



Table 5b. COVID-19 Convalescent Plasma: Selected Clinical Data

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The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for CCP. The studies summarized below are those that have had the greatest impact on the Panel’s recommendations.

Methods	Results	Limitations and Interpretation
REMAP-CAP: Multinational, Open-Label RCT of High-Titer CCP in Hospitalized Patients With Critical COVID-19¹		
<p>Key Inclusion Criterion:</p> <ul style="list-style-type: none"> Admitted to ICU while receiving respiratory support (HFNC oxygen, NIV, MV, ECMO) and/or vasopressor or inotrope support <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> CCP contraindicated Death imminent <p>Interventions:</p> <ul style="list-style-type: none"> High-titer CCP (550 mL +/- 150 mL) within 48 hours of randomization (n = 1,084) Usual care (n = 916) <p>Primary Endpoint:</p> <ul style="list-style-type: none"> Organ support-free days by Day 21 <p>Key Secondary Endpoints:</p> <ul style="list-style-type: none"> In-hospital mortality Mortality by Day 28 and Day 90 Respiratory support-free days ICU LOS 	<p>Participant Characteristics:</p> <ul style="list-style-type: none"> 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 <p>Primary Outcome:</p> <ul style="list-style-type: none"> No difference between arms in 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) <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> No difference between arms in: <ul style="list-style-type: none"> 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 	<p>Key Limitations:</p> <ul style="list-style-type: none"> Open-label study Not all patients in CCP arm received CCP (86% received CCP as per protocol and 95% received some CCP). <p>Interpretation:</p> <ul style="list-style-type: none"> 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 Brazil²		
<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Receipt of supplemental oxygen • Within 12 days of respiratory symptom onset <p>Key Exclusion Criterion:</p> <ul style="list-style-type: none"> • Imminent or current intubation <p>Interventions:</p> <ul style="list-style-type: none"> • 1–2 units CCP (approximately 500 mL) from 1–2 donors (n = 625) • SOC (n = 313) <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Intubation or death by Day 30 <p>Key Secondary Endpoints:</p> <ul style="list-style-type: none"> • 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 	<p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age 68 years; 59% men • 84% receiving systemic corticosteroids at enrollment <p>Primary Outcome:</p> <ul style="list-style-type: none"> • 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, <i>P</i> = 0.18) <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> • By Day 30, no difference between arms in: <ul style="list-style-type: none"> • 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 	<p>Key Limitations:</p> <ul style="list-style-type: none"> • Open-label study • Trial stopped at 78% of planned enrollment after meeting prespecified futility criteria for early termination. <p>Interpretation:</p> <ul style="list-style-type: none"> • There was no benefit of CCP in oxygen-dependent, hospitalized COVID-19 patients within 12 days of symptom onset.
RECOVERY: Open-Label RCT of High-Titer CCP in Hospitalized Patients in the United Kingdom³		
<p>Key Inclusion Criterion:</p> <ul style="list-style-type: none"> • Clinically suspected or laboratory-confirmed SARS-CoV-2 infection <p>Key Exclusion Criterion:</p> <ul style="list-style-type: none"> • CCP contraindicated <p>Interventions:</p> <ul style="list-style-type: none"> • Approximately 275 mL per unit of CCP with IgG against SARS-CoV-2 spike protein, with sample to cutoff ratio ≥ 6.0. Administered as 2 units of high-titer CCP (first unit ASAP after randomization, second unit ≥ 12 hours later the next day) (n = 5,795) • Usual care (n = 5,763) 	<p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age 64 years; 64% men • 5% on MV • 92% received corticosteroids <p>Primary Outcomes:</p> <ul style="list-style-type: none"> • No difference between arms in: <ul style="list-style-type: none"> • Mortality: 24% in each arm • Mortality in patients without detectable SARS-CoV-2 antibodies: 32% in CCP arm vs. 34% in usual care arm <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> • No difference between arms in: 	<p>Key Limitation:</p> <ul style="list-style-type: none"> • Open-label study <p>Interpretation:</p> <ul style="list-style-type: none"> • 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 Kingdom³, continued		
<p>Primary Endpoint:</p> <ul style="list-style-type: none"> All-cause mortality by Day 28 <p>Key Secondary Endpoints:</p> <ul style="list-style-type: none"> Time to hospital discharge by Day 28 Among patients not receiving MV, progression to MV or death by Day 28 	<ul style="list-style-type: none"> 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 	
CSSC-004: RCT of Early Treatment With High-Titer CCP in Outpatients With COVID-19 in the United States⁴		
<p>Key Inclusion Criterion:</p> <ul style="list-style-type: none"> COVID-19 symptoms for <8 days <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> Prior or planned COVID-19–related hospitalization Receipt of anti-SARS-CoV-2 mAbs <p>Interventions:</p> <ul style="list-style-type: none"> Approximately 250 mL of CCP with SARS-CoV-2 spike-RBD IgG titer $\geq 1:320$ (n = 592) Non-SARS-CoV-2 plasma (n = 589) <p>Primary Endpoint:</p> <ul style="list-style-type: none"> COVID-19–related hospitalization or all-cause death within 28 days 	<p>Participant Characteristics:</p> <ul style="list-style-type: none"> 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 time from symptom onset to transfusion was 6 days <p>Primary Outcomes:</p> <ul style="list-style-type: none"> COVID-19–related hospitalization within 28 days: 2.9% in CCP arm vs. 6.3% in control arm (absolute risk reduction of 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 	<p>Key Limitation:</p> <ul style="list-style-type: none"> Patients were at relatively low risk for disease progression. <p>Interpretation:</p> <ul style="list-style-type: none"> This trial demonstrated a benefit of CCP in unvaccinated outpatients with <8 days of COVID-19 symptoms.

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 Spain⁵		
<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥ 50 years • Mild or moderate COVID-19 symptoms for ≤ 7 days <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Severe COVID-19 symptoms or requirement for hospitalization for any reason • Previous SARS-CoV-2 infection • Receipt of >1 COVID-19 vaccination <p>Interventions:</p> <ul style="list-style-type: none"> • 250–300 mL of high-titer, methylene blue-treated CCP (n = 188) • 0.9% saline (n = 188) <p>Primary Endpoints:</p> <ul style="list-style-type: none"> • Hospitalization within 28 days • Mean change in SARS-CoV-2 VL from baseline to Day 7 <p>Key Secondary Endpoints:</p> <ul style="list-style-type: none"> • Death by Day 60 • Time to complete symptom resolution 	<p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age 56 years; 54% men • 75% with ≥ 1 risk factor for COVID-19 progression • 97% with mild COVID-19 • Median 4.4 days of symptoms prior to enrollment • Among the 369 patients for whom baseline serologic testing was available, 88% were negative for both IgG anti-SARS-CoV-2 spike and IgM anti-SARS-CoV-2 S1-RBD <p>Primary Outcomes:</p> <ul style="list-style-type: none"> • Hospitalization within 28 days: 12% in CCP arm vs. 11% in placebo arm (relative risk 1.05; 95% CrI, 0.78–1.41) • 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 <p>Key Secondary Outcomes:</p> <ul style="list-style-type: none"> • Death: 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) 	<p>Key Limitations:</p> <ul style="list-style-type: none"> • 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 immunoglobulins and negatively impacted product efficacy and blinding. <p>Interpretation:</p> <ul style="list-style-type: none"> • This trial did not demonstrate a benefit of CCP in unvaccinated outpatients with <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 Argentina⁶		
<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥ 75 years or aged 65–74 years with ≥ 1 coexisting condition • Mild COVID-19 symptoms for <72 hours <p>Key Exclusion Criterion:</p> <ul style="list-style-type: none"> • Severe respiratory disease <p>Interventions:</p> <ul style="list-style-type: none"> • 250 mL of CCP with IgG against SARS-CoV-2 spike protein $>1:1,000$ (n = 80) • Saline (n = 80) 	<p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age 77 years; 38% men • Most with comorbidities <p>Primary Outcome:</p> <ul style="list-style-type: none"> • 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; $P = 0.03$) 	<p>Key Limitations:</p> <ul style="list-style-type: none"> • Small sample size • Early termination because number of COVID-19 cases decreased <p>Interpretation:</p> <ul style="list-style-type: none"> • This trial demonstrated a benefit of CCP in older adult outpatients with <72 hours of mild COVID-19 symptoms.

Methods	Results	Limitations and Interpretation
Double-Blind RCT of Early High-Titer CCP Therapy to Prevent Severe COVID-19 in Nonhospitalized Older Adults in Argentina⁶		
<p>Primary Endpoint:</p> <ul style="list-style-type: none"> Severe respiratory disease, defined as respiratory rate ≥ 30 breaths/min and/or $SpO_2 < 93\%$ on room air by Day 15 		
SIREN-C3PO: Multicenter, Single-Blind RCT of High-Titer CCP in the United States⁷		
<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> ED patient with ≤ 7 days of symptoms PCR-confirmed SARS-CoV-2 infection Aged ≥ 50 years or aged ≥ 18 years with ≥ 1 risk factor for disease progression <p>Key Exclusion Criterion:</p> <ul style="list-style-type: none"> Need for supplemental oxygen <p>Interventions:</p> <ul style="list-style-type: none"> 250 mL high-titer CCP (median titer 1:641) (n = 257) Saline (n = 254) <p>Primary Endpoint:</p> <ul style="list-style-type: none"> Disease progression, defined as hospital admission, death, or seeking emergency or urgent care within 15 days of randomization <p>Key Secondary Endpoints:</p> <ul style="list-style-type: none"> Severity of illness, as measured by an OS All-cause mortality within 30 days Hospital-free days over 30 days 	<p>Participant Characteristics:</p> <ul style="list-style-type: none"> 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%) <p>Primary Outcomes:</p> <ul style="list-style-type: none"> 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 and 6 in placebo arm) required hospitalization during the 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%). <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> All-cause mortality within 30 days: 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 	<p>Key Limitations:</p> <ul style="list-style-type: none"> Imbalance of patients who required hospital admission during the index visit included in the primary analysis Slightly more patients with multiple risk factors, including immunosuppression, in CCP arm <p>Interpretation:</p> <ul style="list-style-type: none"> 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.

Methods	Results	Limitations and Interpretation
Retrospective Evaluation of CCP Antibody Levels and the Risk of Death From COVID-19 in the United States⁸		
<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Severe or life-threatening COVID-19 • Patients for whom samples of transfused CCP were available for retrospective analysis of antibody titer <p>Interventions:</p> <ul style="list-style-type: none"> • High-titer CCP (n = 515), medium-titer CCP (n = 2,006), or low-titer CCP (n = 561), characterized retrospectively <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Mortality at 30 days after CCP transfusion 	<p>Participant Characteristics:</p> <ul style="list-style-type: none"> • 31% aged ≥70 years; 61% men; 48% White, 37% Hispanic/Latinx • 61% in ICU; 33% on MV • 51% received corticosteroids, 31% received RDV <p>Primary Outcomes:</p> <ul style="list-style-type: none"> • Mortality at 30 days after transfusion: 22% in high-titer CCP arm vs. 27% in medium-titer CCP arm vs. 30% in low-titer CCP arm <ul style="list-style-type: none"> • High-titer CCP arm had a lower risk of death than low-titer CCP arm (relative risk 0.75; 95% CI, 0.61–0.93) • Mortality was lower among patients who were not receiving MV before CCP transfusion (relative risk 0.66; 95% CI, 0.48–0.91) • Among patients who were on MV before CCP transfusion, there was no difference in mortality between high-titer and low-titer arms (relative risk 1.02; 95% CI, 0.78–1.32) 	<p>Key Limitation:</p> <ul style="list-style-type: none"> • Lack of untreated control arm <p>Interpretation:</p> <ul style="list-style-type: none"> • The study data are not sufficient to establish the efficacy or safety of COVID-19 CCP.

Key: ASAP = as soon as possible; BMI = body mass index; CCP = COVID-19 convalescent plasma; CVD = cardiovascular disease; DM = diabetes mellitus; ECMO = extracorporeal membrane oxygenation; ED = emergency department; Fc = fragment crystallizable; 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; PCR = polymerase chain reaction; RBD = receptor binding domain; RCT = randomized controlled trial; RDV = remdesivir; SAE = serious adverse event; SOC = standard of care; SpO₂ = oxygen saturation; VL = viral load

References

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