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The Emerging Role of Convalescent Plasma in the Treatment of COVID-19

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Abstract

Various agents are currently under evaluation as potential treatments in the fight against coronavirus disease 2019 (COVID-19). Plasma from patients that have overcome COVID-19 infection, referred to as convalescent plasma, is a treatment option with considerable background in viral diseases such as Spanish influenza, H1N1, Ebola, Severe Acute Respiratory Syndrome (SARS), and Middle East Respiratory Syndrome (MERS). Although convalescent plasma has historically proven beneficial in the treatment of some viral diseases, its use is still explorative in the context of COVID-19. To date, preliminary evidence from case series is favorable as significant clinical, biochemical improvement and hospital discharge have been reported. A detailed overview of randomized as well non-randomized trials of treatment with convalescent plasma, which have been registered worldwide, is provided in this review. Based on these studies, data from thousands of patients is anticipated in the near future. Convalescent plasma seems to be a safe option, but potential risks such as transfusion-related acute lung injury and antibody-dependent enhancement are discussed. Authorities including the Food and Drug Administration (FDA), and scientific associations such as the International Society of Blood Transfusion (ISBT) and the European Blood Alliance (EBA), have provided guidance into the selection criteria for donors and recipients. A debatable, pivotal issue pertains to the optimal timing of convalescent plasma transfusion. This treatment should be administered as early as possible to maximize efficacy, but at the same time be reserved for severe cases. Emerging risk stratification algorithms integrating clinical and biochemical markers to trace the cases at risk of significant deterioration can prove valuable in this direction.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia was first noted in Wuhan (China) in December 2019[1] and the disease induced by the virus has been termed coronavirus infectious disease 2019 (COVID-19). To date, various treatment regimens are being evaluated as potential tools in COVID-19 in addition to the standard supportive care including oxygen supply, intensive care admission, or even extracorporeal membrane oxygenation for critically ill patients.[2] Among agents, antiviral drugs such as remdesivir,[3] lopinavir/ritonavir,[4] the antimalarial agent hydroxychloroquine in combination with azithromycin,[5] and monoclonal antibodies, such the anti-interleukin-6 receptor tocilizumab,[6–8] are currently under evaluation for treatment of COVID-19.

Plasma from patients that have overcome COVID-19 infection, namely convalescent plasma, is a treatment with considerable historical background in other diseases, but still explorative in the context of SARS-CoV-2. In a pandemic, convalescent plasma could provide an easily accessible source of antiviral antibodies. Indeed, fresh frozen plasma (FFP) is an established treatment in many clinical indications with a well-known safety profile. The present article summarizes available evidence about convalescent plasma in COVID-19, registered trials, and guidance from authorities, providing a critical overview of published studies and perspectives.

Historical evidence for convalescent plasma in other epidemics

In recent history, convalescent plasma has been successfully used in viral outbreaks and epidemics. In as early as the 1918–1925 Spanish influenza pandemic, studies evaluated convalescent blood products to treat pneumonia due to Spanish influenza in

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hospitals, presenting assessment versus a control or comparison group. A meta-analysis conducted almost a century later (2006) showed a sizable reduction in overall crude fatality rate, from 37% among controls to 16% among patients treated with convalescent plasma. Benefit was maximized among patients receiving the treatment early, namely within the first four days of pneumonia complications.[9] Although these early epidemiological studies had been rather rudimentary in their design and were not blinded, randomized, nor placebo-controlled, they underlined the beneficial role of convalescent plasma that prompted modern researchers to support a role of this regimen in a possible future H5N1 influenza pandemic. Convalescent serum had also been used during the first half of the 20th century for measles,[10] poliomyelitis,[11] and mumps.[12]

Several decades later, in the context of pandemic influenza A (H1N1) 2009 virus infection, convalescent plasma treatment was able to significantly reduce respiratory tract viral load, serum cytokine response (interleukin-6, interleukin-19, tumor necrosis factor-alpha), and mortality in a comparative study recruiting 99 patients. In that study, the decrease in mortality was rather impressive, as the odds of death decreased by 80%.[13] A subsequent systematic review and meta-analysis synthesized 32 studies of severe acute respiratory syndrome (SARS) coronavirus infection and severe influenza and highlighted the consistent evidence for a reduction in mortality, especially in case of early administration of convalescent plasma and hyperimmune immunoglobulin after symptom onset. The meta-analysis confirmed the sizable reduction in the odds of mortality, pointing to a decrease by 75% in the odds of death.[14]

In the case of Middle East Respiratory Syndrome (MERS), a protocol of convalescent plasma therapy for patients with the disease was established in 2015. According to this protocol, subjects with an anti-MERS-coronavirus indirect fluorescent antibody titer of 1:160 or more would be screened for eligibility for plasma donation in line with standard donation criteria, provided that they were free of clinical or laboratory evidence of active MERS infection.[15] Nevertheless, challenges of this approach were highlighted in the Korean MERS outbreak where Ko et al supported that donor plasma with a neutralization activity of a titer 1:80 or more in the plaque reduction neutralization test should be adopted, whereas ELISA IgG could provide an alternative for the neutralization test in conditions where the former is not available.[16]

In the context of Ebola virus, a meta-analysis of clinical studies was conducted during the West Africa Ebola virus disease outbreak, gathering a pool of 1147 individuals. This analysis acknowledged that studies were considerably limited by the lack of randomization.[17] A large, non-randomized study of 84 patients pointed to a non-significant 7% decrease in death risk following transfusion of up to 500 mL of convalescent plasma, albeit with unknown levels of neutralizing antibodies.[18] Nevertheless, transfusion of convalescent plasma or whole blood collected from patients that recovered from Ebola virus has been recommended by the World Health Organization as an empirical treatment for the Ebola outbreaks, with provision of guidance also about the selection of donors, screening, and handling of blood and plasma units.[19]

Convalescent plasma in COVID-19 disease: emerging evidence from published studies

Table 1 presents the results of published studies that have evaluated transfusion of convalescent plasma in COVID-19 patients.[20–26] Shen et al[20] first presented the experience on critically ill patients in Shenzhen (China). All patients received a single dose of 400 mL convalescent plasma from donors with neutralizing antibody titer ranging between 1:80 and 1:480. After the transfusion, the titers of anti-SARS-CoV-2 IgG and IgM in recipients increased in a time-dependent manner. Three patients were discharged, whereas the remaining 2 remained hospitalized until the end of the study, with improvement in body temperature and clinical and biochemical indices. Notably, convalescent plasma was administered relatively late during the disease in all patients, namely between days 19 and 22 of hospitalization, except for 1 patient who received the treatment on day 10.[20] All patients at the time of convalescent plasma administration had detectable IgM and IgG antibodies and neutralizing antibodies titers ranging from 1:40 to 1:160. All titers of antibodies increased in a time-dependent manner after transfusion.

Zhang et al[21] adopted a richer regimen of convalescent plasma transfusions in their series of four COVID-19 patients in Guangdong (China), with total volumes administered ranging between 200 and 2400 mL. All patients in severe condition received convalescent plasma after day 12 of hospitalization. Very positive outcomes were reported, as three of 4 patients were discharged from the hospital, whereas the remaining one was finally PCR negative for the virus and was transferred to an unfenced intensive care unit. Two cases produced anti-SARS-CoV-2 IgG approximately 14 days after transfusion.[21]

The largest series published up to date is the one by Duan et al,[22] encompassing 10 COVID-19 patients in China, administering convalescent plasma with neutralizing antibody titers above 1:640. Among them, those who received the transfusion relatively early during the disease (days 10 and 11 from initiation of symptoms) showed a rapid increase in lymphocyte counts, decrease in serum CRP levels, and a notable remission of lung lesions in CT. The neutralizing antibody titers of 5 patients increased rapidly up to 1:640, whereas 4 patients remained at the same high level (1:640) after transfusion. Overall, the results were excellent, as no deaths were noted, 3 patients were discharged, and the remaining 7 were ready for discharge; this is in contrast to a historical control group presented by the study authors, where a death rate of 30% was noted. No serious adverse effects were documented following transfusion of convalescent plasma; only a minor effect was reported by a patient, namely an evanescent facial red spot.[22]

The study by Ye et al[23] in Wuhan (China) encompassed 6 patients and examined the transfusion of convalescent plasma in a spectrum of clinical scenarios, including persistent SARS-CoV-2 detection, consolidation or extensive lesions in chest CT, comorbidity with Sjögren syndrome and post-discharge positivity to SARS-CoV-2; improvement and promising results were noted in all cases. Similarly, Zhang et al[24] reported improvement in a patient from Nanjing (China) receiving convalescent plasma. Ahn et al[25] provided the first report on 2 cases from Korea, where the administration of convalescent plasma was linked to beneficial effects, namely successful weaning from mechanical ventilator in one patient and hospital discharge in the other patient. On the other hand, the study by Zeng et al,[26] from Zhengzhou (China), published in late April, 2020, highlighted the limitations of the new treatment; administration of convalescent plasma in critical, end-stage respiratory failure, at a late stage during the course of the disease (median: 21.5 days after first detection) was associated with suppression of viral shedding but ultimately death in 5 out of 6 examined cases.[26]

In line with the published case series concerning the optimal timing of convalescent plasma administration, a recent review by

Table 1

Studies and Main Findings of Published Studies Examining Convalescent Plasma in COVID-19 Patients.

First author (year)	Patient gender, age	Clinical condition at transfusion	Other treatments	Transfusion features	Outcome
Ahn (2020) – patient 1	M, 71	Severe ARDS	Lopinavir/ritonavir, hydroxychloroquine and empirical antibiotics, methylprednisolone	Hosp day 9 (500 mL divided into two doses and administered to the patient at 12 hours interval). Anti-SARS-CoV-2 IgG antibody measured by ELISA (OD ratio for IgG = 0.586 vs. a cut-off value 0.22)	No adverse reaction; fever subsided, oxygen demand decreased; condition much improved with decreased CRP and IL-6 to normal range. Further resolution of lung infiltrates on chest X-ray; SARS-CoV-2 was negative after day 26. Patient successfully weaned from mechanical ventilator.
Ahn (2020) – patient 2	F, 67	Severe ARDS	Lopinavir/ritonavir, hydroxychloroquine and empirical antibiotics, methylprednisolone	Symptom day 6 (500 mL divided into two doses and administered to the patient at 12 hours interval). Anti-SARS-CoV-2 IgG antibody measured by ELISA (OD ratio for IgG = 0.532)	No adverse reaction. Leukocytosis and lymphopenia immediately recovered; three days later bilateral infiltration on chest X-ray much improved. CRP and IL-6 also recovered to normal. SARS-CoV-2 was negative after day 20. Patient successfully extubated and discharged from hospital on day 24.
Duan (2020) – patient 1	M, 46	Severe	Arbidol, ribavirin, cefoperazone	Symptom day 11 (200 mL)	Pooled reporting[a]
Duan (2020) – patient 2	F, 34	Severe, clustering infection	Arbidol, cefoperazone	Symptom day 11 (200 mL)	An evanescent facial red spot as a non-serious adverse effect; pooled reporting[a]
Duan (2020) – patient 3	M, 42	Severe, clustering infection	Arbidol, moxifloxacin, methyprednisolone	Symptom day 19 (200 mL)	Pooled reporting[a]
Duan (2020) – patient 4	F, 55	Severe	Ribavirin, linezolid, imipenem-silastatin, methyprednisolone	Symptom day 19 (200 mL)	Pooled reporting[a]
Duan (2020) – patient 5	M, 57	Severe	Arbidol, remdesivir, IFN-a, moxifloxacin, cefoperazone/tazobactam, methyprednisolone	Symptom day 14 (200 mL)	Pooled reporting[a]
Duan (2020) – patient 6	F, 78	Severe, clustering infection	Arbidol, cefoperazone, levofloxacin, methyprednisolone	Symptom day 17 (200 mL)	Pooled reporting[a]
Duan (2020) – patient 7	M, 56	Severe	Arbidol, cefoperazone/ tazobactam, fluconazole, methyprednisolone	Symptom day 16 (200 mL)	Pooled reporting[a]
Duan (2020) – patient 8	M, 67	Severe	Arbidol, ribavirin	Symptom day 20 (200 mL)	Pooled reporting[a]
Duan (2020) – patient 9	F, 49	Severe	Arbidol, oseltamivir, peramivir	Symptom day 10 (200 mL)	Pooled reporting[a]
Duan (2020) – patient 10	M, 50	Severe	Arbidol, IFN-a, cefoperazone, caspofungin, methyprednisolone	Symptom day 20 (200 mL)	Pooled reporting[a]
Shen (2020) – patient 1	M, 70s	Critical - Bacterial pneumonia; severe ARDS; MODS	Methylprednisolone, Lop/rit, IFNa-1b, favipiravir	Hosp day 22, 400 mL, 1:240 neutralizing	Remained hospitalized and intubated till case report (day 37 of hospitalization); Improvement in body temperature, SOFA score, viral load, CRP, procalcitonin and IL-6
Shen (2020) – patient 2	M, 60s	Critical - Bacterial pneumonia; fungal pneumonia; severe ARDS; myocardial damage	Methylprednisolone, Lop/rit, arbidol; darunavir	Hosp day 10, 400 mL, 1:80 neutralizing	Remained hospitalized and intubated till case report (day 37 of hospitalization); Improvement in body temperature, SOFA score, viral load, CRP, procalcitonin and IL-6
Shen (2020) – patient 3	F, 50s	Critical – Severe ARDS	Methylprednisolone, Lop/rit, IFNa-1b	Hosp day 20, 400 mL, 1:120 neutralizing	Discharged home, after clinical and biochemical marker improvement
Shen (2020) – patient 4	F, 30s	Critical – Severe ARDS	Methylprednisolone, IFNa-1b, favipiravir	Hosp day 19, 400 mL, 1:240 neutralizing	Discharged home, after clinical and biochemical marker improvement
Shen (2020) – patient 5	M, 60s	Critical – Severe ARDS	Methylprednisolone, Lop/rit, IFNa-1b	Hosp day 20, 400 mL, 1:480 neutralizing	Discharged home, after clinical and biochemical marker improvement
Ye (2020) – patient 1	M, 69	Persistent positive results for SARS-CoV-2	Levofloxacin at disease onset	Symptom days 33, 36 and 39 (3 cycles)	Resolution of GGOs in chest CT 4 days after transfusion; negative tests for SARS-CoV-2 10 days after transfusion; discharged from hospital
Ye (2020) – patient 2	F, 75	Consolidation lesions in chest CT	Not reported	Symptom days 33 and 37 (2 cycles)	Symptom and radiologic improvement (consolidation turned to scattered GGOs) and two-fold increase in anti-SARS-CoV-2 IgM and IgG titers; negative SARS-CoV-2 tests
Ye (2020) – patient 3	M. 56	Respiratory distress	Not reported	Symptom days 33, 34 and 37 (3 cycles)	Symptom improvement, serum anti-SARS-CoV-2 IgM and IgG titers increased and resolution of lesions in chest CT; patient discharged from hospital
Ye (2020) – patient 4	F, 63	GGOs in chest CT, comorbidity with Sjögren syndrome	Levofloxacin at disease onset, arbidol	Symptom day 40 (1 cycle)	Density of GGOs reduced, negative SARS-CoV-2 test, discharged from hospital

(*continued*)

Table 1
(continued).

First author (year)	Patient gender, age	Clinical condition at transfusion	Other treatments	Transfusion features	Outcome
Ye (2020) – patient 5	F, 28	Post-discharge SARS-CoV-2-positive COVID-19 patient	Not reported	Symptom day 33 (1 cycle)	After transfusion, several consecutive SARS-CoV-2 tests negative, discharged from hospital
Ye (2020) – patient 6	M, 57	GGOs in chest CT, having turned negative in the SARS-CoV-2 test but with respiratory distress	Not reported	Symptom day 60 (1 cycle)	Symptom relief and GGO resolution, discharged from hospital
Zeng (2020), six patients pooled	Five males, one female; median age: 61.5, IQR: 31.5–77.8	Critical, end-stage respiratory failure in ICU, high flow nasal cannula oxygen therapy, mechanical ventilation (5/6), ECMO (4/6), CRRT (3/6)	Antibiotics, antiviral therapy (4/6), traditional Chinese medicine (3/6), intravenous immunoglobulin (5/6), glucocorticoids (4/6)	Median of 21.5 days after first detection of viral shedding; median volume of plasma infused: 300 mL	No adverse effects; all patients tested negative for SARS-CoV-2 RNA by 3 days after transfusion, but 5 died eventually
Zhang B (2020) – patient 1	F, 69	Intubated in ICU, ARDS, septic shock, pneumorrhagia	Arbidol, lop/rit, IFNa-1b, human albumin, zadaxin and immunoglobulin, antibacterial and antifungal drugs	Three transfusions: Hosp day 19 (200 mL), Hosp day 29 (400 mL), Hosp day 30 (300 mL)	Extubated on hosp day 32, PCR (-) on hosp day 40 and discharged on hosp day 44
Zhang B (2020) – patient 2	M, 55	ARDS, in non-invasive mechanical ventilation and high-flow nasal cannula	Arbidol, lop/rit, IFNa-1b	Hosp day 12 (200 mL)	PCR (-) on hosp day 16, discharged on hosp day 19
Zhang B (2020) – patient 3	M, 73	ARDS, CRRT multiple organ failure, septic shock, veno-venous ECMO	Arbidol, lop/rit, oseltamivir, ribavirin, IFNa-1b	A total of 2400 mL in 8 transfusions from hosp day 15 to hosp day 41	PCR (-) on hosp day 44, transferred to unfenced ICU on hosp day 51
Zhang B (2020) – patient 4	F, 31	Cesarean section (but newborn dead of endouterine asphyxia) on day 1 due to ARDS, multiple organ dysfunction syndrome and septic shock; CRRT on day 2, veno-venous ECMO on day 6	Lop/rit, ribavirin, imipenem, vancomycin	Hosp day 19 (300 mL)	CRRT and ECMO removed on hosp day 27, PCR (-) and extubation on hosp day 40, discharged on hosp day 46
Zhang L (2020) – one patient	F, 64	ICU, invasive mechanical ventilation	Not reported	Hosp day 17 (200 mL), anti-SARS-CoV-2 IgM levels OD ratio = 1.22 and IgG levels OD ratio = 6.59	No adverse event; no change in blood examinations and lymphopenia; however, the patient did not require mechanical ventilation 11 days after plasma transfusion and was transferred to a general ward.

[a] Pooled reporting: In the study by Duan et al, patients 1, 2, and 9 (transfusion before day 14 of symptoms) showed a rapid increase of lymphocyte counts and a decrease of CRP, with remarkable absorption of lung lesions in CT. The neutralizing antibody titers of five patients increased rapidly up to 1:640, whereas four patients remained at the same high level (1:640) after transfusion. No deaths were noted among 10 examined patients; three patients were discharged and the remaining seven were ready for discharge. ARDS = acute respiratory distress syndrome; CRP = C-reactive protein; CRRT = continuous renal replacement therapy; ECMO = extracorporeal membrane oxygenation; ELISA = enzyme-linked immunosorbent assay; GGOs = ground glass opacities; Hosp = hospitalization; IFN = interferon; IL = interleukin; IQR = interquartile range; Lop/rit = lopinavir/ritonavir; OD = optical density; SOFA = Sequential Organ Failure Assessment.

Tiberghien et al[27] has presented a strategy of administration for high-risk patients (older than age 70 or dependent on oxygen with a baseline oxygen saturation <94%). According to preliminary remarks by the aforementioned research team, early treatment with convalescent plasma (not later than day 5) is preferred before seroconversion for SARS-CoV-2, which may occur on days 6 to 12. A regimen proposed by Tiberghien et al is the slow transfusion of two plasma units, under careful monitoring, for patients whose weight is within the 50 to 80 kg range. The volume is adjusted according to weight, whereas a second infusion of 2 additional units 1 or 2 days later can also be considered.[27] The need for early administration is in line with observations in other diseases, such as pneumococcal pneumonia, where no benefit is noted if the antibody is administered after day 3 of the disease.[28,29]

In light of the promising evidence from case series presented above, there is a clear need for randomized controlled trials on large patient numbers to evaluate the efficacy of the process. Apart from sample size and the non-comparative, non-randomized study design, numerous limitations hamper the interpretation of the aforementioned studies, such as the superimposition of effects mediated by other antiviral treatments, antibiotics, and glucocorticoids administered concomitantly with convalescent plasma. As a whole, these studies indicate that patients receiving transfusions earlier than 14 days post infection may benefit from convalescent plasma treatment.

Mechanism of actions

Convalescent plasma may offer various beneficial actions in COVID-19 disease (Fig. 1). First and foremost, the apparent mechanism pertains to the fact that antibodies from convalescent plasma can suppress viremia.[1] Similar to the strategies implemented in the SARS epidemic, theoretically the administration of convalescent plasma at the early stage of the disease would be more effective.[30] Viremia peak is noted in the first week of infection in the majority of viral illnesses and a primary immune response of the host is usually developed by days 10 to 14 of infection[31] (beginning somewhat earlier according to other researchers),[27] signaling the clearance of the viruses. Other potential mechanisms include antibody-dependent cellular cytotoxicity, complement activation and phagocytosis (ADCP).[29] Moreover, the presence of non-neutralizing antibodies binding to the pathogens may also be helpful.[32] In any case, the administered antibody modifies inflammatory response and this can be optimally achieved during the early response, even at the

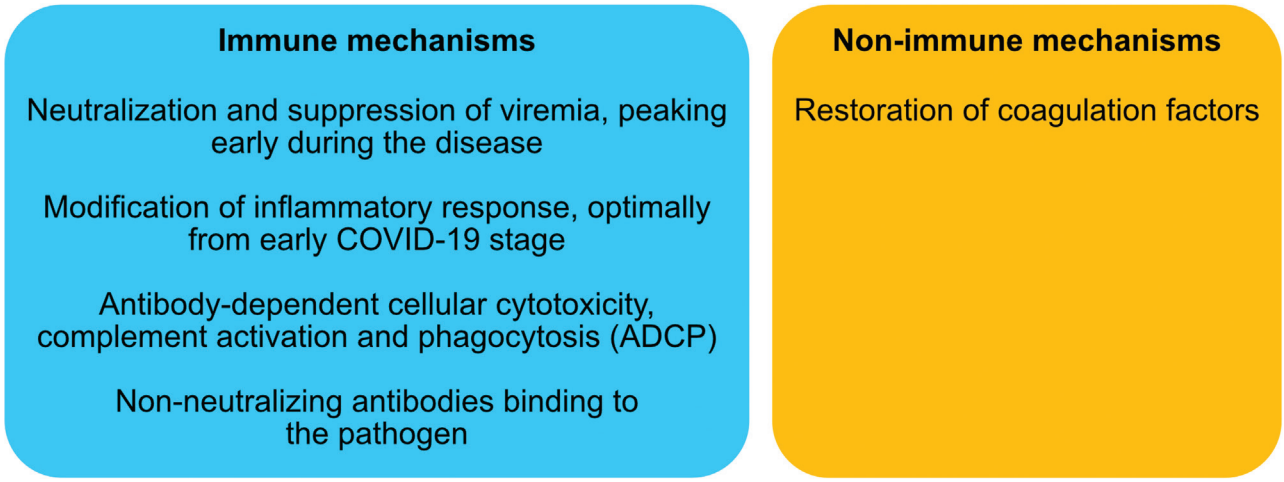

Figure 1. **Potential mechanisms of action of convalescent plasma in COVID-19.**

asymptomatic stage.[33] It has also been suggested that apart from the direct anti-viral properties, plasma components can provide other beneficial actions, such as restoring coagulation factors.[34]

So far, information on immune response to SARS-CoV-2 is rather limited. According to studies in process, a detailed analysis of 9 cases with mild upper respiratory tract symptoms revealed that seroconversion occurred 6 to 12 days after onset of symptoms, while antibodies were not detectable between day 3 and 6, and all patients showed neutralizing antibodies after 2 weeks. Seroconversion coincided with a slow but steady decline of sputum viral load.[35] In another study, the majority of PCR-confirmed SARS-CoV-2-infected persons seroconverted by 2 weeks after disease onset.[36] A study on 173 COVID-19 patients showed that the presence of antibodies was less than 40% within the first week since onset, increasing to 94.3% for IgM and 79.8% for IgG since day 15 after onset, and higher titer of total antibodies correlated with worsened clinical classification.[37] To further assess the time for seroconversion and its correlation with disease severity and antibody titers, additional longitudinal studies evaluating large numbers of serum samples from COVID-19 patients with a broad spectrum of clinical symptoms are needed.

Registered trials on convalescent plasma in COVID-19 disease

Tracing the progression of research on the potential utilization of convalescent plasma in COVID-19, 11 studies were identified in the clinicaltrials.gov register and their main features are summarized in Table 2. Of these 11 studies, 6 were single-arm, 4 were randomized comparative studies, and 1 pertained to the expanded access status for convalescent plasma (NCT04338360). Various countries have been implicated in these studies, including the USA, China, Colombia, Iran, Italy, Mexico, and the Netherlands. If completed, these studies would examine a minimum total of 1106 patients. At present, 5 studies are either recruiting, enrolling by invitation, or active and providing expanded access; six studies are not yet recruiting.

A cardinal point pertains to the timing of convalescent plasma administration in the study protocols, but the majority of studies did not provide this information. However, some studies necessitated an interval of 3 to 7 days from the beginning of illness (NCT04333251) or, less strictly, acute respiratory distress syndrome (ARDS) lasting less than 10 days (NCT04321421). Variable degrees of severity have been adopted as inclusion criteria; some studies focus on severe cases, whereas there were also studies focusing on less severe cases, as intubation (NCT04327349) or critical illness (NCT04332380) was an exclusion criterion. The total amount of convalescent plasma ranges from 1 to 3 units.

A particularly interesting study protocol (NCT04323800) involves the use of convalescent plasma as a prophylaxis for COVID-19. According to this protocol, convalescent plasma administration will be tested within 120 hours after high-risk contact exposure with a person with confirmed COVID-19. Individuals at high risk for a severe COVID-19 illness will be recruited, including elderly subjects and patients suffering from chronic conditions. This strategy of prophylaxis has been successfully implemented in the prevention of other viral diseases via passive immunity, such as the case of administration of hepatitis B immune globulin, human rabies immune globulin, and polyclonal hyperimmune globulin for respiratory syncytial virus (RSV), or more recently palivizumab, a humanized murine monoclonal antibody for high-risk infants.[29,38] In addition to these studies, reports in the media have been appearing about other countries, such as Canada, starting to test convalescent plasma in COVID-19.[39]

Concerning immunoglobulin therapy in COVID-19, 2 studies were identified (Table 2, lower panels). The first one (NCT04261426) focuses on early administration of the immunoglobulin in severe cases, adopting an eligibility interval between the onset of symptoms and randomization that should not surpass 7 days. The second (NCT04261426) is a small exploratory study on 10 patients with the aim to evaluate this experimental treatment in severe COVID-19 pneumonia cases in China.

The examination of studies registered in the Chinese Clinical Trial Registry (Table 3) revealed a different pattern. In the registry, 10 studies on convalescent plasma were identified; among them, the majority (6 trials) were randomized comparative (vs conventional treatment with/without ordinary plasma), three were non-randomized comparative, and only was a single-

Table 2

Studies Registered in Clinicaltrials.gov, to Evaluate Convalescent Plasma or Immunoglobulin Therapy in COVID-19 Patients (updated on April 09, 2020). Withdrawn Studies were not Included.

Principal Investigator, Affiliation	Registration date (identifier)	Current status (as per April 10, 2020)	Actual study start date- estimated study completion date	Participating centers	Sample size	Study design	Eligibility criteria for donors	Inclusion criteria for recipients	Exclusion criteria for recipients	Details about intervention	Outcomes
Studies on convalescent plasma											
Dr Hongzhou Lu, Shanghai Public Health Clinical Center	March 03, 2020 (NCT04292340)	Recruiting	February 1 to December 31, 2020	Shanghai Public Health Clinical Center	15	Single Group	Not stated	COVID-19; written informed consent	Lack of detailed medical history	No details provided	Primary: Virological clearance rate at PCR in throat swabs, sputum, or lower respiratory tract secretions (day 1,3 and 7 from plasma transfusion), clinical outcomes including death, critical illness, recovery Secondary: Adverse events as assessed by CTCAE v5.0 (4 weeks after from plasma transfusion)
Dr Cesare Perotti, Foundation IRCCS San Matteo Hospital, Italy	March 25, 2020 (NCT04321421)	Active, not recruiting	March 17 to May 31, 2020	4 hospitals in Italy	49	Single Group Assignment; no masking	Males, age ≥18 years, evaluated for transmissible diseases. Adjunctive tests for hepatitis A virus, hepatitis E virus and Parvovirus B-19	1. Age ≥18 years, 2. positive for RT-PCR SARS-CoV-2, 3. ARDS moderate to severe, lasting less than 10 days, 4. PCR increased by 3.5 with respect to baseline or >18 mg/dl, 5. need for mechanical ventilation or CPAP, 6. signed informed consent	1. Moderate to severe ARDS lasting more than 10 days; 2. Proven hypersensitivity or allergic reaction to hemoderivatives or immunoglobulins, 3. Consent denied	Each plasma bag obtained from plasmapheresis will be divided in two units and frozen. 500–600 mL of plasma will be obtained from each donor; 250–300 mL to treat each patient at most 3 times over 5 days.	Primary: death from any cause (within 7 days) Secondary: time to extubation (within 7 days), length of intensive care unit stay (within 7 days), time to CPAP weaning (within 7 days), viral load (nasopharyngeal swab, sputum and BAL - day 1, 3 and 7), immune response (neutralizing title at days 1, 3 and 7)
Dr Shmuel Shoham, Johns Hopkins University, USA	March 27, 2020 (NCT04323800)	Not yet recruiting	May 1, 2020 - January 2023	Johns Hopkins University	150 (75 intervention; 75 controls)	Randomized; triple masking (Participant, Care Provider, Investigator). High-titer Anti- SARS-CoV-2 plasma versus control (SARS-CoV-2 non-immune plasma)	Volunteer who recovered from COVID-19 disease, titer of neutralizing antibody >1:64)	1. Age 18 years of age or older; 2. Close contact exposure to person with COVID-19 within 96 hours of enrollment (and 120 hours of receipt of plasma); 3. High risk exposure as defined by CDC: (Living in the same household as, being an intimate partner of, or providing care in a nonhealthcare setting for a person with confirmed COVID-19 infection without using recommended precautions) AND Higher risk for severe illness as defined by CDC (any of 65 years of age; residence in a nursing home or long-term care facility; Chronic lung disease or moderate to severe asthma; Heart disease; Immunocompromising condition including cancer treatment; Severe obesity i.e., BMI>40; Uncontrolled diabetes; Renal failure; Liver disease)	1. Receipt any blood product in past 120 days; 2. Psychiatric or cognitive illness or recreational drug/ alcohol use affecting safety and/or compliance; 3. Symptoms consistent with COVID-19 infection at screening; 4. Nucleic acid testing evidence of COVID-19 infection at screening; 5. History of prior reactions to transfusion blood products; 6. Inability to complete therapy with the study product within 24 hours after enrollment	1 unit; ~200–250 mL collected by apheresis	Primary (day 28) Cumulative incidence of composite outcome of disease severity (death; requiring mechanical ventilation and/or in ICU; non-ICU hospitalization, requiring or not supplemental oxygen; not hospitalized, but with clinical and laboratory evidence of COVID-19 infection; not hospitalized, no clinical evidence of COVID-19 infection, but with positive PCR for SARS-CoV-2) Secondary: Anti-SARS-CoV-2 titers (baseline, days 1, 3, 7, 14, 90), rates and duration of SARS-CoV-2 PCR positivity (up to day 28), peak quantity levels of SARS-CoV-2 RNA (up to day 28), cumulative incidence of disease severity (up to day 28)

(*continued*)

Table 2
(continued).

Principal Investigator, Affiliation	Registration date (identifier)	Current status (as per April 10, 2020)	Actual study start date- estimated study completion date	Participating centers	Sample size	Study design	Eligibility criteria for donors	Inclusion criteria for recipients	Exclusion criteria for recipients	Details about intervention	Outcomes
Dr Amir Shamshirian, Imam Khomeini Hospital, Mazandaran University of Medical Sciences, Iran	March 31, 2020 (NCT04327349)	Enrolling by invitation	March 28 – September 30, 2020	Khomeini Hospital, Mazandaran University of Medical Sciences, Iran	30	Single Group Assignment; no masking	1. Complete recovery from severe COVID-19 disease and hospital discharge; 2. Consent to donate blood; 3. Age 30 to 60 years; 4. Normal CBC test results; 5. negative COVID-19 RT-PCR test. Exclusion criteria for donors: blood-borne viral / infectious diseases; underlying heart disease, low or high blood pressure, diabetes, epilepsy; use of banned drugs for blood donation; other prohibitions on transfusion standards	1. COVID-19; 2. Consent; 3. Age 30 to 70 years; 4. No intubation; 5. PaO2 / FiO2 is above 200 or SpO2 is greater than 85%.	1. History of hypersensitivity to blood transfusions or its products; 2. History of IgA deficiency; 3. Heart failure or any other factor that prevents the transmission of of 500 ml plasma; 4. Entering the intubation stage	No details provided	Primary: Mortality (day 10, 30 after transfusion), CRP (days 1, 3, 7), IL-6 (days 1, 3, 7), TNF-alpha (days 1, 3, 7), PaO2/FiO2 Ratio (days 1, 3, 7). Secondary (days 1, 3, 7): CD3, CD4, CD8, CD4/CD8 ratio, lymphocyte count, leukocyte count, ALT, AST, ALP, LDH, CPK, CK-MB, specific IgG, CT Scan and Chest X-Ray (2hours after admission and day 14), Number of days ventilated, Length of hospitalization
Dr Juan M Anaya Cabrera, Universidad del Rosario, Colombia	April 02, 2020 (NCT04332380)	Not yet recruiting	April 1 to December 31, 2020	Universidad del Rosario, Colombia	10	Single Group Assignment; no masking	Not stated	1. Aged between 18 and 60 years, male or female; 2. Hospitalized participants with diagnosis for COVID 19 by RT-PCR; 3. Without treatment; 4. Moderate cases according to the official guideline 5. Confusion, Urea, Respiratory rate, Blood pressure-65 (CURB-65) $>=2$; 6. SOFA score <6; 7. Written informed consent.	1. Females pregnant or breastfeeding; 2. Prior allergic reactions to transfusions; 3. Critical illness; 4. Surgical procedures in the last 30 days. 5. Active treatment for cancer (Radiotherapy or Chemotherapy); 6. HIV with viral failure; 7. Suspicion or evidence of coinfections; 8. End-stage chronic kidney disease; 9. Child Pugh C stage liver cirrhosis. 10. High cardiac output diseases; 11. Autoimmune diseases or Immunoglobulin A nephropathy; 12. Other judgement of inappropriateness.	500 mL of convalescent plasma, distributed in two 250 mL transfusions on the first and second protocol day.	Primary (days 0, 4, 7, 14 and 28): COVID-19 Viral Load, IgM and IgG COVID-19 titers Secondary (days 7, 14 and 28): ICU admission requirement; Length of ICU stay; Length of hospital stay; Requirement of mechanical ventilation; Duration of mechanical ventilation; Clinical status assessed according to the WHO guideline; Mortality.
Dr Juan M Anaya Cabrera, Universidad del Rosario, Colombia	April 03, 2020 (NCT04332835)	Not yet recruiting	April 1 to December 31, 2020	Universidad del Rosario, Colombia	80	Randomized; no masking; Convalescent plasma plus hydroxychloroquine plus azithromycin vs. hydroxychloroquine plus azithromycin	Not stated	Same as NCT04332380	Same as NCT04332380	500 mL of convalescent plasma, distributed in two 250 mL transfusions on the first and second protocol day.	Same as NCT04332380
Dr José Fe Castilleja-Leal, Hospital San José, Tecnologico de Monterrey, Mexico	April 03, 2020 (NCT04333355)	Not yet recruiting	April 15, 2020- April 30, 2021	Hospital San José, Tecnologico de Monterrey, Mexico	20	Single Group Assignment; no masking	Convalescent individuals with proven COVID-19 and symptom-free for a period of not less than 10 days. Donors will be screened for infectious diseases including SARS-CoV-2.	1. Age ≥18 years, 2. Confirmed SARS-CoV-2 Infection by RT-PCR, 3. Serious or life-threatening infection. (Serious: Dyspnea; RR≥30 cycles/minute; Blood oxygen saturation ≤to 93% with an oxygen supply >60%; $PaO_2/FiO_2<$ 300; a 50% increase in pulmonary infiltrates defined by CT scans in 24 to 48 hours). (Life-threatening infection: respiratory failure; septic shock; dysfunction or multiple organ failure); 4.	1. History of allergic reaction to any type of previous transfusion; 2. Heart failure at risk of volume overload; 3. History of chronic kidney failure in the dialysis phase; 4. Previous hematological diseases (anemia less than 10 grams of hemoglobin, platelets greater than 100,000 / μl); 5. Not suitable for protocol.	Plasma will be fractioned in 250 ml; if no adverse event is present, infusion will be repeated after 24 hours.	Primary: Side effects (time frame: 14 days) Secondary: Heart Failure (time frame: 14 days), Pulmonary Edema (time frame: 14 days), Allergic Reaction (time frame: 14 days), Lung infiltrates in thorax CT(48 hrs, 14 days), Viral load of SARS-CoV-2 in RT PCR (48 hrs, 14 days)

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Principal Investigator, Affiliation	Registration date (identifier)	Current status (as per April 10, 2020)	Actual study start date- estimated study completion date	Participating centers	Sample size	Study design	Eligibility criteria for donors	Inclusion criteria for recipients	Exclusion criteria for recipients	Details about intervention	Outcomes
								Refractory to treatment with azithromycin / hydroxychloroquine or chloroquine / ritonavir / lopinavir defined as: 48 hours with no improvement. 5. Signed Informed consent.			
PI not stated, Baylor Research Institute, USA	April 03, 2020 (NCT04333251)	Not yet recruiting	April 1, 2020 – December 31, 2022	Baylor Research Institute, USA	115	Randomized; no masking (convalescent plasma vs. best supportive care)	1. Neutralization antibody titer >1:64; 2. Age ≥18 years; 3. Hospitalized with COVID-19 respiratory symptoms and confirmation via RT-PCR but are at the moment PCR negative by two nasopharyngeal testings; 4. Negative serum pregnancy test; 5. written informed consent; 6. agreement for storage of specimens for future testing	1. Age ≥18 years; 2. Hospitalized with COVID-19 respiratory symptoms within 3 to 7 days from the beginning of illness; 3. Written informed consent; 4. Agreement for storage of specimens for future testing	1. Receipt of pooled immunoglobulin in past 30 days; 2. Contraindication to transfusion or history of prior reactions to transfusion blood products 3. Females not pregnant	Recipients will receive 1–2 units of ABO matched donor plasma	Primary: Reduction in oxygen and ventilation support (during an average of 4 weeks) Secondary: not specified
Dr Michael Joyner, Mayo Clinic, USA	April 08, 2020 (NCT04338360)	Expanded Access Status : Available	Expanded Access	12 locations in the USA	Intermediate-size population	Expanded Access	Not stated	1. Age ≥18 years; 2. Laboratory confirmed diagnosis; 3. Admitted to acute care facility for COVID-19 complications; 4. Severe (one or more of: dyspnea, RR≥ 30/min, blood oxygen saturation ≤ 93%. PaO_2/FiO_2< 300, lung infiltrates > 50% within 24 to 48 hours) or life threatening (respiratory failure, septic shock, multiple organ dysfunction or failure) COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease; 5. Informed consent	None	One unit of ABO compatible COVID-19 convalescent plasma	Not stated
Dr Maria Lucia Madariaga, University of Chicago	April 09, 2020 (NCT04340050)	Not yet recruiting	April 30, 2020 - December 31, 2021	University of Chicago	10	Single Group; no masking	1. Age greater or equal to 18; 2. Able to donate blood per standard guidelines; 3. Prior confirmed diagnosis of COVID-19; 4. Complete resolution of symptoms at least 28 days prior to donation; 5. Female donors who have never been pregnant, previously pregnant female donors negative for HLA antibodies, or male donors; Exclusion	1. Age≥18 years; 2. Laboratory-confirmed COVID-19; 3. Severe (defined as dyspnea, RR≥ 30/min, blood oxygen saturation ≤ 93%, PaO_2/FiO_2< 300, and/or lung infiltrates > 50% within 24 to 48 hours or immediately life-threatening COVID-19) or life-threatening COVID-19 (defined as respiratory failure, septic shock, and/or multiple organ dysfunction or failure). Lower priority to patients with septic shock or	1. Positive pregnancy test, breastfeeding, or planning to become pregnant/breastfeed; 2. Receipt of pooled immunoglobulin in past 30 days; 3. Contraindication or history of prior reactions to transfusion blood products; 4. Enrolment in other drug trials	Infusion of one unit of anti-SARS-CoV-2 convalescent plasma ~300 mL over 4 hours	Primary (till day 28): Feasibility of performing study pathway (number of donors and recipients; type of respiratory support Secondary (till day 28): Cardiac arrest; Transfer to ICU; ICU mortality; ICU length of stay; Hospital mortality; Hospital length of stay; Ventilator-free days; Overall survival

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Table 2
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Principal Investigator, Affiliation	Registration date (identifier)	Current status (as per April 10, 2020)	Actual study start date- estimated study completion date	Participating centers	Sample size	Study design	Eligibility criteria for donors	Inclusion criteria for recipients	Exclusion criteria for recipients	Details about intervention	Outcomes
							Criteria: no consent, does not meet standard blood bank donation guidelines, unsuccessful blood donation	multiple organ dysfunction; as they may benefit less 4. Less than 21 days from start of illness; 5. Written informed consent 6. Agreement to storage of specimens for future testing; 7. Approval of eIND application			
Bart Rijnders, Erasmus Medical Center	April 10, 2020 (NCT04342182)	Recruiting	April 1 – July 1, 2020	Two hospitals in the Netherlands	426	Randomized; participant masking (Convalescent plasma versus standard of care)	1. History of COVID infection documented by PCR; 2. Known ABO-Rhesus(D) blood group; 3. Negative screening for irregular antibodies; 4. Asymptomatic for at least 24 hours; 5. Symptomatic COVID infection (fever >38.0 C for at least 48 hours); 6. Written informed consent. Exclusion Criteria: Age <18 years; Weight <45kg; History of heart failure; History of transfusion with red blood cells, platelets or plasma; Born as a female person.	1. PCR confirmed COVID disease; 2. Written informed consent; 3. Age >18 years	Patient in which a "no ICU admission" or "no invasive ventilation" restriction was implemented	250 mL convalescent plasma	Primary: Overall mortality (until 60 days) Secondary: Hospital days; Weaning from oxygen therapy; Overall mortality in patients admitted to the ICU within 24 hours; Mortality in patients with a duration of symptoms less or more the median; ICU days in patients admitted to the ICU within 24 hours; SARS-CoV2 shedding from airways (day 1, 3, 5, 7, 10, 14, at discharge)
Studies on immunoglobulin therapy											
Dr Li Taisheng, Peking Union Medical College Hospital	February 7, 2020 (NCT04261426)	Not yet recruiting	February 10 – June 30, 2020	2 hospitals in China	80	Randomized, no masking (Intravenous immunoglobulin versus standard care)	No details provided	1. Age ≥18 years; 2. RT-PCR confirmation in throat swab and/or sputum and/or lower respiratory tract samples; 3. Interval between onset of symptoms and randomization is within 7 days; 4. Any of the following criteria for severe or critical ill conditions: (RR≥30/min; or Rest SPO2<=90%; or $PaO_2/FiO_2 \leq 300$mmHg; or Respiratory failure and needs mechanical ventilation; or Shock occurs; or Multiple organ failure and needs ICU monitoring; 5. Written informed consent	1. Other evidences that can explain pneumonia (such as influenza A virus, influenza B virus, bacterial pneumonia, fungal pneumonia, noninfectious causes); 2. Allergy to Intravenous Immunoglobulin or its preparation components; 3. Selective IgA deficiency; 4. Women pregnant or breastfeeding; 5. Researchers consider unsuitable.	Intravenous Immunoglobulin (IVIG) 0.5g/kg/d for 5 days	Primary: Clinical improvement based on the 7-point scale (day 28 from randomization), Lower Murray lung injury score (days 7 and 14) Secondary: 28-day mortality, Duration of mechanical ventilation, Duration of hospitalization (up to day 28), Proportion of patients with negative RT-PCR (days 7 and 14), Proportion of patients in each category of the 7-point scale (days 7, 14 and 28), Normalization of inflammation factors (days 7 and 14), Adverse Drug Events (through day 28), Serious Adverse Drug Events (through day 28)
Dr Xiang Cheng, Wuhan Union Hospital, China	February 11, 2020 (NCT04264858)	Not yet recruiting	March 17, 2020 – May 31, 2020	Union Hospital, Tongji Medical College, Huazhong University of Science and Technology,	10 Immunoglobulin of cured patients vs. control gamma-globulin	Non-Randomized; no masking	No details specified	1. Written informed consent; 2. Age ≥18 years, no limitation about gender; 3. Acute severe 2019-nCoV pneumonia: RT-PCR confirmed infection, pulmonary CT scan, At least one of the following	1. Viral pneumonia with other viruses besides 2019-nCoV; 2. Not suitable for immunoglobulin therapy; 3. Participation in other studies; 4.	Immunoglobulin of cured patients: 0.2 g/kg, intravenous drip, once a day, for 3 days	Primary: Time to Clinical Improvement (up to 28 days) Secondary (up to day 28): Clinical status assessed by the ordinal scale; Differences in oxygen

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Table 2
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Principal Investigator, Affiliation	Registration date (identifier)	Current status (as per April 10, 2020)	Actual study start date- estimated study completion date	Participating centers	Sample size	Study design	Eligibility criteria for donors	Inclusion criteria for recipients	Exclusion criteria for recipients	Details about intervention	Outcomes
				Wuhan, Hubei, China				should be met: respiratory distress, RR ≥ 30 times/min; oxygen saturation ≤ 93% in resting state; PaO_2/FiO_2 ≤ 300mmHg; respiratory failure and mechanical ventilation; shock occurs; ICU required, in combination with other organ failure.	Other circumstances not suitable		intake methods; Duration of supplemental oxygenation; Duration (days) of mechanical ventilation; Mean PaO2/FiO2; Lesions of pulmonary segment in pulmonary CT (every 7 days); Time to 2019-nCoV RT-PCR negativity in respiratory tract specimens, Dynamic changes of 2019-nCoV antibody titer in blood (day 3 and 28), Length of hospital stay, All-cause mortality

ALT = alanine aminotransferase; ARDS = acute respiratory distress syndrome; AST = aspartate aminotransferase; CBC = complete blood count; CPAP = continuous positive airway pressure; CPK = creatine phosphokinase; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; eIND = Emergency Investigational New Drug; HIV = human immunodeficiency virus; ICU = intensive care unit; LDH = lactate dehydrogenase; NSAIDs = non-steroidal anti-inflammatory drugs; PaO_2/FiO_2 = Partial pressure of arterial oxygen to fraction of inspired oxygen ratio; PCR = polymerase chain reaction; PI = principal investigator; RR = respiratory rate; SARS = severe acute respiratory syndrome; SOFA = Sequential Organ Failure Assessment; TNF = tumor necrosis factor; WHO = World Health Organization.

arm trial. If all studies are complete, a total of 680 patients will have been evaluated. All studies are focusing primarily on severe or critical cases; among the exclusion criteria, pregnancy, lactation, immunoglobulin allergy/allergy to plasma, immunoglobulin A deficiency, and other contraindications for plasma transfusion (such as heart failure) have been often stated. Interestingly, some studies (ChiCTR2000029757, ChiCTR2000030010, ChiCTR2000030702, ChiCTR2000030929) provide shock and disseminated intravascular coagulation as an exclusion criterion. No details have been provided regarding the selection of donors. Regarding immunoglobulin therapy for COVID-19, the identified study in the Chinese Clinical Trial Registry (ChiCTR20000308410) seemed to correspond to the previously presented study in clinicaltrials.gov by the same principal investigator (NCT04264858).

Current situation – American and European framework for donors

On March 24, 2020, the Food and Drug Administration (FDA) took an important step facilitating access to COVID-19 convalescent plasma to be used in COVID-19 patients at a serious or immediately life-threatening stage of the disease, allowing the process of single patient emergency Investigational New Drug Applications (referred to as eINDs) under Title 21 of the Code of Federal Regulations (CFR) 312.310. Under this process, convalescent plasma can be used for the treatment of an individual patient by a licensed physician upon the authorization of the FDA.

According to the FDA, eligible donors could be recovered COVID-19 patients who had been proven positive either by a diagnostic test such as nasopharyngeal swab at the time of illness, or antibody-positive patients on whom a diagnostic test had not been performed during their illness. The level of neutralizing antibody titers should be greater than 1:160, whereas a titer of 1:80 could be deemed acceptable if alternative matching units are not available. Symptoms should have resolved completely at least 28 days prior to donation; alternatively, a symptom-free interval of at least 14 days prior to donation and negative results in one or more nasopharyngeal swabs or in blood-based molecular diagnostic tests are necessitated. Male donors are eligible; special attention is paid to female donors who should be negative for human leukocyte antigen (HLA) antibodies in case of previous pregnancy. General donor eligibility requirements along with the additional criteria for plasmapheresis should be also met, including infection status control. The FDA has also provided guidance on blood establishment standards, labeling, and recordkeeping.[40]

Regarding donors, the International Society of Blood Transfusion (ISBT) Working Party set an interval of 14 days or more after full recovery and necessitated a non-reactivity of the sample for human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), syphilis, and locally transmitted infections. As a means to avoid the incidence of transfusion-related acute lung injury (TRALI)—a serious condition emerging within 6 hours from transfusion—donors should preferably be either males or females who have never been pregnant, including abortions.[41] On April 4, 2020, the European Commission issued the guidance document on the collection and transfusion of convalescent COVID-19 plasma, adopting similar criteria regarding donor eligibility. Notably, the titers of neutralizing antibodies for donors according to the document were set at a level greater than 1:320, although it was recognized that lower thresholds could also be effective.[42]

Table 3

Studies Registered in the Chinese Clinical Trial Registry, to Evaluate Convalescent Plasma or Immunoglobulin Therapy in COVID-19 Patients (updated on April 10, 2020). Cancelled Studies have not been Included.

Study leader and affiliation	Registration date (registration number)	Participating centers	Sample size	Study design	Inclusion criteria	Exclusion criteria	Details about intervention	Outcomes
Studies on convalescent plasma								
Dr Cao Bin, China-Japan Friendship Hospital	February 12, 2020 (ChiCTR2000029757)	12 hospitals in China	200 (100 intervention; 100 control)	Randomized with experimental group (conventional treatment combined with convalescent plasma) vs. control (conventional treatment group), not blinded	1. Informed consent, 2. Age ≥18, 3. COVID-19 diagnosed by PCR; 4. Nucleic acid positive within 72 hours before blood transfusion; 5. Pneumonia confirmed by imaging; 6. Clinical symptoms severe (RR ≥ 30, oxygen saturation ≤93%; in resting state, $PaO_2/(FiO_2 \leq 300)$ or critical (respiratory failure and mechanical ventilation, shock, other organ failure needing ICU); 7. Accept randomization; 8. Hospitalized before the end of the clinical study. 9. Willing to participate in directions and follow-up; 10. No participation in clinical trials.	1. Lack of cooperation. 2.Pregnant or lactating women; 3. Immunoglobulin allergy; 4.Immunoglobulin A deficiency; 5. Diseases increasing the risk of thrombosis. 6. High titer of anti-novel coronavirus antibody RBD IgG (higher than 1). 7. Received any experimental treatment for COVID-19 within 30 days before screening; 8.Life-threatening conditions, near-death state or expected survival time <24 hours, severe septic shock or DIC, 9. Severe congestive heart failure, or other relative contraindications for transfusion.	Convalescent plasma of patients with COVID-19 is collected, and the clinical treatment plan is explored; no further details provided.	Primary: number of days between randomization and clinical improvement within 28 days admission Secondary: 28-day mortality, Hospitalization time, ICU hospitalization, Invasive mechanical ventilation, ECMO duration, Proportion of viral nucleic acid negative (3 days after transfusion), Results of laboratory tests and vital signs, Cumulative incidence of AE, severe AE, grades 3 and 4 AE, Incidence of adverse plasma transfusion reactions
Dr Xiaowei Xu, First Affiliated Hospital of Zhejiang University School of Medicine	February 15, 2020 (ChiCTR2000029850)	First Affiliated Hospital of Zhejiang University School of Medicine	20 (10 intervention; 10 control)	Non-randomized research; no statement about blinding. Standardized comprehensive treatment combined with convalescent plasma treatment vs. standardized comprehensive treatment.	1. Laboratory confirmed diagnosis of COVID-19 infection by RT-PCR; 2. Aged > 18 years; 3. Written informed consent; 4. Clinical deterioration requiring ICU.	1. Hypersensitive to immunoglobulin; 2 IgA deficiency.	No details provided	Primary: Fatality rate Secondary: ICU stay duration, Viral titers in respiratory samples, Hospital stay duration, Intubation period, PaO2/FiO2, Cytokines/ chemokines
Dr Zhang Dingyu, Wuhan Jinyintan Hospital (Wuhan Infectious Diseases Hospital)	February 19, 2020 (ChiCTR2000030010)	Wuhan Jinyintan Hospital (Wuhan Infectious Diseases Hospital) 8 hospitals in China	100 (50 intervention; 50 control)	Patients stratified according to the respiratory support conditions and randomized to the intervention (anti-SARS-CoV-2 virus inactivated plasma) and the control group (ordinary plasma) at a ratio of 1: 1. Blinding not stated.	1. Aged 18 to 70 years old, inpatients, male or female; 2. Severe COVID-19, meeting any of the following: Respiratory distress, RR≥30/min; oxygen saturation is ≤93% In the resting state; PaO_2/FiO_2 ≤300. 3. Signed informed consent.	1. Clinically, any of the following: a) Respiratory failure and mechanical ventilation; b) Shock; 3) Combined failure of other organs requiring ICU; 2. Allergy to blood products or plasma components and auxiliary materials (sodium citrate); 3. Multiple organ failure, estimated survival time is <3 days; 4. HIV positive; 5. Women pregnant, breastfeeding or having a birth plan; 6. Participants in other clinical trials within 3 months; Poor adherence or other conditions (such as poor physical condition).	No details provided	Primary: Improvement of clinical symptoms (reduction of 2 points on the 6-point scale of the patient's admission status or discharge from the hospital) Secondary: Main clinical manifestations subsided or significantly improved (fever, dry cough, fatigue, etc.), ICU hospitalization days, 14 and 28-day all-cause mortality

(continued)

Table 3
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Study leader and affiliation	Registration date (registration number)	Participating centers	Sample size	Study design	Inclusion criteria	Exclusion criteria	Details about intervention	Outcomes
Dr Xuebing Yan, Affiliated Hospital of Xuzhou Medical University	Feb 21, 2020 (ChiCTR2000030039)		90 (30 intervention; 60 control)	Non randomized; no blinding.	1. COVID-19 confirmed diagnosis; 2. Clinical classification is normal, severe or critical; 3. Subject aged ≥18 years old; 4. Signed informed consent.	1. Highly allergic constitution or history of severe allergy, especially plasma allergy; 2. Other reasons according to doctors not to include the patient.	Conventional therapy with infusion of convalescent plasma: 200–500 ml, two infusions are recommended	Primary (infusion day1 and recheck according to patient's condition): SARS-CoV-2 DNA, SARS-CoV-2 antibody levels Secondary (day1, day 3, day 7, day 14, infusion day1, day 2, 14 days after discharge): CRP, IL-6, LDH, CK, liver function, renal function, respiratory rate, SiO2, thoracic spiral CT
Dr Bende Liu, First People's Hospital of Jiangxia District, Wuhan (Union Jiangnan Hospital)	February 21, 2020 (ChiCTR2000030046)	3 hospitals in China	10	Single-arm; case series with anti-2019-nCoV virus inactivated plasma	1. Age 18 to 80 years old, male or female; 2. Confirmed diagnosis, whose clinical classification is common or severe case; 3. Effective contraceptive measures within 3 months after this trial; 4. Confirmation by doctors; 5. Written informed consent	1. Previous or current allergic history to human plasma protein products or excipients; 2. Severe COVID-19; 3. Pneumonia due to other causes; 4. History of DVT, pulmonary embolism or arterial embolism within 1 year before; 5. Severe heart disease, including myocardial infarction and chronic heart failure (NYHA grades III and IV); 6. Severe liver and kidney diseases; 7. Positive HBsAg, (or nucleic acid test), HCV, HIV or Treponema pallidum; 8. Unwilling to take contraceptive measures during the study; 9. Participated in clinical trials within 1 month; 10. Mental illness or epilepsy; acute diseases; current or previous malignancies; Incapable of behavior or cognition; 11. Alcoholics, drug addicts; 12. Poor compliance or other conditions (e.g. expected survival time <3 months).	No details provided	Primary (3 days after transfusion): Oxyhemoglobin saturation, Dyspnea, Body temperature, Radiological characteristic sign, Blood routine, CRP, lymphocyte count, liver function (total bilirubin, AST and ALT), neutralization antibody level, Secondary (within 7 days after transfusion) copy number of 2019-nCoV RNA
Dr Le Aiping, The First Affiliated Hospital of Nanchang University	February 24, 2020 (ChiCTR2000030179)	The First Affiliated Hospital of Nanchang University	100 (50 intervention; 50 control)	Randomized; blinding not stated (Routine treatment plus plasma treatment versus Routine treatment)	1) Written informed consent; 2) Aged 18 to 65 years; 3) Real-time fluorescent RT-PCR of respiratory specimens or blood specimens positive; 4) Severe and critical illness, with rapid disease progression	1) No safety; 2) Allergic constitution, allergic to plasma or drugs; 3) Old age with severe underlying diseases that affect survival, 4) Severe respiratory failure, heart failure, and multiple organ failure; 5) Participants in other clinical trials.	No details provided	Primary: Cure rate, Mortality Secondary: Length of stay
Dr Guojun Zhang, The First Affiliated Hospital of Zhengzhou University	March 08, 2020 (ChiCTR2000030627)	The First Affiliated Hospital of Zhengzhou University	30 (15 intervention; 15 control)	Randomized; blinding not stated (convalescent plasma therapy plus routine treatment versus routine treatment)	Confirmed COVID-19 by nucleic acid test and; clinical classification of severe or critical illness.	Hypersensitivity to plasma products; severe transfusion reactions in the past; acute pulmonary edema, congestive heart failure, pulmonary embolism, malignant hypertension, polycythemia vera, extreme renal failure and other diseases.	No details provided	Primary: Temperature, Virus nucleic acid detection Secondary: Laboratory examination, Length of admission, Mortality rate, Incidence of adverse events in blood transfusion
Dr Cao Bin, China-Japan Friendship Hospital	March 10, 2020 (ChiCTR2000030702), retrospective registration	4 hospitals in China	50 (25 intervention; 25control)	Randomized with experimental group (conventional treatment plus convalescent	1. Written informed consent; 2. Aged ≥18 years old; 3. COVID-19 patients diagnosed by PCR; 4. Nucleic acid positive within 72 hours	1. Lack of cooperation. 2. Pregnant or lactating women; 3. Immunoglobulin allergy; 4. IgA deficiency; 5. The clinical symptoms are mild (no pneumonia on imaging) or reach the standard of severe, (RR≥30/min, oxygen saturation	Convalescent plasma of patients with COVID-19 is collected, and the clinical treatment plan is explored;	Primary: Time to clinical recovery after randomization Secondary: 28-day mortality, hospitalization time, Incidence of breathing exacerbations, Time for conscious cough

(*continued*)

Table 3
(continued).

Study leader and affiliation	Registration date (registration number)	Participating centers	Sample size	Study design	Inclusion criteria	Exclusion criteria	Details about intervention	Outcomes
				plasma) vs. control (conventional treatment group), not blinded	before blood transfusion; 5. Pneumonia confirmed by imaging; 6. Hospitalization reason: Fever and RR>24/min or cough (at least one of the two); 7. Severe clinical warning indicators: such as a progressive decrease in peripheral blood lymphocytes, a progressive increase in peripheral blood inflammatory factors, lactic acid, and rapid progression of lung lesions, etc. 8. Accept randomization; 9. Hospitalization before the end of the clinical study. 10. Willing to participate in directions and follow-up; 11. No participation in other clinical trials.	is ≤93% in resting state, PaO_2/FiO_2 ≤300) or critical (respiratory failure and need mechanical ventilation; shock; organ failure needing ICU). 6. Diseases that may increase the risk of thrombosis. 7. High titer of anti-novel coronavirus antibody RBD IgG (higher than 1). 8. Received any experimental treatment for COVID-19 within 30 days before screening; 9. Life-threatening conditions, near-death state or expected survival time <24 hours, severe septic shock or DIC, etc., 10. Severe congestive heart failure, or other relative contraindications for transfusion.	no further details provided.	relief during infection (cough present when enrolled), Time to remission of conscious dyspnea during infection (existed dyspnea upon enrolment), 28-day assisted oxygen therapy or non-invasive mechanical ventilation rate, Incidence of ICU surveillance required during infection, Incidence of clinical support measures increased during infection, Proportion of viral nucleic acid negative, Cumulative incidence of severe adverse events (SAE), Cumulative incidence of adverse events (AE), grades 3 and 4 AE, Incidence of adverse plasma transfusion reactions
Dr Binghong Zhang, Renmin Hospital of Wuhan University	March 17, 2020 (ChiCTR2000030929)	Renmin Hospital of Wuhan University	60 (30 intervention; 30 control)	Randomized, double-blind study (Anti-SARS-CoV-2 virus inactivated plasma vs. Ordinary plasma)	1. Aged 18 to 70 years old, inpatients, male or female; 2. Patients with severe confirmed COVID-19; Adult patients with severe COVID-19 shall meet any of the following: respiratory distress, RR≥30/minute; oxygen saturation ≤93% in resting state; lesion more than 50% in lung radiology; PaO_2/FiO_2 ≤300 mmHg; 3. Written informed consent.	1) Respiratory failure with mechanical ventilation; 2) Shock; 3) Combined failure of other organs requiring ICU; 2. Allergic to blood products or plasma components and auxiliary; 3. Multiple organ failure, estimated survival time < 3 days; 4. HIV positive before enrollment; 5. Women pregnant or breastfeeding or with a birth plan; 6. Participants in other clinical trials within 1 month before; 7.Poor adherence or other conditions (such as poor physical condition).	No details provided.	Primary: Improvement of clinical symptoms (defined as a reduction of 2 points on the 6-point scale of the patient's admission status or discharge from the hospital) Secondary: Improving time of main clinical symptoms (wheezing, cough, sputum, etc), ICU hospitalization days, 14 and 28-day all-cause mortality
Dr Weiqin Li, Eastern Theater General Hospital	April 02, 2020 ChiCTR2000031501	Huoshenshan hospital, Wuhan	20 (10 intervention; 10 control)	Pragmatic, prospective, non randomized trial; no blinding (Routine treatment plus Infusion of convalescent plasma versus Routine treatment)	1. Severe or critical patients with confirmed COVID-19 pneumonia; 2. 18–85 years old; 3. Obtained informed consent	1. Patients participating in clinical trials of other drugs; 2. Pregnant or lactating women; 3. ALT / AST > 5-fold ULN, neutrophil < 0.5x10^9/L, platelet < 50x10^9/L; 4. Rheumatic, immune-related diseases; 5. Long term oral anti rejection drugs or immunomodulatory drugs; 6. Hypersensitive reaction to mAb or any adjuvant; 7. Active tuberculosis with definite bacterial and fungal infection; 8. Organ transplantation within three months; 9. History of PCI in the past 60 days; 10.	No details provided	Primary: hospital mortality Secondary: Time to 2019-nCoV RT-PCR negative in surviving patients, Time of medical imaging improvement, New receipt of high flow oxygen absorption, New receipt of non-invasive mechanical ventilation, New receipt of invasive mechanical ventilation, New receipt of CRRT, New receipt of ECMO, Lymphocyte count (day

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Table 3
(continued).

Study leader and affiliation	Registration date (registration number)	Participating centers	Sample size	Study design	Inclusion criteria	Exclusion criteria	Details about intervention	Outcomes
						COPD with end-stage chronic diseases, including NYHA heart failure above grade III, chronic kidney disease with CCR < 40 ml/min or requiring family oxygen therapy.		0,3,7,14), CRP (day 3, 7, 14), IL-6 (day 3, 7, 14), New onset of organ failure, New ICU admission rate, Length of hospital stay, Length of ICU stay, Incidence of secondary bacterial infection, Incidence of secondary fungal infection, Incidence of critical illness, Day90 mortality, Day90 readmission for COVID-19 pneumonia
Studies on immunoglobulin therapy								
Dr Xiang Cheng, Union hospital of Tongji Medical College, Huazhong University of Science and Technology	March 15, 2020 (ChiCTR2000030841)	Union hospital of Tongji Medical College, Huazhong University of Science and Technology	10 (5 intervention; 5 control)	Non-randomized research, no blinding (Immunoglobulin of cured patients versus control gamma-globulin)	1. Written informed consent; 2. Aged ≥18 years; 3. Acute confirmed, severe 2019-nCoV pneumonia: Severe, at least one of: RR ≥30/min; oxygen saturation ≤93% in resting state; PaO2/FiO2<300mmHg; respiratory failure and mechanical ventilation required; shock; ICU required in combination with other organ failure.	1. Viral pneumonia with other viruses besides 2019-nCoV; 2. Patients not suitable for immunoglobulin therapy; 3. Participation in other studies; 4. Other circumstances of patient not being suitable for the clinical trial.	No details provided	Primary: Time to Clinical Improvement Secondary: Clinical status assessed by the ordinal scale; Differences in oxygen intake methods; Duration of supplemental oxygenation; Duration (days) of mechanical ventilation; Mean PaO_2/FiO_2; Lesions of the pulmonary segment numbers involved in pulmonary CT; Time to 2019-nCoV RT-PCR negativity in respiratory tract specimens, Dynamic changes of 2019-nCoV antibody titer in blood, Length of hospital stay, All-cause mortality

AE = adverse events; ALT = alanine aminotransferase; AST = aspartate aminotransferase; COPD = Chronic obstructive pulmonary disease; COVID-19 = Coronavirus disease 2019; CRP = C-reactive protein; CRRT = Continuous Renal Replacement Therapies; CT = computed tomography; DIC = disseminated intravascular coagulation; DVT = deep vein thrombosis; ECMO = extracorporeal membrane oxygenation; HIV = human immunodeficiency virus; ICU = intensive care unit; LDH = lactate dehydrogenase; NYHA = New York Heart Association; PaO_2/FiO_2 = Partial pressure of arterial oxygen to fraction of inspired oxygen ratio; PCI = percutaneous coronary intervention; RBD = receptor binding domain; RR = respiratory rate; SARS = severe acute respiratory syndrome; ULN = upper limit normal.

Convalescent plasma recipients and blood establishments

According to the FDA, eligible recipients of convalescent plasma should be COVID-19 positive patients with severe disease (dyspnea, respiratory frequency ≥ 30/min, blood oxygen saturation 93% or less, partial pressure of arterial oxygen to fraction of inspired oxygen ratio less than 300, and/or lung infiltrates > 50% within 24 to 48 hours) or a life-threatening disease (respiratory failure, septic shock, multiple organ dysfunction) who have given informed consent for the procedure.[40] Nevertheless, as evidenced by the registered trials (Tables 2 and 3), a wide variety of selection criteria have been envisaged. Following the FDA's National Expanded Access Treatment Protocol, 2115 sites have registered to participate to convalescent plasma administration by April 27, 2020, enrolled a total of 5,968 patients, with 2576 receiving convalescent plasma.[43]

Convalescent plasma administration seems to be a safe procedure free from serious adverse effects. Meticulous selection of donors can minimize the risk of TRALI. Another potentially concerning phenomenon pertains to antibody-dependent enhancement (ADE) of coronavirus entry. This has been reported in viral diseases and refers to an enhancement of disease in the presence of certain antibodies.[44] Keeping in mind the high titers of neutralizing antibodies that convalescent plasma includes against the same virus (SARS-CoV-2), as well as the previously documented safe experience in SARS and MERS, the occurrence of ADE does not seem to represent a major problem; however, surveillance is warranted.[29]

In accordance to the Infectious Diseases Society of America Guidelines on the treatment and management of patients with COVID-19 infection, convalescent plasma is recommended in the framework of a clinical trial.[45] Similarly, the International Society of Blood Transfusion (ISBT) Working Party on Global Blood Safety has underlined that the clinical use of convalescent plasma should be performed as an experimental therapy, ideally in the context of an organized research trial.

Plasma should be collected in certified blood establishments through legally approved blood collection or plasmapheresis equipment by trained professionals; 200 to 600 mL of plasma can be collected and in most cases, the interval between potential subsequent new donations should be longer than 7 days. Regarding collection workflow, the existing blood transfusion infrastructure can be useful. However, along with increased numbers of survivors, the increasing pool of potential donors may entail logistical challenges, spanning the assessment of donor eligibility, coordination of donor recruitment and collections, as well as transfusion.[32]

Facing the COVID-19 pandemic, the European Blood Alliance (EBA), together with the European Commission's Directorate-General for Informatics (DIGIT) and Directorate-General for Health and Food Safety (DG SANTE), has been developing an open database hosted on a platform by the European Commission with the aim to collect, monitor, and share all information on convalescent plasma.[46] Blood establishments will organize collection, enter donor data in the database to supply plasma to hospitals, and research projects and the industry; afterwards, the patient outcomes of transfusion can serve as the basis of aggregated data, reports, and pragmatic assessment of convalescent plasma effectiveness. According to the guidance document by the European Commission, the data should include gender, age, comorbidities, time point of transfusion, number, volume and antibody titer of the unit, other therapies administered, clinical symptoms (prior to transfusion, 5 days later and at discharge for survivors), serious adverse events, and length of hospitalization.[42]

Critical appraisal, perspectives, and conclusions

As of April 2020, more than 350,000 people have recovered from COVID-19 worldwide.[47] These individuals may offer a valuable pool of a life-saving treatment for future patients during the pandemic. Asymptomatic, antibody positive carriers may also prove helpful as donors of the disease. For instance, there is anecdotal evidence that in Northern Italy among 60 volunteer blood donors in the town of Castiglione d' Adda, Lombardy, 67% were antibody positive although asymptomatic; nevertheless, their specific antibody titers were not declared in detail.[48,49] If proven in larger cohorts, these results may be promising in terms of identifying a large number of eligible convalescent plasma donors. Thorough research into the evaluation of humoral response and neutralizing antibodies[50] in the context of COVID-19 seems an important step in designing strategies pertaining to convalescent plasma.

Until now the number of COVID-19 patients with known outcomes of convalescent plasma administration is particularly limited, stemming from 6 case series.[20–26] The follow-up of cases reaching hospitalizations of 51 days[21] and 60 days after onset of symptoms[23] highlights the need for adequate observation, but also underlines the time needed from the early, sizable Chinese cohorts (reportedly reaching 245 COVID-19 patients, with improvement in 91 of them)[51] to provide robust results in relevant scientific publications.

A pivotal and controversial point is the time of convalescent plasma administration in COVID-19; that should be as early as possible to maximize efficacy, but at the same time oriented to severe cases. To this direction, the examination of risk markers and integrating clinical (gender, age, comorbidities) and biochemical aspects in a comprehensive risk stratification can provide a valuable tool for decision making, promptly tracing those patients with forthcoming poor prognosis who would most need early intervention with convalescent plasma. Emerging markers with such potential are lymphocytopenia, elevated procalcitonin, ferritin, D-dimer, and C-reactive protein.[52]

Along with the evaluation of convalescent plasma from blood donors, the plasma industry could take future steps, manufacturing concentrated hyperimmune globulin preparations that contain standardized antibody doses and could provide a further reach in terms of health setting administering therapy.[34] As a whole, the promising results of convalescent plasma transfusion could change the course of COVID-19. The formulation, namely convalescent plasma or hyperimmune globulin, as well as the optimal time frame, remain to be identified in the future.

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