International Survey of Trials of Convalescent Plasma to Treat COVID-19 Infection

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ABSTRACT

The collection and clinical use of COVID-19 convalescent plasma (CCP) as a therapy for COVID-19 infection is under development and early use in many centers worldwide. We conducted an international survey of centers undertaking studies of CCP to provide understanding of the common themes and differences between them. Sixty-four studies in 22 countries were identified from clinical trial registries and personal contacts of the authors. Twenty of the 64 centers (31%) from 12 of 22 countries (55%) responded to the survey. Of the 20 studies, 11 were randomized controlled trials (RCTs), and 9 were case series. Only 4 of the RCTs plan to recruit 400 patients or more, and only 3 RCTs were blinded. The majority of studies will study the effect of CCP on sick patients requiring hospitalization and those requiring critical care, and none is examining the role of CCP in non-infected at-risk individuals. A wide variety of primary and secondary outcomes are being used. The donor eligibility criteria among the studies are very similar, and the use of plasmapheresis for the collection of CCP is almost universal. The planned dose of CCP ranges from as little as 200 mL to well over 1 L, but is 400 to 800 mL or 4 mL/kg or greater in all the RCTs. There is considerable variability in donor antibody testing with no consistency regarding the cut-off for antibody titer for acceptance as CCP or the use of pathogen-inactivation. Our survey provides an understanding of the similarities and differences among the studies of CCP, and that by virtue of their design some studies may be more informative than others.

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Contents

There are huge efforts to find effective therapies for COVID-19 infection. Numerous trials are in progress; indeed, more than 1000 studies addressing various aspects of COVID-19 were found to be registered on ClinicalTrials.gov on 15 May 2020, including more than 600 interventional studies and randomized clinical trials (RCTs) [1].

The collection and clinical use of COVID-19 convalescent plasma (CCP) is under development and early use in many centers and countries. Those implementing CCP are likely to prepare and administer it in different ways. This variation is not surprising given the urgency of the situation, and the limited evidence base for the safety and effectiveness of convalescent plasma against the several infectious agents against which it has been used [2,3].

There are several key questions surrounding the use of CCP as a therapeutic. These include antibody testing and donor selection, methods of collection and storage, dose and duration of treatment, lot to lot

variability, adverse effects, selection of the patients most likely to bene-fit, and measurement of efficacy. A number of publications have already addressed some of these issues and a few have provided either recom-mendations [3-8] or preliminary results [9]. Links to some websites pro-viding information and/or recommendations about CCP are provided in Appendix 1.

Before being offered for routine use, this new intervention should be rigorously tested in clinical trials designed to define both safety and ef-ficacy. This leads to questions about the design and conduct of these tri-als so that valid data are provided for analysis as quickly as possible. If CCP is found to be safe and effective, the lessons learned from the trials about the optimal methods for preparing and administering CCP will need to be implemented as a matter of urgency.

We report the results of an international survey of centers undertak-ing early studies of CCP to provide an understanding of the common themes and differences between them in the preparation and investiga-tion of CCP and that by virtue of their design some studies may be more informative than others.

Methods

A survey tool was developed to collect information from centers planning to collect and administer CCP to patients with COVID-19 infec-tion. The centers were identified on 1st May 2020 from a search of Clinicaltrials.gov, the Chinese Clinical Trial Registry (ChiCTR) and personal contacts of the authors. The survey tool was written in English and designed to gather information on the whole process of the collec-tion and administration of CCP from the identification of suitable donors including antibody testing, through the collection and storage of the product, the identification of patients suitable for its administration and details of the design of clinical trials. We did not ask about the planned completion dates of the studies so it is not known when the re-sults will be available.

Results

The survey was sent electronically to the study contacts for 64 stud-ies in 22 countries shown in Fig. 1 and listed in Appendix 2 with a re-quest to complete and return it within 7 days. We received responses from 20 of 64 (31%) studies from 12 of 22 (55%) countries, and they pro-vide the data for this report.

The first survey questions were about the design of the studies. Of the 20 studies, 11 were randomized controlled trials (RCTs) and 9 were case series (Table 1A). There was blinding of the investigators to the intervention in 3 of 11 RCTs where standard plasma was used as a comparator, and no blinding in the other 8. Among the RCTs, there was huge variation in the number of study sites (range, 1-250), and this was even more marked in the non-RCTs (range, 1-1300+). There was also considerable variation in the number of patients receiving CCP in both the RCTs (range, 40-5000) and in the case series (6-10 000).
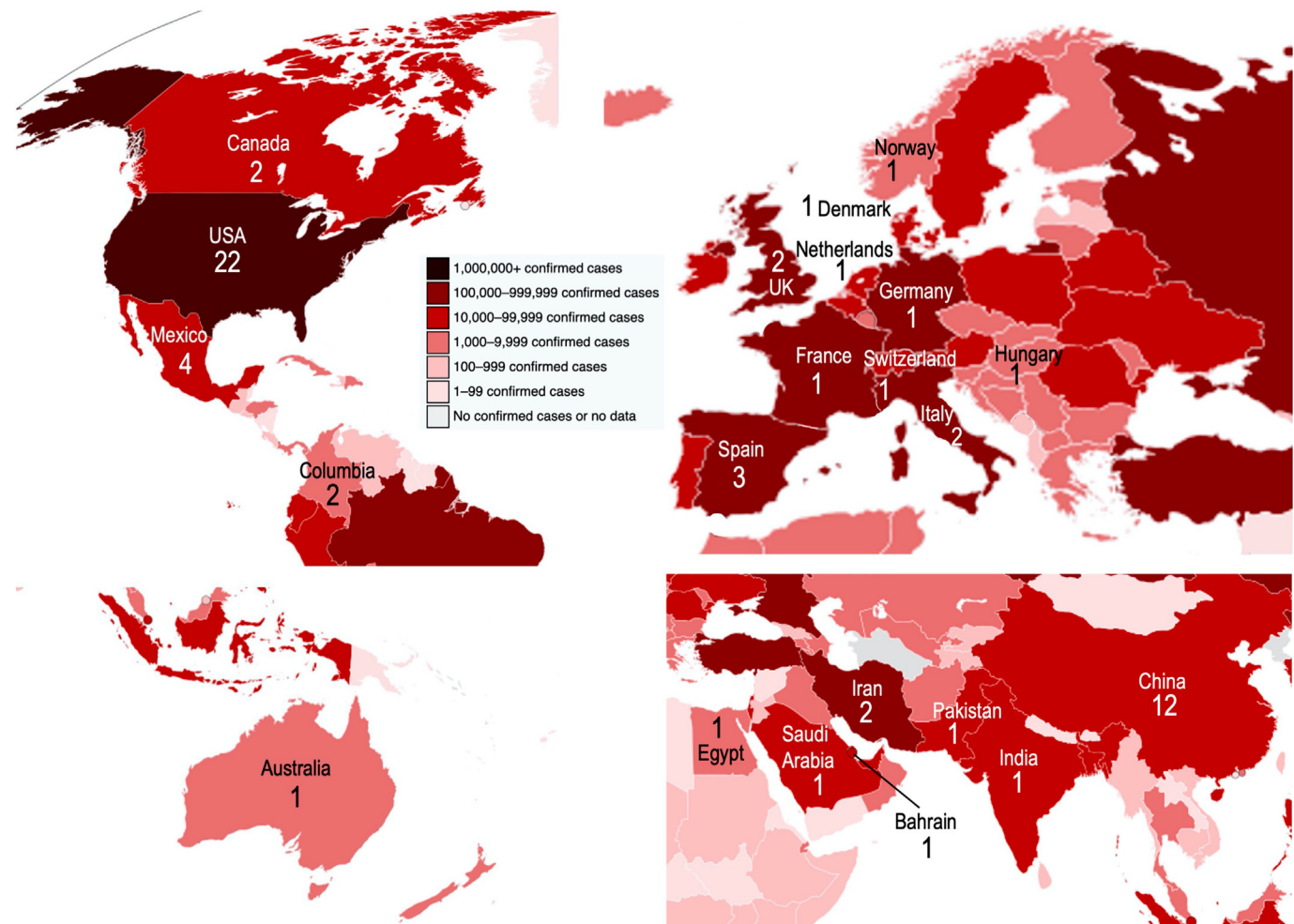

Fig. 1. World map showing the number of CCP studies and the confirmed number of cases of COVID-19 by country as of May 15, 2020.

Table 1A
Study design.

Study identifier	Design	Number of study sites	Number of patients receiving CCP	Age of patients (years)	Upper age limit
USA 1	Case series	1300+	10 000	>18	No
USA 2	RCT (blinded)	1–10	103	>18	No
USA 3	RCT (blinded)	1	400	>18	No
USA 4	Case series	1	30	>18	No
USA 5	Case series	20	100	Adults	No
USA 6	RCT (blinded)	2–10	110	>18	No
China 1	Case series	1	6	Not stated	No
Mexico 1	Case series	1	10	>18	No
Spain 1	RCT (un-blinded)	25	139	Not stated	No
Spain 2	RCT (un-blinded)	1	60	18–69	69
Canada 1	RCT (un-blinded)	53	800	≥16	No
Canada 2	RCT (un-blinded)	16	100	0–18	18
Iran 1	Case series	1	30	30–70	70
UK 1	RCT (un-blinded)	120	1000	>18	No
UK 2	RCT (un-blinded)	250	5000	>0	No
Egypt 1	Case series	1	40	>18	No
France 1	RCT (un-blinded)	9	60	>18	No
Germany 1	RCT (un-blinded)	1	40	<75	75
Saudi Arabia 1	Case series	17	40	>18	No
Switzerland 1	Case series	1	10	18–75	75

RCT, randomized control trial.

The comparison intervention to CCP was standard plasma in 3 of 11 RCTs, and no plasma in the others (although not stated in one study) (Table 1B). The clinical stages of illness targeted by the different trials are shown in Fig. 2. Most RCTs (9/11) included symptomatic, infected but not critically ill patients; 6 RCTs included critically ill patients; and 2 included asymptomatic infected patients. In

Table 1B
Study design (continued)

Study identifier	Comparison group for the RCTs	Exclusions	Adverse effects
USA 1	Non-randomized patients	None	Febrile, allergic, anaphylaxis; TACO
USA 2	Standard plasma	Admission to hospital for ventilation	Anaphylaxis; TACO, TRALI; TTI
USA 3	Standard plasma	Pregnancy	Febrile, allergic, anaphylaxis; TACO
USA 4	Non-randomized patients	Ventilator dependent	Not stated
USA 5	Non-randomized patients	None	Febrile, allergic, anaphylaxis; TACO, TRALI
USA 6	Standard plasma	Cardiac or respiratory failure; Participation in other trials	Febrile, allergic, anaphylaxis; TACO
China 1	Non-randomized patients	Pregnancy	Febrile, allergic, anaphylaxis; TACO
Mexico 1	Non-randomized patients	Renal failure; ECMO; Pregnancy	Febrile, allergic, anaphylaxis; TACO
Spain 1	Not stated	Symptoms >12 days prior; Ventilator or high flow O$_2$; Renal failure; Participation in other trials	Febrile, allergic, anaphylaxis; TACO, TRALI; ADE
Spain 2	No plasma	Participation in other trials	Febrile, allergic, anaphylaxis; TACO
Canada 1	No plasma	Ventilator or ECMO; Symptoms >12 days prior	Febrile, allergic, anaphylaxis; TACO
Canada 2	No plasma	Not stated	Febrile, allergic, anaphylaxis; TACO
Iran 1	Non-randomized patients	Pre-intubation; Ventilator dependent; Heart failure	Not stated
UK 1	No plasma	Participation in other trials	Febrile, allergic, anaphylaxis; TACO, TRALI, TAD; ADE; Thrombosis
UK 2	No plasma	Participation in other trials	Febrile, allergic, anaphylaxis; TACO, TRALI; ADE
Egypt 1	Non-randomized patients	Ventilator or ECMO; Cardiac, pulmonary, renal, or liver failure; Participation in other trials	Not defined at time of survey
France 1	No plasma	Ventilator or ECMO; Cardiac, pulmonary, renal, or liver failure; Pregnancy; Uncontrolled infection; Participation in other trials	Febrile, allergic, anaphylaxis; TACO; ADE
Germany 1	No plasma	Liver failure; Pregnancy; Participation in other trials	Febrile, allergic, anaphylaxis; TACO
Saudi Arabia 1	Non-randomized patients	Not defined at time of survey	Transfusion reactions per aaBB
Switzerland 1	Non-randomized patients	Ventilator or ECMO; Cardiac, pulmonary failure; Pregnancy; Participation in other trials	Febrile, allergic, anaphylaxis; TACO; Other adverse events

'No plasma' indicates no infusion of any fluid.
TACO, transfusion associated circulatory overload; TRALI, transfusion related acute lung injury; TTI, transfusion transmitted infection; ADE, antibody dependent enhancement of infection; TAD, transfusion associated dyspnea; aaBB, American Association of Blood Banks.
All studies require a positive PCR test of the recipient except France-1 and Iran-1.
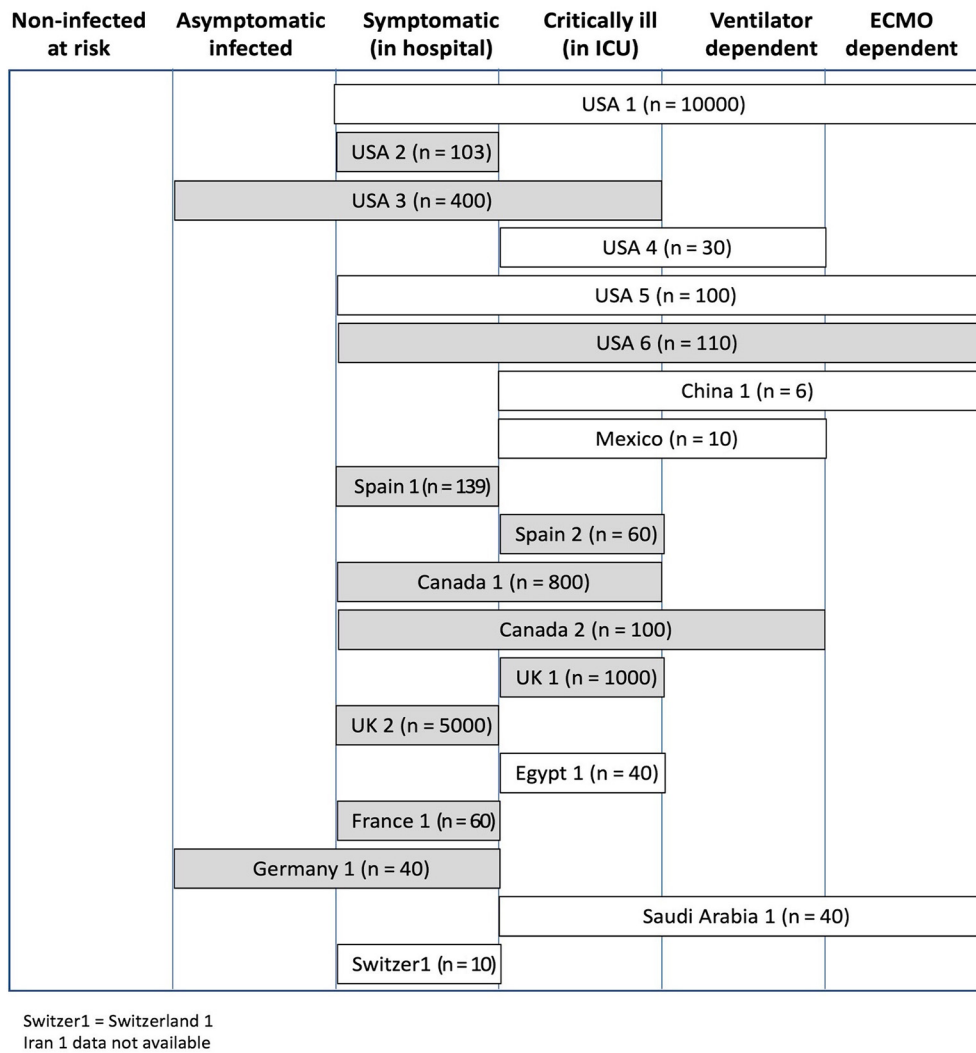
Fig. 2. Study enrolment according to clinical stage of disease based on survey responses. The number in parentheses is the number of subjects planned to receive CCP. The shaded boxes indicate randomized controlled trials.

contrast, all but one of the case series included critically ill patients. None of the studies focused on non-infected at risk individuals. Children were included as study participants in 3 of the RCTs. All studies required a positive PCR test of the recipient except for one of the studies in Iran (Iran-1) and the study in France. The collection of possible adverse effects was similar for all studies, although only 4 studies specifically included antibody dependent enhancement of infection (ADE).

There was considerable variability in the primary and secondary outcomes for the studies (Table 2). Fig. 3 provides a summary of the primary outcomes with the most frequent being clinical change and mortality. The primary outcomes for the 3 largest RCTs were a composite of intubation or death at day 30 (USA-6), ventilation-free days (Canada-1) and mortality at 28 days (UK-2).

The donor eligibility criteria for the collection of CCP were very similar among the studies (Table 3). In 15 of 16 studies where this information was provided, the respondents indicated the requirement for a prior positive polymerase chain reaction (PCR) assay for SARS-COV2. The time required from recovery of symptoms of COVID-19 infection before collection of CCP varied from 14 to 28 days. Nearly all studies indicated that female donors would be tested for HLA or HLA and HNA antibodies to minimize the risk of transfusion-related acute lung injury (TRALI). Plasmapheresis was selected as the method of collection of CCP by nearly all investigators.

The dose of plasma was 400 to 800 mL or 4 mL/kg or greater in all 10 RCTs and in 6 of 8 of the case series providing this information (Table 4). Protocols called for CCP to be stored in the frozen state prior to thawing before administration in all 16 studies that provided this information apart from one study (Germany-1). Six studies including only 2 of the RCTs indicated that the CCP would be pathogen-inactivated.

Responses were received to questions about donor antibody testing from 15 of 20 of survey participants (Table 5). Eleven of 15 of all studies and 8 of 11 of the RCTs indicated that antibody testing would be carried out before the administration of CCP, and the remainder after its administration. Eleven of 15 of all studies and 6 of 11 of the RCTs indicated that testing would include neutralizing antibodies sometimes with additional testing for non-neutralizing antibodies. Only 8 studies provided information about cut-off levels or titers of antibodies used to qualify donors.

Discussion

The COVID-19 pandemic represents a major threat to global health and has caused enormous strain on healthcare systems worldwide. One of the major research challenges is to develop trials to determine the effectiveness of any promising therapies, and one of these treatment options is CCP. A systematic review has shown that

Table 2
Primary and secondary outcomes

Study identifier	Primary outcome	Main secondary outcomes
USA 1	Availability of convalescent plasma	Serious adverse events
USA 2	Time to progression using outpatient ordinal scale	Not recorded
USA 3	Days on ventilation	Mortality at day 90
USA 4	Feasibility of treating ICU patients	Not recorded
USA 5	Not yet decided	Days on ventilation; LOS in ICU; Hospital LOS
USA 6	Modified WHO score at day 14	Days on ventilation; Hospital LOS; Change in viral load; Mortality at day 28
China 1	Change in viral load	Days on ventilation
Mexico 1	Change in lung injury (Kirby index)	Mortality at day 15 & 30
Spain 1	Proportion in level 5 or higher of 7-level ordinal scale	Days on ventilation; Hospital LOS; Change in viral load; Time to clinical worsening; Mortality at 15 days
Spain 2	Feasibility and safety (pilot study)	Days on ventilation; LOS in ICU
Canada 1	Composite of intubation or death at day 30	Days on ventilation; LOS in ICU; Hospital LOS; Change in viral load
Canada 2	Time to recovery or discharge by day 30	LOS in ICU; Hospital LOS; Change in viral load; Others not specified
Iran 1	Mortality at days 10 & 30	Days on ventilation; Hospital LOS; Changes to laboratory tests at day 1, 3 & 7
UK 1	Ventilator-free days at day 21	Days on ventilation; Hospital LOS; Change in viral load; Level of respiratory support at day 15
UK 2	Mortality (date not yet specified)	Days on ventilation; LOS in ICU; Hospital LOS; Renal impairment
Egypt 1	LOS in ICU	Hospital LOS
France 1	Ventilation-free survival at day 14	Days on ventilation; LOS in ICU; Hospital LOS; Disease severity (WHO scale) at day 7 & 14
Germany 1	Mortality at day 28	Days on ventilation; LOS in ICU; Hospital LOS; Change in viral load
Saudi Arabia 1	LOS in ICU	Days on ventilation; Days to clinical recovery
Switzerland 1	Immune markers before vs after infusion	Clinical change (7-point ordinal scale); serious adverse events

ICU, intensive care unit; LOS, length of stay.

convalescent plasma (CP) may have clinical benefit for people with acute viral diseases such as influenza and severe acute respiratory syndrome (SARS) [10], but its effectiveness in patients with COVID-19 is as yet uncertain [8]. One reason for this is that many outbreaks are regional and short-lived not providing sufficient time to collect and carefully study the safety and efficacy of CP. The current COVID-19 pandemic may not be bound by such limitations and there is likely to be sufficient time to collect CCP to treat newly infected patients. The logical first research questions are to determine the safety and effectiveness of CCP; and not surprisingly, numerous studies have been established to do this worldwide. We have undertaken an international survey of centers who have instituted studies of CCP to provide an understanding of the similarities and differences between them.

We identified 64 CCP studies in 22 countries by searching trial registries and through personal contacts. This probably represents an unprecedented upsurge in studies of any single topic in transfusion medicine. We recognize that we may not have identified all CCP studies, and that further studies will have been initiated since we began the survey. We contacted those we identified as the
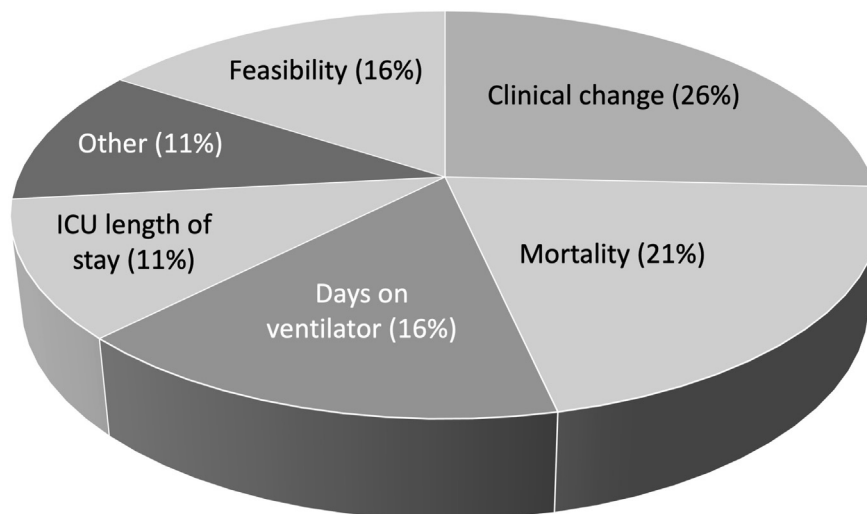

Fig. 3. Primary outcomes of CCP trials based on survey responses.

Table 3
Donor eligibility

Study identifier	Donor category	Prior SARS-CoV2 in donor	Other donor qualifications	Method of collection
USA 1	Uncertain	Not stated	Not stated	Not stated
USA 2	Males; Females negative for HLA antibodies	Positive PCR	Neg PCR if 14–28 days; ≥ 28 d after symptoms	Plasmapheresis
USA 3	Males; Females negative for HLA & HNA antibodies	Positive PCR or antibody	≥ 14 d after symptoms	Plasmapheresis
USA 4	Males; Females negative for HLA & HNA antibodies	Positive PCR	≥ 14 d after symptoms	Plasmapheresis
USA 5	Males; Females negative for HLA & HNA antibodies	Positive PCR	≥ 28 d after symptoms	Plasmapheresis
USA 6	Males; Females negative for HLA antibodies	Positive PCR	Neg PCR if 14–28 days; ≥ 28 d after symptoms	Plasmapheresis
China 1	Males; Females negative for HLA & HNA antibodies	Positive PCR	≥ 14 d after symptoms	Not stated
Mexico 1	Males; Females negative for HLA antibodies	Positive PCR	≥ 14 d after symptoms	Mainly plasmapheresis
Spain 1	Not stated	Not stated	Not stated	Not stated
Spain 2	Males; Females negative for HLA & HNA antibodies	Positive PCR	≥ 14 d after symptoms	Plasmapheresis
Canada 1	Males; Females negative for HLA antibodies	Positive PCR	Neg PCR if 14–28 days; ≥ 28 d after symptoms	Plasmapheresis
Canada 2	Males; Females negative for HLA & HNA antibodies	Positive PCR	≥ 28 d after symptoms (Canadian Blood Services); ≥ 14 d after symptoms (HemaQuebec)	Plasmapheresis
Iran 1	Not stated	Not stated	Recovery from illness	Not stated
UK 1	Males; Females negative for HLA & HNA antibodies	Positive PCR plus antibody	≥ 28 d after symptoms	Mainly plasmapheresis
UK 2	Males; Females negative for HLA & HNA antibodies	Positive PCR plus antibody	≥ 28 d after symptoms	Mainly plasmapheresis
Egypt 1	Male donors only	Positive PCR	≥ 14 d after symptoms	Plasmapheresis
France 1	Males; Females negative for HLA antibodies	Clinical illness test not required	≥ 14 d after symptoms	Plasmapheresis
Germany 1	Uncertain	Uncertain at time of survey	Not stated	Plasmapheresis
Saudi Arabia 1	Males; Females negative for HLA antibodies	Positive PCR	≥ 14 d after negative PCR	Plasmapheresis
Switzerland 1	Male donors only	Positive PCR	≥ 28 d after symptoms	Plasmapheresis

PCR, polymerase chain reaction.

principal investigators by email requesting rapid completion of the survey and received 20 responses from 64 studies (31%) from 12 of 22 countries (55%).

The responses raise concerns about their ability to determine the effectiveness of CCP across the clinical spectrum of COVID-19 infected patients. These concerns include the lack of randomization in 11 of 20 studies and small sample size in 10 of 20. Only 4 of the RCTs plan to recruit 400 patients or more so that the majority of studies are unlikely to have sufficient power to detect significant changes in key outcomes. A substantial proportion of survey respondents noted that mortality would be a primary outcome. Current estimates would suggest that the mortality rate of among hospitalized patients is approximately 15%, and in order to detect a 10% relative reduction in death rate (from 15% to 13.5%) with 80% power and alpha = 0.05 would require a study with over 15 000 participants. Furthermore, 8 RCTs are unblinded which may introduce bias in the assessment of outcomes other than mortality. On the other hand, the 3 blinded RCTs, where standard plasma is being used as the comparator to CCP, may have a reduced ability to detect harms from the transfusion of plasma in COVID-19 infected patients. Among those who responded to the survey, the majority of studies place emphasis on the effect of CCP on sick patients requiring hospitalization and those requiring critical care, and none is examining the role of CCP in non-infected at-risk individuals. A wide variety of primary and secondary outcomes were selected by investigators which likely reflects uncertainty regarding the most appropriate study outcome for CCP at different stages of COVID-19 infection.

The donor eligibility criteria for the collection of CCP are very similar among the studies in the almost universal requirement for a prior positive PCR assay for SARS-COV2 although there is variation in the time from recovery of symptoms of COVID-19 infection before collection of CCP. Nearly all survey respondents plan to use plasmapheresis to collect CCP and only some plan to use pathogen-inactivation. The planned dose of CCP ranges from as little as 200 mL to well over 1 L, but is 400 to 800 mL or 4 mL/kg or greater in all the RCTs. There is considerable variability in donor antibody testing with testing for neutralizing antibodies or non-neutralizing antibodies alone, or a combination of the two; and there is no consistency regarding the cut-off for antibody titer for acceptance as CCP or the use of pathogen-inactivation. Individual units of CCP would be expected to have a range of viral neutralizing capacity depending on their characteristics such as the dose, antibody titer, and antibody affinity, thereby further complicating inferences about efficacy.

As shown in Appendix 2, a large number of studies of CCP are planned worldwide. Our survey provides an informative sampling of these and indicates shared similarities and differences among them. By virtue of randomization, blinding, and sample size some studies may be more informative than others. The survey clearly shows an initial focus on sick hospitalized patients. Whether passive transfer of antibody may prove to be more effective in very recently infected individuals or non-infected persons at high risk for infection will await other studies not represented here. Results of all well-designed trials are eagerly awaited. The COVID-19 pandemic provides the first opportunity in history to rigorously define the role of convalescent plasma in a critically important viral respiratory disease.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tmrv.2020.06.003.

Table 4
Details of plasma dosing

Study identifier	Dose (mL)	Number of infusions	Control plasma details	Storage conditions of CCP	Pathogen inactivation
USA 1	200–500	1	No control plasma (case series)	Not stated	Not stated
USA 2	4–6 mL/kg*	1	Given prior to discharge	Frozen then thawed	No
USA 3	500	1	Low antibody for SARS-CoV2	Frozen then thawed	Uncertain at time of survey
USA 4	40 mL/kg	1	No control plasma (case series)	Not stated	Not stated
USA 5	200–500	1	No control plasma (case series)	Frozen then thawed	No
USA 6	500	2 (day 1 and 2)	2 doses of FFP or FP24	Frozen then thawed	No
China 1	200	Depends on availability	No control plasma (case series)	Frozen then thawed	Yes
Mexico 1	200	1	No control plasma (case series)	Frozen then thawed	No
Spain 1	Not stated	Not stated	Not stated	Not stated	Not stated
Spain 2	600 (200 × 3)	Every 8 h up to 3 doses	No control plasma (unblinded)	Frozen then thawed	Methylene blue or amotosalen
Canada 1	500 (250 x2)	1	No control plasma (unblinded)	Frozen then thawed	No
Canada 2	10 mL/kg (500 max)	1	No control plasma (unblinded)	Frozen then thawed	Uncertain at time of survey
Iran 1	Not stated	Not stated	Not stated (case series)	Not stated	Not stated
UK 1	400–700 (200–300 × 2)	2 (day 1 and 2)	No control plasma (unblinded)	Frozen then thawed	No
UK 2	400–700 (200–300 × 2)	2 (day 1 and 2)	No control plasma (unblinded)	Frozen then thawed	No
Egypt 1	400–500	1	No control plasma (case series)	Frozen then thawed	Mixture
France 1	800–880 (400–440 × 2)	2 (day 1 and 2)	No control plasma (unblinded)	Frozen then thawed	Yes
Germany 1	400	1	No control plasma (unblinded)	Stored at 4C (not frozen)	No
Saudi Arabia 1	200–400	Daily up to 5 times	No control plasma (case series)	Frozen then thawed	Yes
Switzerland 1	600 (200 × 3)	3	No control plasma (case series)	Frozen then thawed	Yes

* Ideal body weight.

Table 5
Antibody testing of donor

Study identifier	Donor antibody testing before or after infusion	Antibody test details
USA 1	Not stated	Not stated
USA 2	Before	Non-neutralizing titer >1:80
USA 3	Before	Non-neutralizing per FDA guidelines
USA 4	Uncertain at time of survey	Uncertain at time of survey
USA 5	Before	Neutralizing antibody >1:100 (Euroimmune)
USA 6	Before	Neutralizing plus non-neutralizing >1:160
China 1	Before	Non-neutralizing >1:160
Mexico 1	After	Neutralizing plus non-neutralizing (no cut-off)
Spain 1	Not stated	Not stated
Spain 2	Before	Non-neutralizing EIA O.D. >1.0
Canada 1	Before	Neutralizing antibody >1:160 or EIA
Canada 2	After	Neutralizing plus non-neutralizing (cut-off not decided)
Iran 1	Not stated	Not stated
UK 1	Before	Neutralizing plus non-neutralizing (cut-off not decided)
UK 2	Before	Neutralizing plus non-neutralizing (cut-off not decided)
Egypt 1	After	Neutralizing antibody >1:40
France 1	Before	Neutralizing >1:30 plus non-neutralizing
Germany 1	Uncertain at time of survey	Uncertain at time of survey
Saudi Arabia 1	Before	Neutralizing plus non-neutralizing (no cut-off)
Switzerland 1	After	Neutralizing plus non-neutralizing (no cut-off)

Declaration of competing interest

The authors have no conflicts to declare.

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