	50	Mar, 2020	—	—	China
ChiCTR2000030381	Pending	Clinical improvement rate	N/A	40	Feb, 2020	—	—	China
ISRCTN85216856	Recruiting	Mortality	Phase 2/3	200	May, 2020	—	Dec, 2020	Ecuador
IRCT20200404046948N1	Recruiting	Clinical improvement	Phase 3	60	Apr, 2020	—	—	Iran
IRCT20200413047056N1	Recruiting	Imaging and laboratory values, hospital length of stay, mechanical ventilation	Phase 3	15	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/2020/06/025803	Recruiting	Time to clinical improvement	Phase 3	400	Jun, 2020	—	—	India
ISRCTN50189673	Recruiting	Mortality	Phase 2/3	15000	Mar, 2020	—	—	UK
CTRI/2020/05/025346	Not Recruiting	ARDS and mortality	Phase 2	90	Jun, 2020	—	—	India
NL8633	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.

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

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 co-morbidities 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, 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.

Funding

This work was supported by the Canadian Institutes of Health Research (CIHR) grant Canadian 2019 Novel Coronavirus (COVID-19) Rapid Research Funding Opportunity (No. OV3-170627) Therapeutics to HB.

Transparency declaration

HB reports grants from Canadian Institute of Health Research during the conduct of the study. DJW has nothing to disclose.

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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