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

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\textbf{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 \cite{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 \cite{2}. The emergence of new variants highlights the importance of surveillance systems to update vaccination strategies and treatment approaches \cite{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 \cite{4}. Moreover, some vaccines may offer suboptimal protection against new variants \cite{5}.

Patients with COVID-19 are often asymptomatic or present with mild respiratory symptoms \cite{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 (NAb) [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 “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/infiltrancies, 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 | 185 patients (86 %) | Detectable NAb titer: SoC (antivirals, broad spectrum antibiotics, immunomodulators and supportive management) + 2 doses of CovCP (200 mL) 24 h apart | NR | 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 | 163 patients (80 %) | Detectable NAb titer: 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 (antivirals, 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) |
| 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, Preprint [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 |

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| 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 |
| 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 |
| Control group | 51 | Hospitalized, severe or life-threatening disease | Symptom onset to randomization, median (IQR): 30 days (19–58) | 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) |
| 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 \( ^ {1} \) | 3 |

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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 |                       | 4                     |
| Control group                                            | 40                | Severe          | NR                       | NR                     | NAb titers comparable in both groups at the day of enrollment | SoC         | NA                       | NA                       | NA                  |
| Avendaño-Solá, 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                  | 3                     |
| 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          | 5 (17 %) patients        | NR                     | SoC                       | NA                       | 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

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| 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]       | 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 patients + 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 |
| CovCP group                                             |                    |                 |                          |                        |                           |              |                             |                        |                         |
| 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]        | 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 |
| CovCP group                                             |                    |                 |                          |                        |                           |              |                             |                        |                         |
| 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]            | 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 |
| CovCP group                                             |                    |                 |                          |                        |                           |              |                             |                        |                         |
| Control group                                           | 21 (historical controls) | Critical | NR | NR | NR | SoC for ICU patients + steroids (70 %) | NA | NA | |
| Kurtz, Brazil, Peer-reviewed publication [53]            | 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 [enoxaparin]) + 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 |

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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]                                           | 29                 | Hospitalized mild/ moderately ill, non-ICU | NR                      | 0 % (exclusion criteria) | NA¹                      | Naive       | Remdesivir and corticosteroids in some patients + 2 units of CovCP within 72 h of admission (except 1 patient who received 1 unit) | NR                       | 5                      |
| Franchini, Italy, Peer-reviewed publication [48]         | 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                      |
| Rasheed, Iraq, Peer-reviewed publication [55]           | 21                 | Hospitalized, early-stage critically-ill | Symptom onset to enrollment, mean ± SD: 14.8 days (SD: 7.5) | 81 % of patients on ventilators | 14.9 % weakly positive for SARS-CoV-2 IgG | SoC (hydroxychloroquine, 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                                           | 733                | Moderate to severe |                          |                         |                           |             |                         |                          | NA                      |
| Acosta–Ampudia, Colombia, Peer-reviewed publication [46] | 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 (hydroxychloroquine, azithromycin, oxygen therapy, methylprednisolone) | NA                       | NA                     |
| Control group                                           | 9                  | Severe (not life-threatening) | Symptom onset to CovCP transfusion, mean ± SD: 8.667 ± 2.693 days | 22.2 % | NA¹ | 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                      |

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| 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 |
|----------------------------------------------------------|--------------------|------------------|--------------------------|------------------------|-----------------------------|--------------|---------------------------|--------------------------|--------------------------|
| 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 favipiravir, lopinavir, ritonavir, hydroxychloroquine, high dose vitamin C, azithromycin) + CovCP | Resolution of symptoms ≥ 14 days | NR | 4 |

Salazar, US, Peer-reviewed publication [20]

| CovCP group | 351 | Hospitalized, severe and/or life-threatening | MV or ECMO: 4.0 % of patients | NR | 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 | NA | 4 |

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 |

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 %) | NA | NAb titer of 40 in 108 donors; 80 in 74 donors; 160 in 27 donors; 320 in 12 donors and 640 in 5 donors | NA | 4 |

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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 of patients | Oxford Level of Evidence |
|-------------------------------------------------------|--------------------|-----------------|--------------------------|------------------------|---------------------------|-------------|----------------------------|-------------------------------|--------------------------|
| **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                         | 4                           |
| 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                           | 4                           |
| 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                         | 4                           |
| 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                           | 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): **| 9 (12.3 %) patients | Ab (1/titer, median with IQR) | 200 mL-unit of CovCP transfused within 72 h of hospital admission | Asymptomatic for ≥ 14 days | Median IgG, IgM, and IgA titer 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)
| 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 |
|----------------------------------------------------------|-------------------|-----------------|-------------------------|------------------------|---------------------------|-------------|---------------------------|------------------------|--------------------------|
| 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]               | 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]             | 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]   | 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]                  | 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 |

(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 |
|----------------------------------------------------------|--------------------|-----------------|--------------------------|------------------------|---------------------------|-------------|---------------------------|------------------------|-------------------------|
| **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                     | 4                      |
| 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                      |
| 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    | First-line treatment (hydroxychloroquine, corticosteroid and broad-spectrum antibiotics) + 1 cycle (600 mL) of CovCP | Asymptomatic for ≥ 14 days | NR | 4                      |
| Control group                                           | 61                 | Severe or immediately life-threatening | NR                       | 7 (11 %) patients      | NR                        | First-line treatment | NA                     | NA                     | 4                      |
| 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                        | NA | NA                     | NA                     | 4                      |
| 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                      |

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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 [25,27,30,32,35,37,38,42,44,46,50–53,56] 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 NAb levels [67]. The improvement in high NAb levels rather than high IgG levels to select appropriate CovCP of patients who received larger amount of NAb [67]. The importance of NAb levels rather than high IgG levels to select appropriate CovCP of patients who received larger amount of NAb [67]. The importance of NAb levels rather than high IgG levels to select appropriate CovCP of patients who received larger amount of NAb [67]. The importance of NAb levels rather than high IgG levels to select appropriate CovCP of patients who received larger amount of NAb [67]. The importance of NAb levels rather than high IgG levels to select appropriate CovCP of patients who received larger amount of NAb [67]. The importance of NAb levels rather than high IgG levels to select appropriate CovCP of patients who received larger amount of NAb [67]. The importance of NAb levels rather than high IgG levels to select appropriate CovCP of patients who received larger amount of NAb [67]. The importance of NAb levels rather than high IgG levels to select appropriate CovCP of patients who received larger amount of NAb [67]. The importance of NAb levels rather than high IgG levels to select appropriate CovCP of patients who received larger amount of NAb [67]. The importance of NAb levels rather than high IgG levels to select appropriate CovCP of patients who received larger amount of NAb [67]. The importance of NAb levels rather than high IgG levels to select appropriate CovCP of patients who received larger amount of NAb [67]. The importance of NAb levels rather than high IgG levels to select appropriate CovCP of patients who received larger amount of NAb [67]. The importance of NAb levels rather than high IgG levels to select appropriate CovCP of patients who received larger amount of NAb [67]. The importance of NAb levels rather than high IgG levels to select appropriate CovCP of patients who received larger amount of NAb [67]. The importance of NAb levels rather than high IgG levels to select appropriate CovCP of patients who received larger amount of NAb [67]. The importance of NAb levels rather than high IgG levels to select appropriate CovCP of patients who received larger amount of NAb [67]. The importance of NAb levels rather than high IgG levels to select appropriate CovCP [67].

Because screening 2 identified only two controlled studies in 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.

 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 subgroup. 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 | 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 |
|--------------------------------------------------------|--------------------|-----------------|--------------------------|------------------------|--------------------------|----------------------------|----------------------------|---------------------------|--------------------------|
| Thompson, US, Peer-reviewed publication [43] CovCP group | 143 (propensity-score matched) | 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 (non-matched)  | Mild (with hospitalization) to severe, in patients with hematologic malignancies | NR | 29 (20.3%) matched controls | NR | Medication | NA | NA |
| 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 |
| 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 | Not detectable at baseline | NR | 3 units of CovCP (11 patients), 2 units (2 patients) or 1 unit (1 patient), each unit of 200 mL | 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 |

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### 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 |
|----------------------------------------------------------|--------------------|-----------------|--------------------------|------------------------|---------------------------|-------------------------------|---------------------------|--------------------------|--------------------------|
| **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 | 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 | NR | NAb titer of ≥ 1:320 | 4 |
| **Jin, US, Peer-reviewed publication [63]**               | 3                  | Any, in hospitalized patients with X-linked agammaglobulinemia | Symptom onset to hospital admission: 5–42 days | 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 | 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 | 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] | 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 |
| CovCP group                                               |                        |                  |                             |           |                        |                      |
| Control group                                             | 5763                   | NR               |                             | 28-day: 24 % | Median (IQR): 11 days (6–28) | NR |
| Agarwal, India, Peer-reviewed publication [28]            | 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 |
| CovCP group                                               |                        |                  |                             |           |                        |                      |
| Control group                                             | 229                    | NR               |                             | 28-day: 14 % | Median (IQR): 13 days (10–18) | NR |
| Simonovich, Argentina, Peer-reviewed publication [26]     | 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 % |
| CP group                                                  |                        |                  |                             |           |                        |                      |
| 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]     | 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) |
| CovCP group                                               |                        |                  |                             |           |                        |                      |
| Control group                                             | 73                     | NR               |                             | 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]                           | 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      |                        |                  |                             |           |                        |                      |
| CovCP group                                               |                        | NR               |                             | 28-day: 43 % | All follow-up: 53.3 % |                      |
| Control group                                             | 60                     | NR               |                             |           |                        |                      |
| Libster, Argentina, Peer-reviewed publication [25]        | 80                     | No               | NR                          | 25-day: 2.5 % | NA                     |                      |
| CovCP group                                               |                        | NR               |                             |           |                        |                      |
| Control group                                             | 80                     | NR               |                             | 25-day: 5 % | NA                     |                      |

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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]                | 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] | 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                                           | 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 % |
| Avendañoa-Solá, 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: 5 % | Median (IQR) time to discharge: 9.0 days (6.0–11.0) | Improvement in 8-point WHO severity score: 53.33 % |
| 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: 26.66 % |
| 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), O₂ saturations (10 %), SOFA scores (~5), PaO₂/FiO₂ (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), O₂ saturations (7.5 %), SOFA scores (~3), PaO₂/FiO₂ (77.01) at day 7 |

Prospective controlled clinical trials (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 |
|--------------------------------------------------------|------------------------|------------------|-------------------------------|-----------|------------------------|----------------------|
| AlSharidah, Kuwait, Peer-reviewed publication [34] | 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) |
| CovCP group | | | | | | |
| 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] | 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 |
| CovCP group | | | | | | |
| 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] | 73 | No | NR | All follow-up: 19 % | 12 days | Extubated patients: 42 %. Composite endpoint of extubation/discharged home alive: 64 % |
| CovCP group | | | | | | |
| 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] | 41 | Yes | No | 7-day: 17 % | 28-day: 49 % | Median (IQR): 17 (7–28) days |
| CovCP group | | | | | | |
| Control group | 72 | NR | NR | 7-day: 29 % | 28-day: 56 % | Median (IQR): 14 (4–26) days |
| | | | | | | |

Sturek US, Pre-print [37] | 29 | Yes | At least one related AE was reported for 4/29 patients | 28-day: 6.9 % | NR | Rate of ICU transfer: 13.8 % |
| CovCP group | | | | | | |
| Control group | 48 | NR | NR | 28-day: 10.4 % | NR | Rate of ICU transfer: 27.1 % |

Franchini Italy, Peer-reviewed publication [48] | 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 |
| CovCP group | | | | | | |
| Control group | 733 (historical controls) | NR | NR | All follow-up: 38.3 % | NR | NR |

Rasheed, Iraq, Peer-reviewed publication [55] | 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 |
| CovCP group | | | | | | |
| Control group | 28 | NR | NR | All follow-up: 28.6 % | NR | |

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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 |
|----------------------------------------------------------|------------------------|------------------|------------------------------|-----------|------------------------|---------------------|
| Acosta-Ampudia, Colombia, Peer-reviewed publication [46] | 9                      | Yes              | No                           | All follow-up: 22.2 % | Mean ± SD: 9.333 ± 3.937 days | Recovery time from critical illness, mean ± SD: 8.45 ± 1.8 days, Whole duration of infection, mean ± SD: 23.4 ± 6.4 days |
| CovCP group                                             |                        |                  |                              |            |                        | 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] | 888 | No | NR | Case fatality rate: 24.7 % | Median (range): 17 days (0–74), MV rate: 49.3 % |
| CovCP group                                      |    |    |    |                            |            |
| 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] | 351 | No | NR | 28-day: 3.7 % | 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 % |
| CovCP group                                     |    |    |    |                |            |
| Control group                                    | 594 | NR | NR | 28-day: 9.8 % | 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] | 263 | Yes | No | 7-day: 9.13 % 14-day:14.83 % | Overall: mean ± SD: 15.67 ± 13.65 days Duration of MV, median: 11 days, Improvement in oxygen device delivery category: 3 days |
| CovCP group                                     |    |    |    |                |            |
| 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 [411] | 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 |
| CovCP group                                     |    |    |    |                |            |
| Control group                                    | 226 | NR | NR | 10-day: 14.2 % 28-day: 22.1 % | NR |

| Thompson, US, Peer-reviewed publication [43] | 143 | No | NR | 30-day: 13.3 % | NR |
| CovCP group                                     |    |    |    |                |            |
| Control group                                    | 823 | NR | NR | 30-day: 24.8 % | NR |

| Tworek, Poland, Peer-reviewed publication | 102 | No | NR | All follow-up: 13.7 % | Median (range):  |
|                                       |    |    |    |                |            |

(continued on next page)
### Table 3 (continued)

| First author, country, type of publication | Number of participants | Safety assessment | Transfusion-related reactions | Mortality | Length of hospital stay | Clinical improvement |
|-------------------------------------------|------------------------|------------------|--------------------------------|-----------|------------------------|----------------------|
| **CovCP group**                           |                        |                  |                                |           |                        |                      |
| **Control group**                         | 102                    | NR               | NR                             | All follow-up: 34.3 % | Median (range): All follow-up: 34.3 % |                      |
| Ventilator time, median (IQR): 6 days (1–29) | 13 days (0–59)         |                  |                                |           |                        |                      |
| **Mesina, Philippines, Pre-print** [45]   | 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**   | 73                     | Yes              | No                             | 28-day: 31.5 % | NR | Clinical status improvement was statistically significant in patients < 65 years (88.2 %) |
| **CovCP group**                           |                        |                  |                                |           |                        |                      |
| **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** | 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 |
| **Klapholz, US, Peer-reviewed publication** | 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 |
| **AlShehry, Saudi Arabia, Peer-reviewed publication** | 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) |
| **Liu, US, Peer-reviewed publication**    | 124                    | NR               | NR                             | 30-day: 39.3 % | Median (IQR): 14 days (10–20) | Time to clinical recovery, median (IQR): 15 days (11–21) |
| **Sostin, US, Peer-reviewed publication** | 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** | 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 % | | | |

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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 % vs 24.8 %) in patients with COVID-19 and hematologic malignancies [43]. In the non-matched case-control series, a significantly reduced mortality rate (13 % vs 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 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] | CovCP group | Control group | 32 | NR | NR | 28-day: 43.8 % | Mean ± SD (range): 15.34 ± 10.11 days (5–56) |
| | | | | | | PaO2/FiO2 levels: 213.41 |
| Hegerova, US, Peer-reviewed publication [52] | CovCP group | Control group | 20 | No | NR | 14-day: 10 % | Median: 15 days |
| | | | | | Discharge rate: 45 % |
| Khanna, Switzerland, Congress abstract [42] | CovCP group | Control group | 15 | No | NR | 28-day: 0 % | Median (IQR): 13 days (7–18) |
| | | | | | Ordinal WHO scale score on day 14, mean ± SD: 3.45 ± 3.6 |
| | | | | | Trend towards decreased inflammatory response in CovCP group |
| | | | | | Progression to intubation not significantly different between groups |

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; PaO2/FiO2, 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.
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                    | Mildly 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     | 28-day: 53.3 % | Overall: 45.5 % 14-day: 24.2 % | For 9/10 patients: normalized body temperature, decreased inflammatory markers and improvement of PaO$_2$/FiO$_2$ after CovCP transfusion |
| 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 last hospital stay: 8-31 days (NR for all patients) |
| Ferrari, Italy, Peer-reviewed publication [61]           | 7                   | Chemo-immunotherapy due to hematologic disorders and related immunodeficiency | Yes              | No                            | 0 %       | 8-28 days from CovCP    | 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 severely 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...
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 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 might improve clinical outcome in specific subpopulations.

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 sub-populations 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.

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Author contributions

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

Declaration of Competing Interest

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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, Canabelli AM, Jackson B, Gupta RK, Thomson EC, Harrison EM, et al. SARS-CoV-2 variants, spike mutations and immune escape. Nat Rev Microbiol 2021;19:809-24. https://doi.org/10.1038/s41579-021-00573-z.
[4] Wouters OJ, Shadlen KC, Salscher-Konrad M, Pollard AJ, Larson HJ, Tearawattananon 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)00586-8.
[5] Martínez-Flores D, Zepeda-Cervantes J, Cruz-Restindiz A, Aguirre-Samperio 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, Peng 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] Heussten AM, Allard MA, Thompson DK, Fasini 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, Senfeld JW, Johnson PW, Carter RE, Wiggins CC, Shoham S, et al. The effect of convalescent plasma therapy on mortality among patients with COVID-19: a 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, Papella 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 YD, 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 Grensveld 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/NEJMoai1511812.
[16] Piechotta V, Iamxintorn 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.pub2.
[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/ocemm-levels-of-evidence/.
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.
jid.2021.02.034.

Budnikova AV, Kostin AL, Petrikov SS, Lysenko MA, Popugayev K, Fomina DS, et al. Convalescent plasma therapy of a new coronavirus infection: an experience of Moscow city hospitals. Anestesiologiya i reanimatsiya 2020;6:33. https://doi.org/10.17116/ar20200633.

Khankina N, Weiser M, Hedberg A, Birkenmaier ST, Roesch S, Battegay M, et al. Effect 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.2020013786.

Thompson MA, Henderson JP, Shak PB, Rubinstein SM, Joyner MJ, Cheoueit 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.2021.0001.

Alshehry N, Zaidi SZA, Al-Akbar A, Al Odayani A, Alobait AI, Al-Saheer 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 Sci 2021;8:26–33. https://doi.org/10.1016/j.sjms.2021.02.009.

Menina FZ, Mangahas G, 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/10.1101/2021.02.12.21251852.

Acosta-Ampudia YM, Monsalve DM, Rojas M, Rodriguez Y, Gallo JE, Salazar-Urbie 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.

Allahyari A, Seddigh-Shamsi M, Mahmoodi M, Amel Jamehdar S, Amini M, Mozoudian M, et al. Efficacy and safety of convalescent plasma therapy in COVID-19 patients with acute respiratory distress syndrome. Int Immunopharmacol 2021;93:107239. https://doi.org/10.1016/j.intimp.2021.107239.

Franchini M, Cinglani C, Morandi M, Corghi G, Cerzoso 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.mayoecoj.2021.01.010.

Shenoy AG, Hetttinger AZ, Fernandez SJ, Blumenthal J, Baev V. Early mortality benefit with COVID-19 convalescent plasma: a matched control study. Br J Haematol 2021;192:769–77. https://doi.org/10.1111/bjh.17722.

Abolghasemi H, Eshghi P, Cheraghalig AM, Imani Fooladi AA, Boloosi Moghadam F, Imanzadeh S, et al. Clinical efficacy of convalescent plasma for treatment of COVID-19 infections: results of a multicenter clinical study. Transfus Apher Sci 2020;65:102579. https://doi.org/10.1016/j.transci.2020.102579.

Alantus F, Ata N, Yigengolu TN, Baci M, Kazankova SA, et al. Convalescent plasma therapy in patients with COVID-19. Transfus Apher Sci 2021;60:102955. https://doi.org/10.1016/j.transci.2021.102955.

Hegerova L, Goeley TA, Sweerts 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.202006964.

Kurtz P, Rigby C, Gadelha M, Palmer AE, Gonzales B, et al. Effect of convalescent plasma in COVID-19: a randomized controlled trial. medRxiv 2020. https://doi.org/10.1101/2020.10.25.20219337.

Robianini RO, Biener A, Spieth P, Achleitner M, Hegerova L, Gooley TA, et al. Convalescent plasma for COVID-19: a multicenter, randomized controlled trial. medRxiv 2020. https://doi.org/10.1101/2020.10.25.20219337.

Lovato E, Christensen PA, Graviss EA, Nguyen DT, Castillo B, Chen J, et al. Effect of convalescent plasma on COVID-19-related cytokine storm. Intern Emerg Med 2021:384:610–8. https://doi.org/10.1007/s11739-021-01304-7.

Sanchez J, Hegerova L, Gooley TA, Sweerts KA, Maree C, Bailey N, Bailey M, et al. Use of convalescent plasma therapy in hospitalized COVID-19 patients: a syst summary. Transfus Apher Sci 2021;62:102993. https://doi.org/10.1016/j.transci.2020.102993.

Hegerova L, Goeley TA, Sweerts 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.202006964.

Hegerova L, Goeley TA, Sweerts KA, Maree C, Bailey N, Bailey M, et al. Use of convalescent plasma therapy for COVID-19 patients with acute respiratory distress syndrome. Int Immunopharmacol 2021;93:107239. https://doi.org/10.1016/j.intimp.2021.107239.

Fahmy AH, Al-Hajj MB, Al-Masarir H, Al-Majed M, Atab B, Stas M, et al. Convalescent plasma therapy in severe COVID-19 patients. Transfus Apher Sci 2021;60:102955. https://doi.org/10.1016/j.transci.2021.102955.

Hegerova L, Goeley TA, Sweerts KA, Maree C, Bailey N, Bailey M, et al. Use of convalescent plasma therapy in patients with COVID-19: an observational study. Front Med (Lausanne) 2021;8:630982. https://doi.org/10.3389/ fmed.2021.630982.

Loft S, Lin HM, Baine I, Wojcieszek JP, Rahmann 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.

Rizk RM, Fatah DF, Hashim HA, Manold MP, 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. Infect Med 2020;28:357–66. https://doi.org/10.3109/02644469.2020.1767876.
hemodialysis patients treated with convalescent plasma. J Med Virol 2021;93: 3047-54. https://doi.org/10.1002/jmv.26846.

[63] Jin H, Reed JC, Liu STH, Ho HE, Lopes JP, Ramsey NB, et al. Three patients with X-linked agammaglobulinemia for COVID-19 improved with convalescent plasma. J Allergy Clin Immunol Pract 2020;8:3594-6. https://doi.org/10.1016/j.jaci.2020.08.050.

[64] Delgado-Fernández M, García-Gematsu F, Fuentes-López A, Muñoz-Pérez MI, Oyarte-Gómez S, Ruiz-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.2021.03.011. 0213-005X(21)00058-5.

[65] Bainbridge ED, Hsue PY, Esensten JH, Lynch KL, Hendrickson CM, Doernberg SB, et al. Early convalescent plasma for high-risk outpatients with COVID-19. J Curr Med Res Opin 2021;4. https://doi.org/10.15520/jcmro.v4i05.419.

[66] Bloch EM, Shoham S, 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/jci137845.

[67] Franchini M, Liubunro GM, Placentini G, Giangiani C, Zaffanella M. The three pillars of COVID-19 convalescent plasma therapy. Life (Basel) 2021;11:354. https://doi.org/10.3390/life11040354.