Contents lists available at ScienceDirect

Transfusion and Apheresis Science

Lessons learned from the use of convalescent plasma for the treatment of COVID-19 and specific considerations for immunocompromised patients

Mickael Beraud [a,1], Erin Goodhue Meyer [b,1], Miquel Lozano [c], Aicha Bah [a], Ralph Vassallo [d], Bethany L. Brown [e,*]

[a] *Terumo Blood and Cell Technologies Europe NV, Ikaroslaan 41, 1930, Zaventem, Belgium*
[b] *Terumo Blood and Cell Technologies, 10811 W Collins Ave, Lakewood, CO, 80215, United States*
[c] *Department of Hemotherapy and Hemostasis, ICMHO, University Clinic Hospital, IDIBAPS, University of Barcelona, Villarroel 170, 08036, Barcelona, Catalonia, Spain*
[d] *Vitalant, 6210 E Oak St, Scottsdale, AZ, 85257, United States*
[e] *American Red Cross, Biomedical Services, Holland Laboratory for the Biomedical Sciences, 15601 Crabbs Branch Way, Rockville, MD, 20855, United States*

ARTICLE INFO

ABSTRACT

Coronavirus disease 2019 (COVID-19) convalescent plasma (CovCP) infusions have been widely used for the treatment of hospitalized patients with COVID-19. The aims of this narrative review were to analyze the safety and efficacy of CovCP infusions in the overall population and in immunocompromised patients with COVID-19 and to identify the lessons learned concerning the use of convalescent plasma (CP) to fill treatment gaps for emerging viruses. Systematic searches (PubMed, Scopus, and COVID-19 Research) were conducted to identify peer-reviewed articles and pre-prints published between March 1, 2020 and May 1, 2021 on the use of CovCP for the treatment of patients with COVID-19. From 261 retrieved articles, 37 articles reporting robust controlled studies in the overall population of patients with COVID-19 and 9 articles in immunocompromised patients with COVID-19 were selected. While CovCP infusions are well tolerated in both populations, they do not seem to improve clinical outcomes in critically-ill patients with COVID-19 and no conclusion could be drawn concerning their potential benefits in immunocompromised patients with COVID-19. To be better prepared for future epidemics/pandemics and to evaluate potential benefits of CP treatment, only CP units with high neutralizing antibodies (NAbs) titers should be infused in patients with low NAb titers, patient eligibility criteria should be based on the disease pathophysiology, and measured clinical outcomes and methods should be comparable across studies. Even if CovCP infusions did not improve clinical outcomes in patients with COVID-19, NAb-containing CP infusions remain a safe, widely available and potentially beneficial treatment option for future epidemics/pandemics.

1. Introduction

The global coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been responsible for more than 240 million infections and more than 4.8 million deaths up to October 17, 2021 [1]. While the number of people fully vaccinated against COVID-19 is globally increasing as several vaccines are available, there are still many active infections and the infectivity, transmission, and lethality of SARS-CoV-2 are evolving [2]. The emergence of new variants highlights the importance of surveillance systems to update vaccination strategies and treatment approaches [3]. These variants cause particular concern as many world areas struggle to vaccinate their citizens due to the lack of infrastructure for production and deployment at scale, affordability, and timely allocation [4]. Moreover, some vaccines may offer suboptimal protection against new variants [5].

Patients with COVID-19 are often asymptomatic or present with mild respiratory symptoms [6]. However, SARS-CoV-2 can also lead to severe complications caused by mechanisms other than the direct viral infection, such as acute respiratory distress syndrome, coagulation disorders,

multi-organ dysfunction syndrome, or septic shock. In some patients, adaptive immunity is suppressed, leading to delayed clearance of the virus, hyperactivation of the innate immune response, overproduction of various inflammatory factors, and increases in the number of active immune cells at the inflammation sites [7]. This imbalance in the immune system resulting in a cytokine storm is a major cause of disease exacerbation and death in patients with COVID-19 [7].

Even though several pharmacological agents have been developed or repurposed for the treatment of COVID-19 and monoclonal antibodies are now available, approved treatment options remain limited globally [8]. COVID-19 convalescent plasma (CovCP) is one treatment that has been extensively used in hospitalized patients with COVID-19 since the first months after the pandemic start [9]. CovCP is obtained from patients who have fully recovered from the infection and ideally contains high titers of virus neutralizing antibodies (NAbs) [10]. Convalescent plasma (CP) infusion is a method of passive immunization that was also previously used during the Spanish influenza pandemic in 1918 [11,12] and later for the treatment of other severe viral infections (severe acute respiratory syndrome [SARS], Middle East respiratory syndrome [MERS], H1N1 influenza, and Ebola virus) [13–15].

Despite the high level of investment and the numerous studies that evaluated the use of CovCP to treat COVID-19, inconsistencies in study design, efficacy endpoints, and reported data have limited the ability to compare results among trials [16]. The objectives of this narrative review are to analyze available data on the safety and efficacy of CovCP infusions for the treatment of COVID-19, to evaluate whether CovCP could be useful for specific subpopulations of patients with COVID-19, and to identify the lessons learned concerning the use of CP to inform future treatment and investigations for emerging viruses.

2. Material and methods

Systematic searches of PubMed, Scopus, and the Dialog database "COVID-19 Research" were conducted to identify peer-reviewed articles and pre-prints published between March 1, 2020 and May 1, 2021 on the use of CovCP to treat patients with COVID-19. The searches were performed with the following terms: ("convalescent plasma" OR "convalescent sera") AND ("covid-19" OR "novel coronavirus" OR ("wuhan" AND "virus") OR "SARS-CoV-2" OR "coronavirus 2019" OR "2019-nCoV" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia"). The systematic literature search was initially performed on May 4, 2020, and weekly updates using the established criteria were conducted until May 1, 2021.

Screening of the retrieved articles was performed by an independent reviewer to identify (i) robust studies evaluating the efficacy and/or safety of CovCP in patients with COVID-19 versus control patients with COVID-19 who did not receive CovCP (screening 1), and (ii) all studies evaluating the use of CovCP in immunocompromised patients with COVID-19 who were identified as a specific subpopulation potentially benefiting from CovCP treatment (screening 2). During screening 1, eligible robust studies included randomized controlled trials (RCTs), prospective controlled clinical trials, and matched case-control studies. During screening 2, eligible immunocompromised patients included organ transplant recipients or patients with primary or secondary immunodeficiency, B-cell depletion, hematological cancers/malignancies, lymphomas, or other cancers. During both screenings, systematic and narrative literature reviews and meta-analyses were excluded, but their reference lists were checked for relevant articles that might have been overlooked. Reference lists of selected articles were also checked for relevant articles.

Data were extracted from the selected articles. Methodological classification was performed using the Oxford Centre for Evidence-Based Medicine levels by two independent assessors with differences resolved by consensus [17]. As decided *a priori*, any article published on a pre-print server was downgraded to the lower Oxford level of evidence (LoE). The other downgrading criteria included early study termination,

small sample size, absence of systematic measurements of NAb levels in CovCP, and inclusion of CovCP units with low NAb levels.

3. Results and discussion

3.1. General information on search results

The systematic literature search identified 1708 peer-reviewed articles, pre-prints and abstracts, of which 261 were selected for further screening.

During screening 1, which was performed to evaluate the efficacy and safety of CovCP for the treatment of COVID-19 and to improve preparedness for future emerging viruses, 222 articles were excluded (case reports, non-matched case-control series, reviews, viewpoints, recommendations, meta-analyses, studies that were not conducted in patients with COVID-19 or did not include CovCP administration, or absence of control patients who did not receive CovCP). Two articles presenting results of the same study were further excluded [18,19] and only the most recent analysis was kept [20]. In total, 36 articles and one abstract [20–56] were included (Table 1). There were 13 RCTs, of which four were categorized as Oxford LoE 2 [25,26,28,33], seven were downgraded to Oxford LoE 3 [21–23,29–32], and two to Oxford LoE 4 [24,27]. Of the remaining papers, eight were prospective controlled clinical trials, of which three were categorized as Oxford LoE 3 [34,35, 50], four as Oxford LoE 4 [46,48,53,55], and one as Oxford LoE 5 [37]. Of the 16 matched case-control series, 14 were categorized as Oxford LoE 4 [20,36,38–41,43,44,47,49,51,52,54,56] and two as Oxford LoE 5 [42,45].

During screening 2, which was performed to identify studies evaluating the potential benefit of CovCP in immunocompromised patients with COVID-19, nine articles were selected (one matched case-control study [43], one non-matched case-control series [57], and seven uncontrolled case series [58–64]) (Table 2). All the selected articles were categorized as Oxford LoE 4 or 5.

Besides differences in study design and LoEs between studies, characteristics of patients (disease severity and duration, mechanical ventilation [MV] status, NAb titers, and concomitant treatment) and of CovCP (timing of CovCP collection and infusion, NAb titers, and volume) were also highly variable (Tables 1 and 2).

Additionally, the results of seven RCTs evaluating the use of CovCP to treat COVID-19 published after May 2021, hence not identified by the systematic literature search, are also briefly discussed [65–71].

3.2. What is the safety and efficacy of CovCP in patients with COVID-19?

3.2.1. Safety

Among 37 articles identified during screening 1, safety was evaluated in 24 studies (Table 3). They confirmed that CovCP treatment has a clinically acceptable safety profile in patients with COVID-19, which was similar to that of standard plasma infusions. The potentially CovCP-related reactions included local reactions at the injection site (pain, chills, rash, redness, and itching); intravenous catheter blockage; transfusion-related acute lung injury (TRALI); transfusion-associated circulatory overload (TACO); pulmonary, allergic, febrile non-hemolytic, and hypotensive reactions; anemia; urticaria; nausea; dyspnea; bradycardia; and tachycardia. No case of antibody-dependent enhancement of infection, listed as a theoretical risk of CovCP administrations by the United States (US) Food and Drug Administration (FDA) [72], was reported.

While the results of most of the seven recently published RCTs support the reassuring safety profile of CovCP [65–69], patients receiving CovCP experienced more serious adverse events than control patients in two of these RCTs [70,71].

3.2.2. Efficacy

There have been inconsistencies and significant biases in efficacy

Table 1
Characteristics of the selected studies evaluating the efficacy and safety of CovCP for the treatment of COVID-19.

First author, country, type of publication*, study group[†]	Number of patients	Disease severity	Time since symptom onset	Mechanical ventilation	Antibody titer in patients	Intervention	Donor eligibility criteria	Antibody titer in CovCP	Oxford Level of Evidence
RCTs									
The RECOVERY Collaborative Group UK, Peer-reviewed publication [33] CovCP group	5795	Any	Symptom onset to randomization, median (range): 9 days (6–12)	302 (5 %) patients	34.7 % seronegative, 53.1 % seropositive, 12.1 % unknown	Usual care (NR) + 2 units of CovCP (275 mL [200–350]) intravenously, the first as soon as possible after randomization and the second (from a different donor) the following day (≥ 12 h after the first unit)	NR	NR	2
Control group	5763	Any	9 days (6–12)	315 (5 %) patients	28.8 % seronegative, 48.8 % seropositive, 22.4 % unknown	Usual care	NA	NA	
Agarwal, India, Peer-reviewed publication [28] CovCP group	235	Hospitalized, moderately ill	Symptom onset to enrollment, median (IQR): 8 days (6–11)	NR	Detectable NAb titer: 185 patients (86 %)	SoC (antivirals, broad spectrum antibiotics, immunomodulators and supportive management) + 2 doses of CovCP (200 mL) 24 h apart	Completely resolved for 28 days or 14 days with 2 negative RT-PCR tests 24 h apart	NAb titer, median (IQR): 1:40 (1:30–1:80)	2
Control group	229	Hospitalized, moderately ill	Symptom onset to enrollment, median (IQR): 8 days (6–11)	NR	Detectable NAb titer: 163 patients (80 %)	SoC (antivirals, broad spectrum antibiotics, immunomodulators and supportive management)	NA	NA	
Simonovich, Argentina Peer-reviewed publication [26] CP group	228	Hospitalized, severe pneumonia	Symptom onset to enrollment, median (IQR): 8 days (5–10)	No MV	Anti-SARS-CoV-2 IgG antibody level, median (IQR): 1:50 (0–1:800); 44.8 % of patients had no detectable antibody level	SoC (antiviral agents, glucocorticoids, or both) + 415–600 mL CovCP	Fully recovered from a clinical perspective after 28 days of COVID-19 diagnosis and discharged from the hospital for ≥ 2 weeks	Anti-SARS-CoV-2 antibody titer, median (IQR): 1:3200 (1:800–1:3200)	2
Control group	105	Hospitalized, severe pneumonia	Symptom onset to enrollment, median (IQR): 8 days (5–10)	No MV	Anti-SARS-CoV-2 IgG antibody level, median (IQR): 1:50 (0–1:1600); 48.6 % of patients had no detectable antibody level	SoC (antiviral agents, glucocorticoids, or both) + 400–600 mL placebo	NA	NA	
O'Donnell, US, Brazil Peer-reviewed publication [29] CovCP group	150	Severe and critical	Symptom onset to randomization, median (IQR): 10 days (7–13)	Invasive MV, ECMO or both: 17 (11 %) patients	NR	SoC (corticosteroids, remdesivir, hydroxychloroquine, antibacterial agents) +CovCP (~200–250 mL infused in 2 h)	Completely resolved for ≥ 14 days and negative PCR test from nasopharyngeal swab	NAb titer, median (IQR): 1:160 (1:80–1:320)	3
Control group	73	Severe and critical	9 days (7–13)	11 (15 %) patients	NR	SoC + normal plasma	NA	NA	
Gonzalez Mexico, Pre-print [31] CovCP group	130	Severe or critical	NR	Invasive MV 162/190 (85.2 %) patients in both groups	NR	Medication (antibiotics, carbapenem drugs, dexamethasone, ivermectin)	Two consecutive negative tests and asymptomatic for ≥ 14 days, or ≥ 28 days	Detectable NAb in CovCP received by 23 patients	3

Table 1 (*continued*)

First author, country, type of publication*, study group[†]	Number of patients	Disease severity	Time since symptom onset	Mechanical ventilation	Antibody titer in patients	Intervention	Donor eligibility criteria	Antibody titer in CovCP	Oxford Level of Evidence
						+200 mL of CovCP infused in 2 h, for 2 days	disease course and asymptomatic for ≥ 14 days prior to donation in the absence of a second RT-PCR		
Control group	60	Severe or critical	NR	Invasive MV 162/190 (85.2 %) patients in both groups	NR	Medication + IVIg at a dose of 0.3 g/kg of ideal weight, 8- h infusion daily, for 5 days	NA	NA	
Libster, Argentina Peer-reviewed publication [25] CovCP group	80	Mildly symptomatic residents of geriatric institutions	< 72 h from symptom onset	No MV	NR	250 mL CovCP over 1.5 h to 2 h	Infected with SARS-CoV-2 for ≥ 10 days, asymptomatic for ≥ 3 days, and with 2 negative RT-PCR tests	S-specific IgG titers: > 1:1000	2
Control group	80	Mildly symptomatic residents of geriatric institutions	< 72 h from symptom onset	No MV	NR	250 mL placebo	NA	NA	
Li, China, Peer-reviewed publication [22] CovCP group	52	Hospitalized, severe or life-threatening disease	Symptom onset to randomization, median (IQR): 27 days (22–39)	ECMO and/or invasive MV: 14/51 patients (27.5 %)	NR	SoC (antiviral or antibacterial medications, steroids, human immunoglobulin, Chinese herbal medicines, and other medications) + CovCP with a median (IQR) volume of 200 mL (200–300). 96 % received a single dose of CovCP	Fully recovered and discharged from the hospital for > 2 weeks	S-RBD-specific IgG titer: ≥ 1:640	3
Control group	51	Hospitalized, severe or life-threatening disease	Symptom onset to randomization, median (IQR): 30 days (19–38)	ECMO and/or invasive MV: 11/50 patients (22.0 %)	NR	SoC (antiviral or antibacterial medications, steroids, human immunoglobulin, Chinese herbal medicines, and other medications)	NA	NA	
Gharbharan, The Netherlands, Peer-reviewed publication [21] CovCP group	43	Hospitalized, variable severity	Symptom onset to enrollment, median (IQR): 9 days (7–13)	Intubation or ventilation and additional organ support: 5 (12 %)	NAb titers, median (IQR): 1:320 (20–1280)	SoC +300 mL CovCP. Second plasma unit after 5 days in unresponsive patients	Asymptomatic for ≥ 14 days	NAb titer, median (IQR): 1:640 (320–1,280)	3
Control group	43	Hospitalized, variable severity	Symptom onset to enrollment, median (IQR): 11 days (6–16)	Intubation or ventilation and additional organ support: 8 (19 %)	NAb titers, median (IQR): 1:80 (20–640)	SoC	NA	NA	
	40	Severe	NR	NR				NA[‡]	3

(*continued on next page*)

Table 1 (*continued*)

First author, country, type of publication*, study group†	Number of patients	Disease severity	Time since symptom onset	Mechanical ventilation	Antibody titer in patients	Intervention	Donor eligibility criteria	Antibody titer in CovCP	Oxford Level of Evidence
Ray, India, Pre-print [30] CovCP group					NAb titers comparable in both groups at the day of enrolment	SoC (hydroxychloroquine, azithromycin, ivermectin doxycycline) + 2 doses of CovCP (200 mL) on 2 consecutive days	Complete resolution of symptoms for ≥ 28 days prior to screening and negative RT-PCR test 40–80 days prior to donation		
Control group	40	Severe	NR	NR	NAb titers comparable in both groups at the day of enrollment	SoC	NA	NA	NA
Avendaño-Solà, Spain Pre-print [27] CovCP group	38	Hospitalized	Symptom onset to inclusion, median (IQR): 8 days (6–9) across both groups	No MV	49.4 % of patients were positive for anti-SARS-CoV-2 IgG antibodies	SoC (supportive and specific treatments with off-label marketed medicines) + 1 dose (250–300 mL) of CovCP	Asymptomatic for ≥ 14 days	NAb titer: > 1:80, median (IQR): 1:292 (1:238–1:451)	4
Control group	43	Hospitalized	Symptom onset to inclusion, median (IQR): 8 days (6–9) across both groups	No MV	49.4 % of patients were positive for anti-SARS-CoV-2 IgG antibodies	SoC (supportive and specific treatments with off-label marketed medicines)	NA	NA	
Pouladzadeh, Iran, Peer-reviewed publication [32] CovCP group	30	Severe	< 7 days	3 (10 %) patients	NR	SoC (chloroquine phosphate, lopinavir/ritonavir, others) +500 mL CovCP on admission day; first unit within 4 h after admission (a second unit if no improvement within 24 h)	Completely recovered for ≥ 14 days and negative RT-PCR test	NR	3
Control group	30	Severe	NR	5 (17 %) patients	NR	SoC	NA	NA	
AlQahtani, Bahrain Peer-reviewed publication [23] CovCP group	20	Hospitalized, hypoxic patients with severe or life-threatening disease	NR	Oxygen therapy, but no MV	NR	SoC (paracetamol and possible therapy including antiviral medications, tocilizumab and antibacterial medication) +400 mL of ABO compatible CovCP given as 200 mL over 2 h over 2 successive days	Asymptomatic and discharged from hospital for > 2 weeks	Antibody level, mean ± SD in 13 CovCPs: 63.8 ± 46.8 AU/mL	3
Control group	20	Hospitalized, hypoxic patients with severe or life-threatening disease	NR	Oxygen therapy, but no MV	NR	SoC (paracetamol and possible therapy including antiviral medications, tocilizumab and antibacterial medication)	NA	NA	
Bajpai, India Pre-print [24] CovCP group	14	Hospitalized, severe disease	Onset of symptoms of severe COVID-19: 3 days	No MV	NR	SoC (hydroxychloroquine, azithromycin) +500 mL CovCP in 2 divided doses on consecutive days	≥ 14 days of complete resolution of symptoms with 2 negative RT-PCR tests 24 h apart	S1-RBD-specific IgG titers, median: ≥ 640 (range: 10–≥ 640) NAb titer, median: ≥ 80 (range: 10–≥ 80)	4
Control group	15	Hospitalized, severe disease	Onset of symptoms of severe COVID-19: 3 days	No MV	NR	SoC (hydroxychloroquine, azithromycin) +500 mL fresh frozen plasma in 2 divided doses on consecutive days	NA	NA	

Prospective controlled trials

Table 1 (*continued*)

First author, country, type of publication*, study group†	Number of patients	Disease severity	Time since symptom onset	Mechanical ventilation	Antibody titer in patients	Intervention	Donor eligibility criteria	Antibody titer in CovCP	Oxford Level of Evidence
Alsharidah, Kuwait, Peer-reviewed publication [34] CovCP group	135	Moderate to severe	NR	IMV or ECMO: 3.7 %; HFNC or non-invasive MV: 33.3 %	NR	Standard treatment (paracetamol, antihistamine, steroids) + antibiotics and low molecular weight heparin in most patents + steroids and/or tocilizumab at the discretion of treating physicians + 2 units (200 mL each) of CovCP, 12 h apart, within 24 h from admission (79.3 %) or 1 unit of CovCP according to the treating physician and protocol dosage range (200–400 mL) (20.7 %)	recovered from COVID-19	NR	3
Control group	233	Moderate to severe	NR	IMV or ECMO: 1.7 %; HFNC or non-invasive MV: 25.3 %	NR	Standard treatment	NA	NA	
Abolghasemi, Iran, Peer-reviewed publication [50] CovCP group	115	Hospitalized	Symptom onset to enrolment: ≤ 7 days	No MV	NR	Routine antiviral therapy (lopinavir/ritonavir, hydroxychloroquine, anti-inflammatory agent) +500 mL CovCP within 4 h. Second CovCP unit after 24 h in unresponsive patients	Asymptomatic for ≥ 14 days	Cut off index higher than 1.1	3
Control group	74	Hospitalized	Symptom onset to enrollment: ≤ 7 days	No MV	NR	Routine antiviral therapy (lopinavir/ritonavir, hydroxychloroquine, anti-inflammatory agent)	NA	NA	
Khamis, Oman, Peer-reviewed publication [35] CovCP group	73	Critical	≤ 14 days	NR	NR	SoC for ICU patients (including hydroxychloroquine and lopinavir/ritonavir) + steroids (70 %) + 200 mL of CovCP at enrollment and a second dose 24 h – 48 h after first dose if the patient did not significantly improve and/or remained in critical respiratory condition.	Completed 14 days free of symptoms	NR	3
Control group	21 (historical controls)	Critical	NR	NR	NR	SoC for ICU patients + steroids (70 %)	NA	NA	
Kurtz, Brazil, Peer-reviewed publication [53] CovCP group	41	Critical	Symptom onset to ICU admission, median (IQR): 10 days (8–14) ICU admission to: -first CovCP: 1 day (1–3)	34 (83 %) patients	Baseline IgG titers ≥ 1:1080 in > 29 patients	SoC (oxygen or MV, prophylactic anticoagulant [enoxapar]) + hydrocortisone for shock and methylprednisolone or dexamethasone for ARDS at the discretion of treating physicians + 1 unit (200–250 mL) CovCP up to 3 days after	Asymptomatic for ≥ 14 days and negative RT-PCR test for virus in plasma	NR	4

Table 1 (*continued*)

First author, country, type of publication*, study group[†]	Number of patients	Disease severity	Time since symptom onset	Mechanical ventilation	Antibody titer in patients	Intervention	Donor eligibility criteria	Antibody titer in CovCP	Oxford Level of Evidence
			-second CovCP: 6 days (5–9)			ICU admission and a second one within a week for all but first 10 patients			
Control group	72	Critical	Symptom onset to ICU admission, median (IQR): 9 days (5–12)	63 (88 %) patients	NR	SoC	–	–	
Sturek, US Pre-print [37] CovCP group	29	Hospitalized mild/moderately ill, non-ICU	NR	0 % (exclusion criteria)	NA[‡]	Remdesivir and corticosteroids in some patients + 2 units of CovCP within 72 h of admission (except 1 patient who received 1 unit)	NR	Median (min–max) Anti-S µg/mL, 7.7 (0.1–112.1) -IgG; 3.0 (0–106.6) -IgM; 2.9 (0–24.7) -IgA Anti-RBD µg/mL:2.7 (0.1–83.9) -IgG; 2.9 (0–27.7) -IgM; 2.6 (0–23.5) -IgA Anti-nucleocapsid EU/mL:0.52 (0.0–8.67) -IgG; 1.3 (0–10.0) -IgM; 0 (0–2.3) -IgA	5
Control group	48	Hospitalized mild/moderately ill, non-ICU	NR	0 % (exclusion criteria)	NA[‡]	Remdesivir and corticosteroids in some patients	NA	NA	
Franchini, Italy, Peer-reviewed publication [48] CovCP group	22	Moderate to severe	Symptom onset to first CovCP transfusion, median (IQR): 7 days (4.5–8)	Oxygen therapy, but no MV in 19 patients	Anti–SARS-CoV-2 IgG (U/mL), median (IQR): 127.0 (64.4–205.7) at baseline	Medication (antiviral, antibacterial treatment, hydroxychloroquine, steroids, anticoagulants) +1 (300 mL) to 3 units of CovCP, according to clinical response	SARS-CoV-2 infection completely resolved for ≥ 14 days + 2 negative PCR tests 24 h apart	Anti–SARS-CoV-2 NAb titer of ≥ 1:80	4
Control group	733	Moderate to severe	NR	NR	NR	NR	NA	NA	
Rasheed, Iraq, Peer-reviewed publication [55] CovCP group	21	Hospitalized, early-stage critically-ill	Symptom onset to enrollment, mean: 14.8 days (SD: 7.5)	81 % of patients on ventilators	14.9 % weakly positive for SARS-CoV-2 IgGs	SoC (hydroxychloquine, azithromycin, oxygen therapy, methylprednisolone) +400 mL of frozen CovCP infused over 2 h	Recovered for 2 weeks	Anti-SARS-CoV-2 IgG index: ≥ 1.25	4
Control group	28	Hospitalized, early-stage critically-ill	Symptom onset to enrollment, mean ± SD: 16.6 ± 6.0 days	57 % of patients on ventilators	No significant difference with CovCP group	SoC (hydroxychloquine, azithromycin, oxygen therapy, methylprednisolone)	NA	NA	
Acosta-Ampudia, Colombia, Peer-reviewed publication [46] CovCP group	9	Severe (not life-threatening)	Symptom onset to CovCP transfusion, mean ± SD: 8.667 ± 2.693 days	22.2 %	NA[‡]	Standard treatment (e.g., antibiotics, corticosteroids, oxygen, anticoagulants) + 2 units (250 mL each) of CovCP within 48 h after study inclusion	Recovered 14–30 days before the pre-donation assessment and 2 consecutive negative RT-PCR results within 48 h before donation	IgG antibody titers ≥ 1:3200 and IgA antibody titers ≥ 1:800 to SARS-CoV-2	4

(*continued on next page*)

Table 1 (*continued*)

First author, country, type of publication*, study group[ǀ]	Number of patients	Disease severity	Time since symptom onset	Mechanical ventilation	Antibody titer in patients	Intervention	Donor eligibility criteria	Antibody titer in CovCP	Oxford Level of Evidence
Control group	9	Severe (not life-threatening)	NR	33.3 %	NR	Standard treatment	NA	NA	
Matched case control studies									
Altuntas, Turkey, Peer-reviewed publication [51] CovCP group	888	Hospitalized, severe or critically-ill	Symptom onset to CovCP infusion: ≤ 5 days: 11.3 %; 6–10 days: 25.9 %; 11–15 days: 27.9 %; 16–20 days: 14.2 %; > 20 days: 20.7 %	NR	NR	SoC (including favipravir, lopinavir, ritonavir, hydroxychloroquine, high dose vitamin C, azithromycin) + CovCP	Resolution of symptoms ≥ 14 days	NR	4
Control group	888	Hospitalized, severe or critically-ill	NR	NR	NR	SoC (including favipravir, lopinavir, ritonavir, hydroxychloroquine, high dose vitamin C, azithromycin)	NA	NA	
Salazar, US, Peer-reviewed publication [20] CovCP group	351	Hospitalized, severe and/or life-threatening	NR	MV or ECMO: 4.0 % of patients	NR	SoC + 1 (79 % of patients) or 2 units of CovCP (~300 mL)	Asymptomatic for > 14 days	Anti-RBD IgG titer: ≥ 1:1,350: 91 %; > 1:150 but < 1:1,350: 6.8 %; < 1:150: 1.7 % for the first transfusion	4
Control group	594	Hospitalized, severe and/or life-threatening	NR	MV or ECMO: 4.5 % of patients	NR	SoC	NA	NA	
Shenoy, US, Peer-reviewed publication [49] CovCP group	263	Hospitalized, severe	NR	NR	NR	Medication (azithromycin, dexamethasone, hydrocortisone, hydroxychloroquine, methylprednisolone, prednisone, remdesivir, sarilumab, tocilizumab) + 1–2 units of CovCP (~200–500 mL)	NR	NR	4
Control group	263	Hospitalized, severe	NR	NR	NR	Medication	NA	NA	
Bulanov, Russia, Peer-reviewed publication [41] CovCP group	226	Hospitalized, moderate to severe	NR	29 (12.8 %) (MV); 2 (0.9 %) (ECMO) patients	NR	Medication (hydroxychloroquine, azithromycin, lopinavir, Ritonavir) + biological therapy, including tocilizumab (23.4 %	NR	NAb titer of 40 in 108 donors; 80 in 74 donors; 160 in 27 donors; 320 in 12 donors and 640 in 5 donors	4

Table 1 (*continued*)

First author, country, type of publication[*], study group[†]	Number of patients	Disease severity	Time since symptom onset	Mechanical ventilation	Antibody titer in patients	Intervention	Donor eligibility criteria	Antibody titer in CovCP	Oxford Level of Evidence
						of patients) + 200–800 mL of CovCP (average 287.5 mL)			
Control group	226	Hospitalized, moderate to severe	NR	32 (14.2 %) (AV); 3 (1.3 %) (ECMO) patients	NR	Medication + biological therapy, including tocilizumab (20.4 % of patients)	NA	NA	
Thompson, US, Peer-reviewed publication [43] CovCP group	143	Mild to severe (with hospitalization), in patients with hematologic malignancies	NR	45 (31.5 %) patients	NR	Medication (corticosteroid, remdesivir, hydroxychloroquine, tocilizumab) + CovCP (details NR)	NR	NR	4
Control group	143 (propensity-score matched) 823 (non-matched)	Mild to severe (with hospitalization) in patients with hematologic malignancies	NR	29 (20.3 %) matched controls 182 (22.1 %) non-matched controls	NR	Medication	NA	NA	
Tworek, Poland, Peer-reviewed publication [40] CovCP group	102	Hospitalized, severe	≤14 days	Ventilator: 12 (11.8 %) patients	NR	SoC + 1 (or more) 200 mL infusion of CovCP on the 14th day from COVID-19 diagnosis (if more, 24 h apart)	10 days after double-negative test with a minimum 24-h interval between tests	NAb level: 142.75 (SEM ± 12.0057); 2/44 donors were negative for NAbs	4
Control group	102 (propensity-matched)	Hospitalized, severe	NR	22 (21.6 %) patients	NR	SoC	NA	NA	
Mesina Philippines, Pre-print [45] CovCP group	75	Hospitalized, moderate pneumonia, severe and critical	Median time from admission to CovCP: 3 days	Intubation: 20 (26.67 %) patients	NR	Medication (dexamethasone, remdesivir, antibiotics, tocilizumab), hemoperfusion or combination of these + CovCP 3 days (IQR: 2–5) from admission	NR	NR	5
Control group	75 (historical)	Hospitalized, moderate pneumonia, severe and critical	NR	NR		NR	NA	NA	
Yoon, US, Peer-reviewed publication [38] CovCP group	73	Hospitalized, severe or life-threatening	Symptom onset to CovCP transfusion in 90 CovCP recipients before propensity score matching, median (IQR): 7 days (5–9)	9 (12.3 %) patients	Ab (1/titer, median with IQR) < 65 YOA: 18,225 (2430–196829)- IgG; 2430 (810–2430)-IgM;	200 mL-unit of CovCP transfused within 72 h of hospital admission	Asymptomatic for ≥ 14 days	Median IgG, IgM, and IgA titers were, respectively, 1:47385 (IQR, 21870–65610; n = 46), 1:810 (IQR, 810–2430; n = 43), and 1:90 (IQR, 90–270; n = 43). Median NAb titer by pseudovirus neutralization assay:	4

(*continued on next page*)

Table 1 (*continued*)

First author, country, type of publication[*], study group[ǂ]	Number of patients	Disease severity	Time since symptom onset	Mechanical ventilation	Antibody titer in patients	Intervention	Donor eligibility criteria	Antibody titer in CovCP	Oxford Level of Evidence
					180 (90–2430)-IgA ≥ 65 YOA: 54,675 (7290–196829)-IgG, 2,430 (810–21870)-IgM; 810 (270–7290)-IgA			1:938 (IQR, 407–2784; n = 42)	
Control group	73 (propensity score-matched)	Hospitalized, severe or life-threatening	NR	9 (12.3 %) patients	NR	NR	NA	NA	
Rogers, US, Peer-reviewed publication [56] CovCP group	64	Hospitalized, severe	Symptom onset to transfusion, median (IQR): 7 days (5–9)	Supplemental oxygen (but not invasive ventilation)	NR	SoC (remdesivir: 28.1 %; corticosteroids: 40.6 %) + 1 (3 patients) or 2 units of CovCP	NR	Anti-SARS-CoV-2 IgG antibody index < 1.4: 13 %	4
Control group	177	Hospitalized, severe	Symptom onset to enrollment: ≤10 days	Supplemental oxygen (but not invasive ventilation)	NR	SoC (remdesivir: 33.3 %; corticosteroids: 22.6 %)	NA	NA	
Klapholz, US, Peer-reviewed publication [39] CovCP group	47	Hospitalized, severe or life-threatening	Admission to transfusion, mean (SD): 4.9 (3.2) days	9 (19.2 %) patients	NR	SoC (hydroxychloroquine, azithromycin, doxycycline, interleukin-6 inhibitors [mostly tocilizumab], antimicrobials, steroids, and anticoagulants) + 1 unit (200 mL) of CovCP infused at baseline, and ≥ 2 additional units during follow-up based on plasma availability	NR	NR	4
Control group	47 (contemporaneous)	Hospitalized, severe or life-threatening	NR	9 (19.2 %) patients	NR	SoC	NA	NA	
AlShehry, Saudi Arabia, Peer-reviewed publication [44] CovCP group	40	Hospitalized, with severe symptoms, ICU requirement or life-threatening condition	NR	Intubation: 25 (62.5 %) patients	NR	Best SoC +300 mL (200–400 mL/treatment dose) CovCP at least once, and if required, daily for up to 5 sessions	≥ 14 days from the last negative PCR test or 28 days from the initial symptoms	NR	4
Control group	124 (propensity score-matched)	Hospitalized, with severe symptoms, ICU requirement or life-threatening condition	NR	Intubation: 79 (63.7 %) patients	NR	Best SoC	NA	NA	
Liu, US, Peer-reviewed publication [54] CovCP group	39	Hospitalized, severe or life-threatening infection	Symptom onset to admission, median (range): 7 days (0–14). Admission to transfusion,	4 patients (10 %)	NR	SoC (including azithromycin, hydroxychloroquine, broad-spectrum antibiotics, therapeutic-dose anticoagulation,	NR	Anti-S antibody titer: ≥ 1:320	4

Table 1 (*continued*)

First author, country, type of publication*, study group[†]	Number of patients	Disease severity	Time since symptom onset	Mechanical ventilation	Antibody titer in patients	Intervention	Donor eligibility criteria	Antibody titer in CovCP	Oxford Level of Evidence
			median (range): 4 days (0–7).			corticosteroids, remdesivir, mesenchymal stem cells and IL-1 and IL-6 inhibitors) + 2 units of ABO–compatible CovCP (~250 mL) infused over 1 h – 2 h			
Control group	156	Hospitalized	NR	10.3 % of patients	NR	SoC (including azithromycin, hydroxychloroquine, broad-spectrum antibiotics, therapeutic-dose anticoagulation, corticosteroids, remdesivir, mesenchymal stem cells and IL-1 and IL-6 inhibitors)	NA	NA	
Sostin, US, Peer-reviewed publication [36] CovCP group	35	Severe or immediately life-threatening	Symptom onset to transfusion, median (IQR): 10 days (7–13)	4 (11 %) patients	NR	1 to 2 units (based on the body mass index) of 200–250 mL CovCP on the same day or the day following transfusion of the first unit	Asymptomatic for ≥ 14 days and tested negative by RT-PCR test prior to donation	NR	4
Control group	61	Severe or immediately life-threatening	NR	7 (11 %) patients	NR	NR	NA	NA	
Allahyari, Iran, Peer-reviewed publication [47] CovCP group	32	Severe (ARDS)	Symptom onset to transfusion, mean ± SD: 10.44 ± 2.95 days	0 % (exclusion criteria) Intubation: 8 patients	ELISA at baseline, mean ± SD: 5.87 ± 5.95- IgM, mean ± SD; 11.55 ± 9.48 - IgG	First-line treatment (hydroxychloroquine, corticosteroid and broad-spectrum antibiotics) + 1 cycle (600 mL) of CovCP	Asymptomatic for ≥ 14 days	NR	4
Control group	32	Severe (ARDS)	NR	0 % (exclusion criteria) Intubation: 14 patients	NR	First-line treatment	NA	NA	
Hegerova, US, Peer-reviewed publication [52] CovCP group	20	Hospitalized, severe or life-threatening infection	Symptom onset to enrollment, median (IQR): 2 days (1–4.3)	6 patients (30 %)	NR	One unit of ABO-compatible CovCP. Most patients received additional therapies, including azithromycin (60 %), hydroxychloroquine (55 %), remdesivir (5 %) or multiple combinations	Asymptomatic for ≥ 28 days	NR	4
Control group	20	Hospitalized, severe or life-threatening infection	NR	6 patients (30 %)	NR	50 % of patients received remdesivir	NA	NA	
Khanna, Switzerland and US,	15	Moderate to severe	Symptom onset to CovCP, median (IQR):	Intubation: 5 (33.3 %) patients	2/15 (13.33 %) patients had detectable IgG	SoC (including tocilizumab) +400 mL of CovCP from 2 donors over 48 h	Negative nasopharyngeal PCR test + outpatients with	12/15 (80 %) of donors had effective RVPN titers (> 1:80)	5

Table 1 (continued)

First author, country, type of publication*, study group†	Number of patients	Disease severity	Time since symptom onset	Mechanical ventilation	Antibody titer in patients	Intervention	Donor eligibility criteria	Antibody titer in CovCP	Oxford Level of Evidence
Congress abstract [42] CovCP group	30	Moderate to severe	11 days (8–17)	NA	antibody to SARS CoV-2 S1 antigen		2 PCR negative tests or ≥ 28 days after symptom resolution	NA	NA
Control group				NA	Intubation: 7 (23.3 %) patients	NR	SoC	NA	NA

Ab, antibody; ARDS, acute respiratory distress syndrome; AU, arbitrary units; AV, artificial ventilation; CovCP, COVID-19 convalescent plasma; CP, convalescent plasma; ECMO, extracorporeal membrane oxygenation; ELISA, enzyme-linked immunosorbent assay; EU, ELISA unit; HFNC, high flow nasal cannula; ICU, intensive care unit; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; IL, interleukin; IMV, invasive mechanical ventilation; IQR, interquartile range; IVIg, intravenous immunoglobulin; MV, mechanical ventilation; NA, not available (†reported as figures); NAb, neutralizing antibody; NR, not reported; PCR, polymerase chain reaction; RCT, randomized controlled trial; RBD, receptor-binding domain; RT-PCR, reverse transcription PCR; RVPN, reporter viral particle neutralization; S, spike protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; SEM, standard error of the mean; SoC, standard of care; UK, United Kingdom; US, United States; YOA, years of age.

* Type of publication at the time of writing of this review.
† All publications were from 2020 or 2021.

evaluations performed during this global pandemic. Estimations of the direct impact of CovCP infusions and comparisons among studies have been prevented by differences in study design, methods, analyses, and standard practices. Early in this pandemic, standard practices were heavily influenced by clinical observations and variability in clinical judgement by geographies.

In 25 of 37 articles identified during screening 1, mortality rates were significantly lower [20,29,34,40,41,43,47–49,54,55] or tended to be lower [25,27,30,32,35,37,38,42,44,50–53,56] in all patients or specific subpopulations of patients with COVID-19 who received CovCP compared with control patients (Table 3). In other studies, no positive impact of CovCP infusions on mortality rates was detected [21–24,26, 28,31,33,36,39,45,46].

Duration of hospitalization and length of stay in intensive care unit (ICU) were difficult to compare among studies due to the variability in the evaluated parameters. While some studies assessed the total duration of hospitalization or length of ICU stay, others evaluated the duration of hospitalization or length of ICU stay after CovCP administration. The duration of hospitalization tended to be longer in CovCP-treated patients in some studies [26,28,29,32,33,35,36,40,42,44,45, 49,52,53], but the opposite was observed in others [22,24,27,30,46,47, 50,51] (Table 3). In two studies, similar lengths of stay were observed in both groups [20,56].

The impact of CovCP on the clinical status of patients with COVID-19 was also difficult to assess because the parameters evaluated in the studies with available results were inconsistent (Table 3). In some studies, no statistically significant improvements in clinical outcomes were observed [21,22,26,28,29,31,33,37,39,40,42,44,46,49,52,53]. In contrast, other studies showed benefits of CovCP in terms of disease progression [23,25,27], mitigation of hypoxia [30], World Health Organization (WHO) severity score [32], respiratory parameters [24,54], rate and time to clinical improvement [20,34], need for intubation [50], extubation rate [35], recovery time from critical illness [55], rate of MV and vasopressor support [51], rate of transfer to MV [41], and clinical status [38] in the overall study population or specific subgroups of patients with COVID-19.

Among the seven recently published RCTS, the use of CovCP seemed associated with improved outcomes in one study in 20 patients with COVID-19 [66]. Another study showed no improvements in survival and outcomes in 53 patients who received CovCP infusions versus 52 control patients, but a significant benefit of CovCP was observed in the subgroup of patients who received larger amount of NAbs [67]. The importance of high NAb levels rather than high IgG levels to select appropriate CovCP samples was also highlighted in another RCT [65]. In contrast, a large RCT in 940 patients with COVID-19 showed that CovCP did not reduce the risk of intubation or death and that CovCP infusions with unfavorable antibody profile were even associated with a worsening of clinical outcomes [70]. Other RCTs also showed that CovCP did not improve clinical outcomes in 1084 critically-ill patients with COVID-19 versus 916 controls [71], early administration of CovCP did not prevent disease progression in 257 high-risk patients versus 254 controls [69], and CovCP was associated with increased antibody levels but not with improved outcomes in 59 patients versus 15 controls [68].

3.3. What is the safety and efficacy of CovCP in immunocompromised patients with COVID-19?

3.3.1. Safety

Among nine articles identified during screening 2, safety was evaluated in one non-matched case-control study and three single-group case series in immunocompromised patients with COVID-19 (Table 4). These studies showed that CovCP infusions were well tolerated in this subpopulation. No transfusion-related reactions were reported.

3.3.2. Efficacy

Because screening 2 identified only two controlled studies in

Table 2
Characteristics of selected studies evaluating the use of CovCP in immunocompromised patients with COVID-19.

First author, country, type of publication *, study group[j]	Number of patients	Disease severity	Time since symptom onset	Mechanical ventilation	Antibody titer in patient	Intervention to treat COVID-19	Timing of CovCP collection	Antibody titer in CovCP	Oxford Level of Evidence
Matched case control studies									
Thompson, US, Peer-reviewed publication [43] CovCP group	143	Mild (with hospitalization) to severe, in patients with hematologic malignancies	NR	45 (31.5 %) patients	NR	Medication (corticosteroid, remdesivir, hydroxychloroquine, tocilizumab) + CovCP (details NR)	NR	NR	4
Control group	143 (propensity-score matched) 823 (non-matched)	Mild (with hospitalization) to severe, in patients with hematologic malignancies	NR	29 (20.3 %) matched controls 182 (22.1 %) non-matched controls	NR	Medication	NA	NA	
Non-matched case control studies									
Biernat, Poland, Peer-reviewed publication [57] CovCP group	23	Mild, moderate and severe, in patients with hematologic malignancies	NR	3 (13 %) patients	NR	Medication (dexamethasone) + 1 or 2 CovCP units (200–250 mL) administered 48 h – 72 h after diagnosis of infection + supportive care	EU guidelines [99]	Anti-S-RBD-specific IgG titer > 1:1,000	4
Control group	22 (historical)	Mild, moderate and severe, in patients with hematologic malignancies	NR	4 (18.2 %) patients	NR	Medication (hydroxychloroquine, remdesivir, tocilizumab, lopinavir/ritonavir, dexamethasone) + supportive care	NA	NA	
Case series									
Jeyaraman, India, Peer-reviewed publication [58]	33	Severe, in patients with hematologic malignancies	Diagnosis of COVID-19 infection to CovCP infusion, median (range): 4 (2–25) days	Invasive ventilation: 14 (42.4 %) patients	NR	1 unit (200 mL) CovCP infused over 1 h – 1.5 h; a second one after 24 h if no improvement	NR	Anti-S-RBD-specific IgG titer > 1:640	4
Rodionov, Germany, Peer-reviewed publication [59]	14	Median initial disease severity on the 10-point WHO Clinical Progression Scale was 5 (range: 4–6), in patients with solid organ transplantation (n = 8), allogeneic stem cell transplantation (n = 4), or active hematological malignancy (n = 2)	Positive PCR to transfusion, mean ± SD: 5.14 ± 5.14 days	NR	Not detectable at baseline	3 units of CovCP (11 patients), 2 units (2 patients) or 1 unit (1 patient), each unit of 200 mL	NR	PRNT50 values ≥ 1:40	4
Gupta, India, Peer-reviewed publication [60]	10	Severe, in kidney transplant recipients in ICU	Symptoms to hospital admission, median (IQR): 3 days (2–5); symptoms to transfusion,	Invasive ventilation: 1 (10 %) patient	NR	Medication (antiviral therapy, glucocorticoids), other supportive care + 2 units (200 mL each) of CovCP, 24 h apart	Asymptomatic, complete resolution of symptoms ≥ 14 days before donation, preferably with 1 negative RT-PCR test or complete	NAb titer > 1:640	4

Table 2 (*continued*)

First author, country, type of publication *, study group†	Number of patients	Disease severity	Time since symptom onset	Mechanical ventilation	Antibody titer in patient	Intervention to treat COVID-19	Timing of CovCP collection	Antibody titer in CovCP	Oxford Level of Evidence
			median (IQR): 5 days (3–8)				resolution of symptoms for 28 days		
Ferrari, Italy, Peer-reviewed publication [61]	7	Persistent symptoms of infection due to SARS-CoV-2, in patients with immunologic deficiency after chemo-immunotherapy, due to hematological disorders	Symptoms to CovCP: 6–10 days	Intubation: 1 (14.3 %) patient	NR	Medication (antibiotics, low molecular weight heparin, corticosteroid and hydroxychloroquine) + 3 infusions of CovCP (210 mL each)	NR	Hyperimmune	4
Lindemann, Germany, Peer-reviewed publication [62]	4	Moderate to severe, in kidney transplant recipients (n = 2) and hemodialysis patients (n = 2)	Symptom onset to transfusion: 3–13 days	0 %	NAb detectable at baseline (≤ 1:40 for 3 patients and 1:640 for 1 patient)	Oxygen administration, tacrolimus, mycophenolate mofetil, and prednisone or dexamethasone + 1 or 2 cycles of 3 units (200–280 mL) each, applied at days 1, 3, and 5	NR	NAb titers 1:160–1:1280	4
Jin, US, Peer-reviewed publication [63]	3	Any, in hospitalized patients with X-linked agammaglobulinemia	Symptom onset to hospital admission: 5–42 days Symptoms onset to CovCP transfusion: 61–44 days	0 %	Not detectable at baseline for patients 1 and 2 ; NR for patient 2	2 units (200 mL each) of CovCP on days 22 and 23 for patient 1; day 16 for patient 2 and day 44 for patient 3 + remdesivir for patient 1; subcutaneous heparin and oral azithromycin for patient 2	NR	Anti-S titer of ≥ 1:320	5
Delgado-Fernández, Spain, Peer-reviewed publication [64]	3	Any, in patients with humoral immunodeficiency	Symptom onset to hospital admission: 7–13 days Symptoms to CovCP transfusion: 36–56 days	NR	IgG/IgA/IgM before CovCP detectable for 1/3 patients	Medication (antibiotics, antimicrobials, corticosteroid boluses, tocilizumab, dexamethasone, remdesivir), IVIg + 1 dose (300 mL) of CovCP administered during 3 h – 4 h with no premedication (second one after 4–6 days, if patients had no serum antibodies after first transfusion)	Recovered from COVID-19 and had a negative RNA test 14 days before donation	OD CovCP/cut-off index > 1.5 (ELISA IgG; hyperimmune plasma), could have neutralizing activity in > 80.8 % of donations	5

CovCP, COVID-19 convalescent plasma; ELISA, enzyme-linked immunosorbent assay; EU, European Union; ICU, intensive care unit; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; IQR, interquartile range; IVIg, intravenous immunoglobulin; n, number of patients; NA, not available; NAb, neutralizing antibody; NR, not reported; OD, optical density; PCR, polymerase chain reaction; PRNT, plaque reduction neutralization test; RBD, receptor-binding domain; RT-PCR, reverse transcription PCR; S, spike protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; US, United States; WHO, World Health Organization.

* Type of publication at the time of writing of this review.
† All publications were from 2020 or 2021.

Table 3

Safety-related information and clinical outcomes in the selected studies evaluating the efficacy and safety of CovCP for the treatment of COVID-19.

First author, country, type of publication*, study group†	Number of participants	Safety assessment	Transfusion-related reactions	Mortality	Length of hospital stay	Clinical improvement
RCTs						
The RECOVERY Collaborative Group UK, Peer-reviewed publication [33] CovCP group	5795	Yes	9 patients with pulmonary reactions (none considered to be transfusion-related acute lung injury, including 3 deaths possibly related to transfusion), and 4 patients with serious febrile, allergic, or hypotensive reactions (all recovered).	28-day: 24 %	Median (IQR): 12 days (6–28)	NR
Control group	5763	NR	NR	28-day: 24 %	Median (IQR): 11 days (6–28)	NR
Agarwal, India, Peer-reviewed publication [28] CovCP group	235	Yes	Minor AEs (pain in local infusion site, chills, nausea, bradycardia and dizziness) in 1 patient each. Fever and tachycardia in 3 patients each. Dyspnea and intravenous catheter blockage in 2 participants each.	28-day: 15 %	Median (IQR): 14 days (10–19)	NR
Control group	229	NR	NR	28-day: 14 %	Median (IQR): 13 days (10–18)	NR
Simonovich, Argentina Peer-reviewed publication [26] CP group	228	Yes	Infusion-related AEs: 4.8 % (11 patients). 5 patients with nonhemolytic febrile reactions.	30-day: 10.96 %	Time from enrollment to hospital discharge, median (IQR): 13 days (8–30)	Proportion of ICU admissions and invasive MV requirements: 53.9 % and 26.8 %
Control group	106	Yes	Infusion-related AEs: 1.9 % (2 patients)	30-day: 11.43 %	Time from enrollment to hospital discharge, median (IQR): 12 days (7–30)	Proportion of ICU admissions and invasive MV requirements: 60.6 % and 22.9 %
O'Donnell, US, Brazil Peer-reviewed publication [29] CovCP group	150	Yes	4/147 (2.7 %) patients (included worsening anemia, urticaria, skin rash, and transfusion-associated circulatory overload)	28-day: 12.6 %	Median (IQR): 9 days (6–28)	Time-to-clinical improvement, median, (IQR):5 days (4–6)
Control group	73		3/72 (4.2 %) patients receiving control plasma (included transfusion-associated circulatory overload, worsening anemia, urticaria and possible febrile non-hemolytic transfusion)	28-day: 24.6 %	Median (IQR): 8 days (6–22)	Time-to-clinical improvement, median, (IQR): 7 days (5–8)
Gonzalez Mexico, Pre-print [31] CovCP group	130	Yes	No	28-day: 46.2 % All follow-up: 53.8 %	Median (IQR): 12 days (6–22) (NR by group)	No statistically significant difference between groups
Control group	60	NR	NR	28-day: 43 % All follow-up: 53.3 %		
Libster, Argentina Peer-reviewed [25] CovCP group	80	No	NR	25-day: 2.5 %	NA	16.2 % and 5 % of patients experienced severe and life-threatening respiratory disease and 6.2 % critical systemic illness; median time to development of severe COVID-19: 15 days.
Control group	80	NR	NR	25-day: 5 %	NA	31.2 % and 12.5 % of patients experienced severe and life-threatening respiratory disease and 7.5 % critical systemic illness; median time to development

(continued on next page)

Table 3 (*continued*)

First author, country, type of publication*, study group†	Number of participants	Safety assessment	Transfusion-related reactions	Mortality	Length of hospital stay	Clinical improvement
						of severe COVID-19: 15 days.
Li, China, Peer-reviewed publication [22] CovCP group	52	Yes	Two participants with transfusion-related AEs (non-severe allergic transfusion reaction and febrile nonhemolytic transfusion reaction in 1 patient and possible severe transfusion-associated dyspnea in 1 patient)	28-day: 15.7 %	Median (IQR): 41 days (31–indeterminate)	On day 28: 51.9 %
Control group	51	NR	NR	28-day: 24.0 %	Median (IQR): 53 days (35–indeterminate)	On day 28: 43.1 %
Gharbharan, The Netherlands, Peer-reviewed publication [21] CovCP group	43	No	NR	15-day: 14 %	NR	On day 15: 58 %
Control group	43	NR	NR	15-day: 26 %	NR	On day 15: 58 %
Ray, India, Pre-print [30] CovCP group	40	NR	NR	30-days post-enrollment: no statistically significant differences between groups, except in CovCP patients < 67 years of age with ARDS and severe COVID-19 in CovCP group ($P = 0.0442$) (significant survival benefit in CovCP group)	No statistically significant differences between SoC and CovCP groups, except in patients < 67 years of age with ARDS and severe COVID-19 ($P = 0.031$) (reduction in hospital stay in CovCP group; median of 17 days for SoC and 13 days for CovCP group)	No statistically significant differences between groups, except in patients < 67 years of age with ARDS and severe COVID-19 in CovCP group (mitigation of hypoxia)
Control group	40	NR	NR			
Avendaño-Solà, Spain Pre-print [27] CovCP group	38	Yes	Two CovCP infusion-related AE and suspected TRALI (TRALI was ruled out after full assessment).	15-day: 0 %	Median (IQR) time to discharge: 8.5 days (6.0–13.0)	Progression to categories 5–7 at day 15: 0 %
Control group	43	NR	NR	29-day: 9.3 %	Median (IQR) time to discharge: 9.0 days (6.0–11.0)	Progression to categories 5–7 at day 15: 14 %
Pouladzadeh, Iran, Peer-reviewed publication [32] CovCP group	30	Yes	No serious side effects on patients	All follow-up: 10 %	Mean ± SD: 8.66 ± 3.94 days	Improvement in 8-point WHO severity score: 53.33 %
Control group	30	NR	NR	All follow-up: 16.7 %	Mean ± SD: 6.66 ± 4.30 days	Improvement in 8-point WHO severity score: 26.66 %
AlQahtani, Bahrain Peer-reviewed publication [23] CovCP group	20	No	NR	28-day: 5 %	NR	At day 28, 20 % were ventilated
Control group	20	NR	NR	28-day: 10 %	NR	At day 28, 30 % were ventilated
Bajpai, India Pre-print [24] CovCP group	14	Yes	One patient showed signs of mild urticaria during transfusion	28-day: 21.4 %	Mean: 12.1 days (SD: 4.27)	MV within 7 days: 21.4 %. Significant improvement in respiratory rate (−14.5 per min), O_2 saturations (10 %), SOFA scores (−5), PaO_2/FiO_2 (231.15) at day 7
Control group	15	Yes	One patient showed signs of mild urticaria during transfusion	28-day: 6.7 %	Mean: 16.1 (SD: 5.6)	MV within 7 days: 6.7 %. Respiratory rate (−10 per min), O_2 saturations (7.5 %), SOFA scores (−3), PaO_2/FiO_2 (77.01) at day 7

Prospective controlled clinical trials

Table 3 (*continued*)

First author, country, type of publication*, study group[†]	Number of participants	Safety assessment	Transfusion-related reactions	Mortality	Length of hospital stay	Clinical improvement
AlSharidah, Kuwait, Peer-reviewed publication [34] CovCP group	135	Yes	3 (2 %) patients with allergic skin reactions (completely resolved after transfusion)	30-day: 17.8 %	NR	30-day: 86.5 % (moderate disease) 60.8 % (severe disease) 80.6 % (overall). Time to improvement, median (IQR): 7 days (5–9)
Control group	233	NR	NR	30-day: 38.8 %	NR	30-day: 68.4 % (moderate disease) 34.6 % (severe disease) 58.6 % (overall). Time to improvement, median (IQR): 10 (6–15) days
Abolghasemi, Iran, Peer-reviewed publication [50] CovCP group	115	Yes	One case of transient mild fever and chills	All follow-up: 14.8 %	Mean ± SD: 9.54 ± 5.07 days	7.0 % intubated
Control group	74	NR	NR	All follow-up: 24.3 %	Mean ± SD: 12.88 ± 7.19 days	20.3 % intubated
Khamis, Oman, Peer-reviewed publication [35] CovCP group	73	No	NR	All follow-up: 19 %	12 days	Extubated patients: 42 %. Composite endpoint of extubation/discharged home alive: 64 %
Control group	21 (historical controls)	NR	NR	All follow-up: 29 %	8 days	Extubated patients: 33 %. Composite endpoint of extubation/discharged home alive: 24 %
Kurtz Brazil, Peer-reviewed publication [53] CovCP group	41	Yes	No	7-day: 17 % 28-day: 49 %	Median (IQR): 17 (7–28) days	2-point reduction from patients' admission status on a 10-point ordinal scale: 46 % (within 28 days)
Control group	72	NR	NR	7-day: 29 % 28-day: 56 %	Median (IQR): 14 (4–26) days	2-point reduction from patients' admission status on a 10-point ordinal scale: 32 % (within 28 days)
Sturek US, Pre-print [37] CovCP group	29	Yes	At least one related AE was reported for 4/29 patients	28-day: 6.9 %	NR	Rate of ICU transfer: 13.8 %
Control group	48	NR	NR	28-day: 10.4 %	NR	Rate of ICU transfer: 27.1 %
Franchini Italy, Peer-reviewed publication [48] CovCP group	22	Yes	No	All follow-up: 13.6 %	NA (treatment at the elderly LTCF, only 2 patients were eventually hospitalized)	Proportion of patients with ≥ 3 symptoms decreased by 63.1 % within 14 days following CovCP transfusion
Control group	733 (historical controls)	NR	NR	All follow-up: 38.3 %	NR	NR
Rasheed, Iraq, Peer-reviewed publication [55] CovCP group	21	Yes	Allergic reaction in 1 patient (mild skin redness and itching)	All follow-up: 4.8 %	NR	Recovery time from critical illness, mean ± SD: 4.52 ± 2.35 days. Whole duration of infection, mean ± SD: 19.3 ± 6.9 days
Control group	28	NR	NR	All follow-up: 28.6 %	NR	

Table 3 (*continued*)

First author, country, type of publication*, study group†	Number of participants	Safety assessment	Transfusion-related reactions	Mortality	Length of hospital stay	Clinical improvement
						Recovery time from critical illness, mean ± SD: 8.45 ± 1.8 days. Whole duration of infection, mean ± SD: 23.4 ± 6.4 days
Acosta-Ampudia Colombia, Peer-reviewed publication [46] CovCP group	9	Yes	No	All follow-up: 22.2 %	Mean ± SD: 9.333 ± 3.937 days	No significant differences in clinical outcomes
Control group	9	NR	NR	All follow-up: 11.1 %	Mean ± SD: 17.222 ± 10.244 days	No significant differences in clinical outcomes
Matched case control studies						
Altuntas, Turkey, Peer-reviewed publication [51] CovCP group	888	No	NR	Case fatality rate: 24.7 %	Median (range): 17 days (0–74). Median duration in ICU (range): 9 days (0–68)	MV rate: 49.3 %
Control group	888	NR	NR	Case fatality rate: 27.7 %	Median (range): 18 days (0–77). Median duration in ICU (range): 12 days (0–74)	MV rate: 55 %
Salazar, US, Peer-reviewed publication [20] CovCP group	351	No	NR	28-day: 3.7 % 60-day: 6.2 % for patients infused with CovCP with anti-RBD IgG titers ≥ 1:1,350	Median (IQR) post-day 0: 5.9 days (3.2–11.7) for patients infused with CovCP with anti-RBD IgG titers ≥ 1:1,350	On day 7: 64.2 % On day 14: 82.9 % On day 28: 90.0 % On day 60: 92.2 % for patients infused with CovCP with anti-RBD IgG titers ≥ 1:1,350
Control group	594	NR	NR	28-day: 9.8 % 60-day: 12.5 %	Median (IQR) post-day 0: 5.9 days (3.1–12.9)	On day 7: 57.2 % On day 14: 73.5 % On day 28: 79.2 % On day 60: 82.8 %
Shenoy, US, Peer-reviewed publication [49] CovCP group	263	Yes	No	7-day: 9.13 % 14-day:14.83 % 28-day: 25.48 %	Overall: mean ± SD: 15.67 ± 13.65 days	Duration of MV, median: 11 days. Improvement in oxygen device delivery category: 3 days
Control group	263	NR	NR	7-day: 19.77 % 14-day: 23.57 % 28-day: 27.00 %	Overall: mean ± SD: 10 ± 10.86 days	Duration of MV, median: 15 days. Improvement in oxygen device delivery category: 6 days
Bulanov, Russia, Peer-reviewed publication [41] CovCP group	226	Yes	2 moderate febrile non-hemolytic reactions	10-day: 5.3 % 28-day: 14.2 %	NR	Likelihood of transfer to MV during hospitalization was statistically significantly lower in CovCP patients: RR = 0.411, P < 0.05.
Control group	226	NR	NR	10-day: 14.2 % 28-day: 22.1 %	NR	
Thompson, US, Peer-reviewed publication [43] CovCP group	143	No	NR	30-day: 13.3 %	NR	NR
Control group	823	NR	NR	30-day: 24.8 %	NR	NR
Tworek, Poland, Peer-reviewed	102	No	NR	All follow-up: 13.7 %	Median (range):	Ventilator time, median (IQR): 8 days (1–28)

Table 3 (*continued*)

First author, country, type of publication*, study group†	Number of participants	Safety assessment	Transfusion-related reactions	Mortality	Length of hospital stay	Clinical improvement
publication [40] CovCP group					20 days (0–63)	
Ventilator time, median (IQR): 6 days (1–29)	Control group 13 days (0–59)	102	NR	NR	All follow-up: 34.3 %	Median (range):
Mesina, Philippines, Pre-print [45] CovCP group	75	Yes	1 (1.33 %) patient with mild transfusion reaction	All follow-up: 25.33 %	Median (IQR): 14 days (9–20)	Improvement in pulmonary parameters. Improvement in inflammatory markers
Control group	75	NR	NR	All follow-up: 26.67 %	Median (IQR): 11 days (8–17)	NR
Yoon, US, Peer-reviewed publication [38] CovCP group	73	Yes	No	28-day: 31.5 %	NR	28-day, stable/improved: 64.4 % Clinical status improvement was statistically significant in patients < 65 years (88.2 %)
Control group	73	NR	NR	28-day: 38.4 %	NR	28-day, stable/improved: 57.5 % Clinical status improvement was statistically significant in patients < 65 years (64.7 %)
Rogers, US, Peer-reviewed publication [56] CovCP group	64	Yes	Two patients were judged to have a TRALI reaction. One patient was judged to have a TACO reaction.	28-day: 12.5 %	Median: 8 days	NR
Control group	177	NR	NR	28-day: 15.8 %	Median: 8 days	NR
Klapholz, US, Peer-reviewed publication [39] CovCP group	47	Yes	No serious adverse transfusion reaction	7-day: 21.3 %	NR	7-day: no significant clinical benefit in the composite outcome of worsening oxygen support or mortality
Control group	47	NR	NR	7-day: 19.1 %	NR	
AlShehry Saudi Arabia, Peer-reviewed publication [44] CovCP group	40	Yes	No	30-day: 26.3 %	Median (IQR): 15.5 days (11–31)	Time to clinical recovery, median (IQR): 16.5 days (12–36.5)
Control group	124	NR	NR	30-day: 39.3 %	Median (IQR): 14 days (10–20)	Time to clinical recovery, median (IQR): 15 days (11–21)
Liu, US, Peer-reviewed publication [54] CovCP group	39	No	NR	11-day: 12.8 %	Discharge rate: 71.8 %	Clinical condition had worsened on day 14 in 17.9 % of patients
Control group	156	NR	NR	9-day: 24.4 %	Discharge rate: 66.7 %	Clinical condition had worsened on day 14 in 28.2 % of patients
Sostin, US, Peer-reviewed publication [36] CovCP group	35	No	NR	All follow-up: 20.0 %	Median (IQR): 10 days (6–17)	NR
Control group	61	NR	NR	All follow-up: 24.6 %	Median (IQR): 7 days (4–11)	NR
	32	Yes	No	28-day: 21.9 %		

Table 3 (*continued*)

First author, country, type of publication*, study group[†]	Number of participants	Safety assessment	Transfusion-related reactions	Mortality	Length of hospital stay	Clinical improvement
Allahyari, Iran, Peer-reviewed publication [47]					Mean ± SD (range): 13.91 ± 8.43 days (5–51)	PaO$_2$/FiO$_2$ levels: 275.03 were significantly higher compared to the control (P = 0.034)
CovCP group Control group	32	NR	NR	28-day: 43.8 %		Mean ± SD (range): 15.34 ± 10.11 days (5–56)
PaO$_2$/FiO$_2$ levels: 213.41						
Hegerova, US, Peer-reviewed publication [52] CovCP group	20	No	NR	14-day: 10 %	Median: 15 days. Discharge rate: 45 %	Ordinal WHO scale score on day 14, mean ± SD: 3.1 ± 3.1
Control group	20	NR	NR	14-day: 30 %	Median: 9 days. Discharge rate: 45 %	Ordinal WHO scale score on day 14, mean ± SD: 3.45 ± 3.6
Khanna, Switzerland, Congress abstract [42] CovCP group	15	No	NR	28-day: 0 %	Median (IQR): 13 (7–18)	Trend towards decreased inflammatory response in CovCP group. Progression to intubation not significantly different between groups.
Control group	30	NR	NR	28-day: 17.86 %	Median (IQR): 12 (8–18)	

AE, adverse event; ARDS, acute respiratory distress syndrome; CovCP, COVID-19 convalescent plasma; CP, convalescent plasma; h, hour; ICU, intensive care unit; IgG, immunoglobulin G; IQR, interquartile; LTCF, long-term care facility; MV, mechanical ventilation; NA, not available; NR, not reported; PaO$_2$/FiO$_2$, ratio of arterial oxygen partial pressure to fractional inspired oxygen; RCT, randomized controlled trial; RBD, receptor binding domain; RR, relative risk; SD, standard deviation; SoC, standard of care; SOFA, sequential organ failure assessment; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury; UK, United Kingdom; US, United States; WHO, World Health Organization.

* Type of publication at the time of writing of this review.

† All publications were from 2020 or 2021.

immunocompromised patients with COVID-19, conclusions about efficacy were difficult to draw in this subpopulation (Table 4). Nevertheless, the only matched case-control study showed that CovCP treatment was associated with significantly improved 30-day mortality (13.3 % versus 24.8 %) in patients with COVID-19 and hematologic malignancies [43]. In the non-matched case-control series, a significantly reduced mortality rate (13 % versus 41 %) following CovCP treatment was observed in patients with hematologic malignancies [57]. In this study, CovCP-treated patients showed a significantly milder course of infection, less severe symptoms, and faster recovery. In the uncontrolled case series conducted in immunocompromised patients with COVID-19, mortality rates and lengths of hospital stay were highly variable, and conclusions were difficult to draw. Improvements in clinical symptoms were reported in 8 of 14 patients within 5 days in one case series [59], in three of four patients in another case series [62], and in all patients in three other case series [61,63,64].

A recently published RCT suggested that CovCP with high NAb levels in addition to high IgG levels should be used if further studies evaluate its use in patients with an impaired humoral immunity [65].

3.4. Why was CovCP broadly used at the early stages of the pandemic?

Before the COVID-19 pandemic, CP was used during previous epidemics or outbreaks caused by other coronaviruses (MERS and SARS) and emerging viruses [11–15,73–77]. While data on CP use were scarce for MERS [73,74], studies in a limited number of patients with SARS suggested that CP might improve clinical outcomes when administered at an early disease stage or in patients with severe disease [13,75,76]. A meta-analysis on the use of CP for the treatment of severe acute respiratory infections caused by SARS and influenza showed consistent

evidence for a reduction in mortality when CP was administered early after the onset of symptoms [77]. Although the LoE was low for CP efficacy against other coronaviruses, these results suggested that CovCP could be a potentially effective treatment for patients with COVID-19.

Therefore, CovCP treatment was initiated during the early months of the pandemic as a short-term strategy for conferring immediate passive immunity to susceptible individuals and to manage the disease before effective and targeted pharmacotherapy was found [78]. CovCP was used in various countries because passive antibody administration was the only immediately available therapy potentially able to prevent cellular infection by SARS-CoV-2, block viral replication, and treat COVID-19 [78,79].

In high-income countries, CovCP could be rapidly obtained using established blood collection and transfusion infrastructures as the number of patients who recovered from the disease had been increasing [78]. In low- and middle-income countries, CovCP was less frequently used in the early stages of the pandemic due to the challenges related to donor recruitment, blood collection, capacity to procure CovCP, and characterization of CovCP units [80].

The safety profile of CovCP was considered comparable to that of standard plasma infusions since the only difference was the presence of anti-SARS-CoV-2 antibodies in CovCP. In high-income countries, the risk of transfusion-transmitted infections is very low and the safety profile of CovCP infusions is considered as clinically acceptable [81]. In these countries, the main CovCP transfusion-related risks include allergic transfusion reactions, TRALIs, and TACOs, which are manageable reactions. The other theoretical risk of CovCP infusions was antibody-dependent enhancement of infection, a process whereby non-neutralizing antibodies, sometimes developed during a prior infection with a different viral serotype, enhance viral cellular entry,

Table 4

Safety-related information and clinical outcomes in the selected studies evaluating the use of CovCP in immunocompromised patients with COVID-19.

First author, country, type of publication*, study group†	Number of patients	Condition triggering immuno-suppression/-compression	Safety assessment	Transfusion-related reactions	Mortality	Length of hospital stay	Clinical improvement
Matched case-control studies							
Thompson, US, Peer-reviewed publication [43] CovCP group	143	Hematologic malignancies	No	NR	30-day: 13.3 %	NR	NR
Control group	823	Hematologic malignancies	NR	NR	30-day: 24.8 %	NR	NR
Non-matched case-control studies							
Biernat, Poland, Peer-reviewed publication [57] CovCP group	23	Hematologic malignancies	Yes	No	13 %	NR	Milder course of infection ($P = 0.03807$), characterized by less severe symptoms and faster recovery ($P = 0.00001$); pulmonary infiltrates resolved significantly faster ($P = 0.02480$) and a shorter oxygen therapy was required ($P = 0.02355$) in CovCP recipients compared with controls
Control group	22 historical controls	Hematologic malignancies	NR	NR	41 %	NR	
Case series							
Jeyaraman, India, Peer-reviewed publication [58]	33	Hematologic malignancies	Yes	No severe adverse effects	Overall: 45.5 % 14-day: 24.2 % 28-day: 33.3 %	Overall median length (range): 14 days (2–39) Mean ± SD: 12.7 ± 6.5 days (early [< 7 days] CovCP initiation) and 24.3 ± 9.5 days (late [≥ 7 days] CovCP initiation)	NR
Rodionov, Germany, Peer-reviewed publication [59]	14	Solid organ transplantation (n = 8), allogeneic stem cell transplantation (n = 4), or active hematologic malignancy (n = 2)	No	NR	14 %	NR	5-day post-last transfusion: 8 (57 %) patients showed improvement of 1 point or more on the WHO Clinical Progression Scale.
Gupta, India, Peer-reviewed publication [60]	10	Kidney transplant	No	NR	10 %	Mean ± SD: 16.3 ± 7.2 days	For 9/10 patients: normalized body temperature, decreased inflammatory markers and improvement of PaO_2/FiO_2 after CovCP transfusion
Ferrari, Italy, Peer-reviewed publication [61]	7	Chemo-immunotherapy due to hematologic disorders and related immunodeficiency	Yes	No	0 %	For last hospital stay: 8–31days (NR for all patients)	Resolved/improved COVID-19 symptoms in all patients. Regression of fever, cough and/or dyspnea, less intensive oxygen requirement and rapid fall of the inflammatory marker CRP
Lindemann, Germany, Peer-reviewed publication [62]	4	Kidney transplant (n = 2) and hemodialysis (n = 2)	No	NR	25 %	8–28 days from CovCP	3/4 patients clinically improved and could be discharged from the hospital
Jin, US, Peer-reviewed publication [63]	3	X-linked agammaglobulinemia	No	NR	0 %	3–29 days	100 % at 1–3 days post-CovCP
Delgado-Fernandez, Spain, Peer-reviewed publication [64]	3	Humoral immunodeficiency	Yes	NR	0 %	43–57 days (NR for patient 1)	Observed in all cases by discharge

CovCP, COVID-19 convalescent plasma; n, number of patients; NR, not reported; PaO_2/FiO_2, ratio of arterial oxygen partial pressure to fractional inspired oxygen; SD, standard deviation; US, United States; WHO, World Health Organization.

* Type of publication at the time of writing of this review.

exacerbating the severity of symptoms [72,82,83]. This theoretical risk has not been observed with CovCP infusions.

3.5. How was CovCP implemented during the COVID-19 pandemic?

At the onset of the COVID-19 pandemic, the decision to implement CovCP was guided by urgency, and the lessons learned from CP use in previous epidemics with respiratory viruses were initially difficult to apply [77]. Several studies were conducted before routine assays were available to determine NAb titers in CovCP units [23,28,30,32–37,39, 41,43–45,47,49,51–53]. Therefore, CovCP with low NAb titers was infused during the early months of the pandemic, which may have led to negative or inconclusive results. The variability in NAb quantity in CovCP was further amplified by the differences in treatment protocols, including timing and volume of CovCP infusions [81]. The facts that the plasma of many patients who recovered from COVID-19 does not contain sufficient NAb levels to provide therapeutic benefit and that NAb titers decrease with time highlight the importance of determining NAb titers with reliable and consistent testing methods in CovCP before infusion [65,67]. A consensus concerning the choice of the assay to measure antibody levels in CovCP in clinical trials is critical to allow comparisons among studies. Several assays are currently used, such as viral plaque neutralization tests and binding antibody surrogate immunoassays (enzyme-linked immunosorbent assay [ELISA] and chemiluminescent immunoassays [CLIA]), of which 12 are considered acceptable by the US FDA to qualify CovCP units for clinical use in hospitalized patients [84].

The timing of CovCP infusion was also highly variable among the studies evaluating CovCP in patients with COVID-19. Early in the pandemic, CovCP was mainly given to severe or critically-ill patients, who were often in the ICU units and/or mechanically ventilated [20, 22–24,29–32,35,36,38–40,44,46,47,49,51–56]. While CP infusions may be an effective treatment option in severely ill patients suffering from other diseases, no positive effect of CovCP was observed in patients with COVID-19 at a late disease stage who were at high risk of mortality mainly from hyperinflammation (cytokine storm) or secondary infections and less from the SARS-CoV-2 infection itself [25,79]. A few studies suggested that CovCP might be beneficial when administered to patients at an earlier stage of disease [25,85,86], but these results were not confirmed in more recent RCTs [69,70]. At the early disease stages, the blocking of viral entry and intracellular replication by the CovCP NAbs might help prevent disease progression and activation of the inflammatory cascade leading to cytokine storm [25,79]. For any future use of CP in the setting of an emerging infectious pandemic/epidemic, well-defined patient grading scales are needed, which should be based on additional factors beyond the time since symptom onset or admission to hospital or ICU. Standardized definitions should be based on viral physiopathology, disease severity (e.g., with or without MV) and number of days post-hospital admission (correlated to disease severity) in addition to symptom duration (though disease progression varies from patient to patient). Antibody testing later in the disease course may also be important to identify patients who have not yet formed sufficient levels of antibodies and may benefit from CP. Moreover, binding antibody signal in patients with early infection may not accurately reflect NAb levels and should not be the only criterion used to initiate CP infusions [65,67]. Another option to describe disease stages is the consistent use of the WHO clinical progression scale [87].

In this narrative review, we discussed whether clinical outcomes could be improved with CovCP in specific subpopulations of patients with COVID-19 since its use in the general population does not seem beneficial. Based on published studies, our experience, and the pathophysiology of COVID-19, we identified immunocompromised patients (e.g., organ transplant recipients, or patients with primary or secondary

immunodeficiency, B-cell depletion, or cancers), who are at increased risk for mortality, as a potential target population who might benefit more from CovCP therapy [59,88,89]. In this population, two controlled studies showed that CovCP treatment was associated with significantly improved survival rates [43,57], and uncontrolled case series suggested that CovCP infusions resulted in clinical improvements [60,61,63,64]. A pilot study suggested that immunosuppressed patients with COVID-19 at an early disease stage and without detectable anti-SARS-CoV-2 antibodies are potential candidates for CovCP treatment, and patients with high post-transfusion antibody titers have the highest chance of treatment success [59]. A recent review has also suggested that CovCP with high NAb titers is a safe and effective treatment for immunocompromised patients [90]. The observed benefits of CovCP in these patients could potentially be explained by their lower risk for hyperinflammation and cytokine storm and their higher risk for chronic SARS-CoV-2 infections that can be treated with CovCP infusions [59,88]. Of note, the available results in this subpopulation should be interpreted with caution because potential confounding factors, such as co-administered treatments (e.g., steroids), were not considered in the analyses. Additional studies are needed to determine whether CovCP administration prevents or favors the development of viral mutations, which were previously reported in immunocompromised patients with chronic SARS-CoV-2 infections [91,92].

The above-mentioned observations are in line with the revisions made by the FDA in March 2021 concerning the Emergency Use Authorization (EUA) of CovCP initially issued on August 23, 2020 to facilitate access for hospitalized patients in the US [93]. In the revised EUA, CovCP use was limited to units with high anti-SARS-CoV-2 antibody titers for the treatment of hospitalized patients with COVID-19 early in the course of disease (even if there is currently no consensus concerning the definition of early disease stage) and hospitalized patients with COVID-19 and impaired humoral immunity [84]. This updated EUA is also in line with the interim recommendations of the Association for the Advancement of Blood and Biotherapies (AABB, formerly the American Association of Blood Banks) mentioning that the risks of CovCP are comparable to those of standard plasma, CovCP is optimally effective when transfused as close to symptom onset as possible, and CovCP effectiveness is related to the anti-SARS-CoV-2 antibody quantity within a unit [81]. In the US, the FDA requirement for higher NAb titers has complicated the collection of CovCP meeting the various binding NAb titer criteria. These complexities and data inconsistencies have resulted in a halt to reimbursement for CovCP treatment and a decrease in demand in the US.

3.6. What are the lessons learned for the next pandemic?

CP is a potentially useful treatment, but data reported to date on its efficacy do not provide rigorously evaluated and consistent conclusions. There are currently no guidelines for its collection and administration during pandemics. Major problems are the difficulties to collect enough CP with high NAb titers to treat large numbers of patients and to rapidly and timely implement RCTs with reduced risks of biases during a pandemic. More than 1.5 year after the onset of the COVID-19 pandemic, we have more insight on how to be better prepared for a next epidemic or pandemic. Fig. 1 provides a list of elements that should be considered during the implementation of a CP program for emerging viruses.

During the first months of the COVID-19 pandemic, NAb levels were not measured in CovCP units due to the clinical urgency—even if existing literature based on previous epidemics had shown that CP is beneficial only if antibody levels are high in infused units—and the disease pathophysiology was not sufficiently understood to determine the optimal treatment strategies. The first lesson that we have learned is
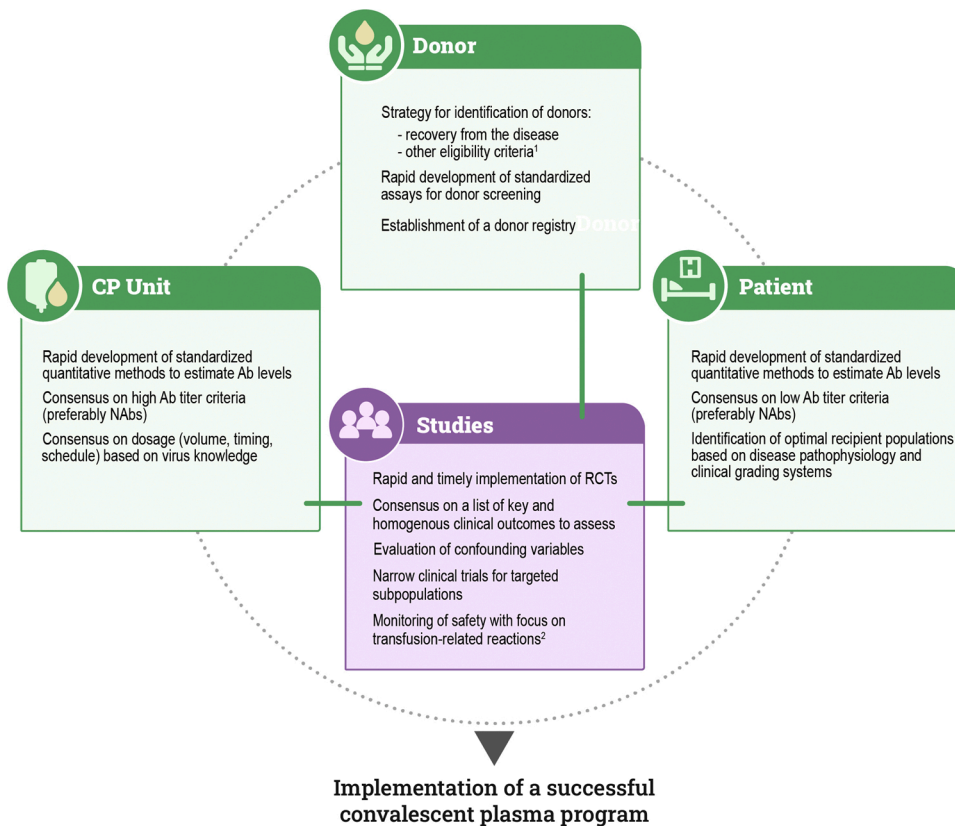
Fig. 1. Key elements that should be considered during the implementation of a CP program for emerging viruses.
Footnote: Ab, antibody; CP, convalescent plasma; NAb, neutralizing antibody; RCT, randomized controlled trial. 1. Negative for anti-human leukocyte antigen or no history of pregnancy/transfusion; 2. E.g., antibody-dependent enhancement of infection, transfusion-associated circulatory overload or transfusion-related acute lung injury.

that it is essential to rapidly develop standardized quantitative methods with capacity for high throughput (preferably neutralization tests or validated surrogates) and to define optimal criteria for the selection of CP units with high antibody titers in the early stages of pandemics. A clear strategy should be established for the identification of potential donors who recovered from the disease. Therefore, standardized viral nucleic acid tests and antibody assays should be rapidly developed for screening. Because eligible donors should be negative for anti-human leukocyte antigen [80], only men or nulliparous women with no history of transfusion should be considered as donors in the absence of testing. The establishment of a CP donor registry may be useful to identify eligible candidates for possible future donations. A plasma bank of frozen and ready-to-use CP could also be built by collecting plasma once or twice from all potential donors, especially in the early stages of a pandemic. Of note, it is important to determine whether the virus can be transmitted by transfusion and pathogen inactivation methods should be considered until this is confirmed, especially if prophylactic CP infusion post-potential exposure is considered. Moreover, the identification of CP recipients lacking high existing antibody levels is also essential to establish an efficient CP strategy in epidemics/pandemics.

While several studies have shown that CovCP infusions are not effective to treat patients suffering from COVID-19, a question that still needs to be addressed is whether plasma from vaccinated individuals might be beneficial. It has been recently shown that the *in vitro* neutralization activity induced by vaccination was lower against some variants, but that vaccinated individuals retained neutralization capability against most emerging variants [94]. Another study has shown that antibody responses to the first dose of mRNA vaccines (BNT162b2/Pfizer; mRNA-1273/Moderna) in individuals with pre-existing immunity from infection were equal to and frequently exceeded the titers found in naïve individuals after their second dose [95]. Thus, the collection of CovCP from vaccinated individuals who have recovered from primary infection is an area of interest [96]. Storage of plasma collected after vaccination could play a role in case of

emergence of a more aggressive variant or during the existing vaccination gap in some countries and can be helpful to be better prepared for a next wave of infections.

A second lesson learned is that early understanding of disease pathophysiology is necessary to identify target populations optimally benefiting from any treatment, including NAb-containing CP infusions. Previous studies have suggested with a low LoE that CP infusions might be beneficial in critically-ill patients affected by some respiratory viruses, such as SARS or MERS [13,73–77]. For other viral infections whose life-threatening effects are not the direct result of viral cellular damage, such as COVID-19, CP infusions do not seem effective in critically-ill patients but might improve clinical outcome in specific subpopulations. For COVID-19, additional studies are needed to determine whether CovCP infusions may be beneficial at early disease stages in immunocompromised patients. These observations highlight the importance of the early characterization of the disease pathophysiology to determine the optimal timing and schedule of CP infusions and to design narrow clinical trials in targeted subpopulations. Since the disease pathophysiology is always unknown during the first months of new epidemics/pandemics, safe and broadly available approaches, such as CP infusions, remain valuable treatment options during the emerging phase. CP treatment may stop infections and should not be restricted to critically-ill patients but should be used at earlier disease stages for all patients or specific subpopulations of vulnerable patients in future pandemics/epidemics.

A third lesson learned is that there is a need for increased rigor and consistency in terms of treatment protocols and testing methodologies in studies evaluating the use of CP. At the onset of a pandemic, high-quality RCTs should be rapidly implemented and a consensus concerning key clinical outcomes to assess should be established to allow for comparisons between studies. The evaluation of confounding variables, such as concomitant treatments, and the monitoring of safety are also essential. Ideally, a standard protocol for RCTs evaluating CP safety and efficacy should be drafted and made publicly available and ready to be

implemented worldwide.

A fourth lesson learned is that CP treatment implementation and use in later stages of pandemics may vary from one country to another. The implementation of CP treatment at the early stages may be more complicated and require adapted strategies in developing countries due to operational considerations [80]. However, CP treatment may be useful in the longer term in countries with limited resources owing to its low cost, wide availability, and clinically acceptable safety profile, assuming infectious disease safety is ensured by testing or inexpensive plasma pathogen reduction, and cold chain can be maintained [97]. In countries with limited resources where the determination of NAb titers in CP is complicated, the identification of clinical predictors of high NAb titers is also critical. For CovCP, a previous study has shown that male sex, older age, and hospitalization for COVID-19 were associated with increased antibody levels [98]. In countries with limited resources, collection and storage of CP could be another option to improve preparedness for a next wave of infections or the emergence of new variants. If feasible, CP sharing programs between high- and low-income countries should also be established.

4. Conclusion

The evidence of benefit of NAb-containing CP infusions observed during previous epidemics and the reassuring safety profile of plasma treatment led to the widespread use of CovCP at the onset of the COVID-19 pandemic. While CovCP was used to fill a gap in the treatment for this new emerging virus, it was not intended for long-term use and was never considered as the ultimate therapy for COVID-19 since the eventual goals were to find effective targeted therapies and prevention measures through vaccination.

With the insights that we have more than 1.5 year after the onset of the pandemic, we realize that the implementation of CovCP infusions for the treatment of COVID-19 was suboptimal. To be better prepared for future epidemics or pandemics and to evaluate the potential benefits of CP treatment, we should ensure that only CP with high NAb titers is infused in patients with low NAb titers, patient eligibility criteria are based on the pathophysiology of the targeted disease, and measured clinical outcomes and methods are comparable across studies. Future research on the use of CP should focus on increasing scientific rigor for consistency in study design, test methods, and data analyses to allow for improved data interpretation and evidence-based clinical decisions. A standard protocol accounting for confounding variables, such as co-administered drugs and patients' confounding clinical variables, could be developed for the implementation of RCTs.

While CovCP infusions seem ineffective for the treatment of critically-ill patients with COVID-19, additional studies are needed to evaluate their potential benefits in immunocompromised patients. Even if CovCP infusions do not improve clinical outcome in patients with COVID-19, NAb-containing CP infusions remain a safe, widely available and potentially beneficial treatment option to fill treatment gaps for emerging viruses. An early characterization of the disease pathophysiology will be essential to determine the optimal timing and schedule of CP infusions and to design narrow clinical trials in targeted subpopulations for future global pandemics or local epidemics.

Data availability

No data was used for the research described in the article.
Data will be made available on request.

Funding

Author contributions

All authors contributed to the literature review interpretation, critically revised the manuscript, and approved the final version.

Declaration of Competing Interest

Acknowledgements

References

[1] World Health Organization. Weekly epidemiological update. 2021. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/.

[2] Boehm E, Kronig I, Neher RA, Eckerle I, Vetter P, Kaiser L. Novel SARS-CoV-2 variants: the pandemics within the pandemic. Clin Microbiol Infect 2021;27: 1109–17. https://doi.org/10.1016/j.cmi.2021.05.022.

[3] Harvey WT, Carabelli AM, Jackson B, Gupta RK, Thomson EC, Harrison EM, et al. SARS-CoV-2 variants, spike mutations and immune escape. Nat Rev Microbiol 2021;19:409–24. https://doi.org/10.1038/s41579-021-00573-0.

[4] Wouters OJ, Shadlen KC, Salcher-Konrad M, Pollard AJ, Larson HJ, Teerawattananon Y, et al. Challenges in ensuring global access to COVID-19 vaccines: production, affordability, allocation, and deployment. Lancet 2021;397: 1023–34. https://doi.org/10.1016/S0140-6736(21)00306-8.

[5] Martínez-Flores D, Zepeda-Cervantes J, Cruz-Reséndiz A, Aguirre-Sampieri S, Sampieri A, Vaca L. SARS-CoV-2 vaccines based on the Spike glycoprotein and implications of new viral variants. Front Immunol 2021;12:701501. https://doi.org/10.3389/fimmu.2021.701501.

[6] Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA 2020;324:782–93. https://doi.org/10.1001/jama.2020.12839.

[7] Chen R, Lan Z, Ye J, Pang L, Liu Y, Wu W, et al. Cytokine storm: the primary determinant for the pathophysiological evolution of COVID-19 deterioration. Front Immunol 2021;12:589095. https://doi.org/10.3389/fimmu.2021.589095.

[8] Heustess AM, Allard MA, Thompson DK, Fasinu PS. Clinical management of COVID-19: a review of pharmacological treatment options. Pharmaceuticals (Basel) 2021;14:520. https://doi.org/10.3390/ph14060520.

[9] Klassen SA, Senefeld JW, Johnson PW, Carter RE, Wiggins CC, Shoham S, et al. The effect of convalescent plasma therapy on mortality among patients with COVID-19: systematic review and meta-analysis. Mayo Clin Proc 2021;96:1262–75. https://doi.org/10.1016/j.mayocp.2021.02.008.

[10] Casadevall A, Pirofski L-A. The convalescent sera option for containing COVID-19. J Clin Invest 2020;130:1545–8. https://doi.org/10.1172/JCI138003.

[11] Marano G, Vaglio S, Pupella S, Facco G, Catalano L, Liumbruno GM, et al. Convalescent plasma: new evidence for an old therapeutic tool? Blood Transfus 2016;14:152–7. https://doi.org/10.2450/2015.0131-15.

[12] McGuire LW, Redden WR. The use of convalescent human serum in influenza pneumonia - a preliminary report. Am J Public Health (N Y) 1918;8:741–4. https://doi.org/10.2105/ajph.8.10.741.

[13] Cheng Y, Wong R, Soo YO, Wong WS, Lee CK, Ng MH, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis 2005;24:44–6. https://doi.org/10.1007/s10096-004-1271-9.

[14] Hung IF, To KK, Lee CK, Lee KL, Chan K, Yan WW, et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. Clin Infect Dis 2011;52:447–56. https://doi.org/10.1093/cid/ciq106.

[15] van Griensven J, Edwards T, de Lamballerie X, Semple MG, Gallian P, Baize S, et al. Evaluation of convalescent plasma for ebola virus disease in Guinea. N Engl J Med 2016;374:33–42. https://doi.org/10.1056/NEJMoa1511812.

[16] Piechotta V, Iannizzi C, Chai KL, Valk SJ, Kimber C, Dorando E, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database Syst Rev 2021;5:Cd013600. https://doi.org/10.1002/14651858.CD013600.pub4.

[17] Howick J, Chalmers I, Glasziou P, Greenhalgh T, Heneghan C, Liberati A, et al. The oxford levels of evidence 2. Oxford Centre for Evidence-Based Medicine; 2011. https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence.

[18] Salazar E, Christensen PA, Graviss EA, Nguyen DT, Castillo B, Chen J, et al. Treatment of coronavirus disease 2019 patients with convalescent plasma reveals a signal of significantly decreased mortality. Am J Pathol 2020;190:2290–303. https://doi.org/10.1016/j.ajpath.2020.08.001.

[19] Salazar E, Perez KK, Ashraf M, Chen J, Castillo B, Christensen PA, et al. Treatment of coronavirus disease 2019 (COVID-19) patients with convalescent plasma. Am J Pathol 2020;190:1680–90. https://doi.org/10.1016/j.ajpath.2020.05.014.

[20] Salazar E, Christensen PA, Graviss EA, Nguyen DT, Castillo B, Chen J, et al. Significantly decreased mortality in a large cohort of coronavirus disease 2019 (COVID-19) patients transfused early with convalescent plasma containing high-titer anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein IgG. Am J Pathol 2021;191:90–107. https://doi.org/10.1016/j.ajpath.2020.10.008.

[21] Gharbharan A, Jordans CCE, GeurtsvanKessel C, den Hollander JG, Karim F, Mollema FPN, et al. Effects of potent neutralizing antibodies from convalescent plasma in patients hospitalized for severe SARS-CoV-2 infection. Nat Commun 2021;12:3189. https://doi.org/10.1038/s41467-021-23469-2.

[22] Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. JAMA 2020;324:460–70. https://doi.org/10.1001/jama.2020.10044.

[23] AlQahtani M, Abdulrahman A, Almadani A, Alali SY, Al Zamrooni AM, Hejab AH, et al. Randomized controlled trial of convalescent plasma therapy against standard therapy in patients with severe COVID-19 disease. Sci Rep 2021;11:9927. https://doi.org/10.1038/s41598-021-89444-5.

[24] Bajpai M, Kumar S, Maheshwari A, Chhabra K, kale P, Gupta A, et al. Efficacy of convalescent plasma therapy compared to fresh frozen plasma in severely ill COVID-19 patients: a pilot randomized controlled trial. medRxiv 2020. https://doi.org/10.1101/2020.10.25.20219337.

[25] Libster R, Marc GP, Wappner D, Coviello S, Bianchi A, Braem V, et al. Early high-titer plasma therapy to prevent severe covid-19 in older adults. N Engl J Med 2021;384:610–8. https://doi.org/10.1056/NEJMoa2033700.

[26] Simonovich VA, Burgos Pratx LD, Scibona P, Beruto MV, Vallone MG, Vázquez C, et al. A randomized trial of convalescent plasma in Covid-19 severe pneumonia. N Engl J Med 2020;384:619–29. https://doi.org/10.1056/NEJMoa2031304.

[27] Avendano-Sola C, Ramos-Martinez A, Munez-Rubio E, Ruiz-Antoran B, Malo de Molina R, Torres F, et al. Convalescent plasma for COVID-19: a multicenter, randomized clinical trial. medRxiv 2020. https://doi.org/10.1101/2020.08.26.20182444.

[28] Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). BMJ 2020;371:m3939. https://doi.org/10.1136/bmj.m3939.

[29] O'Donnell MR, Grinsztejn B, Cummings MJ, Justman JE, Lamb MR, Eckhardt CM, et al. A randomized double-blind controlled trial of convalescent plasma in adults with severe COVID-19. J Clin Invest 2021;131:e150646. https://doi.org/10.1172/jci150646.

[30] Ray Y, Paul SR, Bandopadhyay P, D'Rozario R, Sarif J, Lahiri A, et al. Clinical and immunological benefits of convalescent plasma therapy in severe COVID-19: insights from a single center open label randomised control trial. medRxiv 2020. https://doi.org/10.1101/2020.11.25.20237883.

[31] Gonzalez JLB, González Gámez M, Mendoza Enciso EA, Esparza Maldonado RJ, Palacios DH, Campos SD, et al. Efficacy and safety of convalescent plasma and intravenous immunoglobulin in critically ill COVID-19 patients. A controlled clinical trial. medRxiv 2021. https://doi.org/10.1101/2021.03.28.21254507.

[32] Pouladzadeh M, Safdarian M, Eshghi P, Abolghasemi H, Bavani AG, Sheibani B, et al. A randomized clinical trial evaluating the immunomodulatory effect of convalescent plasma on COVID-19-related cytokine storm. Intern Emerg Med 2021: 1–11. https://doi.org/10.1007/s11739-021-02734-8.

[33] RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. Lancet 2021;397:2049–59. https://doi.org/10.1016/S0140-6736(21)00897-7.

[34] Alsharidah S, Ayed M, Ameen RM, Alhuraish F, Rouheldeen NA, Alshammari FR, et al. COVID-19 convalescent plasma treatment of moderate and severe cases of SARS-CoV-2 infection: a multicenter interventional study. Int J Infect Dis 2021; 103:439–46. https://doi.org/10.1016/j.ijid.2020.11.198.

[35] Khamis F, Al Arimi Z, Al Naamani H, Al Bahrani M, Pandak N, Al Bolushi Z, et al. Convalescent plasma therapy in critically Ill COVID-19 patients: an open label trial. Omjournal 2021;36:e296. https://doi.org/10.5001/omj.2021.105.

[36] Sostin OV, Rajapakse P, Cruser B, Wakefield D, Cruser D, Petrini J. A matched cohort study of convalescent plasma therapy for COVID-19. J Clin Apher 2021;36: 523–32. https://doi.org/10.1002/jca.21888.

[37] Sturek JM, Thomas TA, Gorham JD, Sheppard CA, Raymond AE, Guex KPD, et al. Convalescent plasma for preventing critical illness in COVID-19: a phase 2 trial and immune profile. medRxiv 2021. https://doi.org/10.1101/2021.02.16.21251849.

[38] Yoon HA, Bartash R, Gendlina I, Rivera J, Nakouzi A, Bortz 3rd RH, et al. Treatment of severe COVID-19 with convalescent plasma in Bronx, NYC. JCI Insight 2021;6:e142270. https://doi.org/10.1172/jci.insight.142270.

[39] Klapholz M, Pentakota SR, Zertuche JP, McKenna M, Roque W, Forsberg M, et al. Matched cohort study of convalescent COVID-19 plasma treatment in severely or life threateningly ill COVID-19 patients. Open Forum Infect Dis 2021;8:ofab001. https://doi.org/10.1093/ofid/ofab001.

[40] Tworek A, Jaroń K, Uszyńska-Kałuża B, Rydzewski A, Gil R, Deptała A, et al. Convalescent plasma treatment is associated with lower mortality and better outcomes in high-risk COVID-19 patients - propensity-score matched case-control study. Int J Infect Dis 2021;105:209–15. https://doi.org/10.1016/j.ijid.2021.02.054.

[41] Bulanov AY, Kostin AI, Petrikov SS, Lysenko MA, Popugaev K, Fomina DS, et al. Convalescent plasma therapy of a new coronavirus infection: an experience of Moscow city hospitals. Anesteziologiya i reanimatologiya 2020;6:33. https://doi.org/10.17116/anaesthesiology202006233.

[42] Khanna N, Weisser M, Hedstueck A, Sutter ST, Roesch S, Battegay M, et al. Efficacy of COVID-19 pathogen inactivated convalescent plasma for patients with moderate to severe acute COVID-19: a case matched control study. Blood 2020;136:29–30. https://doi.org/10.1182/blood-2020-136180.

[43] Thompson MA, Henderson JP, Shah PK, Rubinstein SM, Joyner MJ, Choueiri TK, et al. Association of convalescent plasma therapy with survival in patients with hematologic cancers and COVID-19. JAMA Oncol 2021;7:1167–75. https://doi.org/10.1001/jamaoncol.2021.1799.

[44] AlShehry N, Zaidi SZA, Al Askar A, Al Odayani A, Alotaibi JM, AlSagheir A, et al. Safety and efficacy of convalescent plasma for severe COVID-19: interim report of a multicenter Phase II study from Saudi Arabia. Saudi J Med Med Sci 2021;9:16–23. https://doi.org/10.4103/sjmms.sjmms_731_20.

[45] Mesina FZ, Mangahas CG, Gatchalian EM, Ariola-Ramos MS, Torres RP. Use of convalescent plasma therapy among hospitalized coronavirus disease 2019 (COVID-19) patients: a single-center experience. medRxiv 2021. https://doi.org/10.1101/2021.02.16.21251824.

[46] Acosta-Ampudia Y, Monsalve DM, Rojas M, Rodríguez Y, Gallo JE, Salazar-Uribe JC, et al. COVID-19 convalescent plasma composition and immunological effects in severe patients. J Autoimmun 2021;118:102598. https://doi.org/10.1016/j.jaut.2021.102598.

[47] Allahyari A, Seddigh-Shamsi M, Mahmoudi M, Amel Jamehdar S, Amini M, Mozdourian M, et al. Efficacy and safety of convalescent plasma therapy in severe COVID-19 patients with acute respiratory distress syndrome. Int Immunopharmacol 2021;93:107239. https://doi.org/10.1016/j.intimp.2020.107239.

[48] Franchini M, Glingani C, Morandi M, Corghi G, Cerzosimo S, Beduzzi G, et al. Safety and efficacy of convalescent plasma in elderly COVID-19 patients: the RESCUE trial. Mayo Clin Proc Innov Qual Outcomes 2021;5:403–12. https://doi.org/10.1016/j.mayocpiqo.2021.01.010.

[49] Shenoy AG, Hettinger AZ, Fernandez SJ, Blumenthal J, Baez V. Early mortality benefit with COVID-19 convalescent plasma: a matched control study. Br J Haematol 2021;192:706–13. https://doi.org/10.1111/bjh.17272.

[50] Abolghasemi H, Eshghi P, Cheraghali AM, Imani Fooladi AA, Bolouki Moghaddam F, Imanizadeh S, et al. Clinical efficacy of convalescent plasma for treatment of COVID-19 infections: results of a multicenter clinical study. Transfus Apher Sci 2020;59:102875. https://doi.org/10.1016/j.transci.2020.102875.

[51] Altuntas F, Ata N, Yigenoglu TN, Bascı S, Dal MS, Korkmaz S, et al. Convalescent plasma therapy in patients with COVID-19. Transfus Apher Sci 2021;60:102955. https://doi.org/10.1016/j.transci.2020.102955.

[52] Hegerova L, Gooley TA, Sweerus KA, Maree C, Bailey N, Bailey M, et al. Use of convalescent plasma in hospitalized patients with COVID-19: case series. Blood 2020;136:759–62. https://doi.org/10.1182/blood.2020006964.

[53] Kurtz P, Righy C, Gadelha M, Bozza FA, Bozza PT, Gonçalves B, et al. Effect of convalescent plasma in critically ill patients with COVID-19: an observational study. Front Med (Lausanne) 2021;8:630982. https://doi.org/10.3389/fmed.2021.630982.

[54] Liu STH, Lin H-M, Baine I, Wajnberg A, Gumprecht JP, Rahman F, et al. Convalescent plasma treatment of severe COVID-19: a propensity score–matched control study. Nat Med 2020;26:1708–13. https://doi.org/10.1038/s41591-020-1088-9.

[55] Rasheed AM, Fatak DF, Hashim HA, Maalood MF, Kabah KK, Almusawi YA, et al. The therapeutic potential of convalescent plasma therapy on treating critically-ill COVID-19 patients residing in respiratory care units in hospitals in Baghdad, Iraq. Infez Med 2020;28:357–66.

[56] Rogers R, Shehadeh F, Mylona E, Rich J, Neill M, Touzard-Romo F, et al. Convalescent plasma for patients with severe coronavirus disease 2019 (COVID-19): a matched cohort study. Clin Infect Dis 2021;73:e208–14. https://doi.org/10.1093/cid/ciaa1548.

[57] Biernat MM, Kolasińska A, Kwiatkowski J, Urbaniak-Kujda D, Biernat P, Janocha-Litwin J, et al. Early administration of convalescent plasma improves survival in patients with hematological malignancies and COVID-19. Viruses 2021;13:436. https://doi.org/10.3390/v13030436.

[58] Jeyaraman P, Agrawal N, Bhargava R, Bansal D, Ahmed R, Bhurani D, et al. Convalescent plasma therapy for severe Covid-19 in patients with hematological malignancies. Transfus Apher Sci 2021;60:103075. https://doi.org/10.1016/j.transci.2021.103075.

[59] Rodionov RN, Biener A, Spieth P, Achleitner M, Hölig K, Aringer M, et al. Potential benefit of convalescent plasma transfusions in immunocompromised patients with COVID-19. Lancet Microbe 2021;2:e138. https://doi.org/10.1016/S2666-5247(21)00030-6.

[60] Gupta A, Kute VB, Patel HV, Engineer DP, Banerjee S, Modi PR, et al. Feasibility of convalescent plasma therapy in kidney transplant recipients with severe COVID-19: a single-center prospective cohort study. Exp Clin Transplant 2021;19:304–9. https://doi.org/10.6002/ect.2020.0479.

[61] Ferrari S, Caprioli C, Weber A, Rambaldi A, Lussana F. Convalescent hyperimmune plasma for chemo-immunotherapy induced immunodeficiency in COVID-19 patients with hematological malignancies. Leuk Lymphoma 2021;62:1490–6. https://doi.org/10.1080/10428194.2021.1872070.

[62] Lindemann M, Krawczyk A, Dolff S, Konik M, Rohn H, Platte M, et al. SARS-CoV-2-specific humoral and cellular immunity in two renal transplants and two

hemodialysis patients treated with convalescent plasma. J Med Virol 2021;93:
3047–54. https://doi.org/10.1002/jmv.26840.

[63] Jin H, Reed JC, Liu STH, Ho HE, Lopes JP, Ramsey NB, et al. Three patients with X-
linked agammaglobulinemia hospitalized for COVID-19 improved with
convalescent plasma. J Allergy Clin Immunol Pract 2020;8:3594–6. https://doi.
org/10.1016/j.jaip.2020.08.059.

[64] Delgado-Fernández M, García-Gemar GM, Fuentes-López A, Muñoz-Pérez MI,
Oyonarte-Gómez S, Ruíz-García I, et al. Treatment of COVID-19 with convalescent
plasma in patients with humoral immunodeficiency - three consecutive cases and
review of the literature. Enferm Infecc Microbiol Clin 2021. https://doi.org/
10.1016/j.eimc.2021.01.013. S0213-005X(21)00035-5.

[65] Bainbridge ED, Hsue PY, Esensten JH, Lynch KL, Hendrickson CM, Doernberg SB,
et al. Characteristics of high-titer convalescent plasma and antibody dynamics after
administration in patients with severe coronavirus disease 2019. Open Forum
Infect Dis 2021;8:ofab385. https://doi.org/10.1093/ofid/ofab385.

[66] Pardiwalla B, Yadav A, Bhatia A, Toraskar K, Sharma V, Shah M, et al.
Convalescent plasma to limit coronavirus associated complications: a proof of
concept phase-2 clinical study at a designated COVID-19 hospital in Mumbai city.
J Curr Med Res Opin 2021;4. https://doi.org/10.15520/jcmro.v4i05.419.

[67] Körper S, Weiss M, Zickler D, Wiesmann T, Zacharowski K, Corman VM, et al.
Results of the CAPSID randomized trial for high-dose convalescent plasma in
patients with severe COVID-19. J Clin Invest 2021;131:e152264. https://doi.org/
10.1172/jci152264.

[68] Bennett-Guerrero E, Romeiser JL, Talbot LR, Ahmed T, Mamone LJ, Singh SM,
et al. Severe acute respiratory syndrome coronavirus 2 convalescent plasma versus
standard plasma in coronavirus disease 2019 infected hospitalized patients in New
York: a double-blind randomized trial. Crit Care Med 2021;49:1015–25. https://
doi.org/10.1097/ccm.0000000000005066.

[69] Korley FK, Durkalski-Mauldin V, Yeatts SD, Schulman K, Davenport RD,
Dumont LJ, et al. Early convalescent plasma for high-risk outpatients with covid-
19. N Engl J Med 2020;385(21):1951–60. https://doi.org/10.1056/
NEJMoa2103784.

[70] Bégin P, Callum J, Jamula E, Cook R, Heddle NM, Tinmouth A, et al. Convalescent
plasma for hospitalized patients with COVID-19: an open-label, randomized
controlled trial. Nat Med 2021;27(11):2012–24. https://doi.org/10.1038/s41591-
021-01488-2.

[71] The REMAP-CAP Investigators, Estcourt LJ, Turgeon AF, McQuilten ZK,
McVerry BJ, Al-Beidh F, et al. Convalescent plasma in critically ill patients with
covid-19. medRxiv 2021. https://doi.org/10.1101/2021.06.11.21258760.
2021.06.11.21258760.

[72] Food and Drug Administration. Fact sheet for heathcare providers. Emergency use
authorization (EUA) of COVID-19 convalescent plasma for treatment of COVID-19
hospitalized patients. 2020 (Accessed 3 June 2021), https://www.fda.gov/me
dia/141478/download.

[73] Arabi YM, Hajeer AH, Luke T, Raviprakash K, Balkhy H, Johani S, et al. Feasibility
of using convalescent plasma immunotherapy for MERS-CoV infection, Saudi
Arabia. Emerg Infect Dis 2016;22:1554–61. https://doi.org/10.3201/
eid2209.151164.

[74] Ko JH, Seok H, Cho SY, Ha YE, Baek JY, Kim SH, et al. Challenges of convalescent
plasma infusion therapy in Middle East respiratory coronavirus infection: a single
centre experience. Antivir Ther 2018;23:617–22. https://doi.org/10.3851/
imp3243.

[75] Zhang J-S, Chen J-T, Liu Y-X, Zhang Z-S, Gao H, Liu Y, et al. A serological survey on
neutralizing antibody titer of SARS convalescent sera. J Med Virol 2005;77:
147–50. https://doi.org/10.1002/jmv.20431.

[76] Yeh K-M, Chiueh T-S, Siu LK, Lin J-C, Chan PKS, Peng M-Y, et al. Experience of
using convalescent plasma for severe acute respiratory syndrome among
healthcare workers in a Taiwan hospital. J Antimicrob Chemother 2005;56:
919–22. https://doi.org/10.1093/jac/dki346.

[77] Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw FM, Lim WS, et al.
The effectiveness of convalescent plasma and hyperimmune immunoglobulin for
the treatment of severe acute respiratory infections of viral etiology: a systematic
review and exploratory meta-analysis. J Infect Dis 2015;211:80–90. https://doi.
org/10.1093/infdis/jiu396.

[78] Bloch EM, Shoham S, Casadevall A, Sachais BS, Shaz B, Winters JL, et al.
Deployment of convalescent plasma for the prevention and treatment of COVID-19.
J Clin Invest 2020;130:2757–65. https://doi.org/10.1172/jci138745.

[79] Franchini M, Liumbruno GM, Piacentini G, Glingani C, Zaffanello M. The three
pillars of COVID-19 convalescent plasma therapy. Life (Basel) 2021;11:354.
https://doi.org/10.3390/life11040354.

[80] Bloch EM, Goel R, Wendel S, Burnouf T, Al-Riyami AZ, Ang AL, et al. Guidance for
the procurement of COVID-19 convalescent plasma: differences between high- and
low-middle-income countries. Vox Sang 2021;116:18–35. https://doi.org/
10.1111/vox.12970.

[81] Cohn CS, Estcourt L, Grossman BJ, Pagano MB, Allen ES, Bloch EM, et al. COVID-
19 convalescent plasma: interim recommendations from the AABB. Transfusion
2021;61:1313–23. https://doi.org/10.1111/trf.16328.

[82] Ricke DO. Two different antibody-dependent enhancement (ADE) risks for SARS-
CoV-2 antibodies. Front Immunol 2021;12:640093. https://doi.org/10.3389/
fimmu.2021.640093.

[83] Wen J, Cheng Y, Ling R, Dai Y, Huang B, Huang W, et al. Antibody-dependent
enhancement of coronavirus. Int J Infect Dis 2020;100:483–9. https://doi.org/
10.1016/j.ijid.2020.09.015.

[84] Food and Drug Administration. Emergency Use Authorization (EUA) for the
emergency use of COVID-19 convalescent plasma for the treatment of hospitalized
patients with Coronavirus Disease 2019 (COVID-19) early in the course of disease,
https://www.fda.gov/media/141477/download; 09 March 2021 (Accessed 03
June 2021).

[85] Moniuszko-Malinowska A, Czupryna P, Zarębska-Michaluk D, Tomasiewicz K,
Pancewicz S, Rorat M, et al. Convalescent plasma transfusion for the treatment of
COVID-19-Experience from Poland: a multicenter study. J Clin Med 2020;10:28.
https://doi.org/10.3390/jcm10010028.

[86] Joyner MJ, Carter RE, Senefeld JW, Klassen SA, Mills JR, Johnson PW, et al.
Convalescent plasma antibody levels and the risk of death from Covid-19. N Engl J
Med 2021;384:1015–27. https://doi.org/10.1056/NEJMoa2031893.

[87] Marshall JC, Murthy S, Diaz J, Adhikari NK, Angus DC, Arabi YM, et al. A minimal
common outcome measure set for COVID-19 clinical research. Lancet Infect Dis
2020;20:e192–7. https://doi.org/10.1016/S1473-3099(20)30483-7.

[88] Hueso T, Pouderoux C, Péré H, Beaumont A-L, Raillon L-A, Ader F, et al.
Convalescent plasma therapy for B-cell depleted patients with protracted COVID-
19 disease. Blood 2020;136:2290–5. https://doi.org/10.1182/blood.2020008423.

[89] Fung M, Nambiar A, Pandey S, Aldrich JM, Teraoka J, Freise C, et al. Treatment of
immunocompromised COVID-19 patients with convalescent plasma. Transpl Infect
Dis 2021;23:e13477. https://doi.org/10.1111/tid.13477.

[90] Focosi D, Franchini M. Potential use of convalescent plasma for SARS-CoV-2
prophylaxis and treatment in immunocompromised and vulnerable populations.
Expert Rev Vaccines 2021:1–8. https://doi.org/10.1080/
14760584.2021.1932475.

[91] Kemp SA, Collier DA, Datir RP, Ferreira IATM, Gayed S, Jahun A, et al. SARS-CoV-2
evolution during treatment of chronic infection. Nature 2021;592:277–82. https://
doi.org/10.1038/s41586-021-03291-y.

[92] Choi B, Choudhary MC, Regan J, Sparks JA, Padera RF, Qiu X, et al. Persistence and
evolution of SARS-CoV-2 in an immunocompromised host. N Engl J Med 2020;383:
2291–3. https://doi.org/10.1056/NEJMc2031364.

[93] Food and Drug Administration. EUA 26382: Emergency Use Authorization (EUA)
request (original request 8/12/20; amended request 8/23/20). 2020 (Accessed 03
June 2021), https://www.fda.gov/media/141480/download.

[94] Cevik M, Grubaugh ND, Iwasaki A, Openshaw P. COVID-19 vaccines: keeping pace
with SARS-CoV-2 variants. Cell 2021;184:5077–81. https://doi.org/10.1016/j.
cell.2021.09.010.

[95] Krammer F, Srivastava K, Simon V. Robust spike antibody responses and increased
reactogenicity in seropositive individuals after a single dose of SARS-CoV-2 mRNA
vaccine. medRxiv 2021. https://doi.org/10.1101/2021.01.29.21250653.

[96] Romon I, Arroyo JL, Díaz T, Dominguez-Garcia JJ, Briz M. High-titre anti-SARS-
CoV-2 convalescent plasma donation after donors' vaccination. Vox Sang 2021;
116:930–1. https://doi.org/10.1111/vox.13094.

[97] Focosi D, Franchini M. Impact of pathogen-reduction technologies on COVID-19
convalescent plasma potency. Transfus Clin Biol 2021;28:132–4. https://doi.org/
10.1016/j.tracli.2021.02.005.

[98] Klein SL, Pekosz A, Park HS, Ursin RL, Shapiro JR, Benner SE, et al. Sex, age, and
hospitalization drive antibody responses in a COVID-19 convalescent plasma donor
population. J Clin Invest 2020;130:6141–50. https://doi.org/10.1172/jci142004.

[99] European Commission. Directorate General for Health and Food Safety, An EU
programme of COVID-19 convalescent plasma collection and transfusion. Guidance
on collection, testing, processing, storage, distribution and monitored use, https
://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/guidance_pl
asma_covid19_en.pdf; 10 March 2021 (Accessed 29 June 2021).