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REVIEW

TRANSFUSION

CME/SAM

COVID-19 convalescent plasma: Interim recommendations from the AABB

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1 | INTRODUCTION

Convalescent plasma (CP) has been used as passive immunotherapy for the prevention and treatment of infectious diseases for more than 100 years.[1,2] The lack of proven therapies during the early months of the COVID-19 pandemic, a favorable safety profile[3,4] and early evidence for efficacy in adults[5,6] led to the widespread use of CCP. By early 2021, over 25,000 units of CCP were transfused every week in the United States (US) to patients with COVID-19[7] under conditions that varied in regard to the patient's disease severity, timing of the transfusion, and the number of units transfused. At the time of writing, over 500,000 units of CCP have been transfused in the United States with many more collected and transfused around the world.

Evidence from recently published randomized controlled trials (RCTs) and large observational studies suggests that CCP is most efficacious when high titer units are given early in the course of disease. In the US, the Food and Drug Administration (FDA) has updated the emergency use authorization (EUA) for CCP so that only high titer units may be used; this will likely cause a significant strain on the supply of CCP. As COVID cases surge, the supply of CCP has been outstripped by demand, resulting in the need for more thoughtful use so that transfusions are limited to patients for whom CCP is likely to be effective. Based on the available evidence, AABB developed interim recommendations for CCP use. These interim recommendations will be updated as more peer-reviewed clinical trial data are published.

2 | METHODS

The AABB Board of Directors commissioned a committee of experts to draft clinical practice guidelines for the use of CCP. The primary focus was to evaluate whether CCP is safe and which patient populations would benefit most from CCP. The final guidelines will employ systematic review and meta-analysis of available data using a Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. However, there are currently insufficient data to draft definitive clinical practice guidelines. Given that the AABB recognizes the wide use of CCP in the COVID-19 pandemic in the United States, these recommendations were drafted as interim guidance.

The committee was primarily composed of experts who were current or former members of the AABB clinical transfusion medicine committee (CC, AT, EA, ND, MP, RG, BS, TG, RM, JR). There also were experts appointed by professional organizations as subject matter experts (American Society of Hematology: BG; International Society of Blood Transfusion: DD; Society of Critical Care Medicine: TR; American Society of Anesthesiology: MJ, American Society of Microbiology: AC; and Cochrane: LE). The committee also included several experts on CCP collection and transfusion (EB, JG, JW, RV), a patient representative (GB) and GRADE methodologist (FF). The committee members had no substantial conflicts of interest as defined by the AABB conflict of interest policy.

The committee performed a literature search using the search terms "COVID-19," "SARS-CoV-2", and "convalescent plasma" to identify randomized controlled trials or large observational studies (>350 patients). Published meta-analyses were also consulted for the final analysis. The committee analyzed data from peer-reviewed publications (excluding pre-prints), to reach a consensus for best practice recommendations. However, a formal systematic review and meta-analysis was not performed. The interim recommendations were composed independent of GRADE methodology.

3 | INTERIM RECOMMENDATIONS

3.1 | Interim recommendation 1: When making risk benefit decisions, one should consider the risk of CCP as comparable to standard (SARS-CoV-2 non-immune) plasma

3.1.1 | Rationale for recommendation

The body of evidence suggests that CCP confers similar risk to that of standard (SARS-CoV-2 non-immune) plasma. In the United States and other high-income countries, the risk of transfusion transmitted infections, such as HIV, hepatitis B virus, and hepatitis C virus, are less than one infection per every 2 million transfusions.[8] Non-infectious risks, such as allergic transfusion reactions, transfusion-related acute lung injury (TRALI), and transfusion-associated circulatory overload (TACO), are more common, but manageable.[9] One initial concern was the possibility of antibody-dependent enhancement (ADE), which occurs when antibodies from a prior infection exacerbate the clinical severity of infection with a different viral serotype.[10]

In the six RCTs included in the safety analysis, transfusion-related adverse events occurred in 0%–4.8% of patients receiving CCP (Table 1). While the rates reported by some of the trials are somewhat higher than the 1%–3% reported for allergic transfusion reactions with plasma,[11] this may be ascribed to active—rather than passive—surveillance and reporting mechanisms. Symptoms and signs may also be reported that are temporally related to the transfusion but are due to the patient's underlying

TABLE 1 Data related to safety of COVID-19 convalescent plasma from randomized controlled trials and a large observational study

Author	Study design	CCP arm N	Control arm N	Placebo used	Percentage of CCP patients with AE	Percentage of control patients with AE	Adverse events CCP within 24 h of transfusion
Li L[19]	RCT	52	51	Standard of care	3.80%	NA	2 with non-severe allergic; 1 with severe TAD
Agarwal A[31]	RCT	235	229	Standard of care	3.80%	NA	1 with pain at infusion site, chills, nausea; 3 with fever and tachycardia; 2 with dyspnea and IV catheter blockage; 3 with mortality possibly related to CCP
Salman OH[17]	RCT	15	15	Standard of care	0%	NA	No adverse events
Rasheed AM[16]	RCT	21	28	Standard of care	4.70%	NA	1 with mild allergic reaction
Simonovich VA[18]	RCT	228	105	Normal saline	4.80%	1.90%	13 AE in 11 patients- No significant differences in the overall incidence of AE (OR, 1.21; 95% CI, 0.74–1.95) or SAE.
Libster R[13]	RCT	80	80	Normal saline	0%	0%	No adverse events
Joyner MJ[4]	Observational	20,000	NA	NA	0.39%	NA	78 transfusion reactions [(<1%) - 36 TACO; 21 TRALI; 21 severe allergic] mortality within 4 h of transfusion: 10 reported as related to transfusion. Thrombotic or thromboembolic events: 113 (<1%)

Abbreviations: AE, adverse events; CCP, COVID-19 convalescent plasma; FNHTR, febrile non-hemolytic transfusion reaction; NA, not available; OR, odds ratio; RCT, randomized controlled trial; TACO, transfusion associated circulatory overload; TAD, transfusion associated dyspnea; TRALI, transfusion-related acute lung injury.

illness and unrelated to use of CCP. In the largest observational study of 20,000 patients in the US FDA Expanded Access Program (EAP) who received CCP, the rate of transfusion-related adverse events was 0.39%, with 36 cases of TACO [0.18% (0.13–0.25; 95% CI)], 21 reports of TRALI [0.10% (0.07–0.16; 95%CI)]; and 21 severe allergic reactions [0.10% (0.07–0.16; 95% CI)]. The rate of thrombotic or thromboembolic events was less than 1%.[4] In all trials and studies, there were no deaths that were ascribed definitively to CCP transfusion. There have not been any reported cases of ADE or transfusion-transmitted viral infections.[12] No safety data are available for pediatric patients.

3.2 | Interim recommendation 2: CCP is optimally effective when transfused as close to symptom onset as possible. CCP Is unlikely to provide benefit for patients with late-stage disease or on mechanical ventilation

3.2.1 | Rationale for recommendation

A trial led by Libster et al. enrolled older individuals (>75 years old or between 65–74 years old with at least one coexisting condition) with COVID-19 who were

TABLE 2 Data related to efficacy of COVID-19 convalescent plasma from randomized clinical trials and a large observational study

Author	Study design	CCP arm N	Control arm N	CCP titer	Control	Patient population	Timing of intervention	Primary endpoint	Efficacy CCP (ITT)
Li L[19]	RCT open label	52	51	High titer IgG against S-RBD	Standard of care	Adults with severe or life-threatening COVID-19	Median of 30 days between onset of symptoms and randomization	Clinical improvement within 28 days	51.9% CCP vs. 43.1% control met primary endpoint (HR 1.40 (95% CI 0.79–2.49; $p = .26$)
Agarwal A[31]	RCT open label	235	229	Inconsistent	Standard of care	Adults with moderate COVID-19	Inconsistent	Composite of progression to severe disease or all-cause mortality by day 28	19% CCP vs. 18% control met primary endpoint (RR 1.04; 95% CI 0.71–1.54)
Salman OH[17]	RCT open label	15	15	Inconsistent	Standard of care	Adults with moderate or severe COVID-19	Median of 17 days from onset of illness to hospitalization. Median of 13 days from hospitalization to randomization	At least 50% improvement of the severity of illness at any time during 5- day study period	Gradual decrease in illness severity during the study period in CCP group, $p < .001$, compared to baseline value. No difference seen in control group
Rasheed AM[16]	RCT open label	21	28	High titer IgG (SARS-CoV-2 IgG index >1)	Standard of care	Critically ill adults with COVID-19	Mean 15 (CP) to 17 (control) days after onset of infection to randomization	Improvement in clinical status and mortality	Recovery time from critical illness 4.52 days for CCP vs. 8.45 days for control ($p < .0001$); Mortality was 1/21 (CCP) vs. 8/28 in control group.
Simonovich VA[18]	RCT Double blind	228	105	High titer IgG against SARS-CoV-2	Normal saline	Adults with COVID-19 and severe pneumonia	Median of 8 days between onset of symptoms and randomization	Clinical status 30 days after intervention using WHO 6-point disease severity scale	No significant difference noted between CCP and control group in the distribution of clinical outcomes (OR 0.83; 95% CI 0.52–1.35; $p = .46$)
Libster R[13]	RCT Double blind	80	80	High titers - upper 28th percentile of units tested	Normal saline	65–74 yo with comorbidities or > =75 yo	<72 h between onset of symptoms and transfusion	Severe respiratory disease	16% CCP vs. 31% control met primary endpoint (RR 0.52; 95% CI).29–0.94; $p = .03$)

TABLE 2 (Continued)

Author	Study design	CCP arm N	Control arm N	CCP titer	Control	Patient population	Timing of intervention	Primary endpoint	Efficacy CCP (ITT)
Joyner MJ[14]	Observational	3082	NA	Data stratified by low, middle and high titer CCP	NA	Adults with severe or life-threatening COVID-19	Data stratified by less than and greater than 72 h of admission	30-day all-cause mortality	Among 2014 patients non-ventilated patients, 22.2% in low-titer cohort met the end-point vs. 14.2% in the high-titer cohort (relative risk, 0.75). CCP showed no benefit among patients who received mechanical ventilation (relative risk, 1.02)

Abbreviations: CCP, COVID-19 convalescent plasma; ITT, intention to treat; NA, not available; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

identified in the outpatient setting within 48 h of symptom onset. The patients who were given CCP within 72 h of symptom onset had a 48% reduced risk of progression to severe respiratory disease (Table 2) when compared to those who received placebo.[13] In the intention-to-treat population, severe respiratory disease developed in 13 of 80 patients (16%) who received CCP, compared to 25 of 80 patients (31%) who received placebo. It is important to note that this trial closed at 76% enrollment, preventing adequate statistical power to discern long term outcomes.

The benefit of administering CCP early in the disease course is corroborated by data from observational studies. An analysis of a 3082-patient cohort in the EAP found that high titer CCP given less than 72 h after hospital admission conferred a greater benefit when compared to those receiving CCP later in their hospital stay.[14] The unadjusted mortality within 30 days after transfusion was lower among patients who received a transfusion within 3 days after receiving a diagnosis of COVID-19 (point estimate, 22.2%; 95% CI, 19.9 to 24.8) than among those who received a transfusion 4 or more days after receiving a diagnosis of COVID-19 (point estimate, 29.5%; 95% CI, 27.6 to 31.6).[14] A matched propensity study by Salazar et al. found the greatest effect when patients were given CCP within 44 h of hospital admission[15]; however, these are retrospective data drawn from a smaller study of 351 patients.

Two smaller RCTs did find benefit from later administration of CCP. The trial by Rasheed et al. gave CCP a mean of 15 days after onset of infection to randomization and found a significant reduction in recovery time and mortality when compared to the control group.[16] The second trial enrolled adults with moderate or severe COVID-19 who had a median of 17 days from onset of illness to hospitalization and a median of 13 days from hospitalization to randomization. There was a gradual decrease in illness severity during the study period in the CCP group compared to baseline value ($p < .001$), but no difference seen in the control group.[17]

In contrast, no benefit of CCP was reported in two RCTs in which patients received CCP a median of 8[18] or 30 days[19] after hospitalization; however, the latter study was underpowered due to early termination. Additional RCTs that targeted patients in later stages of disease have closed early due to a lack of efficacy.[20,21]

The sub-analysis of the EAP found no benefit from CCP, regardless of titer level, on the risk of death among patients who also required mechanical ventilation (relative risk, 1.02).[14] Of these 1068 patients, 80 of 183 (43.7%) in the low-titer group died within 30 days of transfusion. Of the medium-titer and high-titer groups, 277 of 666 (41.6%) and 64 of 158 patients (40.5%) died within 30 days of CCP transfusion, respectively. In the US, the

FDA has updated their guidance for clinicians, noting that CCP given "...late in the course of illness (e.g. following respiratory failure requiring intubation and mechanical ventilation) has not been associated with clinical benefit."[22]

3.3 | Interim recommendation 3: The effectiveness of CCP is related to the antibody quantity within a unit; high-titer CCP is superior to low-titer CCP. A single high-titer unit should be sufficient for most patients

3.3.1 | Rationale for recommendation

The primary mechanism of CCP is thought to be by transfusion of neutralizing antibodies. However, there is significant heterogeneity in the antibody levels of CCP donors, including the level of neutralizing antibodies present.[23] Various assays are used to qualify CCP in different jurisdictions and the definition of high- and low-titer units will vary as a result. This variability extends to RCTs, which have used different assays and definitions to determine high-titer units.

Based on available evidence, a high-titer unit will confer the greatest benefit. A sub-analysis from a large observational study of the EAP found that of 2014 patients who did not require mechanical ventilation, 81 of 365 (22.2%) in the low-titer group reached the endpoint of 30-day mortality compared with 50 of 352 (14.2%) in the high-titer (approximately upper half of neutralizing antibody titers) group.[14] Therefore, patients in the high-titer group had a significantly lower relative risk of death within 30 days after transfusion than patients in the low-titer group (relative risk, 0.75; 95% CI, 0.61 to 0.93). In data from one RCT, 3/36 (8%) patients who received a unit with a titer above the median concentration of 3200 (upper 28th percentile of surrogate IgG binding assay against SARS CoV-2) reached the endpoint of advanced respiratory disease compared with 9/42 (21%) patients who received a unit with a titer below the 3200 median titer. This may also be compared with 25/80 (31%) of patients who received the placebo.[13]

In the US, the FDA, responding to this body of evidence, recently revised the EUA for CCP so that only high titer units can be used.[22] But in many countries, low titer or untitered units will still be used. If the titer is unknown or only a low-titer unit is available, the question of how many units of low-titer CCP are equivalent to a single high-titer unit remains. Studies comparing the clinical efficacy of two low titer units versus a high titer unit have not been identified. Because binding antibody assays are qualitative, the actual dose of neutralizing antibody within each CCP unit is usually unknown. Also, since the volume of units collected ranges from ~200 ml with apheresis to ~325 ml from whole blood,[24] the quantity of antibody (volume x titer) transfused in a unit is highly variable. The AABB recommends transfusing one high-titer CCP unit when CCP is indicated. Since the risks from transfusion are low,[4] it is acceptable to transfuse two units of low-titer in lieu of a high-titer unit. Based on the variability of titer and volume, it is possible that two units may deliver a dose equivalent to a single high-titer unit, however, the effectiveness of two low titers is unknown. Patients with impaired cardiac function may require a smaller volume or more prolonged transfusion times to mitigate the risk of TACO when additional units are transfused. A third unit is not encouraged as shortages of CCP limit inventory.[7,25]

3.4 | Interim recommendation 4: In the absence of group B or group AB CCP, the transfusion of group A or group O CCP with low anti-A/B titer may be acceptable for group B and group AB patients

3.4.1 | Rationale for recommendation

Typically, transfused plasma is ABO-identical or ABO-compatible with the recipient to prevent passive hemolysis of the recipient's red cells. For patients with lower prevalence ABO groups, namely, blood groups B and AB, ABO-identical or -compatible CCP may not be available. Published literature and clinical experience have shown that incompatible plasma, such as group A with low-titer anti-B is safe in situations when compatible plasma is not available.[26,27] In addition, some institutions routinely transfuse platelet components that contain incompatible plasma.[28]

3.5 | Interim recommendation 5: Additional randomized, controlled clinical trial data are needed to fully assess CCP efficacy and to identify which specific patient populations would benefit most

3.5.1 | Rationale for recommendation

More than 100 RCTs were initiated to assess whether CCP can either prevent SARS-CoV-2 infection or treat COVID-19. The vast majority of the RCTs have yet to be completed or analyzed with the largest ones highlighted (Table 3). There are many different settings where CCP

TABLE 3 The largest ongoing or completed trials of CCP, no results yet published, with planned recruitment >500 participants to intervention or control

Study name, registration, and recruitment status	Study design country	Planned number of participants		Patient population	Exclusion criteria	CCP volume and titer	Control intervention	Timing of intervention	Primary outcome
		Convalescent plasma	Comparator						
REMAP-CAP[a] trial NCT02735707	Platform RCT Open label	Adaptive design, no sample size, but over 1000 randomized	Adaptive design, no sample size, but over 1000 randomized	Adult Confirmed COVID-19> 90% critically ill (WHO score ≥ 6)	Hospitalized for >14 days Admitted to ITU for >48 h Previous reaction to blood components Known objection to receiving plasma components	550 mls ± 150 ml ≥ Euroimmun 6 in UK Neutralizing Ab titer >1:80 Australia; >1:100 Canada & USA	Standard care	D1 275mls D2 275mls	Organ-support free days - 21 days
Completed recruitment	Australia, Canada, UK, USA								
RECOVERY[a] trial NCT04381936	Platform RCT Open label	Adaptive design, no sample size, but over 5750 randomized	Adaptive design, no sample size, but over 5750 randomized	Any age Suspected or confirmed COVID-19 Hospitalized >90% requiring oxygen therapy (WHO score ≥ 5)	Previous reaction to blood components Known objection to receiving plasma components	550 mls ± 150 ml ≥ Euroimmun 6	Standard care	D1 275mls D2 275mls	All-cause mortality - 28 days
Completed recruitment	UK								
CCAP NCT04345289	RCT Double blind	733	367	Adult Confirmed COVID-19 Moderate to severe (WHO score ≥ 5)	Pregnant or breastfeeding	600mls	Saline 600 ml	Unclear	All-cause mortality or need of invasive mechanical ventilation 28 -days
Recruiting	Denmark								
CONCOR-1[a] NCT04348656 NCT04418518	RCT Open label	800	400	Adult Confirmed COVID-19 Moderate to severe (WHO score 5 to 6)	Symptoms for >12 days Intubated or plan in place for intubation Plasma is contraindicated	500mls	Standard care	Unclear	Intubation or death in hospital - 30 days
Stopped recruitment	Canada, USA								
PassITON NCT04362176	RCT Double blind, placebo-controlled	500	500	Adult Confirmed COVID-19 Hospitalized with hypoxia	Symptoms for >14 days	250-400mls with demonstrated neutralizing capacity	Lactated Ringer's solution with multivitamin	Within 72 h of hospitalization	WHO 7-point ordinal scale at day 15
Recruiting	USA								
NCT04516811	RCT Double blind	300	300	Adult Confirmed COVID-19 Moderate to severe (WHO score 5 to 6)	Participation in another therapeutic clinical trial for COVID-19. Invasive mechanical ventilation. Expected survival <24 h	200–250 ml Contains anti-SARS-CoV-2 – titer not specified	Saline	Unclear	Clinical Improvement (≥ 2 points on WHO scale) – 28 days
Recruiting	South Africa								

(Continues)

TABLE 3 (Continued)

Study name, registration, and recruitment status	Study design country	Planned number of participants		Patient population	Exclusion criteria	CCP volume and titer	Control intervention	Timing of intervention	Primary outcome
		Convalescent plasma	Comparator						
VA CURES-1 NCT04539275	RCT Double blind	351	351	Adult Confirmed COVID-19 Moderate (WHO score 5) Admitted ≤72 h	Respiratory failure or anticipated to develop it or die within 24 h. Anticipated discharge ≤72 h. Previous transfusion reaction. Serum IgA deficiency (<7 mg/dL) Received convalescent plasma in the last 60 days	200-500 ml SARS-CoV-2 titer not specified	Saline	two equally divided doses, less than 12 h apart	Proportion of participants developing acute hypoxemic respiratory failure or all-cause death – 28 days
Recruiting	USA								
NCT04649879	RCT Open label	613	307	Adult Confirmed COVID-19 SARS-CoV-2 detected in blood	Estimated glomerular filtration rate < 30 (kidney failure stage III or more) Pregnant or breastfeeding	200mls up to 10x Neutralizing Ab titer ≥1:640 or Euroimmun >9	Standard care	Daily until SARS-CoV-2 is no longer detectable in the blood or 10 transfusions	COVID-19 related mortality - 28 days
Not yet recruiting	Sweden								
ASCOT NCT04483960	RCT Open label	800	1600	Adult Confirmed COVID-19 Moderate (WHO score 4 to 5) Symptoms ≤12 days Expected to be inpatient ≥48 h	Requiring non-invasive or invasive ventilation or vasopressor support Pregnant	Volume not reported Neutralizing Ab titer >1:80	Lopinavir/ritonavir OR Lopinavir/ritonavir+ hydroxychloroquine	Unclear	Proportion of participants alive and not requiring organ support – 28 days
Recruiting	Australia								
CSSC-004 NCT04373460	RCT Double blind	672	672	Adult Confirmed COVID-19 Mild (WHO score 2 to 3) Symptoms ≤8 days First positive SARS-CoV-2 ≤ 8 days	Hospitalized or expect to be hospitalized within 24 h History of prior reactions to transfusion blood products Receiving any treatment drug for COVID-19 ≤ 14 days prior to screening	200-250mls SARS-CoV-2 antibody titers ≥1:320	Non-immune plasma 200-250mls	Unclear	Cumulative incidence of hospitalization or death prior to hospitalization – 28 days
Recruiting	USA								

TABLE 3 (Continued)

Study name, registration, and recruitment status	Study design country	Planned number of participants		Patient population	Exclusion criteria	CCP volume and titer	Control intervention	Timing of intervention	Primary outcome
		Convalescent plasma	Comparator						
CoV-Early Study NCT04589949	RCT Double blind	345	345	Adult Confirmed COVID-19 Mild (WHO score 2 to 3) 70 years or older OR 50–69 years and 1 or more risk factors	Life expectancy <28 days Symptoms ≥8 days Hospitalized Previous history of transfusion-related acute lung injury Immunoglobulin A (IgA) deficiency	300mls Contains anti-SARS-CoV-2 -titer not specified	Non-immune plasma 300mls	Unclear	Highest disease status – 28 days
Recruiting	Netherlands								
C3PO NCT04355767	RCT Double blind	300	300	Adult Confirmed COVID-19 Mild (WHO score 2 to 3) Symptoms ≤7 days	Prisoner Prior adverse reaction(s) from blood product transfusion Receipt of any blood product within the past 120 days	1 unit SARS-CoV2 antibodies titers of ≥1:160	Saline + multivitamin (equivalent volume)	Unclear	Number of patients with disease progression (death or hospital admission or seeking emergency or urgent care) – 15 days
Recruiting	USA								

[a]Trials recently closed.

could be used, including post-exposure prophylaxis, early outpatient treatment, early inpatient treatment, late-stage disease, and severe disease requiring mechanical ventilation. In addition, there are specific patient populations who could possibly benefit, including pediatric patients, pregnant women, immunosuppressed patients, and other populations at high risk for development of severe or critical COVID-19 disease. While RCT data may not be able to address all of these settings and patient populations, they will help with the overall understanding of CCP's therapeutic potential and limitations, and they will dramatically improve the ability to provide concrete recommendations. As the data from these trials become available, these recommendations will be updated with formal clinical practice guidelines.

4 | DISCUSSION

The interim recommendations from the AABB are based on a general analysis of the peer-reviewed data currently available. This is not meant to be a systematic review with a rigorous analysis of the data. Instead, this is intended as a tool to guide current practice with updates made as new data become available. There is no published trial data of CCP use in pediatric patients; therefore, all recommendations are limited to the adult population.

The two most important factors in determining effectiveness are the quality of the CCP (neutralizing antibody titer) and the disease state of the patients. However, the rapidly changing landscape of the pandemic has introduced confounding factors, making it difficult to assess the efficacy of CCP in RCTs. The individual trials and observational studies have used different (often surrogate) assays to quantify neutralizing antibody titers as well as different patient populations and time to transfusion. Other confounding factors also contribute, such as changes in therapies that occurred while trials were ongoing. As a result, the evidence for efficacy from RCTs is mixed; however, some data suggest that using high-titer CCP early after symptom onset provides benefit.[13]

The three studies[13–15] that evaluated patients who had been transfused with CCP early after symptom onset/admission showed benefit of CCP either when compared to patients who received a placebo[13] or were transfused later in the disease course.[14,15] This is in contrast to two trials in which CCP was transfused a median of either 8[18] or 30[19] days after symptom onset. In both trials, no benefit was demonstrated for CCP. As live SARS-CoV-2 virus is generally not detected beyond day 9,[29] it may be that the time to transfusion of CCP was too late.

The neutralizing titer of the unit is also a critical factor. As noted in interim recommendation number three,

there is significant variability between assays and it is not always possible to make direct comparisons between different assays and correlate antibody levels with efficacy.[30] It is worth noting that one trial[31] that used a mix of low- and high-titer units reported no overall benefit of CCP for reducing mortality, although some symptomatic improvement was observed. However, the broad principle that 'more antibody is better' (when delivered early in disease) is seen in the analysis by Joyner.[14] Similarly, Libster et al reported overall risk reductions of 73.3% and 31.4% for groups receiving plasma at or above the median and below the median concentrations, respectively.[13] This principle is also guiding the FDA, which has revised the CCP EUA so that only high titer units may be used.[22] Thus, although the interim recommendation to give two low titer doses when no high-titer unit is available is not evidence based, it is a reasonable strategy for delivering the maximum dose of antibody.

These interim recommendations have limitations. The recommendations are a consensus of experts, rather than developed after a systematic review of the literature and rigorous GRADE-based analysis. This more substantive approach will be taken after the major RCTs are finished and more evidence is available. Since the high-quality evidence from RCTs is currently limited, many of these recommendations are not generalizable to a wider population and may change as new evidence emerges.

The strength of these recommendations lies in the practical approach of using the best available evidence to develop urgently needed recommendations so that CCP is transfused at an appropriate dosage to the patient population most likely to benefit. While the efficacy of CCP remains uncertain, the current evidence indicates that high titer units administered early in symptomatic patients confer some benefit when compared to untreated patients. CCP has emerged as one of the primary treatments used for patients with COVID-19 in the United States and many other countries. The emergence of RCT data will assist the medical community in determining which clinical setting and patient populations will benefit most.

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CONFLICT OF INTEREST

The authors have no substantial conflicts of interest.

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