Table 4c. COVID-19 Convalescent Plasma: Selected Clinical Trial Data

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The studies described in this table are those that had the greatest impact on the Panel's recommendations. The Panel reviewed other clinical studies of CCP for the treatment of COVID-19.[1-5] However, those studies have limitations that make them less definitive and informative than the studies summarized in the table.

Methods	Results	Limitations and Interpretation
REMAP-CAP: Multinational, Open-Label RCT of High-Titer CCP in Hospitalized Patients With Critical COVID-19 in Australia, Canada, the United Kingdom, and the United States[6]		

Key Inclusion Criterion
• Admitted to ICU while receiving respiratory support (HFNC oxygen, NIV, MV, ECMO) and/or vasopressor or inotrope support
Key Exclusion Criteria
• CCP contraindicated
• Death imminent
Interventions
• High-titer CCP (550 mL +/- 150 mL) within 48 hours of randomization (n = 1,084)
• Usual care (n = 916)
Primary Endpoint
• Number of organ support-free days by Day 21
Key Secondary Endpoints
• In-hospital mortality
• Mortality by Day 28 and Day 90
• Number of respiratory support-free days
• ICU LOS
	Participant Characteristics
	• Mean age 61 years; 68% men
	• 32% on MV
	• 29% were SARS-CoV-2 antibody negative at baseline.
	• 94% received corticosteroids; 45% received RDV; 39% received IL-6 inhibitors.
	Primary Outcome
	• Median number of organ support-free days by Day 21: 0 days in CCP arm vs. 3 days in usual care arm (OR 0.97; 95% CrI, 0.82–1.14)
	Secondary Outcomes
	• No difference between arms in:
	  • In-hospital mortality: 37% in CCP arm vs. 38% in usual care arm
	  • Mortality by Day 28 or Day 90
	  • Median number of respiratory support-free days: 0 days in CCP arm vs. 2 days in usual care arm
	  • Median ICU LOS: 21 days in CCP arm vs. 17 days in usual care arm
		Key Limitations
		• Open-label study
		• Not all patients in CCP arm received CCP (86% received CCP as per protocol and 95% received some CCP).
		Interpretation
		• There was no benefit of CCP in hospitalized patients with critical COVID-19.

Methods	Results	Limitations and Interpretation
CONCOR-1: Multinational, Open-Label RCT of CCP for Hospitalized Patients With COVID-19 in Canada, the United States, and Brazil[7]		

Key Inclusion Criteria
• Receipt of supplemental oxygen
• Availability of ABO–compatible CCP
Key Exclusion Criteria
• Imminent or current intubation
• >12 days from respiratory symptom onset
Interventions
• 1–2 units of CCP (approximately 500 mL) from 1–2 donors (n = 625)
• SOC (n = 313)
Primary Endpoint
• Composite of intubation or death by Day 30
Key Secondary Endpoints
• Time to intubation or death by Day 30
• Mortality by Day 30
• ICU LOS by Day 30
• Need for renal dialysis by Day 30
• Frequency of SAEs by Day 30
	Participant Characteristics
	• Mean age 68 years; 59% men
	• 84% were receiving systemic corticosteroids at enrollment.
	Primary Outcome
	• Composite of intubation or death by Day 30: 32% in CCP arm vs. 28% in SOC arm (relative risk 1.16; 95% CI, 0.94–1.43; $P = 0.18$)
	Secondary Outcomes
	• By Day 30, no difference between arms in:
	  • Time to intubation or death
	  • Mortality: 23% in CCP arm vs. 21% in SOC arm
	  • Mean ICU LOS: 4.3 days in CCP arm vs. 3.7 days in SOC arm
	  • Need for renal dialysis: 1.6% in CCP arm vs. 2.0% in SOC arm
	• Frequency of SAEs by Day 30: 33% in CCP arm vs. 26% in SOC arm
		Key Limitations
		• Open-label study
		• Trial stopped at 78% of planned enrollment after meeting prespecified futility criteria for early termination.
		Interpretation
		• There was no benefit of CCP in oxygen-dependent, hospitalized patients with COVID-19 who were within 12 days of symptom onset.

RECOVERY: Open-Label RCT of High-Titer CCP in Hospitalized Patients in the United Kingdom[8]		

Key Inclusion Criterion
• Clinically suspected or laboratory-confirmed SARS-CoV-2 infection
Key Exclusion Criterion
• CCP contraindicated
Interventions
• 2 units of high-titer CCP (approximately 275 mL/unit) with IgG against SARS-CoV-2 spike protein and sample to cutoff ratio ≥6.0. First unit administered ASAP after randomization; second unit administered ≥12 hours later (n = 5,795).
	Participant Characteristics
	• Mean age 64 years; 64% men
	• 5% on MV
	• 92% received corticosteroids.
	Primary Outcomes
	• No difference between arms in:
	  • All-cause mortality by Day 28: 24% in each arm
	  • Mortality in patients without detectable SARS-CoV-2 antibodies: 32% in CCP arm vs. 34% in usual care arm
		Key Limitation
		• Open-label study
		Interpretation
		• There was no benefit of CCP in hospitalized patients with COVID-19.

Methods	Results	Limitations and Interpretation
RECOVERY: Open-Label RCT of High-Titer CCP in Hospitalized Patients in the United Kingdom[8], continued		

• Usual care (n = 5,763)
Primary Endpoint
• All-cause mortality by Day 28
Key Secondary Endpoints
• Time to hospital discharge by Day 28
• Among patients not on MV, progression to MV or death by Day 28
	Secondary Outcomes
	• No difference between arms in:
	  • Proportion discharged by Day 28: 66% in both arms
	  • Proportion who progressed to MV or death by Day 28: 29% in CCP arm vs. 29% in usual care arm	

RECOVER: Open-Label RCT of High-Titer CCP in Hospitalized Patients With Severe COVID-19 in 4 Risk Groups in Germany[9]		

Key Inclusion Criteria
• PCR-confirmed SARS-CoV-2 infection
• Hospitalized with SpO_2 ≤94% on room air or PaO_2/FiO_2 <300 mm Hg
• ≥1 of the following criteria:
  • Hematologic cancer and/or receipt of active cancer therapy in past 24 months for any cancer
  • Chronic immunosuppression due to medications and/or underlying disease
  • Aged >50 to ≤75 years with ALC <0.8 x 10^9 cells/L and/or D-dimer >1 µg/mL
  • Aged >75 years without other listed criteria
Key Exclusion Criterion
• Required MV or NIV
Interventions
• 2 units (238–337 mL) of high-titer CCP (≥1:80) or vaccinated donor plasma from 2 donors on Days 1 and 2 (n = 68)
• SOC (n = 66)
Primary Endpoint
• Time to 2-point improvement on a 7-point OS or hospital discharge
	Participant Characteristics
	• 136 participants were enrolled between September 2020 and January 2022.
	• Mean age 69 years; 68% men; 97% White
	• Participants were enrolled from 4 mutually exclusive patient groups:
	  • Patients with cancer (n = 56)
	  • Patients with immunosuppression who did not have cancer (n = 16, including 12 solid organ transplant recipients)
	  • Patients aged >50 to ≤75 years with lymphopenia and/or elevated D-dimer levels (n = 36)
	  • Patients aged >75 years without other criteria (n = 26)
	• 11% were fully vaccinated.
	• 8% received small-molecule antiviral drugs (12% in plasma arm vs. 5% in SOC arm); 37% received anti-inflammatory drugs (40% in plasma arm vs. 33% in SOC arm).
	• 60% received supplemental oxygen via nasal cannula; 21% on HFNC oxygen or NIV
	• Median 7 days between symptom onset and randomization
	Primary Outcome
	• Median time to 2-point improvement on OS or hospital discharge: 13 days in plasma arm vs. 18 days in SOC arm
		Key Limitations
		• Open-label study
		• The live-virus neutralization assay used to select plasma for this trial may not produce the same results as the assays used to qualify high-titer CCP in the current FDA EUA.
		• Small sample size
		• Trial was terminated early because the neutralizing activity of stored plasma against the Omicron variant was not known.
		• Low proportion of vaccinated participants and limited use of current SOC therapies, such as antiviral or immunomodulatory agents
		• Subgroup analyses were not adjusted for multiple comparisons.
		Interpretation
		• The trial did not demonstrate a benefit of high-titer CCP or vaccinated donor plasma in the overall study population.

Methods	Results	Limitations and Interpretation
RECOVER: Open-Label RCT of High-Titer CCP in Hospitalized Patients With Severe COVID-19 in 4 Risk Groups in Germany[9], continued		
Key Secondary Endpoints • 28-day, 56-day, and 84-day overall survival rate	(HR 1.29; 95% CI, 0.86–1.93; $P = 0.205$) • Median time to improvement or hospital discharge among patients with cancer: 13 days in plasma arm vs. 31 days in SOC arm (HR 2.50; 95% CI, 1.34–4.79; $P = 0.003$) **Key Secondary Outcomes** • No difference between arms in overall survival; 27 patients (19.9%) died (HR for survival 0.72; 95% CI, 0.33–1.55; $P = 0.403$). • Fewer patients with cancer died in plasma arm than in SOC arm (HR 0.28; 95% CI, 0.06–0.96; $P = 0.042$).	• Results from the predefined subgroup analysis of patients with cancer suggest a potential benefit of CCP or vaccinated donor plasma. However, this analysis was conducted largely before the emergence of Omicron subvariants, so the results should be interpreted with caution.
CONFIDENT: Open-Label RCT of High-Titer CCP in Hospitalized Patients With COVID-19–Associated ARDS in Belgium[10]		
Key Inclusion Criteria • PCR-confirmed SARS-CoV-2 infection • Admitted to ICU with COVID-19–associated ARDS and WHO COVID-19 OS score of 7, 8, or 9 • On MV for ≤5 days • Clinical Frailty Scale score of <6 **Key Exclusion Criteria** • Previous transfusion-related side effects • Medical decision to limit therapy **Interventions** • 2 units (400–500 mL total) of high-titer CCP (≥1:320) from donors who fully recovered from COVID-19 between 28 days and 10 months before study. CCP was administered within 24 hours of study randomization (n = 237). • SOC (n = 238) **Primary Endpoint** • Mortality by Day 28	**Participant Characteristics** • Median age 64 years; 68% male • 10% were vaccinated. • 10% with mild ARDS, 58% with moderate ARDS, 32% with severe ARDS • Baseline evidence of ongoing SARS-CoV-2 replication (Ct value of 22 in CCP arm vs. 20 in SOC arm) • 98% received corticosteroids; 6% received RDV; 4% received IL-6 inhibitors. **Primary Outcome** • Mortality by Day 28: 35% in CCP arm vs. 45% in SOC arm ($P = 0.03$) • In patients on MV ≤48 hours: 33% in CCP arm vs. 47% in SOC arm • In patients on MV >48 hours: 42% in CCP arm vs. 40% in SOC arm • Similar outcomes were seen regardless of whether the original SARS-CoV-2 strain (Wuhan-Hu-1) or the Alpha, Delta, or Omicron variants were in circulation.	**Key Limitations** • Open-label study • Trial was stopped after recruiting 95% of the target enrollment due to a low ICU admission rate. • Approximately 18% of patients who were assigned to receive CCP received a lower neutralizing titer of 1:160. • The live-virus neutralization assay used to select plasma for this trial may not produce the same results as the assays used to qualify high-titer CCP in the current FDA EUA. • Low proportion of vaccinated patients and limited use of current SOC therapies, such as antiviral agents or a second immunomodulatory agent • There were differences in treatment effects across sites. **Interpretation** • CCP reduced mortality by Day 28 in patients with COVID-19 and ARDS, and

Methods	Results	Limitations and Interpretation
CONFIDENT: Open-Label RCT of High-Titer CCP in Hospitalized Patients With COVID-19–associated ARDS in Belgium[10], continued		
		the effect was most notable in patients who were randomized ≤48 hours after initiating MV.
CSSC-004: RCT of Early Treatment With High-Titer CCP in Outpatients With COVID-19 in the United States[11]		
Key Inclusion Criterion • COVID-19 symptoms for <8 days **Key Exclusion Criteria** • Prior or planned COVID-19–related hospitalization • Receipt of anti-SARS-CoV-2 mAbs **Interventions** • Approximately 250 mL of CCP with SARS-CoV-2 spike protein IgG (titer ≥1:320) (n = 592) • Non-SARS-CoV-2 plasma (n = 589) **Primary Endpoint** • Composite of COVID-19–related hospitalization or all-cause death within 28 days	**Participant Characteristics** • Median age 44 years; 7% aged ≥65 years; 57% women; 79% White • 8% with type 2 DM; 2% with CVD; 38% with BMI ≥30 • 82% were unvaccinated. • Median of 6 days between symptom onset and transfusion **Primary Outcomes** • COVID-19–related hospitalization within 28 days: 2.9% in CCP arm vs. 6.3% in control arm (absolute risk reduction 3.4 percentage points; 95% CI, 1.0–5.8; *P* = 0.005) • 53 of 54 hospitalizations occurred in unvaccinated individuals. None occurred in fully vaccinated individuals. • All-cause deaths within 28 days: 0 in CCP arm vs. 3 in control arm	**Key Limitation** • Patients were at relatively low risk of disease progression. **Interpretation** • This trial demonstrated a benefit of CCP in unvaccinated outpatients with <8 days of COVID-19 symptoms.
CONV-ERT: RCT of High-Titer, Methylene Blue-Treated CCP as an Early Treatment for Outpatients With COVID-19 in Spain[12]		
Key Inclusion Criteria • Aged ≥50 years • Mild or moderate COVID-19 symptoms for ≤7 days **Key Exclusion Criteria** • Severe COVID-19 symptoms or need for hospitalization for any reason • Previous SARS-CoV-2 infection • Receipt of ≥1 doses of a COVID-19 vaccine **Interventions** • 250–300 mL of high-titer, methylene blue-treated CCP (n = 188)	**Participant Characteristics** • Mean age 56 years; 54% men • 75% with ≥1 risk factors for COVID-19 progression • 97% with mild COVID-19 • Median of 4.4 days of symptoms prior to enrollment • Among 369 patients with available baseline serologic testing, 88% were negative for both IgG anti-SARS-CoV-2 spike and IgM anti-SARS-CoV-2 S1-RBD. **Primary Outcomes** • Hospitalization within 28 days: 12% in CCP arm vs. 11% in placebo arm (relative risk 1.05; 95% CrI, 0.78–1.41)	**Key Limitations** • Trial was underpowered because it was terminated early due to rising vaccination rates among the eligible patient population. • Methylene blue, which was used for pathogen inactivation in donor plasma, could have potentially impaired Fc-region functionality of Ig and negatively impacted product efficacy and blinding. **Interpretation** • This trial did not demonstrate a benefit of CCP in unvaccinated outpatients with

Methods	Results	Limitations and Interpretation
CONV-ERT: RCT of High-Titer, Methylene Blue-Treated CCP as an Early Treatment for Outpatients With COVID-19 in Spain[12], continued		
• 0.9% saline (n = 188) **Primary Endpoints** • Hospitalization within 28 days • Mean change in SARS-CoV-2 VL from baseline to Day 7 **Key Secondary Endpoints** • Death by Day 60 • Time to complete symptom resolution	• Mean change in SARS-CoV-2 VL: -2.41 $\log_{10}$ copies/mL in CCP arm vs. -2.32 $\log_{10}$ copies/mL in placebo arm **Key Secondary Outcomes** • Death by Day 60: 0 in CCP arm vs. 2 in placebo arm (relative risk 0.20; 95% CI 0.01–4.14) • No difference between arms in median time to symptom resolution: 12.0 days for both arms (HR 1.05; 95% CI, 0.85–1.30)	≤7 days of COVID-19 symptoms.
Double-Blind RCT of Early High-Titer CCP Therapy to Prevent Severe COVID-19 in Nonhospitalized Older Adults in Argentina[13]		
Key Inclusion Criteria • Aged ≥75 years or aged 65–74 years with ≥1 coexisting conditions • Mild COVID-19 symptoms for <72 hours **Key Exclusion Criterion** • Severe respiratory disease **Interventions** • 250 mL of CCP with SARS-CoV-2 spike protein IgG (titer >1:1,000) (n = 80) • Saline (n = 80) **Primary Endpoint** • Severe respiratory disease, defined as respiratory rate ≥30 breaths/min and/or SpO_2 <93% on room air, by Day 15	**Participant Characteristics** • Mean age 77 years; 38% men • Most with comorbidities **Primary Outcome** • Severe respiratory disease by Day 15: 16% in CCP arm vs. 31% in placebo arm (relative risk 0.52; 95% CI, 0.29–0.94; *P* = 0.03)	**Key Limitations** • Small sample size • Trial was terminated early because the number of COVID-19 cases decreased. **Interpretation** • This trial demonstrated a benefit of CCP in older adult outpatients with <72 hours of mild COVID-19 symptoms.

Methods	Results	Limitations and Interpretation
SIREN-C3PO: Multicenter, Single-Blind RCT of High-Titer CCP in Adults With COVID-19 in the United States[14]		
Key Inclusion Criteria • ED patient with ≤7 days of symptoms • PCR-confirmed SARS-CoV-2 infection • Aged ≥50 years or aged ≥18 years with ≥1 risk factors for disease progression **Key Exclusion Criterion** • Need for supplemental oxygen **Interventions** • 250 mL of high-titer CCP (median titer 1:641) (n = 257) • Saline (n = 254) **Primary Endpoint** • Disease progression, defined as hospital admission, death, or seeking emergency or urgent care, within 15 days of randomization **Key Secondary Endpoints** • Severity of illness by Day 30, as measured by an OS • All-cause mortality by Day 30 • Number of hospital-free days by Day 30	**Participant Characteristics** • Median age 54 years; 46% men • More patients with immunosuppression in CCP arm than in placebo arm (13% vs. 7%) • More patients with ≥3 risk factors in CCP arm than in placebo arm (55% vs. 48%) **Primary Outcomes** • No difference between arms in proportion with disease progression: 30% in CCP arm vs. 32% in placebo arm (risk difference 1.9%; 95% CrI, -6.0% to 9.8%) • 25 patients (19 in CCP arm vs. 6 in placebo arm) required hospitalization during index visit. In a post hoc analysis that excluded these patients, disease progression occurred in 24% in CCP arm vs. 30% in placebo arm (risk difference 5.8%; 95% CrI, -1.9% to 13.6%). **Secondary Outcomes** • All-cause mortality by Day 30: 5 (1.9%) in CCP arm vs. 1 (0.4%) in placebo arm • No difference between arms in illness severity or mean number of hospital-free days by Day 30	**Key Limitations** • In the primary analysis, the number of patients who required hospital admission during the index visit was not balanced across arms. • The CCP arm included more patients with multiple risk factors, including immunosuppression. **Interpretation** • The use of high-titer CCP within 1 week of symptom onset did not prevent disease progression in outpatients with COVID-19 who were at high risk of severe disease.
CoV-Early: Double-Blind RCT of CCP in Nonhospitalized, High-Risk Adults With COVID-19 in the Netherlands[15]		
Key Inclusion Criteria • Aged ≥70 years, aged ≥50 years with a comorbidity, or aged ≥18 years and severely immunocompromised • Positive SARS-CoV-2 RT-PCR or antigen test result • COVID-19 symptoms for ≤7 days **Key Exclusion Criteria** • Life expectancy <28 days • History of TRALI • IgA deficiency	**Participant Characteristics** • Median age 60 years; 22% women • Median of 5 days of symptoms • Median of 1 comorbidity • Median SpO_2 of 97% at baseline • 7.9% were SARS-CoV-2 IgG antibody negative at baseline. • 2.9% were fully vaccinated; 5.0% received 1 dose of a COVID-19 vaccine.	**Key Limitations** • Study was discontinued after 421 of 690 planned participants were enrolled, resulting in decreased power. • The CCP used was selected based on a PRNT50 assay and may not qualify as high-titer CCP per the current FDA EUA.

Methods	Results	Limitations and Interpretation
CoV-Early: Double-Blind RCT of CCP in Nonhospitalized, High-Risk Adults With COVID-19 in the Netherlands[15], continued		
Interventions • 300 mL of CCP with minimum PRNT50 titer of 1:160 (n = 207) • Non-SARS-CoV-2 plasma collected prior to pandemic (n = 209) **Primary Endpoint** • Improvement based on 5-point OS by Day 28 **Secondary Endpoints** • Percentage of hospital admissions • Number of days of symptoms	**Primary Outcome** • Odds of receiving highest score on 5-point OS by Day 28: OR 0.86; 95% CrI, 0.59–1.22 in CCP arm **Secondary Outcomes** • Percentage of hospital admissions: 4.8% in CCP arm vs. 8.6% in non-SARS-CoV-2 plasma arm (aHR 0.61; 95% CI, 0.28–1.34) • Number of days of symptoms: 13 in CCP arm vs. 12 in non-SARS-CoV-2 plasma arm ($P = 0.99$)	**Interpretation** • This trial did not demonstrate a benefit of CCP in nonhospitalized, high-risk patients with COVID-19.
Retrospective Evaluation of CCP Antibody Levels and the Risk of Death From COVID-19 in the United States[16]		
Key Inclusion Criteria • Severe or life-threatening COVID-19 • Patients for whom samples of transfused CCP were available for retrospective analysis of antibody titer **Interventions** • High-titer CCP (n = 515), medium-titer CCP (n = 2,006), or low-titer CCP (n = 561), characterized retrospectively **Primary Endpoint** • Mortality by Day 30 after CCP transfusion	**Participant Characteristics** • 31% aged ≥70 years; 61% men; 48% White, 37% Hispanic/Latinx • 61% in ICU; 33% on MV • 51% received corticosteroids; 31% received RDV. **Primary Outcomes** • Mortality by Day 30 after transfusion: 22% in high-titer CCP arm vs. 27% in medium-titer CCP arm vs. 30% in low-titer CCP arm • Lower risk of death in high-titer CCP arm than low-titer CCP arm (relative risk 0.75; 95% CI, 0.61–0.93) • Lower mortality among patients not receiving MV before CCP transfusion (relative risk 0.66; 95% CI, 0.48–0.91) • No difference in mortality between high-titer and low-titer arms among patients on MV before CCP transfusion (relative risk 1.02; 95% CI, 0.78–1.32)	**Key Limitation** • Lack of untreated control arm **Interpretation** • The study data are not sufficient to establish the efficacy or safety of CCP.

Key: ALC = absolute lymphocyte count; ARDS = acute respiratory distress syndrome; ASAP = as soon as possible; BMI = body mass index; CCP = COVID-19 convalescent plasma; Ct = cycle threshold; CVD = cardiovascular disease; DM = diabetes mellitus; ECMO = extracorporeal membrane oxygenation; ED = emergency department; EUA = Emergency Use Authorization; Fc = fragment crystallizable; FDA = Food and Drug Administration; HFNC = high-flow nasal cannula; ICU = intensive care unit; Ig = immunoglobulin; IL = interleukin; LOS = length of stay; mAb = monoclonal antibody; MV = mechanical ventilation; NIV = noninvasive ventilation; OS = ordinal scale; the Panel = the COVID-19 Treatment Guidelines Panel; PaO_2/FiO_2 = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; PCR = polymerase chain reaction; PRNT50 = 50% plaque reduction neutralization test; RBD = receptor-binding domain; RCT = randomized controlled trial; RDV = remdesivir; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SOC = standard of care; SpO_2 = oxygen saturation; TRALI = transfusion-related acute lung injury; VL = viral load; WHO = World Health Organization

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