

**CLINICAL MEMORANDUM**

Date: December 27, 2021

From: Carlos H. Villa MD PhD, Associate Director for Special Programs, OBRR

To: Nicole Verdun MD, Director, OBRR

Through: Orijei Illoh MD, Division Director, OBRR/DBCD  
Wendy Paul MD, Deputy Division Director, OBRR/DBCD  
Salim Haddad MD, Team Lead, OBRR/DBCD/CRS

Re: EUA 26382

Product: COVID-19 Convalescent Plasma

Sponsor: Assistant Secretary for Preparedness and Response (ASPR)  
Office of Assistant Secretary for Preparedness and Response  
U.S. Department of Health and Human Services (HHS)

---

## EXECUTIVE SUMMARY

FDA has continued to review emerging evidence from clinical trials of COVID-19 Convalescent Plasma (CCP) and related therapies for the treatment of COVID-19 and determined that revision of the scope of Emergency Use Authorization (EUA) is warranted. FDA issued an EUA for CCP on 8/23/2020 and revised the EUA on 11/30/2020, 2/4/2021, 2/23/2021, 3/9/2021, and 6/2/2021. Several additional randomized controlled trials and observational studies have reported on the use of CCP in both the inpatient and outpatient settings. Review of these data found that the majority of large RCTs of CCP do not demonstrate clinical benefit in the treatment of immunocompetent hospitalized patients with COVID-19. Subgroup analyses have failed to clearly identify and define sub-populations of patients that assure a favorable ratio of potential benefit to risk (for example, criteria based on disease severity, duration of symptoms, or serostatus). However, for immunosuppressed or immunodeficient patients, studies suggest a larger potential benefit, and considering these data and the potential risk for severe outcomes in patients with COVID-19 with immunosuppressive disease or receiving immunosuppressive treatment, EUA criteria for high titer CCP are met in this population in both inpatient and outpatient settings. To more accurately and consistently assure high titers in CCP products, the tests used in the manufacture of CCP should be limited to serology tests that have been issued an EUA that includes an indication for semi-quantitative or quantitative detection of anti-SARS-CoV-2 antibodies, and the cutoffs for qualification should be increased. Randomized trials to better identify patient and product characteristics likely to confer clinical benefit with CCP or other passive immune therapies remain important to assure availability of safe and effective therapeutics in this and potential future pandemics.

**Recommendation:** Based on evaluation of newly reported evidence, the authorized indications for CCP should be limited to the use of CCP with high titers of anti-SARS-CoV-2 antibodies for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment, in either the outpatient or inpatient setting. Testing criteria used for manufacturing tests used in the qualification of CCP should be revised to better assure high neutralization titers in CCP.

## **I. Regulatory History**

FDA issued EUA 26382 on August 23, 2020 for the use of CCP for treatment of hospitalized patients with COVID-19. This authorization was based on the totality of the scientific evidence available at the time, which supported a determination that CCP met the “may be effective” criterion for issuance of an EUA and that the known and potential benefits of CCP outweighed the known and potential risks of CCP for the terms of the EUA. Considering the limited data from adequate and well-controlled randomized trials at the time of the issuance of the EUA, FDA noted in the August 23, 2020 Letter of Authorization that additional data from such trials remained necessary for a definitive demonstration of CCP efficacy and to determine the optimal product attributes and appropriate patient populations for use of CCP. Information derived from ongoing clinical trials of CCP, particularly randomized, controlled trials, as well as clinical trial results from studies of other investigational medical products to treat COVID-19 continue to inform the ongoing benefit:risk assessment of CCP. On February 4, 2021, following evaluation of emerging evidence from randomized controlled trials, the EUA was reissued to authorize the use of high titer CCP for the treatment of hospitalized patients with COVID-19 early in the course of hospitalization or in patients with impaired humoral immunity. The February 4, 2021 EUA reissuance no longer authorized the use of low titer CCP. FDA added additional tests used as manufacturing tests in the qualification of CCP to the EUA on 11/30/2020, 2/4/2021, 2/23/2021, 3/9/2021, and 6/2/2021.

## **II. Summary of Updated Evidence on the Use of CCP for the Treatment of COVID**

### **a. Randomized Controlled Trials (RCTs) in Hospitalized Patients with COVID-19**

At the time of the original issuance of the EUA for CCP, results from two RCTs had been published or made publicly available as pre-print (and later published)[1-3]. Both studies failed to demonstrate a significant benefit with CCP transfusion, but had been stopped early either due to low enrollment[1] or to the presence of high antibody titers in subjects prior to transfusion[2, 3]. Additionally, patients were treated relatively late in illness, at a median of 30 days[1] and 10 days[2, 3] post symptom onset. At the time of the February 4, 2021 EUA reissuance, additional published RCTs included the PLACID study conducted in India[4] and the PlasmAr study in Argentina[5], neither of which observed benefits with CCP transfusion in hospitalized patients in their primary clinical endpoints. However, review of these studies at that time noted some limitations, including low titer of the transfused CCP compared to baseline titers in the transfused subjects in the PLACID study, and, in both studies, small sample sizes that limited the power to detect small but clinically important differences, particularly in subgroups such as those treated early in hospitalization. Additional small, randomized trials published at that time likewise did not observe a significant difference in clinical outcomes in their overall study populations but were underpowered to detect meaningful clinical benefits[6, 7]. The ConPlas-19 study in Spain[8], where results had been posted as a pre-print, observed a trend towards a survival benefit with administration of high titer CCP, but the difference did not meet the prespecified test for statistical significance, and the study was stopped early due to diminished enrollment (this study was later reopened, and the full published results[9] are reviewed below).

In addition to published or publicly posted study results, at the time of the February EUA reissuance, the RECOVERY study in the United Kingdom, a large platform trial that has evaluated multiple COVID-19 therapies[10], reported on a comparison of CCP to standard of

care. However, only an investigator statement had been posted at that time, and the full results of the study had not been published. Preliminary analysis showed no significant difference in the primary endpoint of 28-day mortality in patients treated with CCP compared to standard of care. FDA review of these findings noted that additional information on the timing of product administration relative to symptom onset, baseline patient antibody titers, and antibody titers in the transfused CCP would be important to further evaluate the findings.

After the February 2021 revision of the EUA for CCP, full results of the CCP arm of RECOVERY, and several additional RCTs, have reported on the use of CCP in hospitalized patients with COVID-19. These are summarized as follows:

**RECOVERY [11]** – RECOVERY was a large, open-label platform trial of patients hospitalized with COVID-19 in the United Kingdom, where 16,287 subjects were randomized to either transfusion of two units of CCP (~275 mL each, 80% of subjects received two units, 11% received one unit) or standard of care. CCP was qualified using a serologic test for anti-SARS-CoV-2 spike antibodies. Subjects receiving CCP were randomized at a median of 9 days from onset of symptoms (IQR 6-12), with 29-35% of subjects known to be seronegative for anti-SARS-CoV-2 antibodies at enrollment (12% of CCP subjects and 22% of usual care subjects were missing antibody test results at baseline). 24% of subjects in the CCP arm and 24% of subjects in the standard of care arm died within 28 days (rate ratio 1.00, 95% CI 0.93–1.07;  $p=0.95$ ). No significant differences in mortality were observed in prespecified subgroups of patients, including in those patients seronegative at enrollment, or based on duration of symptoms at enrollment, although trends favored that any potential benefit would be more likely in seronegative subjects or in patients treated earlier from symptom onset or not yet requiring oxygen or steroid therapy. In subjects who were not receiving invasive mechanical ventilation at baseline, for the prespecified composite secondary outcome of invasive mechanical ventilation or death, there was some evidence of heterogeneity by patient SARS-CoV-2 antibody test result, with slightly improved outcomes with CCP in patients who were seronegative at baseline compared with those who were seropositive. Within 72 hours of randomization, a higher number of severe allergic reactions (16 of 5,795, <1%) was reported in the CCP arm compared to the control arm (2 of 5,763, <1%). The frequency of sudden worsening in respiratory status, temperature increase, sudden hypotension, clinical hemolysis, and thrombotic events were broadly similar between the two study arms. 13 subjects transfused with CCP had reports submitted to the national hemovigilance system, including: 9 patients with pulmonary reactions (none considered to represent transfusion related acute lung injury with 3 deaths considered possibly related to transfusion), and 4 patients with serious febrile, allergic, or hypotensive reactions (all of whom recovered).

**REMAP-CAP [12]** – REMAP-CAP was an open-label, randomized, multi-national platform trial conducted in the United Kingdom, Canada, Australia, and the United States, wherein, among the 4,763 total patients who were enrolled, 2,097 patients were enrolled in the immunoglobulin domain, and 2,011 of these hospitalized patients were severely/critically ill (requiring intensive care), and randomized to CCP ( $n=1,084$ ), CCP if clinical deterioration ( $n=11$ ), or no CCP ( $n=916$ ). A smaller subset of patients with moderate disease ( $n=86$ ) were randomized to CCP ( $n=42$ ), CCP if clinical deterioration ( $n=20$ ), or no CCP ( $n=24$ ). Duration of symptoms at enrollment or randomization was not reported. 31% of subjects in the CCP arm and 26.7% of subjects in the control arm were negative for anti-SARS-CoV-2 antibodies at baseline. Subjects were transfused with 2 units of CCP that had been qualified with variable serologic or neutralization criteria according to study region. The study found no significant benefit in organ support-free days, hospital survival, or any of the pre-specified secondary outcomes in subjects treated with CCP. No significant differences in the primary outcome were observed in the

prespecified subgroup analyses, including subjects without detectable baseline anti-SARS-CoV-2 antibodies, subjects not on mechanical ventilation, or subjects enrolled within 72 hours of hospitalization. A signal of potential harm in participants more than 7 days into hospitalization was reported (posterior probability of harm 90.3%). Of 1,980 subjects who experienced adverse events, 32 (3.0%) subjects in the CCP arm and 12 (1.3%) subjects in the control arm experienced serious adverse events. Only 1 event was considered to be possibly or probably related to CCP. A trend toward benefit in immunodeficient subjects was noted (posterior probability of superiority in this subgroup was 89.8%), but the small size of this subgroup (126 subjects) limited the power to detect clinically meaningful benefit in this population.

**CONCOR-1** [13] – CONCOR-1 was an open-label, randomized controlled trial conducted in Canada, the United States, and Brazil of CCP in 940 adults with COVID-19 receiving oxygen within 12 days of respiratory symptom onset (median 7.9 days from symptom onset, IQR 5-10). Subjects were randomized 2:1 to receive either 500 mL of CCP qualified by different methods according to blood supplier (overall median plaque reduction neutralization (PRNT) titer (PRNT50) was 1:160 [IQR 1:80, 1:320]) or standard of care. The trial was stopped early for futility and found no significant benefit with CCP, in either intent-to-treat or per-protocol populations. In the intent-to-treat population, the primary outcome, a composite of intubation or death at day 30, occurred in 32.4% of patients in the CCP arm and 28.0% patients in the standard of care arm (RR 1.16, 95% CI 0.94–1.43, P = 0.18). No significant differences were observed in most subgroups, including time from diagnosis to randomization of less than 3 days (overall median time of diagnosis was 2.9 days after median symptom onset). The study results suggest that the effect of CCP was modulated by antibody content, and a subgroup of patients where CCP was provided by a specific blood supplier had worse outcomes. Patients in the CCP arm had more serious adverse events (33.4% versus 26.4%; RR = 1.27, 95% CI 1.02–1.57, p = 0.034). Transfusion-related complications were recorded in 35 (5.7%) of subjects in the CCP arm. Of the 35 reactions, none were fatal and 4 were considered life-threatening (2 transfusion associated circulatory overload (TACO), 1 possible transfusion related acute lung injury (TRALI), 1 transfusion associated dyspnea). Adverse reactions occurring in more than 1% of subjects included transfusion associated dyspnea (2.1%) and minor allergic reaction (1.5%).

**TSUNAMI** [14] – TSUNAMI was an open-label, randomized trial conducted in Italy. The study enrolled 487 patients hospitalized with COVID-19 pneumonia (median 7 days from symptom onset, IQR 5-9) randomized to either high titer CCP plus standard therapy or standard therapy alone. Among subjects with available baseline antibody testing, 25% of subjects were found to be seropositive in the CCP arm. CCP was qualified by a titer of at least 1:160 using a microneutralization test. Subjects were transfused with 200 mL CCP up a maximum of three infusions (15.1% received 1 infusion, 75.4% received 2 infusions, and 9.5% received 3 infusions). In the modified intent-to-treat population, the primary outcome, a composite of worsening respiratory failure (Pao<sub>2</sub>/Fio<sub>2</sub> ratio <150 mm Hg) or death within 30 days, occurred in 25.5% of patients treated with CCP and 28.0% of patients treated with standard therapy (OR 0.88, 95% CI 0.59-1.33, p=0.54). No significant differences were seen in the pre-specified subgroups, including patients treated within 5 days of symptom onset (OR 0.71, 95% CI 0.34-1.48), patients negative for anti-S IgG antibodies at baseline (OR 0.79, 95% CI 0.43-1.45), or patients transfused with CCP units of a titer of at least 1:320 (OR 0.76, 95% CI 0.42-1.37). Some subgroups were likely to have been underpowered to detect clinically meaningful benefit. Adverse events occurred more frequently in the CCP group (5.0%) compared to the control group (1.6%, p = .04). In subjects transfused with CCP, 5 experienced adverse events requiring treatment interruption, all involving worsening of respiratory failure. Two of these cases, 1 associated with a fever, and 1 with a diffuse skin rash, were considered to have a high causality association with CCP.

**ConPlas-19** [9]– ConPlas-19 was an open-label, randomized trial of CCP conducted in Spain. The study enrolled 350 subjects admitted to the hospital with COVID-19 pneumonia and within 7 days of symptom onset and not requiring high flow oxygen or mechanical ventilation (median 6 days of illness, IQR 4-7). Subjects were transfused with one unit of CCP qualified by qualitative positivity in a serologic test of anti-SARS-CoV-2 IgG, later found to have a median neutralization ID50 of 157 (IQR 64-502). No significant difference was found in the prespecified primary outcome of proportion of patients with a score of 5 (noninvasive ventilation or high-flow oxygen) or worse on an ordinal scale at 14 days (11.7% CCP vs 16.4.0% control,  $p=0.205$ ), although a significant difference was observed at 28 days (8.4% CCP vs 17.0% control,  $p = 0.021$ ). Subgroup analyses did not show a relationship between outcomes and titer of the transfused CCP, or any clear trends based on age, sex, study period, duration of symptoms, concomitant therapies, or baseline serostatus. Subgroup analyses were limited by relatively small subgroup sizes and limited statistical power to detect such trends. Overall rates of serious adverse events were similar in the study arms. CCP transfusion–related events were reported in 10 patients (5.6%); 5 (2.79%) were cases of severe worsening of dyspnea (3 of which were reported by investigators as suspected TRALI, later adjudicated as dyspnea), 2 fevers, 2 allergic reactions, and 1 case of nausea/vomiting.

**O’Donnell et al.**[15] – O’Donnell et al reported on a randomized, double-blind, controlled trial among 223 adults hospitalized with severe and critical COVID-19 in New York, NY and Rio de Janeiro, Brazil (median 10 days of symptom onset, IQR 7-13 in the CCP arm). The majority of subjects required oxygen support at the time of randomization, although only 11-15% required invasive mechanical ventilation, ECMO, or both. Patients were randomized 2:1 to receive a single transfusion (200-250 mL) of either CCP or control plasma. CCP was qualified using a serologic total IgG titer. Post-hoc neutralization testing found a median neutralizing titer of 1:160 (IQR 1:80-1:320). The primary outcome was status on a clinical ordinal scale at 28 days following randomization, analyzed using a proportional odds model. Although no significant improvement in the clinical scale was observed in subjects randomized to CCP (OR 1.50, 95% confidence interval [CI] 0.83–2.68,  $P = 0.180$ ), 28-day mortality was significantly lower in subjects randomized to CCP (19/150 [12.6%] versus 18/73 [24.6%], OR 0.44, 95% CI 0.22–0.91,  $P = 0.034$ ). In the prespecified subgroup analyses no significant between-group differences were observed, including in those based on respiratory support or symptom duration at baseline. Trends toward improved clinical status were seen in patients within 7 days of symptom onset and those who received higher titer CCP. A lower rate of serious adverse events was seen in the CCP arm compared to control plasma. Adverse events considered definitely or probably associated with plasma transfusion were reported in 4 of 147 (2.7%) patients who received CCP and 3 of 72 (4.2%) patients who received control plasma. In patients receiving CCP, these events included worsening anemia, urticaria, skin rash, and transfusion-associated circulatory overload.

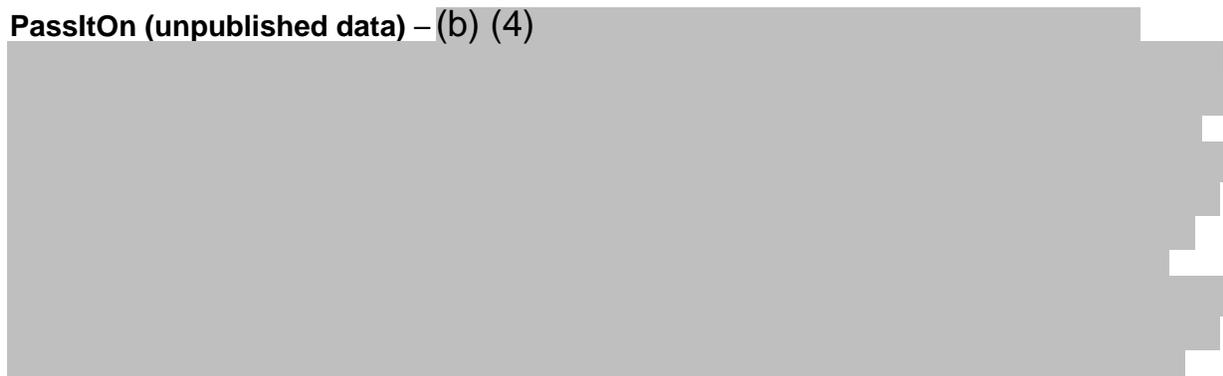
**CAPSID** [16] – CAPSID was a randomized, open-label trial conducted in Germany. The study enrolled 106 hospitalized patients requiring supplemental oxygen or ventilation support or intensive care treatment (median 7 days of symptom onset, IQR 4-10). Among subjects with available data, only 20 of 95 subjects were negative for neutralizing antibodies at baseline. Patients were transfused with a median volume of 846 mL of CCP, relatively higher volume than comparable trials, with a median neutralization ID50 of 1:160. There was no significant difference in the composite primary outcome of no longer requiring ventilation support or ICU treatment and no tachypnea at day 21 (43.4% CCP, 32.7% control,  $p = 0.32$ ). In a prespecified subgroup analysis, in subjects treated with the upper half of CCP titers, the primary outcome occurred in 56.0% compared to 32.1% in subjects receiving lower titer units, with significantly

shorter intervals to clinical improvement and improved survival compared to controls. The proportion of patients with serious adverse events (SAEs) was 41.5% in the CCP group and 48.1% in the control group. 3 adverse events in 53 total subjects were considered possibly related to the intervention in the CCP arm.

**PennCCP2 [17]** – PennCCP2 was a randomized, open label trial conducted in Philadelphia, PA in 80 adults hospitalized with COVID-19 pneumonia (median 6 days of symptoms, IQR 4-9), with a median disease severity score of 5, and requiring supplemental oxygen. Participants had a high frequency of baseline comorbidities, and 60% of subjects were seronegative at baseline. CCP was qualified using a serologic assay, and it was later found that 85% of CCP recipients were expected to have received at least one unit that would have met the EUA criteria for high titer (see Table on page 15). The study found that CCP treatment resulted in benefit in both clinical severity score (the primary endpoint) and 28-day mortality (26% in control arm, 5% in CCP arm,  $p=0.013$ ) compared to randomization to standard of care. As this positive result was reported following the large, negative trials outlined above, the authors speculated that the observation of benefit may have been due to the relatively earlier administration of two units of locally sourced CCP in a highly comorbid, majority seronegative population. Rates of serious adverse events were similar between study arms. There were 3 transfusion-related adverse events including, nausea, pruritis, and an acute allergic reaction, all grade 2.

**CONTAIN [18]** – CONTAIN was a randomized, double-blind, placebo-controlled trial of CCP at 21 hospitals in the United States. The study enrolled 941 adults treated within 3 days of hospitalization or less than 7 days following symptom onset (median 7 days of symptoms, IQR 4-9) and requiring noninvasive oxygen supplementation. In subjects with available baseline anti-SARS-CoV-2 antibody testing, 67% of subjects were found to be seropositive. CCP units were tested for SARS-CoV-2 antibodies using a serologic test (median pseudovirus neutralization titer 1:93, IQR 48-213). The study did not find a significant benefit for the primary outcome of an 11-point ordinal severity scale on day 14, after adjusting for site, baseline risk, WHO score, age, sex, and symptom duration (cOR 0.94, 95% CI 0.75-1.18). Likewise, there was no significant difference in the secondary outcome of ordinal scale score on day 28. Exploratory analyses found a trend towards benefit in subjects treated in the early pandemic (April-June 2020) when there was less use of concomitant remdesivir and corticosteroids. The study did not observe an association of clinical outcome with subject baseline serostatus or CCP neutralizing titer. Median neutralization titer of the CCP during the April-June 2020 period (median 1:175, IQR 1:76-1:379) was higher than seen overall (median 1:93, IQR 1:48-1:213). Exploratory analyses suggested CCP was more likely to be beneficial in those aged 65 or older, or those with less severe disease, but posterior probability distributions showed considerable uncertainty. There were 2 (0.4%) transfusion reactions in placebo recipients and 8 (1.7%) in CCP recipients ( $P = .06$ ), with no cases of TACO or TRALI reported.

**PassItOn (unpublished data) – (b) (4)**



(b) (4)



**DAWn-plasma [19]** - DAWn-plasma was an open-label, multi-center, randomized trial conducted in Belgium in 489 hospitalized patients with laboratory or radiologically confirmed COVID-19 not requiring mechanical ventilation. Subjects were randomized 2:1 to either 4 units (median 884 mL) of high titer CCP plus standard of care (n=326) or standard of care alone (n=163). CCP was qualified with neutralization testing, with titers of at least 1:320 qualifying for transfusion, and titers of 1:160 allowed based on availability of product. 80.7% of transfused CCP came from donors with titers of at least 1:320. The study found no significant difference in the primary outcome of the proportion of patients of patients alive without mechanical ventilation at day 15 (83.7% CCP, 84.1% control, OR 0.99[0.59-1.68]). No differences were observed in the secondary endpoints, including the proportion of patients of patients alive without mechanical ventilation at day 30. There was no significant association between the number of units transfused with titers of at least 1:320 and the primary outcome. Of subjects with available data, 30% of the CCP arm subjects, and 26% of the control subjects had neutralizing titers of at least 1:320 at baseline. There were no significant interactions between the fraction of inhaled oxygen at baseline, or the time from symptoms to randomization, and study arm in the effect on the primary outcome. Transfusion related side effects were reported in 19 of 320 (5.9%) patients in the CCP arm.

**Bennett-Guerrero et al. [20]** – Bennett-Guerrero et al reported the results of a small double-blind randomized trial conducted in Stony Brook, NY of CCP in 74 patients hospitalized with COVID-19 (median 9 days of illness, IQR 6-18). Subjects were randomized 4:1 to either 2 units of CCP qualified by serologic testing (median neutralization titer 1:526) or standard plasma. The study found no difference in ventilator-free days through 28 days (primary study endpoint) between the study arms. All-cause mortality was lower in the CCP group (27%) compared to standard plasma (33%), but did not reach statistical significance, noting the relatively small sample size due to early stopping of the study. Rates of adverse events were similar between study arms.

#### **b. Outpatient Randomized Controlled Trials (RCTs) of CCP**

At the time of the February 2021 EUA reissue, an outpatient RCT of CCP use in the outpatient setting in Argentina by Libster et al.[21] reported the results of a randomized, double-blind, placebo-controlled trial of 250 mL of CCP versus saline placebo in 160 high risk adults. CCP was qualified by ELISA-based serologic testing for IgG titer greater than 1:1000. Study subjects included those 75 years or older, or 65 to 74 with at least one comorbidity (hypertension, diabetes, obesity, chronic renal failure, cardiovascular disease, and COPD) with mild COVID-19 symptoms within 72 hours from onset of symptoms. At 76% of target enrollment, the investigators observed a 48% relative risk reduction in development of severe respiratory disease within 15 days in the CCP arm, with the primary outcome occurring in 25 of 80 subjects (31%) in the placebo arm, and 13 of 80 subjects (16%) in the CCP arm (relative risk, 0.52; 95%

CI, 0.29 to 0.94;  $p=0.03$ ). While secondary end points trended towards benefit, differences were not statistically significant, with wide confidence intervals due to the small number of the events across both groups. A dose dependent effect was described, with a relative risk of 0.27 (95% CI 0.08-0.68) above a median serologic titer of 1:3200.

**C3PO** [22] – C3PO was a multi-center randomized, single-blinded outpatient study at 48 hospitals in the United States. The study enrolled 511 adults presenting to the emergency department with symptomatic COVID-19 and at high risk for progression to severe COVID-19 (age 50 or older, or one or more risk factors for progression). Subjects were eligible if presenting to the emergency department within 7 days after symptoms onset and in stable enough condition for outpatient management. Subjects were randomized to either one unit of CCP or 350 mL of a colored saline/multivitamin solution. CCP was qualified with either a reporter pseudoviral neutralization test or a live viral neutralization test ID50 of 1:250 or greater (median titer 1:641). Subject baseline serostatus was not reported. Disease progression occurred in 30.0% in the CCP arm and 31.9% in the placebo arm (risk difference, 1.9 percentage points; 95% credible interval, -6.0 to 9.8; posterior probability of superiority of convalescent plasma, 0.68). Secondary outcomes, including worst illness severity and hospital-free days were similar between groups. In a post hoc sensitivity analysis excluding patients admitted to the hospital during the index visit (which was observed with greater frequency in the CCP arm), the posterior probability of superiority of CCP was 0.93 in the ITT population and 0.94 in the per-protocol population. However, credible intervals for the risk differences included zero, indicating uncertainty with regards to the differences. Adverse events mostly occurred with similar frequency between the study arms, with the exception of dyspnea, which occurred more frequently in the placebo arm (6.7% placebo, 2.3% CCP, risk difference -4.4%, 95%CI -0.6%, -8.4%), and infusion related reactions, which occurred more frequently in the CCP arm (0.4% placebo, 5.8% CCP, risk difference 5.4%, 95%CI 2.4%, 9.1%). Three subjects in the CCP arm experienced serious infusion reactions resulting in the administration of glucocorticoids or epinephrine or admission to the hospital.

**CSSC-004** [23]– CSSC-004 was a double-blind, randomized, multi-center, placebo-controlled trial at 23 sites in the United States. The study enrolled 1,225 adult outpatients with symptomatic COVID-19 within 8 days of symptom onset, regardless of risk factors for disease progression. Subjects were randomized to either 250 mL of CCP qualified with serologic testing, or placebo standard plasma. Study CCP was qualified using a serologic test, with a median titer of 1:14,580 in a serologic ELISA and 81% meeting the cutoff for high titer using a EUROIMMUN test included in the February 2021 EUA for CCP. The study found that the primary outcome of COVID-19-related hospitalization occurred in 2.9% of participants transfused with CCP compared to 6.3% of subjects transfused with control plasma (RR 0.46, upper limit of 95% CI 0.733, one-sided  $p = 0.004$ ). Subjects in this trial tended to be at a relatively lower risk for progression to severe COVID-19 when compared to other CCP outpatient studies reviewed herein, with only 35% of subjects over age 50. There were 34 grade 3 or 4 adverse events in the CCP arm and 53 grade 3 or 4 adverse events in the control arm. Two severe transfusion reactions were reported in the CCP arm; 1 reported as pneumonia, and 1 reported as infusion related reaction, otherwise unspecified. One transfusion was stopped due to development of diffuse erythema and nausea, and the subject was evaluated in the emergency department and discharged.

**COMPILE<sub>home</sub>** [24] – COMPILE<sub>home</sub> was a consortium of two European double-blind randomized trials of CCP in outpatients with COVID-19 (COV-ert [NCT04621123], CoV-Early [NCT04589949]). The COV-ert study randomized outpatients aged 50 or older within 7 days of symptoms to either one unit of CCP or normal saline. CoV-Early enrolled outpatients aged 50 or

older within 7 days of symptoms and at least one additional risk factor for severe COVID-19 to either CCP or control plasma donated prior to January 2020. CCP was qualified by semi-quantitative serologic testing, and subsequent neutralization testing found a median neutralization titer of 1:386 (IQR 1:233-1:707). Using a Bayesian adaptive individual patient data meta-analysis, the study examined 797 subjects. 93% of subjects were seronegative at baseline. The two primary endpoints were a 5-point ordinal severity scale or a composite of hospitalization or death. The study found that CCP did not significantly improve either outcome (OR 0.936, 95% CI 0.667-1.311 and OR 0.919, CI 0.592-1.416, respectively). Likewise, the study did not find a difference in the secondary endpoint of time to resolution of symptoms. A trend towards benefit of CCP for hospitalization or death in patients within 5 days of symptoms was noted (OR 0.658, CI 0.394-1.085). The study did not observe differences in patients receiving CCP above or below the median titer, or when excluding subjects with anti-SARS-CoV-2 antibodies at baseline. 4 SAE were considered related to the plasma transfusion (3 in the control arm). 3 of these patients were able to leave the hospital within 24 hours from the transfusion, while one patient was hospitalized for 5 days one week after CCP transfusion and diagnosed with thrombophlebitis at the transfusion site and pulmonary embolism. 2 subjects transfused with control plasma experienced anaphylactic transfusion reactions which were categorized as life-threatening.

### **c. Meta-analyses**

In addition to the publication of the studies listed above, several meta-analyses have continued to evaluate emerging data on the use of CCP. Meta-analyses of CCP are challenging to interpret due to the high heterogeneity in patient populations, concomitant therapies (which have evolved over the course of the pandemic), plasma dosing, qualification of the transfused CCP (including evolution of tests used to manufacture CCP, even within studies), and emergence of variants with potential for mismatch in viral strains between donor and recipient populations. While recognizing these limitations, published meta-analyses have largely concluded that the use of CCP in hospitalized patients with COVID-19 does not improve clinical outcomes[25-29].

### **d. Updated FDA Analyses of Patients Treated under the Expanded Access Protocol**

During the early COVID-19 pandemic, a national Expanded Access Protocol (EAP) sponsored by the Mayo Clinic was established to provide access to CCP to hospitalized patients with COVID-19, and to monitor safety. Data collected under the EAP were also analyzed in an exploratory analysis to examine a relationship between viral neutralization titers in the transfused CCP and clinical outcomes. These analyses provided, in part, supportive evidence that CCP may be effective in treated hospitalized patients at the time of original issuance of the EUA. FDA continued to obtain data from the EAP and performed updated analysis on a larger cohort of patients. In the updated analyses, 23,118 patients receiving a single unit of CCP were stratified into two groups based on receipt of “high” (n=13,636) or “low” titer (n=9,482) based on a live viral neutralization assay at a cutoff >250 (50% inhibitory dilution, ID50); 7 and 28-day death rates were analyzed. A multivariable Cox regression that included CCP titer, ventilation status, days from diagnosis to transfusion, age, gender, race, and HHS region was performed to further assess risk factors. Compared to patients transfused with low titer CCP, patients transfused with high titer CCP showed a 1.0% and 1.5% absolute reduction in 7 and 28-day death rates overall. However, reduction in mortality was confined to those with less severe disease. The relative benefit of high titer CCP compared to low titer CCP was confirmed in multivariable Cox regression.

In a separate report of patient characteristics and adverse events observed in the EAP, Senefeld et al[30], found that, after adjudication, 597 serious adverse events out of 112,654 units transfused (0.5%) were judged as related to CCP transfusion, with 163 reports of transfusion associated cardiac overload (TACO), 38 reports of transfusion related acute lung injury (TRALI), 216 TACO/TRALI, 110 allergic transfusion reactions, 47 febrile non-hemolytic transfusion reactions, and 20 hypotensive transfusion reactions.

#### **e. Updated Observational Studies**

At the time of the February 2021 EUA reissuance, observational and non-randomized studies had been published demonstrating potential benefit with early, high titer CCP, or in specific subgroups, but findings were variable. Minimal or no benefit was seen in late disease, particularly once respiratory failure had progressed to the stage of requiring mechanical ventilation/intubation. Many observational studies and case series have continued to be reported since that time. Among the larger retrospective, matched cohort studies reported following the February 2021 EUA reissuance are the following:

Arnold Egloff et al.[31] reported an electronic health records based retrospective study of 3,774 patients in the United States treated with CCP compared to 10,687 matched controls. Mortality was examined using a shared frailty model controlling for concomitant medications, date of admission, and days from admission to transfusion. The study found a reduction in all-cause in-hospital mortality in patients treated with CCP (adjusted hazard ratio [aHR] = 0.71; 95% CI, 0.59–0.86;  $P < 0.001$ ), with greater reduction in those treated within 3 days of admission. That this study observed an effect size much larger than could be reasonably expected from RCTs in comparable populations suggests there is potential for residual confounding.

Cho et al.[32] reported a retrospective observational study of CCP using a hypothetical randomized trial (target trial) approach to estimate the effect of CCP on 30-day mortality in US veterans hospitalized with non-severe COVID-19. The target-trial emulation included 11,269 eligible person-trials contributed by 4,755 patients, with 402 trials assigned to the CCP arm. The study found a 30-day mortality risk of 6.5% (95% CI 4.0-9.7%) in the CCP arm and 6.2% (95% CI 5.6-7.0%) in the control arm. The study concluded there were no meaningful differences in 30-day mortality between non-severe COVID-19 patients transfused with CCP compared to those not transfused with CCP.

Chauhan et al.[33] reported a retrospective observational study of CCP at 16 hospitals in Colorado comparing 188 hospitalized COVID-19 patients transfused with CCP under the EAP to 188 propensity score matched controls. This study found an increased length of hospital stay in CCP-treated patients and no change in inpatient mortality compared to controls. In subgroup analysis of CCP-treated patients within 7 days of admission, there was no difference in length of hospitalization and inpatient mortality.

(b) (4)



(b) (4)

#### **f. Patients with immunosuppressive disease or receiving immunosuppressive treatment**

Several case series and reports have described clinical improvement in patients with immunosuppressive disease or receiving immunosuppressive treatment following treatment with CCP[35-37]. Examples of these conditions have included X-linked agammaglobulinemia[38, 39], hematologic malignancy[40-44], stem cell transplantation[45, 46], solid organ transplant[36, 47], B-cell depleting therapies[45, 46], and common variable immunodeficiency[36, 47]. Such patients may fail to form, or have reduction in, humoral immune responses to either infection or vaccination, and can have prolonged courses of infection compared to immunocompetent patients[48-54]. In some reports of prolonged infection in immunosuppressed or immunodeficient patients lasting several months, infection resolved following administration of CCP[55]. A retrospective matched cohort study using data from a patient registry compared outcomes in 143 patients with hematologic cancers hospitalized with COVID-19 and treated with CCP compared to 823 propensity score matched controls[56]. The study found that CCP was associated with improved 30-day mortality (HR 0.60, 95% CI 0.37-0.97), including in subgroups requiring ICU-level care or mechanical ventilatory support.

In aggregate, while available studies support potential efficacy in patients with immunosuppressive disease or receiving immunosuppressive treatment and suggest a longer potential therapeutic window and larger relative benefit than in immunocompetent patients, well-controlled data in these populations remain lacking and use of CCP in this population should be further examined in randomized controlled trials.

There has been speculation on the association of CCP use and identification of COVID-19 viral variants in immunocompromised patients[57]. However, there is a demonstrated risk of COVID-19 viral mutations in chronically infected immunocompromised patients even in the absence of CCP transfusion[52, 58]. Measures to eliminate viral replication in these patients may decrease this risk. In a small group of patients with B-cell malignancies where prolonged infection and viral variants were identified in the context of monoclonal antibody therapy, patients were apparently able to clear the virus following CCP therapy[59]. Nonetheless, patients with impaired humoral immunity may experience persistent SARS-CoV-2 viral replication and, therefore, may be at risk for developing viral resistance to SARS-CoV-2 antibodies after treatment with CCP.

#### **g. Updated preclinical studies**

Following the February 2021 reissuance of the EUA, Cross et al.[60] reported on the use of convalescent serum for the treatment of COVID-19 in nonhuman primates. These authors found that animals treated with 6.1 mL/kg of high neutralization titer convalescent serum (PRNT ID50 of ~1:2,048) had reduced severity of virus-associated lung pathology, reductions in coagulopathy and inflammatory markers, and lower levels of virus in respiratory compartments. Differences between control animals and animals treated with low neutralization titer sera (PRNT ID50 of ~1:128) were minimal. Notably, animals were treated ten hours post viral challenge. While these studies suggest potential for clinical benefit with early administration of

high titer CCP, the timing of administration was earlier than in comparable clinical studies, and the neutralization titer was higher than has been typically achieved in both clinical studies and in real-world experience with use of CCP in patients with COVID-19.

#### **h. Related passive immune therapies**

As the putative active agent in CCP is anti-SARS-CoV-2 donor antibodies developed in response to SARS-CoV-2 infection, in considering data on the use of CCP in COVID-19, it is also important to consider data on related passive immune therapies for the treatment of COVID-19 (not including post-exposure prophylaxis), such as anti-SARS-CoV-2 monoclonal antibodies and preparations of anti-SARS-CoV-2 immunoglobulin. FDA has issued EUAs for three anti-SARS-CoV-2 monoclonal antibody products for the treatment of mild to moderate COVID-19 in non-hospitalized patients at high risk for progressing to severe disease. These products include bamlanivimab/etesevimab, casirivimab/imdevimab, and sotrovimab (<https://www.fda.gov/media/149532/download>, <https://www.fda.gov/media/145801/download>, <https://www.fda.gov/media/145610/download>). The fact sheets for healthcare providers for these products indicate that they should be administered within 10 days of symptom onset. Studies supporting the safety and efficacy of these products include:

- BLAZE-1[61], which found that a single infusion of bamlanivimab plus etesevimab could reduce COVID-19-related hospitalization or all-cause death in patients treated within 3 days of a positive SARS-CoV-2 test result (70% relative risk reduction,  $p < 0.001$ );
- Phase 3 studies of casirivimab/imdevimab[62], which found that a single infusion could reduce COVID-19-related hospitalization or all-cause death in patients treated within 7 days of symptom onset (71% relative risk reduction,  $p < 0.001$ ); and,
- COMET-ICE[63], which found that a single infusion of sotrovimab could reduce all-cause hospitalization or death in symptomatic patients with at least one risk factor for disease progression, and treated within 5 days of symptom onset (85% relative risk reduction  $p = 0.002$ ).

Compared to the studies of CCP in the outpatient setting outlined above, the relative magnitude of benefit for monoclonal antibodies is larger, the study findings relatively more consistent, and notably, greater efficacy was seen in patients at high risk of disease progression compared to CCP.

In contrast to the successful trials of monoclonal antibodies in the outpatient setting, studies in the hospitalized population have been less conclusive, and, in some cases, negative. Accordingly, monoclonal antibodies are only authorized for use in non-hospitalized patients, and current fact sheets accompanying monoclonal antibody EUAs note that monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. In the ACTIV-3/TICO platform trial of therapeutic agents, the monoclonal antibody bamlanivimab, when co-administered with remdesivir, did not demonstrate efficacy in hospitalized patients with COVID-19 and without end-organ failure[64]. In the RECOVERY platform trial, a single infusion of casirivimab/imdevimab reduced 28-mortality in hospitalized subjects with COVID-19 who were seronegative at baseline compared to usual care alone (from 30 to 24%, rate ratio 0.8, 95% CI

0.7-0.91)[65]. However, no significant difference was seen in the overall randomized population, regardless of baseline antibody status (rate ratio 0.94; 95% CI 0.86-1.03;  $p=0.17$ ). Additional analyses of the ACTIV-3 study found that sustained recovery after administration of bamlanivimab differed by the presence of baseline neutralizing antibodies at study entry[66]. In seronegative patients (particularly those with indicators of high viral replication such as plasma antigen levels, or nasal viral RNA levels) there was evidence of potential benefit, but in seropositive subjects, evidence of potential harm. Other studies of monoclonal antibodies in hospitalized patients were stopped due to futility upon interim DSMB analyses (<https://www.nih.gov/news-events/news-releases/nih-sponsored-activ-3-clinical-trial-closes-enrollment-into-two-sub-studies>). The limited success of monoclonal antibodies in hospitalized COVID-19 patients despite strong efficacy in the early disease, outpatient setting may suggest that the potential for success of any passive immune therapy in hospitalized immunocompetent COVID-19 patients is limited.

In immunodeficient patients, Stein et al. reported a recent retrospective analysis of 64 patients with primary and/or secondary immunodeficiency-associated antibody disorders treated with casirivimab/imdevimab under expanded access[67]. This analysis found that the majority of patients showed rapid viral clearance and clinical improvement in measures such as oxygenation status, including patients who had COVID-19 duration more than 21 days prior to treatment. Patients with disease duration of 21 days or greater included 3 subjects with primary B-cell immunodeficiencies and 34 patients with secondary causes of B-cell deficiency (malignant or drug induced).

Another related passive immune therapy is the use of preparations of hyperimmune globulin from convalescent donors. Preparation of hyperimmune globulin using plasma from infection-recovered donors allows for use of purified immunoglobulin G products with higher concentrations of the immunoglobulins per volume of the product. An early study found that a preparation of anti-SARS-CoV-2 hyperimmune globulin had more than 10-fold greater concentrations of immunoglobulin G in the final product compared to the pooled starting plasma, although with only a roughly 3-fold increase in neutralization titer (to  $1:325\pm 76$ )[68]. While this product is expected to have higher titers than the average random donor unit of CCP, studies of this class of products in hospitalized patients with COVID-19, although not yet published in peer-reviewed literature, failed to demonstrate a reduction in the risk of disease progression in nearly 600 enrolled subjects (<https://www.businesswire.com/news/home/20210402005026/en/CoVlg-19-Plasma-Alliance-Announces-Topline-Results-from-NIH-Sponsored-Clinical-Trial-of-Investigational-COVID-19-Hyperimmune-Globulin-Medicine>).

When considering comparisons between monoclonal antibody therapies, hyperimmune globulins, and CCP, it is instructive to compare the neutralization activity achievable in a typical treatment or transfusion. For a 250 mL CCP unit with a neutralization titer (ID<sub>50</sub>) of 1:450 (the median titer in a subset of >15,000 donations tested for neutralization titers under the EAP), when transfused in a 70kg adult with ~ 3L total plasma volume, the final titer of the transfused antibodies would be expected to be ~1:35. Based on published descriptions of hyperimmune globulin preparations noted above, the achievable titers with such products would potentially be 3 to 10-fold higher.

In the case of monoclonal antibodies, the achievable neutralization activities are much higher. For sotrovimab, the  $C_{max}$  following a 1-hour, IV infusion was 117.6 ug/mL (<https://www.fda.gov/media/149534/download>). As sotrovimab neutralizes a reference strain of SARS-CoV-2 with an average EC<sub>50</sub> of 100.1 ng/mL, the neutralization activity achieved is

~1176-fold above the EC50. For casirivimab/imdevimab, the concentration at the end of infusion is 192 mg/L and 198 mg/L for a 600mg/600mg dose administered intravenously (<https://www.fda.gov/media/145611/download>). The neutralization EC50 of casirivimab is 0.006 mcg/mL, and the neutralization EC50 of imdevimab is 0.006 mcg/mL. Therefore, at  $C_{max}$ , the neutralization activity in recipient serum is 32,000-fold and 33,000-fold the EC50 for casirivimab and imdevimab, respectively. For bamlanivimab/etesevimab, the  $C_{max}$  following IV infusion was 187 mcg/mL and 422 mcg/mL, respectively (<https://www.fda.gov/media/145802/download>). The neutralization EC50 of bamlanivimab is 0.02 mcg/mL and the neutralization EC50 of etesevimab is 0.14 mcg/mL. Therefore, at  $C_{max}$ , the neutralization activity in recipient serum is 9350-fold and 3000-fold the EC50 for bamlanivimab and etesevimab, respectively.

As described, the neutralization activity achievable in any of the currently authorized antibody preparations is orders of magnitude greater than that achievable with a typical transfusion of either single donor CCP, or even the pooled hyperimmune globulin products described to date. While noting these quantitative differences in neutralization activity, it is also important to note the qualitative differences in these therapies. CCP includes the entire polyclonal donor repertoire of plasma antibodies, including various classes and isotypes, as well all the other components of human plasma, which can vary by donors and have variable effects on recipient physiology. In contrast, hyperimmune globulin consists largely of immunoglobulin G, while monoclonal antibody therapies to date consist of one or two clones, with variable profiles of Fc region mediated effects. While polyclonality could theoretically provide advantages with respect to immune evasion by specific mutations, potential relative advantages of the polyclonality of CCP or hyperimmune globulin with regard to clinical efficacy remains to be demonstrated in clinical studies.

#### **i. Antibody responses in COVID-19 and timing of CCP transfusion**

While the variable results in outpatient studies indicate that CCP with high titers of anti-SARS-CoV-2 antibodies is more likely to be beneficial early in the adaptive immune response, the CCP studies summarized above also indicate that transfusion of CCP is unlikely to be beneficial when otherwise immunocompetent subjects have progressed to the stage of where the disease requires hospitalization and where they have largely begun producing their own endogenous antibodies. This is consistent with longstanding historical precedent in passive immune therapies for viral infections, where prophylactic or early use has generally been more effective than in established infections[69].

As noted in the clinical review memorandum at the time of EUA reissuance in February 2021, emerging data on the roles of humoral and cellular immunity in SARS-CoV-2 indicate it is likely that CD4+ T cells, CD8+ T cells, and neutralizing antibody responses all contribute to control of SARS-CoV-2 infection in both non-hospitalized and hospitalized cases of COVID-19[70]. Recent animal studies found both humoral and cellular adaptive immunity contributed to viral clearance in the setting of primary infection[71], while in convalescent or vaccinated animals, protection from subsequent infection was largely mediated by antibody response more so than cellular immunity. The timing of CCP transfusion, should be considered in the context of the kinetics of the humoral immune response. The large majority of patients with SARS-CoV-2 infection will seroconvert within 5-15 days post-symptom onset, with 90% seroconverting by day 10[70, 72, 73]. IgM and IgG antibodies are frequently detected concurrently[74], and peak anti-spike or anti-RBD IgG levels are reached by approximately 15 days post symptom onset[75]. In the RCTs of hospitalized patients treated with CCP outlined above, where serostatus information was available, a range of 25 to 69% of enrolled subjects were noted to be seropositive at

baseline, consistent with the observed range of median duration of symptoms of 6 to 10 days. In the outpatient setting, the benefit of CCP within 3 days in high-risk patients was not consistently observed when administered within 7 days of symptom onset, even when a large fraction were found to be seronegative. In lower risk populations, it appears that CCP had a longer window for potential therapeutic benefit. While there has been some speculation that hospitalized patients who are seronegative at the time of CCP transfusion are more likely to benefit[76], additional data from large RCTs appears to indicate that serostatus alone does not sufficiently discriminate patients likely to benefit from CCP transfusion, at least with the neutralization titers of CCP studied to date. This is likewise true for symptom duration, which is likely to be an imprecise surrogate for duration or stage of infection itself.

### III. Qualification of CCP

At the time of the original issuance of the EUA for CCP, available serologic and neutralization tests that could be used to qualify CCP donations in the manufacture of the product remained limited. In the original EUA issuance, CCP was required to be qualified and labeled as high titer CCP using qualified tests for SARS-CoV-2 antibodies as a manufacturing step to determine CCP suitability before release. Based on a panel of convalescent plasma samples tested against various serologic assays and a live viral neutralization assay developed by the Broad Institute, the original issuance of the EUA only included the Ortho VITROS Anti-SARS-CoV-2 IgG test. Subsequently, FDA received additional data from a panel of specimens tested with various commercial serologic assays and the Broad Institute live virus neutralization assay. Data from this panel, as well as additional data provided by test manufacturers, were used to identify tests that demonstrated acceptable performance for identifying CCP with a neutralization titer of at least 250 (tests with point estimates of at least 50% positive percent agreement and at least 85% negative percent agreement for identification of a neutralization titer of at least 250 were considered qualifying). Based on these assessments, additional tests were included in the CCP EUA on 11/30/2020, 2/4/2021, 2/23/2021, 3/9/2021, and 6/2/2021.

As data on serologic and neutralization testing of convalescent sera and plasma continue to emerge, it remains clear that performance of serologic tests to predict neutralization activity is highly variable[77-80]. While the performance criteria outlined above were established in the context of limited availability of serologic tests, limited data on titers needed for therapeutic efficacy, and limited therapeutic options for the treatment of COVID-19, subsequent progress in all of these three aspects supports the establishment of more rigorous criteria to assure manufacture of CCP with high titers of anti-SARS-CoV-2 antibody. To assure consistent performance, including linearity across the analytical range, it is now reasonable to conclude that tests used in the manufacture of CCP should include only those tests that have been issued an EUA that includes an indication for semi-quantitative or quantitative detection of anti-SARS-CoV-2 antibodies. Thus, tests only authorized for qualitative detection should no longer be considered acceptable for use in the manufacture of CCP. In addition, recognizing the high variability in the correlation between serologic and neutralization testing, more stringent criteria should be established to better assure that neutralization titers meet a minimum requirement. Based on data received by FDA on semi-quantitative tests currently included in the CCP EUA, revised thresholds for qualification of CCP would therefore be as follows:

**Tests Acceptable for Use in the Manufacture of  
COVID-19 Convalescent Plasma with High Titers of Anti-SARS-CoV2 Antibodies**

<b>Manufacturer (listed alphabetically)</b>	<b>Assay</b>	<b>Previous Qualifying Result</b>	<b>Revised Qualifying Result</b>
<b>Abbott</b>	AdviseDx SARSCoV-2 IgG II (ARCHITECT and Alinity i)	≥ 840 AU/mL	≥ 1280 AU/mL
<b>Diasorin</b>	LIAISON SARS-CoV-2 TrimericS IgG	≥ 52 AU/mL	≥ 87 AU/mL
<b>GenScript</b>	cPass SARS-CoV-2 Neutralization Antibody Detection Kit	Inhibition ≥ 68%	Inhibition ≥ 80%
<b>Kantaro</b>	COVID-SeroKlir, Kantaro Semi- Quantitative SARS-CoV-2 IgG Antibody Kit	Spike ELISA > 47 AU/mL	Spike ELISA > 69 AU/mL
<b>Ortho</b>	VITROS Anti-SARS-CoV-2 IgG Quantitative Reagent Pack	N/A	>200 BAU/mL
<b>Roche</b>	Elecsys Anti-SARS-CoV-2 S	≥ 132 U/mL	>210 U/mL

Performance of these assays for the qualification of CCP at the time of testing may vary depending on the variants circulating, including newly emerging strains of SARS-CoV-2 and their prevalence, which change over time. Notably, the potency of CCP as a therapeutic is likely to be impacted by discordance between viral strains infecting donors compared to viral strains infecting CCP recipients. For example, a donor who has recovered from an infection with a given variant, and who may be predicted to have high levels of neutralizing antibodies based on serologic qualification, could have low cross-reactivity with a different or emerging variant such that the CCP would be expected to be inactive against infections with that variant. Therefore, to the extent possible, blood establishments and transfusion services considering the use of CCP as described under this EUA should attempt to minimize discordance between donor and recipient strains, for example by minimizing temporal or geographic differences between donations and use of the product[81]. While plasma from convalescent and vaccinated donors was demonstrated to provide large increases in neutralizing titer levels and improved variant cross-reactivity[82-87], this distinct product remains to be studied under randomized, controlled trials.

## IV. Evaluation of EUA Criteria

FDA may only issue an EUA if several statutory criteria, outlined in section 564 of the Federal Food, Drug, and Cosmetic Act (the Act), (21 USC 360bbb-3) are met. These criteria are further explained in an FDA guidance document, (<https://www.fda.gov/media/97321/download>), and with respect to CCP, are summarized below followed by this reviewer's assessment based on the emerging evidence summarized above. For the purposes of this evaluation, CCP includes only CCP that has been found to contain high titers of anti-SARS-CoV-2 antibodies when manufactured using the tests outlined above. CCP with low titers of anti-SARS-CoV-2 was previously determined to not meet EUA criteria due to evidence demonstrating the product was not effective.

### a. Serious or Life-Threatening Disease or Condition

Under section 564(c)(1), for FDA to issue an EUA for a medical product, the product must be intended to diagnose, treat, or prevent a serious or life-threatening disease or condition that can be caused by a chemical, biological, radiological, or nuclear agent specified in the declaration of emergency. SARS-CoV-2 is a biological agent that can cause a serious or life-threatening disease or condition. COVID-19, the disease caused by infection with the SARS-CoV-2 virus, has resulted in >800,000 deaths in the United States as of December 14, 2021. Large numbers of new infections and deaths continue to be reported ([www.cdc.gov/coronavirus/2019-ncov/cases-updates/us-cases-deaths.html](http://www.cdc.gov/coronavirus/2019-ncov/cases-updates/us-cases-deaths.html)). Although in the United States there is now widespread availability of safe and effective authorized or approved vaccines for the prevention of COVID-19, a substantial proportion of the population (>20% of those ≥5 years old) remains unvaccinated and at increased risk for severe or life-threatening disease. Patients with COVID-19 have an increased risk of serious events such as thromboembolic events, cardiomyopathy and arrhythmia, renal injury, and stroke, which can result in long-term morbidity (<https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html>). Thus, the first statutory criterion is met for CCP intended to treat COVID-19.

### b. Evidence of Effectiveness

The second statutory criterion for issuance of an EUA is that, based on the totality of scientific evidence available, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product "may be effective" in diagnosing, preventing, or treating the serious or life-threatening disease or condition. Section 564(c)(2)(A). As described below, this criterion is met for CCP with high titers of anti-SARS-CoV-2 antibodies when it is used for the treatment of COVID-19 either early in the course of disease (e.g., prior to hospitalization in immunocompetent patients), or, in patients with immunosuppressive disease or receiving immunosuppressive treatment.

Accumulated evidence from RCTs summarized above indicates that transfusion of CCP, including what was considered 'high titer' in prior issuance of this EUA, is unlikely to provide significant clinical benefit for the large majority of hospitalized, immunocompetent patients. In addition, patient characteristics such as baseline serostatus or duration of symptoms appear to be insufficient to reliably identify a subset of hospitalized patients likely to benefit from CCP transfusion. In some outpatient RCTs, where CCP transfusion was examined relatively earlier in the course of illness, results indicate that CCP may be effective in the treatment of COVID-19. However, RCTs also demonstrated that monoclonal antibodies, which typically achieve higher

neutralization activity than CCP, had more consistent, and often greater, efficacy compared to CCP in immunocompetent patients.

In immunodeficient or immunosuppressed patients, particularly those with evidence of inadequate humoral immunity, based on observational data and limited subgroup analyses of RCTs, CCP appears more likely to be associated with clinical benefit. However, well-controlled studies from which to infer causal benefit in the immunosuppressed or immunodeficient population remain limited. Case series and observational studies suggest the time window for therapeutic benefit in this population may be longer than in immunocompetent patients.

Data from RCTs of CCP are complicated by the lack of standardized methods and titer cutoffs used to qualify CCP donations. Review of the testing strategies used to qualify CCP in clinical studies, titers examined in preclinical studies, neutralization activity in related products such as monoclonal antibodies, and titers described as correlates of immune protection, suggests that commonly used acceptance criteria for qualification of CCP, while highly variable, may be too low to provide sufficient potency for clinical benefit in some clinical scenarios. Furthermore, variability in the performance of serologic tests for the purpose of qualifying CCP of a certain neutralization titer is such that more stringent criteria should be used to establish a CCP donation as high titer. There remains significant uncertainty with respect to the appropriate minimum titer of CCP, which would likely also depend on the intended patient population.

Based on the totality of the scientific evidence available, it is reasonable to believe that CCP with high titers of anti-SARS-CoV-2 antibodies may be effective when it is used the treatment of COVID-19 either early in the course of disease (e.g., prior to hospitalization in immunocompetent patients), or, in patients with immunosuppressive disease or receiving immunosuppressive treatment.

### **c. Risk-Benefit Analysis**

The third statutory criterion for issuance of an EUA is that, based on the totality of scientific evidence available, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the known and potential benefits of the product, when used to diagnose, prevent, or treat the disease or condition, outweigh the known and potential risks of the product. Section 564(c)(2)(A). As described below, this criterion is met for CCP with high titers of anti-SARS-CoV-2 antibodies when it is used the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment. This criterion is not met for the treatment of immunocompetent patients with COVID-19.

Potential benefits of CCP as outlined above include reduced progression to severe disease, improved mortality or rates of hospitalization with early treatment, and improved viral clearance. However, these potential benefits appear to be unlikely in the general population of hospitalized immunocompetent patients with COVID19.

Notably, the risks of CCP include those inherent to plasma transfusion[88]:

- Transfusion related acute lung injury (TRALI)
- Transfusion associated cardiac overload (TACO)
- Allergic/Anaphylactic reactions
- Febrile nonhemolytic transfusion reactions
- Transfusion-transmitted infections
- Hemolytic reactions

The risks of these events observed in RCTs and observational studies in the hospitalized population to date, and summarized above, appear to be within the expected rates of these events for transfusion of plasma in critically ill patients[89-92]. Thus, while uncommon, serious adverse reactions judged to be related to CCP transfusion have been described in some of the trials summarized above. While it remains plausible that there is a modest benefit in certain subsets of the hospitalized population, parameters such as baseline serostatus and duration of symptoms do not appear to be adequate to identify those subsets, and subgroup analyses from large trials suggest potential benefit is too small to warrant transfusion in the larger hospitalized population where the known and potential benefits do not outweigh the known and potential risks of plasma transfusion.

Considering the risks of transfusion outlined above, in patient populations where RCTs have shown benefit to be unlikely, such as immunocompetent patients whose disease has progressed to the point of requiring hospitalization, available data demonstrate that the known and potential risks of CCP transfusion outweigh the known and potential benefits. Therefore, in hospitalized, immunocompetent patients, CCP no longer meets the criteria for EUA unless variables that can more reliably predict clinical benefit and assure favorable potential benefit:risk (such as patient characteristics, CCP titer, and timing) can be better defined in randomized, controlled trials.

For patients with COVID-19 with immunosuppressive disease or receiving immunosuppressive treatment, and who may fail to form appropriate antibody responses, the potential benefit of CCP appears to be larger. These patients may also be at risk for more severe outcomes with COVID-19, including relatively prolonged courses of infection. Therefore, in this patient population, in both the inpatient and outpatient setting, it is reasonable to believe that the known and potential benefits of CCP transfusion outweigh the known and potential risks.

In the outpatient trials summarized above, the effectiveness of CCP for the prevention of progression to severe disease or hospitalization was variable, depending on timing and risk profile of the patients. Serious transfusion reactions to plasma components in the outpatient trials occurred at rate of 0.4% overall (range 0-1.2%). Considering the potential risk of transfusion reactions, the potential benefit:risk of CCP should be evaluated in the context of the availability of alternative therapies, including passive immune therapies, such as monoclonal antibodies, and oral antiviral therapies, such as nirmatrelvir/ritonavir (Paxlovid™). Monoclonal antibodies, which are more consistently and precisely manufactured, dosed, and characterized than CCP, have shown mostly larger and more consistent benefits in the outpatient setting compared to CCP, as summarized above (see 'Related passive immune therapies'). FDA recently issued an EUA for the oral antiviral nirmatrelvir/ritonavir based on data from a randomized, controlled trial in non-hospitalized patients with COVID-19 and at least one risk factor for disease progression who were within 5 days post symptom onset. In a modified intent-to-treat analysis (subjects dosed within 5 days of symptom onset who did not receive COVID-19 monoclonal antibody treatment), this study found an 88% (95%CI 75%-94%) relative risk reduction (from 6.3% to 0.8%) in the proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28 (<https://www.fda.gov/media/155050/download>).

Considering the current state of the pandemic, high rates of seropositivity for anti-SARS-CoV-2 antibodies, and the availability of better characterized and effective therapeutics, available data demonstrate that the known and potential benefits of CCP transfusion do not outweigh the known and potential risks (which include known transfusion associated risks such as TACO or severe allergic reactions) for immunocompetent patients in the outpatient setting at this time.

While polyclonality of CCP offers a theoretical benefit with respect to immune escape mutations in potential variants, it remains difficult to qualify variant-specific neutralization activity in individual donations using current approaches to manufacturing and testing of CCP, while monoclonal antibodies, as a more consistent product, are relatively easier to reliably characterize. If monoclonals were to no longer represent a viable alternative therapy due to loss of activity against variant strains, use of CCP in the outpatient setting, and approaches to qualify the CCP, can be reevaluated at that time and should be further studied in controlled clinical trials.

The theoretical risk of antibody-dependent enhancement (ADE) of disease is a concern with passive immune therapies. However, conclusive evidence of antibody-dependent enhancement of disease has not been observed in the studies of CCP summarized above, and the potential for ADE with the use of CCP remains theoretical at this time.

The potential risk of CCP to suppress long-term immunity in recovered or vaccinated patients remains to be evaluated in clinical studies. Currently, there are limited data available on the safety and effectiveness of COVID-19 vaccines in people who received CCP for the treatment of COVID-19. Based on the estimated half-life of antibodies in CCP, CDC currently recommends that COVID-19 vaccination should be temporarily deferred as a precautionary measure for 90 days following treatment with CCP to avoid potential interference of the product with vaccine-induced immune responses. (<https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html> )

#### **d. No Alternatives**

The fourth statutory criterion for issuance of an EUA is that “there is no adequate, approved, and available alternative to the product” for diagnosing, preventing, or treating the disease or condition. Section 564(c)(3). Here, there is no adequate, approved, and available alternative to CCP for the treatment of patients with COVID-19 with immunosuppressive disease or receiving immunosuppressive treatment on both an outpatient and inpatient basis.

Specifically, Veklury® (remdesivir) is the only drug approved by FDA for the treatment of COVID-19 at the time of this review. Remdesivir is a nucleotide analog RNA polymerase inhibitor that has demonstrated antiviral activity against SARS-CoV-2. Remdesivir’s approved indication is limited to the treatment of COVID-19 in adults and pediatric patients (12 years of age and weighing at least 40 kg) requiring hospitalization. Remdesivir is not considered an “adequate” alternative for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment for the following reasons:

- i. The approved indication for remdesivir is limited to hospitalized patients, whereas CCP may be administered to patients with COVID-19 with immunosuppressive disease or receiving immunosuppressive treatment in both inpatient and outpatient settings, based on currently available data. Patients in this population have been treated with CCP in both inpatient and outpatient settings, including in prolonged illness of mild to moderate severity, where resolution of infection was associated with CCP treatment (see ‘*Patients with immunosuppressive disease or receiving immunosuppressive treatment*’, above).

- ii. In patients with COVID-19 with immunosuppressive disease, or on immunosuppressive therapy, remdesivir appears to maintain some degree of antiviral activity[93]. However, in some cases, treatment with remdesivir appeared inadequate to resolve symptomatic illness and completely clear the virus [58, 94-96]. In some of these examples, treatment with CCP after failure of remdesivir to completely clear the infection was associated with improved symptoms and resolution of PCR positivity for SARS-CoV-2[94, 96].
- iii. CCP has a different mechanism of action than remdesivir. The presumptive mechanism of action of CCP is the binding of neutralizing antibodies to the virus that prevent viral infection of host cells, as well as other antibody-mediated pathways, such as complement activation, antibody-dependent cellular cytotoxicity, and phagocytosis that may facilitate viral clearance[97]. These mechanisms facilitate viral clearance in immunocompromised patients who may lack adequate humoral immune function, whereas remdesivir inhibits viral replication. This distinct mechanism of action of CCP can occur in a manner complementary to the inhibition of viral replication provided by remdesivir, as noted above.

## **V. Recommendation**

Based on evaluation of newly reported evidence, the authorized indications for CCP should be limited to the use of CCP with high titers of anti-SARS-CoV-2 antibodies for the treatment of COVID-19 in outpatients or inpatients with immunosuppressive disease or receiving immunosuppressive treatment, in either the outpatient or inpatient setting. Testing criteria used for manufacturing tests used in the qualification of CCP should be revised to better assure high neutralization titers in CCP.

## References

1. Li, L., et al., *Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial*. JAMA, 2020. **324**(5): p. 460-470.
2. Gharbharan, A., et al., *Convalescent Plasma for COVID-19. A randomized clinical trial*. medRxiv, 2020: p. 2020.07.01.20139857.
3. Gharbharan, A., et al., *Effects of potent neutralizing antibodies from convalescent plasma in patients hospitalized for severe SARS-CoV-2 infection*. Nature Communications, 2021. **12**(1): p. 3189.
4. Agarwal, A., et al., *Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial)*. BMJ, 2020. **371**: p. m3939.
5. Simonovich, V.A., et al., *A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia*. N Engl J Med, 2021. **384**(7): p. 619-629.
6. Ray, Y., et al., *Clinical and immunological benefits of convalescent plasma therapy in severe COVID-19: insights from a single center open label randomised control trial*. medRxiv, 2020: p. 2020.11.25.20237883.
7. AlQahtani, M., et al., *Randomized controlled trial of convalescent plasma therapy against standard therapy in patients with severe COVID-19 disease*. medRxiv, 2020: p. 2020.11.02.20224303.
8. Avendaño-Solà, C., et al., *Convalescent Plasma for COVID-19: A multicenter, randomized clinical trial*. medRxiv, 2020: p. 2020.08.26.20182444.
9. Avendano-Sola, C., et al., *A multicenter randomized open-label clinical trial for convalescent plasma in patients hospitalized with COVID-19 pneumonia*. J Clin Invest, 2021. **131**(20).
10. Normand, S.T., *The RECOVERY Platform*. N Engl J Med, 2021. **384**(8): p. 757-758.
11. Abani, O., et al., *Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial*. The Lancet, 2021. **397**(10289): p. 2049-2059.
12. Writing Committee for the REMAP-CAP Investigators, *Effect of Convalescent Plasma on Organ Support–Free Days in Critically Ill Patients With COVID-19: A Randomized Clinical Trial*. JAMA, 2021. **326**(17): p. 1690-1702.
13. Begin, P., et al., *Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial*. Nat Med, 2021. **27**(11): p. 2012-2024.
14. Menichetti, F., et al., *Effect of High-Titer Convalescent Plasma on Progression to Severe Respiratory Failure or Death in Hospitalized Patients With COVID-19 Pneumonia: A Randomized Clinical Trial*. JAMA network open, 2021. **4**(11): p. e2136246-e2136246.
15. O'Donnell, M.R., et al., *A randomized double-blind controlled trial of convalescent plasma in adults with severe COVID-19*. J Clin Invest, 2021. **131**(13).
16. Korper, S., et al., *Results of the CAPSID randomized trial for high-dose convalescent plasma in patients with severe COVID-19*. J Clin Invest, 2021. **131**(20).
17. Bar, K.J., et al., *A randomized controlled study of convalescent plasma for individuals hospitalized with COVID-19 pneumonia*. J Clin Invest, 2021. **131**(24).
18. Ortigoza, M.B., et al., *Efficacy and Safety of COVID-19 Convalescent Plasma in Hospitalized Patients: A Randomized Clinical Trial*. JAMA Intern Med, 2021.
19. Devos, T., et al., *Early high antibody-titre convalescent plasma for hospitalised COVID-19 patients: DAWn-plasma*. Eur Respir J, 2021: p. 2101724.
20. Bennett-Guerrero, E., et al., *Severe Acute Respiratory Syndrome Coronavirus 2 Convalescent Plasma Versus Standard Plasma in Coronavirus Disease 2019 Infected*

- Hospitalized Patients in New York: A Double-Blind Randomized Trial*. Crit Care Med, 2021. **49**(7): p. 1015-1025.
21. Libster, R., et al., *Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults*. N Engl J Med, 2021. **384**(7): p. 610-618.
  22. Korley, F.K., et al., *Early Convalescent Plasma for High-Risk Outpatients with Covid-19*. N Engl J Med, 2021. **385**(21): p. 1951-1960.
  23. Sullivan, D.J., et al., *Randomized Controlled Trial of Early Outpatient COVID-19 Treatment with High-Titer Convalescent Plasma*. medRxiv, 2021: p. 2021.12.10.21267485.
  24. Millat-Martinez, P., et al., *Convalescent plasma for outpatients with early COVID-19*. medRxiv, 2021: p. 2021.11.30.21266810.
  25. Piechotta, V., et al., *Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review*. Cochrane Database Syst Rev, 2021. **5**(5): p. CD013600.
  26. Ling, R.R., et al., *Convalescent Plasma for Patients Hospitalized With Coronavirus Disease 2019: A Meta-Analysis With Trial Sequential Analysis of Randomized Controlled Trials*. Transfus Med Rev, 2021.
  27. Janiaud, P., et al., *Association of Convalescent Plasma Treatment With Clinical Outcomes in Patients With COVID-19: A Systematic Review and Meta-analysis*. JAMA, 2021. **325**(12): p. 1185-1195.
  28. Snow, T.A.C., et al., *Convalescent plasma for COVID-19: a meta-analysis, trial sequential analysis, and meta-regression*. Br J Anaesth, 2021. **127**(6): p. 834-844.
  29. Axfors, C., et al., *Association between convalescent plasma treatment and mortality in COVID-19: a collaborative systematic review and meta-analysis of randomized clinical trials*. BMC Infectious Diseases, 2021. **21**(1): p. 1170.
  30. Senefeld, J.W., et al., *Access to and safety of COVID-19 convalescent plasma in the United States Expanded Access Program: A national registry study*. PLOS Medicine, 2021. **18**(12): p. e1003872.
  31. Arnold Egloff, S.A., et al., *Convalescent plasma associates with reduced mortality and improved clinical trajectory in patients hospitalized with COVID-19*. J Clin Invest, 2021. **131**(20).
  32. Cho, K., et al., *Early Convalescent Plasma Therapy and Mortality Among US Veterans Hospitalized With Nonsevere COVID-19: An Observational Analysis Emulating a Target Trial*. J Infect Dis, 2021. **224**(6): p. 967-975.
  33. Chauhan, L., et al., *A Multi-center, Prospective, Observational-cohort controlled study of Clinical Outcomes following COVID-19 Convalescent plasma therapy in hospitalized COVID-19 patients*. Clin Infect Dis, 2021.
  34. (b) (4)
  35. Senefeld, J.W., et al., *Use of convalescent plasma in COVID-19 patients with immunosuppression*. Transfusion, 2021. **61**(8): p. 2503-2511.
  36. Fung, M., et al., *Treatment of immunocompromised COVID-19 patients with convalescent plasma*. Transpl Infect Dis, 2021. **23**(2): p. e13477-e13477.
  37. Ljungquist, O., et al., *Convalescent plasma treatment in severely immunosuppressed patients hospitalized with COVID-19: an observational study of 28 cases*. Infect Dis (Lond), 2021: p. 1-9.
  38. Jin, H., et al., *Three patients with X-linked agammaglobulinemia hospitalized for COVID-19 improved with convalescent plasma*. J Allergy Clin Immunol Pract, 2020. **8**(10): p. 3594-3596.e3.

39. Mira, E., et al., *Rapid recovery of a SARS-CoV-2-infected X-linked agammaglobulinemia patient after infusion of COVID-19 convalescent plasma*. J Allergy Clin Immunol Pract, 2020. **8**(8): p. 2793-2795.
40. Luetkens, T., et al., *Successful transfer of anti-SARS-CoV-2 immunity using convalescent plasma in an MM patient with hypogammaglobulinemia and COVID-19*. Blood Adv, 2020. **4**(19): p. 4864-4868.
41. Furlan, A., et al., *Dramatic Response to Convalescent Hyperimmune Plasma in Association With an Extended Course of Remdesivir in 4 B Cell-Depleted Non-Hodgkin Lymphoma Patients With SARS-Cov-2 Pneumonia After Rituximab Therapy*. Clin Lymphoma Myeloma Leuk, 2021. **21**(9): p. e731-e735.
42. Zimmerli, A., et al., *Case Report: Stepwise Anti-Inflammatory and Anti-SARS-CoV-2 Effects Following Convalescent Plasma Therapy With Full Clinical Recovery*. Front Immunol, 2021. **12**: p. 613502.
43. Tremblay, D., et al., *Convalescent Plasma for the Treatment of Severe COVID-19 Infection in Cancer Patients*. Cancer Med, 2020. **9**(22): p. 8571-8578.
44. Ferrari, S., et al., *Convalescent hyperimmune plasma for chemo-immunotherapy induced immunodeficiency in COVID-19 patients with hematological malignancies*. Leuk Lymphoma, 2021. **62**(6): p. 1490-1496.
45. Balashov, D., et al., *SARS-CoV-2 convalescent plasma therapy in pediatric patient after hematopoietic stem cell transplantation*. Transfus Apher Sci, 2021. **60**(1): p. 102983.
46. Niu, A., et al., *COVID-19 in allogeneic stem cell transplant: high false-negative probability and role of CRISPR and convalescent plasma*. Bone Marrow Transplantation, 2020. **55**(12): p. 2354-2356.
47. Rahman, F., et al., *Treatment with convalescent plasma in solid organ transplant recipients with COVID-19: Experience at large transplant center in New York City*. Clinical Transplantation, 2020. **34**(12): p. e14089.
48. Adedoyin, O., et al., *Undetectable SARS-CoV-2 active adaptive immunity-post-vaccination or post-COVID-19 severe disease-after immunosuppressants use*. BMJ Case Rep, 2021. **14**(11).
49. Apostolidis, S.A., et al., *Cellular and humoral immune responses following SARS-CoV-2 mRNA vaccination in patients with multiple sclerosis on anti-CD20 therapy*. Nat Med, 2021. **27**(11): p. 1990-2001.
50. Gavriatopoulou, M., et al., *Poor neutralizing antibody responses in 106 patients with WM after vaccination against SARS-CoV-2: a prospective study*. Blood Adv, 2021. **5**(21): p. 4398-4405.
51. Avanzato, V.A., et al., *Case Study: Prolonged Infectious SARS-CoV-2 Shedding from an Asymptomatic Immunocompromised Individual with Cancer*. Cell, 2020. **183**(7): p. 1901-1912.e9.
52. Corey, L., et al., *SARS-CoV-2 Variants in Patients with Immunosuppression*. New England Journal of Medicine, 2021. **385**(6): p. 562-566.
53. Collier, A.Y., et al., *COVID-19 mRNA Vaccine Immunogenicity in Immunosuppressed Individuals*. J Infect Dis, 2021.
54. Tepasse, P.R., et al., *Persisting SARS-CoV-2 viraemia after rituximab therapy: two cases with fatal outcome and a review of the literature*. Br J Haematol, 2020. **190**(2): p. 185-188.
55. Cusi, M.G., et al., *Hyperimmune plasma in three immuno-deficient patients affected by non-severe, prolonged COVID-19: a single-center experience*. BMC Infectious Diseases, 2021. **21**(1): p. 630.
56. Thompson, M.A., et al., *Association of Convalescent Plasma Therapy With Survival in Patients With Hematologic Cancers and COVID-19*. JAMA Oncol, 2021. **7**(8): p. 1167-1175.

57. Kemp, S.A., et al., *SARS-CoV-2 evolution during treatment of chronic infection*. *Nature*, 2021. **592**(7853): p. 277-282.
58. Choi, B., et al., *Persistence and Evolution of SARS-CoV-2 in an Immunocompromised Host*. *The New England journal of medicine*, 2020. **383**(23): p. 2291-2293.
59. Pommeret, F., et al., *Bamlanivimab + etesevimab therapy induces SARS-CoV-2 immune escape mutations and secondary clinical deterioration in COVID-19 patients with B-cell malignancies*. *Ann Oncol*, 2021. **32**(11): p. 1445-1447.
60. Cross, R.W., et al., *Use of convalescent serum reduces severity of COVID-19 in nonhuman primates*. *Cell Reports*, 2021. **34**(10): p. 108837.
61. Dougan, M., et al., *Bamlanivimab plus Etesevimab in Mild or Moderate Covid-19*. *New England Journal of Medicine*, 2021. **385**(15): p. 1382-1392.
62. Weinreich, D.M., et al., *REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19*. *New England Journal of Medicine*, 2021. **385**(23): p. e81.
63. Gupta, A., et al., *Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab*. *New England Journal of Medicine*, 2021. **385**(21): p. 1941-1950.
64. ACTIV-3/TICO LY-CoV555 Study Group, et al., *A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19*. *New England Journal of Medicine*, 2020. **384**(10): p. 905-914.
65. RECOVERY Collaborative Group, et al., *Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial*. *medRxiv*, 2021: p. 2021.06.15.21258542.
66. ACTIV-3/TICO Bamlanivimab Study Group, et al., *Clinical and Virological Response to a Neutralizing Monoclonal Antibody for Hospitalized Patients with COVID-19*. *medRxiv*, 2021: p. 2021.07.19.21260559.
67. Stein, D., et al., *Compassionate Use of REGEN-COV® in Patients with COVID-19 and Immunodeficiency-Associated Antibody Disorders*. *medRxiv*, 2021: p. 2021.11.05.21265911.
68. Vandenberg, P., et al., *Production of anti-SARS-CoV-2 hyperimmune globulin from convalescent plasma*. *Transfusion*, 2021. **61**(6): p. 1705-1709.
69. Casadevall, A., E. Dadachova, and L.-a. Pirofski, *Passive antibody therapy for infectious diseases*. *Nature Reviews Microbiology*, 2004. **2**(9): p. 695-703.
70. Sette, A. and S. Crotty, *Adaptive immunity to SARS-CoV-2 and COVID-19*. *Cell*.
71. Israelow, B., et al., *Adaptive immune determinants of viral clearance and protection in mouse models of SARS-CoV-2*. *Sci Immunol*, 2021. **6**(64): p. eabl4509.
72. Wajnberg, A., et al., *Humoral response and PCR positivity in patients with COVID-19 in the New York City region, USA: an observational study*. *Lancet Microbe*, 2020. **1**(7): p. e283-e289.
73. Röltgen, K., et al., *Defining the features and duration of antibody responses to SARS-CoV-2 infection associated with disease severity and outcome*. *Science Immunology*, 2020. **5**(54): p. eabe0240.
74. Long, Q.-X., et al., *Antibody responses to SARS-CoV-2 in patients with COVID-19*. *Nature Medicine*, 2020. **26**(6): p. 845-848.
75. Lucas, C., et al., *Kinetics of antibody responses dictate COVID-19 outcome*. *medRxiv*, 2020: p. 2020.12.18.20248331.
76. Hamilton, F.W., et al., *Is convalescent plasma futile in COVID-19? A Bayesian re-analysis of the RECOVERY randomized controlled trial*. *International Journal of Infectious Diseases*, 2021. **109**: p. 114-117.
77. Farnsworth, C.W., et al., *Assessment of serological assays for identifying high titer convalescent plasma*. *Transfusion*, 2021. **61**(9): p. 2658-2667.

78. Patel, E.U., et al., *Comparative Performance of Five Commercially Available Serologic Assays To Detect Antibodies to SARS-CoV-2 and Identify Individuals with High Neutralizing Titers*. J Clin Microbiol, 2021. **59**(2).
79. Di Germanio, C., et al., *SARS-CoV-2 antibody persistence in COVID-19 convalescent plasma donors: Dependency on assay format and applicability to serosurveillance*. Transfusion, 2021. **61**(9): p. 2677-2687.
80. Bradley, B.T., et al., *Anti-SARS-CoV-2 Antibody Levels Measured by the AdviseDx SARS-CoV-2 Assay Are Concordant with Previously Available Serologic Assays but Are Not Fully Predictive of Sterilizing Immunity*. Journal of Clinical Microbiology, 2021. **59**(9): p. e00989-21.
81. Kunze, K.L., et al., *Mortality in individuals treated with COVID-19 convalescent plasma varies with the geographic provenance of donors*. Nat Commun, 2021. **12**(1): p. 4864.
82. Vickers, M.A., et al., *Exponential increase in neutralizing and spike specific antibodies following vaccination of COVID-19 convalescent plasma donors*. Transfusion, 2021. **61**(7): p. 2099-2106.
83. Stamatatos, L., et al., *mRNA vaccination boosts cross-variant neutralizing antibodies elicited by SARS-CoV-2 infection*. Science, 2021.
84. Romon, I., et al., *High-titre anti-SARS-CoV-2 convalescent plasma donation after donors' vaccination*. Vox sanguinis, 2021. **116**(8): p. 930-931.
85. Jabal, K.A., K.B. Wiegler, and M. Edelstein, *Convalescent plasma from people vaccinated after COVID-19 infection*. Lancet Microbe, 2021. **2**(5): p. e171-e172.
86. Wang, Z., et al., *Naturally enhanced neutralizing breadth against SARS-CoV-2 one year after infection*. Nature, 2021. **595**(7867): p. 426-431.
87. Gallian, P., et al., *COVID-19 convalescent plasma: Evolving strategies for serological screening in France*. Vox Sang, 2021. **n/a**(n/a).
88. AABB ABC ARC ASBP, *Circular of Information for the Use of Human Blood and Blood Components*. 2017.
89. Roubinian, N.H. and D.J. Triulzi, *Transfusion-Associated Circulatory Overload and Transfusion-Related Acute Lung Injury: Etiology and Prevention*. Hematology/Oncology Clinics of North America, 2019. **33**(5): p. 767-779.
90. Kuldane, S.A., M. Kelher, and C.C. Silliman, *Risk factors, management and prevention of transfusion-related acute lung injury: a comprehensive update*. Expert Rev Hematol, 2019. **12**(9): p. 773-785.
91. Saadah, N.H., et al., *Comparing transfusion reaction risks for various plasma products – an analysis of 7 years of ISTARE haemovigilance data*. British Journal of Haematology, 2018. **180**(5): p. 727-734.
92. Pandey, S. and G.N. Vyas, *Adverse effects of plasma transfusion*. Transfusion, 2012. **52** **Suppl 1**(Suppl 1): p. 65s-79s.
93. Buckland, M.S., et al., *Treatment of COVID-19 with remdesivir in the absence of humoral immunity: a case report*. Nature communications, 2020. **11**(1): p. 6385-6385.
94. Helleberg, M., et al., *Persistent COVID-19 in an Immunocompromised Patient Temporarily Responsive to Two Courses of Remdesivir Therapy*. The Journal of infectious diseases, 2020. **222**(7): p. 1103-1107.
95. Camprubi, D., et al., *Persistent replication of SARS-CoV-2 in a severely immunocompromised patient treated with several courses of remdesivir*. Int J Infect Dis, 2021. **104**: p. 379-381.
96. Malsy, J., et al., *Sustained Response After Remdesivir and Convalescent Plasma Therapy in a B-Cell-Depleted Patient With Protracted Coronavirus Disease 2019 (COVID-19)*. Clin Infect Dis, 2021. **73**(11): p. e4020-e4024.
97. Bloch, E.M., et al., *Deployment of convalescent plasma for the prevention and treatment of COVID-19*. J Clin Invest, 2020. **130**(6): p. 2757-2765.

