

9-1-2022

Clinical Practice Guidelines From the Association for the Advancement of Blood and Biotherapies (AABB): COVID-19 Convalescent Plasma

Lise J. Estcourt

NHS Blood and Transplant and Radcliffe Department of Medicine, University of Oxford, United Kingdom (L.J.E.)

Claudia S. Cohn

University of Minnesota, Department of Laboratory Medicine and Pathology, Minneapolis, Minnesota (C.S.C.)

Monica B. Pagano

University of Washington, Department of Laboratory Medicine and Pathology, Seattle, Washington (M.B.P.)

Claire Iannizzi

Evidence-based Oncology, Department of Internal Medicine, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany (C.I., N.K., N.S.)

Nina Kreuzberger

Evidence-based Oncology, Department of Internal Medicine, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany (C.I., N.K., N.S.)

https://digitalrepository.unm.edu/hsc_path_pubs

Recommended Citation

See next page for additional authors

Estcourt LJ, Cohn CS, Pagano MB, Iannizzi C, Kreuzberger N, Skoetz N, Allen ES, Bloch EM, Beaudoin G, Casadevall A, Devine DV, Foroutan F, Gniadek TJ, Goel R, Gorlin J, Grossman BJ, Joyner MJ, Metcalf RA, Raval JS, Rice TW, Shaz BH, Vassallo RR, Winters JL, Tobian AAR. Clinical Practice Guidelines From the Association for the Advancement of Blood and Biotherapies (AABB): COVID-19 Convalescent Plasma. *Ann Intern Med.* 2022 Sep;175(9):1310-1321. doi: 10.7326/M22-1079. Epub 2022 Aug 16. PMID: 35969859; PMCID: PMC9450870.

This Article is brought to you for free and open access by the Pathology at UNM Digital Repository. It has been accepted for inclusion in Pathology Research and Scholarship by an authorized administrator of UNM Digital Repository. For more information, please contact disc@unm.edu.

Authors

Lise J. Estcourt, Claudia S. Cohn, Monica B. Pagano, Claire Iannizzi, Nina Kreuzberger, Nicole Skoetz, Elizabeth S. Allen, Evan M. Bloch, Gregory Beaudoin, Arturo Casadevall, Dana V. Devine, Farid Foroutan, Thomas J. Gniadek, Ruchika Goel, Jed Gorlin, Brenda J. Grossman, Michael J. Joyner, Ryan A. Metcalf, Jay S. Raval, Todd W. Rice, Ralph R. Vassallo, Jeffrey L. Winters, Aaron A R Tobian, and Beth H. Shaz

Clinical Practice Guidelines From the Association for the Advancement of Blood and Biotherapies (AABB): COVID-19 Convalescent Plasma

Lise J. Estcourt, MB BChir, DPhil*; Claudia S. Cohn, MD, PhD*; Monica B. Pagano, MD; Claire Iannizzi, MSc; Nina Kreuzberger, MPH; Nicole Skoetz, MD; Elizabeth S. Allen, MD; Evan M. Bloch, MBChB, MS; Gregory Beaudoin, BS, RRT; Arturo Casadevall, MD, PhD; Dana V. Devine, PhD; Farid Foroutan, PhD; Thomas J. Gniadek, MD, PhD; Ruchika Goel, MD, MPH; Jed Gorlin, MD, MBA; Brenda J. Grossman, MD, MPH; Michael J. Joyner, MD; Ryan A. Metcalf, MD; Jay S. Raval, MD; Todd W. Rice, MD, MSc; Beth H. Shaz, MD, MBA; Ralph R. Vassallo, MD; Jeffrey L. Winters, MD; and Aaron A.R. Tobian, MD, PhD*

Description: Coronavirus disease 2019 convalescent plasma (CCP) has emerged as a potential treatment of COVID-19. However, meta-analysis data and recommendations are limited. The Association for the Advancement of Blood and Biotherapies (AABB) developed clinical practice guidelines for the appropriate use of CCP.

Methods: These guidelines are based on 2 living systematic reviews of randomized controlled trials (RCTs) evaluating CCP from 1 January 2019 to 26 January 2022. There were 33 RCTs assessing 21 916 participants. The results were summarized using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) method. An expert panel reviewed the data using the GRADE framework to formulate recommendations.

Recommendation 1 (Outpatient): The AABB suggests CCP transfusion in addition to the usual standard of care for outpatients with COVID-19 who are at high risk for disease progression (weak recommendation, moderate-certainty evidence).

Recommendation 2 (Inpatient): The AABB recommends against CCP transfusion for unselected hospitalized persons with moderate or severe disease (strong recommendation, high-certainty evidence). This recommendation does not apply

to immunosuppressed patients or those who lack antibodies against SARS-CoV-2.

Recommendation 3 (Inpatient): The AABB suggests CCP transfusion in addition to the usual standard of care for hospitalized patients with COVID-19 who do not have SARS-CoV-2 antibodies detected at admission (weak recommendation, low-certainty evidence).

Recommendation 4 (Inpatient): The AABB suggests CCP transfusion in addition to the usual standard of care for hospitalized patients with COVID-19 and preexisting immunosuppression (weak recommendation, low-certainty evidence).

Recommendation 5 (Prophylaxis): The AABB suggests against prophylactic CCP transfusion for uninfected persons with close contact exposure to a person with COVID-19 (weak recommendation, low-certainty evidence).

Good Clinical Practice Statement: CCP is most effective when transfused with high neutralizing titers to infected patients early after symptom onset.

Ann Intern Med. doi:10.7326/M22-1079

Annals.org

For author, article, and disclosure information, see end of text.

This article was published at Annals.org on 16 August 2022.

* Drs. Estcourt, Cohn, and Tobian contributed equally to this work.

Convalescent plasma (CP) has been used for more than 100 years for infectious disease outbreaks, including Spanish influenza, Middle East respiratory syndrome, SARS-CoV-1, and others (1–4). Convalescent plasma is collected from persons who were previously infected with the targeted virus using routine plasma collection techniques. Thus, it is relatively easy to obtain and may be available before other specific therapeutics can be developed. Data from previous outbreaks suggest that CP is most effective when it is transfused early in the disease course and contains high titers of neutralizing antibodies against the target pathogen (1–4).

Limited treatment options at the beginning of the COVID-19 pandemic led to widespread global use of COVID-19 CP (CCP). In March 2020, the U.S. Food and Drug Administration (FDA) issued initial guidance and recommendations for CCP. During the late fall and early winter of 2020 to 2021, there were more than 100 000 units of CCP distributed to hospitals in the United States every month (1).

Data from observational studies in previous infectious disease outbreaks show that CP is safe, with a risk profile that is similar to standard plasma transfusion (4). In the United States and other high-income countries, the risk for transfusion-transmitted infections (HIV, hepatitis B virus, hepatitis C virus, and so forth) from plasma transfusions is less than 1 in every 2 million units transfused (5, 6). In an observational analysis that assessed more than 20 000 persons who received CCP, the rate of all reported transfusion reactions (severe allergic transfusion reactions, transfusion-associated circulatory overload, transfusion-related acute lung injury, and so forth) was

See also:

Editorial comment

Web-Only
Supplement

less than 0.5% (7). In addition, there have been no reported cases of transfusion-transmitted viral infections or antibody-dependent enhancement in either CCP trials or the U.S. Expanded Access Program (6, 7).

The Association for the Advancement of Blood and Biotherapies (AABB) issued interim recommendations in early 2021 (6). However, limited data from randomized controlled trials (RCTs) were available at the time, and the recommendations were based on consensus of expert opinion. Many RCTs have subsequently been completed, making it timely to do a more rigorous and formal evaluation. A systematic review was done, and the GRADE (Grading of Recommendations Assessment, Development and Evaluation) method was used to develop these guidelines.

METHODS

Target Population

These guidelines provide recommendations for clinicians who are treating persons infected with SARS-CoV-2 and who are candidates for CCP transfusion.

Guideline Development Process

The AABB Board of Directors commissioned a committee of experts to draft clinical practice guidelines. Consistent with previous clinical practice guidelines from the AABB (8, 9), the committee conducted a formal systematic review and meta-analysis of the data and used the GRADE method to formulate the current recommendations. The committee focused exclusively on randomized trial data to minimize the risk of bias.

The guidelines committee comprised experts with understanding of CCP and the GRADE method (**Supplement Table 1**, available at [Annals.org](#)). There were 9 current or former members of the AABB clinical transfusion medicine committee (C.S.C., M.B.P., E.S.A., T.J.G., R.G., R.A.M., J.S.R., B.H.S., A.A.R.T.). Other professional organizations also appointed subject experts, including the American Society of Anesthesiologists (M.J.J.), American Society of Microbiology (A.C.), American Society of Hematology (B.J.G.), Cochrane (L.J.E., C.I., N.K., N.S.), International Society of Blood Transfusion (D.V.D.), and Society of Critical Care Medicine (T.W.R.). In addition, committee members included experts on CCP collection and transfusion (E.M.B., J.G., R.R.V., J.L.W.), a GRADE methodologist (F.F.), and a patient representative (G.B.). As defined by the AABB conflict of interest policy (10), all committee members were required to disclose financial, professional, intellectual, or personal conflicts, with no substantial conflicts of interest identified. The data were analyzed, and the overall quality of evidence for each outcome was assessed by the 3 nonvoting members of the committee (C.I., N.K., N.S.) who had no involvement with any CCP trials and are authors of the Cochrane Reviews. Five members (L.J.E., A.C., E.M.B., T.W.R., A.A.R.T.) were either principal investigators or helped design a CCP trial. All members voted on each recommendation with the following exceptions: Drs. Tobian, Casadevall, and Bloch were excluded from voting on the recommendations for outpatient and prophylactic use, and Drs. Estcourt and Rice

were excluded from voting on the recommendations for inpatient use. A strong recommendation required more than 70% of the committee to vote “strongly for” the recommendation, and a weak recommendation required more than 70% of the committee to vote “for” the recommendation. Disagreements were handled by additional discussion and final voting.

Evidence Review and Grading

Systematic Review

The guidelines are based on separately published living systematic reviews of the literature on CCP published by Cochrane (11, 12). The systematic review was subsequently updated by Cochrane Haematology for these guidelines. This included all RCTs evaluating CCP that were available as either preprint or published articles between 1 January 2019 and 26 January 2022 (**Appendix Figure**, available at [Annals.org](#)). The intervention group was CCP from donors who had previously tested positive for SARS-CoV-2. The control groups included persons randomly assigned to nonimmune plasma, normal saline, or standard of care. The trials tested the efficacy of CCP for prophylaxis, patients in the outpatient setting, and hospitalized patients. Subgroup analyses were done to evaluate patients with SARS-CoV-2 antibodies detected at baseline compared with those who did not have antibodies, and a second subgroup analysis included patients with preexisting immunosuppression versus immunocompetent patients. The committee also evaluated the following 2 additional subgroups: patients with severity level 4 COVID-19 according to the World Health Organization (WHO) Clinical Progression Scale (**Supplement Table 2**, available at [Annals.org](#)) and duration of symptom onset 7 days or less versus greater than 7 days before receiving CCP; the committee did not vote on these categories (**Supplement Methods**, available at [Annals.org](#)).

Before reviewing the data, the committee voted on the most important primary outcomes for the different trial populations. The primary outcomes in the systematic review were SARS-CoV-2 infection status (postexposure prophylaxis trial), hospitalization or all-cause mortality within 28 days (outpatient trials), all-cause mortality within 28 days, and progression or need for invasive mechanical ventilation (WHO stage ≥ 7) (inpatient trials). Secondary outcomes included transfusion-related reactions, serious adverse events, ventilator-free days, admission to the intensive care unit, and duration of hospitalization.

Each clinical trial was assessed for the risk of bias for sequence generation, allocation concealment, blinding, and incomplete outcome data using methods recommended by Cochrane (13, 14). Additional details are also available in the **Supplement** (available at [Annals.org](#)). Statistical heterogeneity was assessed by both the I^2 and χ^2 tests (13). All analyses were done using Review Manager Web 2022 (Cochrane) (15). For dichotomous outcomes, we calculated the relative risks (RRs) and the corresponding 95% CIs in the intervention group compared with the control group. Meta-analyses were calculated for each comparison and outcome using fixed-effects and random-effects models (14).

Rating Certainty of Evidence

The committee used the GRADE method to develop the guidelines (16–18). The evidence profiles were prepared to display data in terms of benefits and harms for the most important outcomes. The profiles provided judgments by the Cochrane group about the rating for risk of bias, consistency, directness, precision, and publication bias. The credibility of subgroup effects was assessed using the ICEMAN (Instrument to assess the Credibility of Effect Modification Analyses) criteria (19). The panel reviewed the ratings and determined the strength of recommendations during the committee meeting.

Values and Preferences

The committee made their recommendations under the assumption that patients would highly value avoiding risks for disease progression, morbidity, and mortality from COVID-19. Thus, when the data suggested that there was limited harm from CCP transfusions and that there was benefit to CCP, the panel was prepared to make recommendations for CCP.

Guideline Use and Updates

New evidence will be evaluated by the Cochrane living systematic review (11, 12) and may be used to update these guidelines when substantial new findings are published. Use of CCP will depend on its availability at blood collection centers and hospital policies for treating patients with COVID-19.

Comments and Modification

The first, second, and last authors prepared the initial draft guideline document, which was modified and approved by all committee members. Subsequently, the AABB Board of Directors reviewed and approved the guidelines. Before publication, the guidelines were publicly available on the AABB website.

Additional Materials

Additional resources for the clinical use of CCP are available at the AABB Plasma Antibody Network site (www.aabb.org/get-involved/committees-sections/transfusion-medicine-section/plasma-antibody-network).

Disclaimer

This clinical practice guideline is not intended as an absolute standard and will not apply to all individual decisions on when to transfuse or withhold CCP.

RECOMMENDATIONS

Recommendation 1 (Outpatient)

The AABB suggests CCP transfusion in addition to the usual standard of care for outpatients with COVID-19 who are at high risk for disease progression (weak recommendation, moderate-certainty evidence).

Evidence Summary

There were 4 randomized trials that evaluated CCP transfusion to outpatients done in Argentina (Prevention of Severe Covid-19 in Infected Elderly by Early Administration

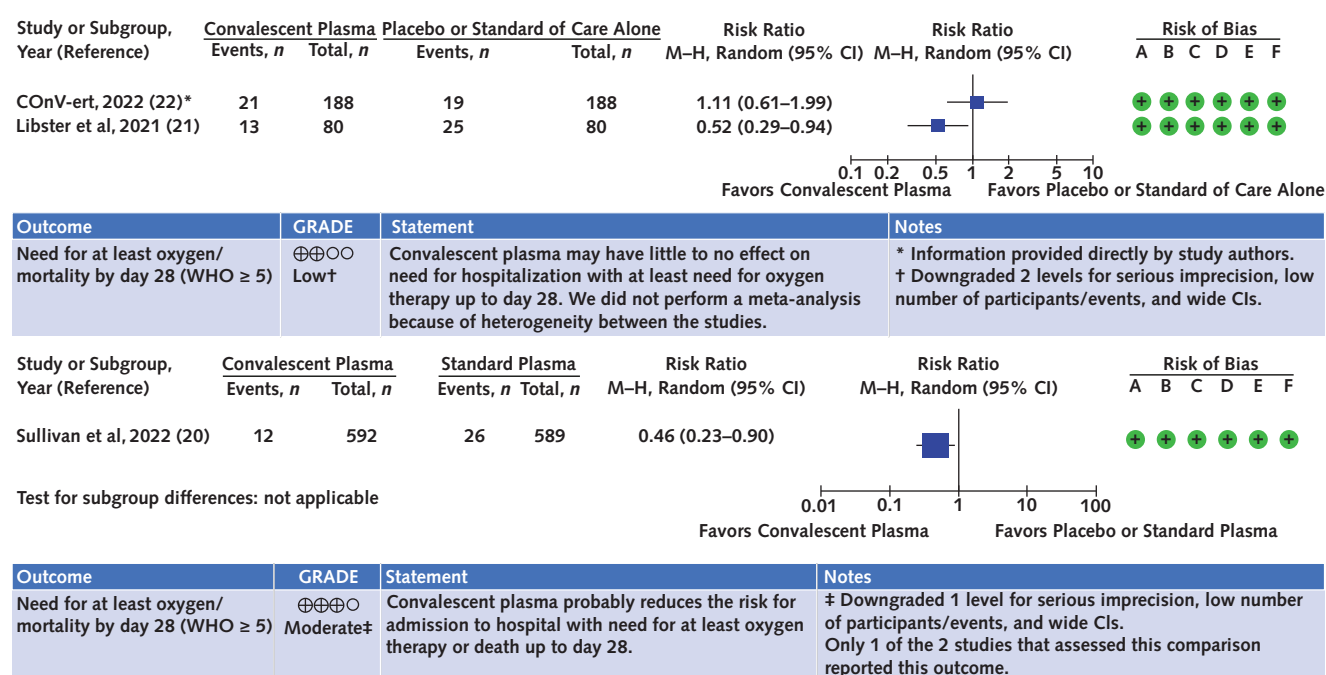
of Convalescent Plasma With High-titers of Antibody Against SARS-CoV2), Spain (CONV-ert [Convalescent Methylene Blue Treated {MBT} Plasma for Early Treatment in Non-hospitalised Mild or Moderate COVID-19 Patients: a Randomized Double Blind Study]), the United States (Convalescent Plasma to Limit SARS-CoV-2 Associated Complications [CSSC-004]), and the Netherlands (CoV-Early Study [Early Convalescent Plasma Therapy for High-risk Patients With COVID-19 in Primary Care]) (20–22). The CONV-ert and CoV-Early trials were published as pooled analyses (22). Data were requested, but only mortality data were available for the trial from the CoV-Early investigators ($n = 406$). The 3 other trials evaluated 1717 participants, including 860 who received 1 unit of high-titer CCP in the intervention group. Two trials compared CCP with a control group of saline placebo ($n = 536$), and 2 trials compared CCP with standard control plasma ($n = 1587$) (Supplement Table 3, available at Annals.org). All 4 trials required CCP transfusion within 9 days of symptom onset, but there was variability in CCP transfusion timing.

The Argentinian trial by Libster and colleagues (21) did not report any adverse events in either the intervention or control group. The CONV-ert trial reported a 5.9% rate of transfusion-related adverse events in the CCP group. The U.S. trial by Sullivan and colleagues (20) reported a 0.2% adverse event rate in the CCP group and a 0.3% adverse event rate in the control plasma group. Most adverse events in all trials were due to mild allergic reactions that are commonly observed with plasma transfusion (Supplement Table 4, available at Annals.org).

The trial analyses were stratified by the control group. For the outcome “need for either hospitalization requiring oxygenation (WHO ≥ 5) or death,” the trial by Sullivan and colleagues showed a statistically significant reduction (RR, 0.46 [95% CI, 0.23 to 0.90]), as did the trial by Libster and colleagues, but the CONV-ert trial did not show a benefit (Figure 1). The overall certainty of evidence for the trial by Libster and colleagues and the CONV-ert trial was low and downgraded for serious imprecision, low number of participants, and wide CIs (Supplement Table 5, available at Annals.org). The overall certainty of the evidence was moderate for the trial by Sullivan and colleagues (Supplement Table 6, available at Annals.org). All 4 trials contributed data to the mortality at 28 days outcome (Supplement Figure 1, available at Annals.org). There may be a reduction in mortality, but it was not statistically significant.

Rationale for Recommendation

As the primary outcome of interest was preventing hospitalizations that required oxygen and death, and because the overall rate and severity of adverse events was low, the committee voted to suggest CCP for outpatients at high risk for disease progression as defined by the WHO. The trials by Libster and colleagues and Sullivan and colleagues provide very similar efficacy estimates. There was concern that data from the CONV-ert trial was not consistent with data from the trials by Libster and colleagues and Sullivan and colleagues. The CONV-ert data inconsistency could reflect the use of methylene blue treated CCP given that methylene blue has been

Figure 1. CCP transfusion for outpatients with COVID-19.

The **top panel** compares CCP to standard of care or placebo with the outcome of need for hospitalization with need of at least oxygen by mask or nasal prongs or death. The **bottom panel** compares CCP to standard plasma with the outcome of need for hospitalization with need of at least oxygen by mask or nasal prongs or death. For risk of bias assessment explanation and GRADE assessment, see the Supplement Methods (available at [Annals.org](#)). For WHO grading, see Supplement Table 8 (available at [Annals.org](#)). CONV-ert = Convalescent Methylene Blue Treated (MBT) Plasma for Early Treatment in Non-hospitalised Mild or Moderate COVID-19 Patients: a Randomized Double Blind Study; GRADE = Grading of Recommendations Assessment, Development and Evaluation; M-H = Mantel-Haenszel; WHO = World Health Organization.

reported to interfere with immunoglobulin function (23). Overall, there is biological plausibility for CCP to be used as a passive immunotherapy for outpatients. This is based on early use of CP with other viruses; monoclonal antibody therapy has also been shown to reduce risk for hospitalization for outpatients recently infected with SARS-CoV-2 (24).

Recommendation 2 (Inpatient)

The AABB recommends against CCP transfusion for unselected hospitalized persons with moderate or severe disease (strong recommendation, high-certainty evidence). This recommendation does not apply to immunosuppressed patients or those who lack antibodies against SARS-CoV-2.

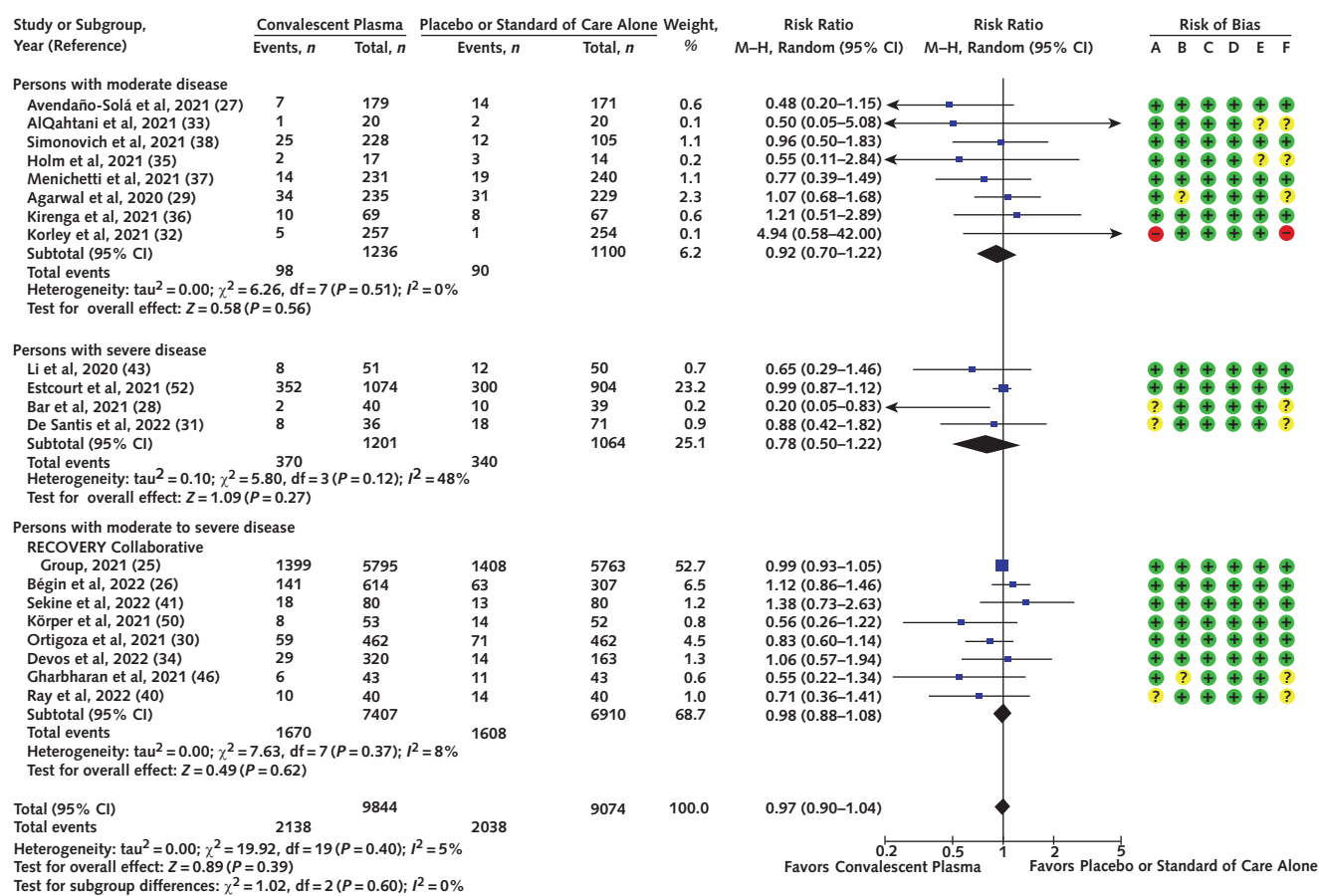
Evidence Summary

There were 28 randomized trials that evaluated CCP in hospitalized patients; 22 trials compared CCP versus placebo or standard of care, 5 trials compared CCP versus standard plasma, and 1 trial compared CCP versus immunoglobulin (Supplement Table 7, available at [Annals.org](#)) (25–52). Hospitalized patients included those requiring emergency department care, and therefore the study by Korley and colleagues (32) was included within the inpatient studies. The primary predefined end points included all-cause mortality at 28 days and disease progression

defined as the need for invasive mechanical ventilation or death (WHO stage ≥7). The trials were done among hospitalized patients with moderate or severe COVID-19 in North America, South America, Europe, Africa, and Australia and involved 19 625 participants. One to 3 units of CCP were transfused in the intervention group of the trials. Although nearly all trials used high-titer CCP, there was substantial variability in the antibody profiles of CCP provided. There was also variability as to when the CCP was transfused, ranging from the emergency department to more than a week after hospital admission.

The transfusion-related adverse events in the intervention group ranged from 0% to 15%. Most of the reported events were minor, transient transfusion reactions. However, 2 trials reported 3 possible deaths each related to CCP (Supplement Table 8, available at [Annals.org](#)) (25, 29).

Among unselected hospitalized patients receiving CCP compared with either placebo or standard of care, CCP did not affect all-cause mortality at 28 days (RR, 0.97 [CI, 0.90 to 1.04]) (Figure 2). The overall certainty of the evidence was high (Supplement Table 9, available at [Annals.org](#)). Among unselected hospitalized patients receiving CCP compared with standard plasma, CCP did not affect all-cause mortality at 28 days (RR, 0.73 [CI, 0.45 to 1.19]) (Supplement Figure 2, available at [Annals.org](#)). The overall certainty in the evidence was low (Supplement

Figure 2. CCP transfusion versus standard of care or placebo for hospitalized patients.

Outcome	GRADE	Statement	Notes
All-cause mortality by day 28	⊕⊕⊕⊕ High	Convalescent plasma does not reduce all-cause mortality at up to day 28.	Twenty of the 22 included studies that compared convalescent plasma versus standard of care or placebo in hospitalized patients reported this outcome.

The primary outcome was all-cause mortality at day 28. For risk of bias assessment explanation and GRADE assessment, see the Supplement Methods (available at [Annals.org](#)). df = degrees of freedom; GRADE = Grading of Recommendations Assessment, Development and Evaluation; M-H = Mantel-Haenszel.

Table 10, available at [Annals.org](#)). The CCP also had no effect on clinical improvement (that is, weaning or liberation of mechanical ventilation) when compared with placebo or standard of care (RR, 1.05 [CI, 0.96 to 1.14]) or plasma (RR, 5.59 [CI, 0.29 to 108.38]) (Supplement Figure 3, available at [Annals.org](#)).

Rationale for Recommendation

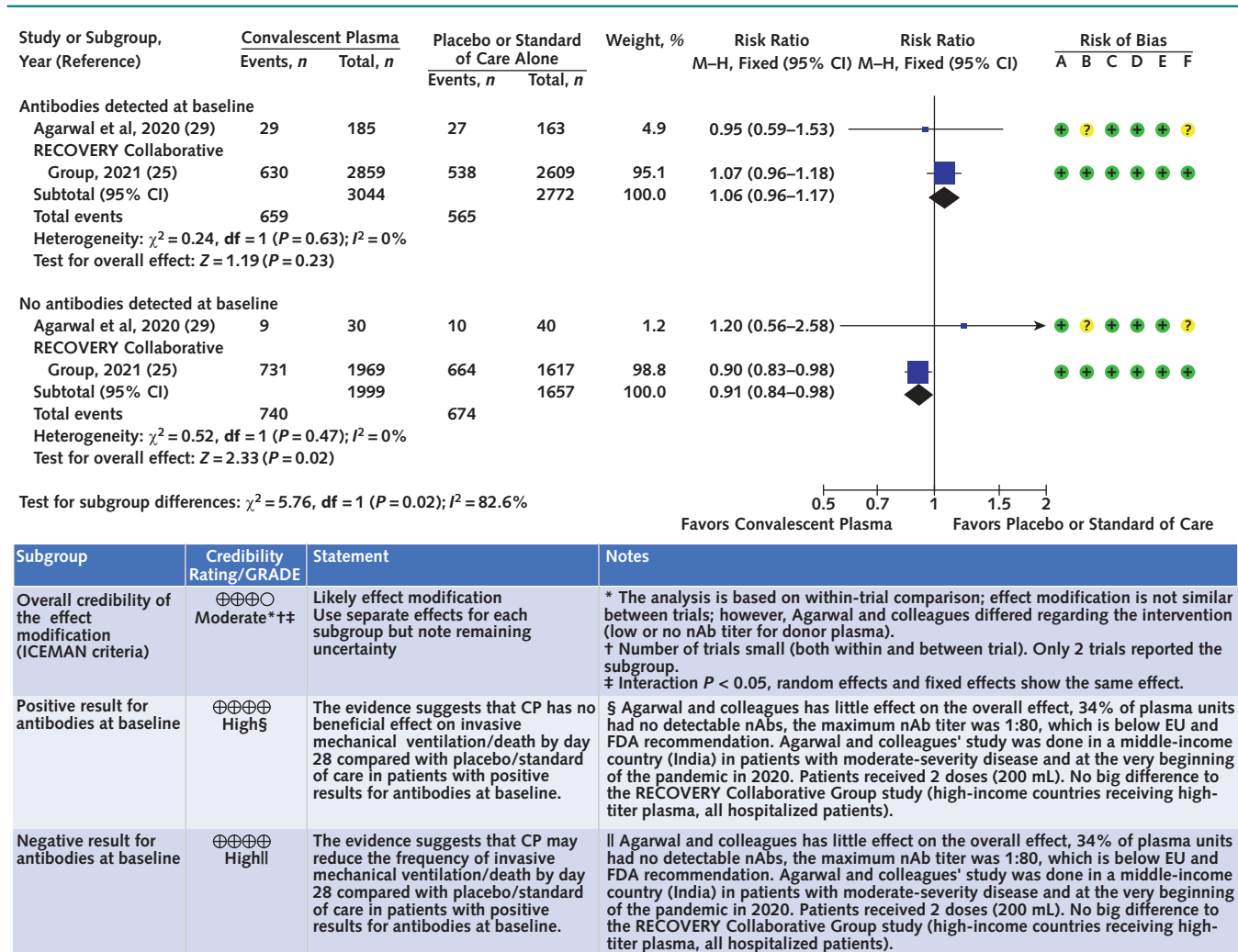
The CCP seemed to be relatively safe as the vast majority of adverse events were minor, transient reactions despite the very rare possibility of death. However, there was no consistent evidence showing that CCP for unselected hospitalized patients reduces mortality or leads to clinical improvement. These data are consistent with biological plausibility that viral neutralization would have no effect on persons with advanced disease who are in the postviral phase of COVID-19 with systemic inflammation and cytokine storm.

Recommendation 3 (Inpatient)

The AABB suggests CCP transfusion in addition to the usual standard of care for hospitalized patients who do not have SARS-CoV-2 antibodies detected at admission (weak recommendation, low-certainty evidence).

Evidence Summary

There were 6 randomized trials of hospitalized patients with data on whether SARS-CoV-2 antibodies were present at baseline to assess whether CCP conferred benefit among patients who lacked antibodies compared with those with antibodies (25, 27-30, 52). There were 2 trials that assessed whether CCP was beneficial for this subgroup using a composite outcome of either need for invasive mechanical ventilation or mortality at 28 days (25, 29). These 2 trials had data for 9472 participants. Among those with antibodies, there was no difference in need for mechanical ventilation or mortality

Figure 3. CCP transfusion versus standard of care or placebo stratified by status of SARS-CoV-2 antibodies at baseline.

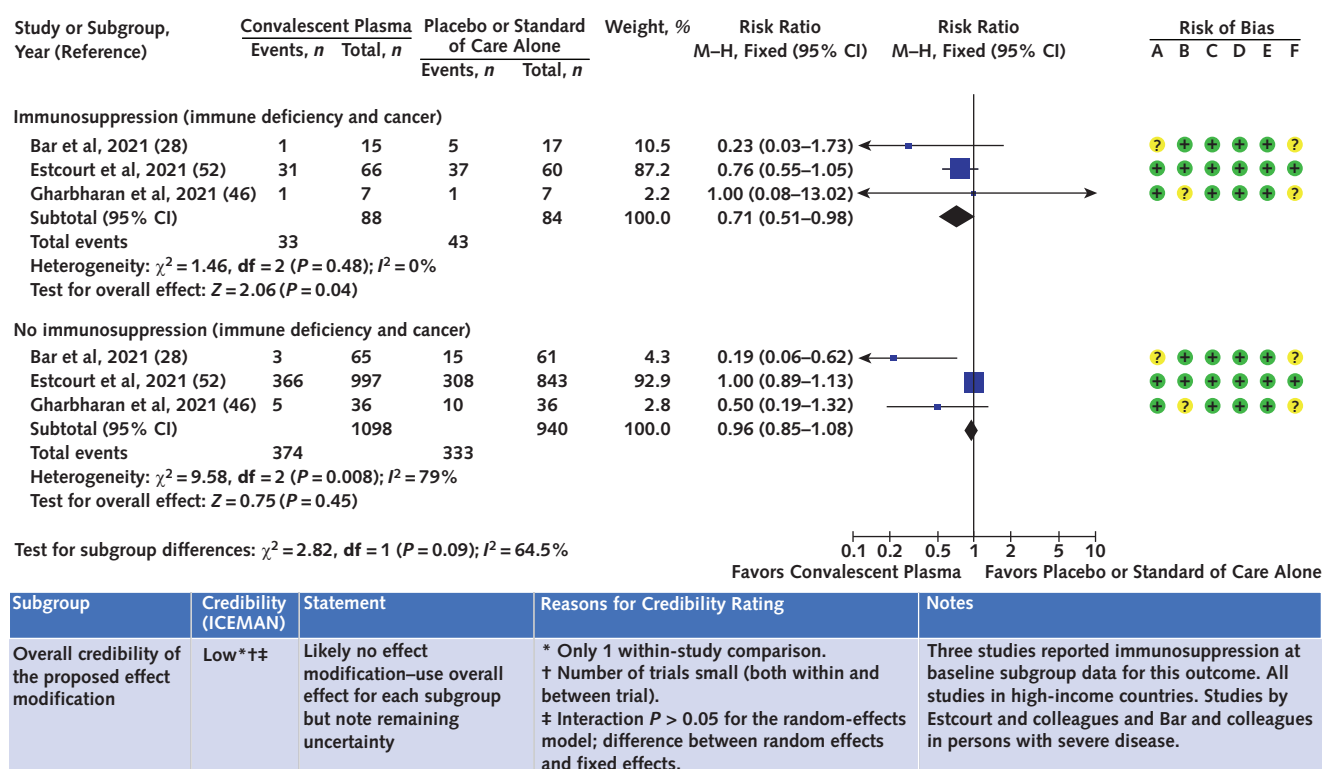
The primary outcome was need for invasive mechanical ventilation or death at 28 days in hospitalized patients. For risk of bias assessment explanation and GRADE assessment, see the Supplement Methods (available at [Annals.org](#)). CP = convalescent plasma; df = degrees of freedom; EU = European Union; FDA = U.S. Food and Drug Administration; GRADE = Grading of Recommendations Assessment, Development and Evaluation; ICEMAN = Instrument to assess the Credibility of Effect Modification Analyses; M-H = Mantel-Haenszel; nAb = neutralizing antibody titer.

between those who received CCP and those who received standard of care or placebo (Figure 3). However, among hospitalized patients who lacked SARS-CoV-2 antibodies at baseline, CCP decreased the need for mechanical ventilation or mortality compared with standard of care or placebo (RR, 0.91 [CI, 0.84 to 0.98]). For this subgroup difference, the I^2 was 82.6% with $P = 0.020$. The overall credibility of the effect modification was moderate. Among the 5 trials that evaluated only mortality, similar direction of effect was seen favoring CCP use for those persons who lacked SARS-CoV-2 antibodies at the time of hospitalization (Supplement Figure 4, available at [Annals.org](#)).

Rationale for Recommendation

Although these subgroup data are in contrast to the overall unselected hospitalized patient data, the committee found that there was moderate certainty of a subgroup difference to suggest that CCP should be transfused to

hospitalized patients without SARS-CoV-2 antibodies at baseline. The subgroup difference was seen with both random- and fixed-effects models. Because of the large quantity of data originating from the RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial, the certainty of the evidence was high. Evaluating the presence or absence of antibodies was also a prespecified outcome for many of the trials. Finally, there is biological plausibility for CCP being most beneficial for those without antibodies. Besides the recipients initially lacking antibodies, the humoral response is not as effective when it initially begins to develop. The SARS-CoV-2 antibody response improves with time, including increased avidity and isotype switching, that likely leads to improved viral neutralization (53). Throughout history, CP has consistently been most effective when provided early in the course of disease. Observational data have also shown that CCP is most effective when provided earlier to hospitalized patients

Figure 4. CCP transfusion versus standard of care or placebo stratified by immunosuppression status.

The primary outcome was all-cause mortality at 28 days in hospitalized patients. For risk of bias assessment explanation and GRADE assessment, see the Supplement Methods (available at [Annals.org](https://www.annals.org)). df = degrees of freedom; GRADE = Grading of Recommendations Assessment, Development and Evaluation; ICEMAN = Instrument to assess the Credibility of Effect Modification Analyses; M-H = Mantel-Haenszel.

(54, 55). Thus, the committee noted that in immunocompetent patients, the lack of a detectable antibody response could be used as a surrogate for early infection.

Recommendation 4 (Inpatient)

The AABB suggests CCP transfusion in addition to the usual standard of care for hospitalized patients with preexisting immunosuppression (weak recommendation, low-certainty evidence).

Evidence Summary

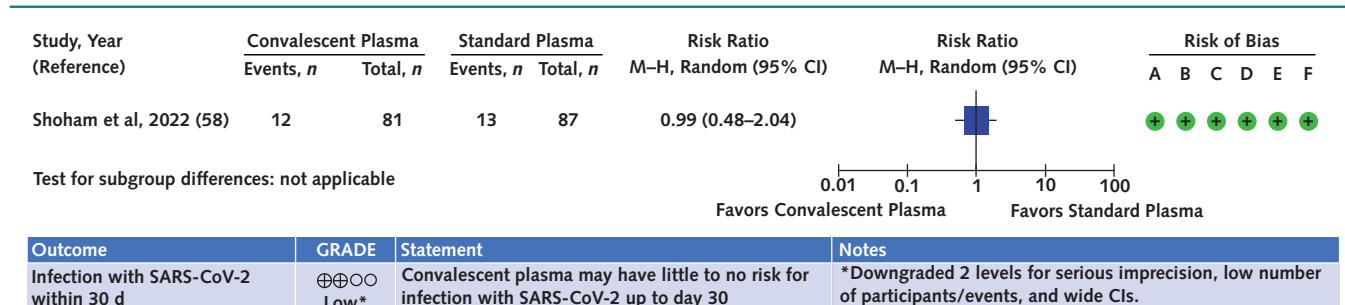
There were 3 randomized trials that evaluated whether CCP was efficacious among hospitalized patients with preexisting immunosuppression (cancer, steroids, B-cell-depleting therapies, and so forth) (28, 46, 52). The 3 trials had immune status data on 2210 enrolled participants. A forest plot shows there was no difference in mortality at 28 days among immunocompetent persons who received CCP versus the standard of care or placebo (Figure 4). However, among immunosuppressed hospitalized patients at baseline, CCP decreased mortality compared with standard of care or placebo (RR, 0.71 [CI, 0.51 to 0.98]). For this subgroup difference, the I^2 was 64.5% with $P = 0.090$. There was no evidence of effect modification. By ICEMAN criteria, the overall credibility of the subgroup effect was low. This was likely because of the small numbers and wide CIs so there was remaining uncertainty.

Rationale for Recommendation

Although the subgroup difference was not statistically significant, the committee suggests with low-certainty evidence that CCP should be provided in addition to the usual standard of care for hospitalized patients with preexisting immunosuppression. Most of the data were derived from the REMAP-CAP (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia) trial, which had a prespecified outcome of evaluating CCP efficacy in immunosuppressed patients. Patient preferences were considered because this patient population has limited therapeutic options. Patients with preexisting immunosuppression do not respond well to SARS-CoV-2 vaccines and are also at the highest risk for severe complications from COVID-19 (56, 57). In addition, there is biological plausibility that CCP would be beneficial as CCP provides antibodies to help neutralize the virus among persons who are not able to mount an antibody response.

Recommendation 5 (Prophylaxis)

The AABB suggests against prophylactic CCP transfusion for uninfected persons with close contact exposure to a person with COVID-19 (weak recommendation, low-certainty evidence).

Figure 5. CCP transfusion versus standard plasma as prophylaxis to prevent infection with SARS-CoV-2 within 30 days.

For risk of bias assessment explanation and GRADE assessment, see the Supplement Methods (available at [Annals.org](#)). df = degrees of freedom; GRADE = Grading of Recommendations Assessment, Development and Evaluation; M-H = Mantel-Haenszel.

Evidence Summary

One trial evaluated 168 adults across 19 sites in the United States who had close contact exposure to a person with confirmed COVID-19 in the previous 5 days and a negative SARS-CoV-2 polymerase chain reaction test within the 24 hours before transfusion (Supplement Table 11, available at [Annals.org](#)) (58). Persons were randomly assigned to 1 unit of high-titer CCP (*n* = 87) or standard plasma (*n* = 81). The median time from exposure to transfusion was 2 days (interquartile range, 1 to 4 days). A forest plot (Figure 5) shows no statistically significant difference in the development of infection between the 2 trial groups (RR, 0.99 [CI, 0.48 to 2.04]). There were no statistically significant differences between trial groups for admission to the hospital within 30 days (RR, 0.21 [CI, 0.01 to 4.39]) or development of clinical COVID-19 symptoms (RR, 0.92 [CI, 0.32 to 2.62]) (Supplement Figures 5 and 6, available at [Annals.org](#)). There were 28 adverse events in the CCP group and 58 in the control group (Supplement Table 12, available at [Annals.org](#)). The overall quality of the RCT evidence for infection within 30 days was low (Supplement Table 13, available at [Annals.org](#)). The data were downgraded 2 levels for serious imprecision, low number of participants and events, and wide CIs.

Rationale for Recommendation

There was no consistent evidence showing that 1 unit of high-titer CCP prevents SARS-CoV-2 infection among highly exposed persons. The CCP data are in contrast to data showing that monoclonal antibodies prevent SARS-CoV-2 infection (59). The differences between CCP and monoclonal antibodies could be due to the quality and/or quantity of antibody present in CCP, different trial populations, and the limited data from only 1 CCP trial. The AABB suggests against prophylactic CCP transfusion because there was no conclusive evidence showing the benefits of CCP in this setting.

GOOD CLINICAL PRACTICE STATEMENT

Both observational data (54, 55, 60) and randomized trial data showed that CCP is most effective when transfused to infected patients at the earliest possible time

and with high neutralizing antibody titers. However, the randomized trial data were difficult to interpret for hospitalized patients with symptoms present less than 7 days or patients with stage 4 COVID-19 severity according to the WHO Clinical Progression Scale (Supplement Figures 7 to 11, available at [Annals.org](#)). For outpatients, it is good practice to transfuse CCP within 5 days of symptom onset, and CCP transfusion continues to be effective up to 9 days after symptom onset (20). In addition to the timing, high-titer CCP units are the most effective (21, 54), and high-titer CCP can now be obtained from persons who have had a primary infection and vaccination (61).

DISCUSSION

During the initial waves of the pandemic, CCP became one of the most commonly used therapies despite limited data on its efficacy. Now that data are available, the AABB suggests high-titer CCP transfusion for infected patients who are outpatients with risk for progression, those without detectable SARS-CoV-2 antibodies, and those who are immunosuppressed. The AABB recommends against CCP transfusion for those patients with later-stage COVID-19.

The beneficial effects of CCP are primarily associated with its neutralizing antibodies, which target SARS-CoV-2 and assist in viral clearance (62, 63). Thus, persons who benefit the most from CCP are those treated early and who have not yet developed their own neutralizing antibodies. As SARS-CoV-2 antibody detection is easily available at most hospitals and also by point-of-care assays, the recommendations could be easily implemented. In addition to neutralization, CCP antibodies provide additional benefits, as they can also stimulate phagocytosis, complement activation and antibody dependent cellular cytotoxicity against SARS-CoV-2 (64). Overall, the efficacy is likely related to antibody avidity, the inflammatory environment, and multiple functions of the antibodies in CCP (53, 64, 65).

There are several advantages of CCP, especially as SARS-CoV-2 evolves and new variants of concern (VOCs) emerge. In vitro data suggest that high-titer CCP continues to be effective against the Omicron VOC (66, 67), which has many mutations in the spike glycoprotein. However, data indicate that the Omicron VOC and 2

sublineages of Omicron can evade most available monoclonal antibodies (68). Also, CCP can be collected from persons who have been both infected with SARS-CoV-2 and vaccinated, thus ensuring very high titers of neutralizing antibodies. Finally, CCP is relatively easy to collect, making it a less expensive therapeutic option than other passive antibody therapies.

There are limitations to these guidelines. Although the committee waited until most of the RCT data were available, there are still ongoing trials, and the evidence base remains incomplete. There is substantial variability in the quantity of neutralizing antibodies present in CCP units (63), and it is difficult to compare antibody titers across all trials because different assays were used to quantify the presence of antibodies. In addition, the ideal quantity of CCP needed is unknown. Fortunately, the FDA's emergency use authorization has now set minimum standards for titers permitted for CCP to be used, and these levels are higher than most of the CCP used in the trials. Many of the trials were initiated near the beginning of the pandemic, which led to confounding factors that have affected the trial results; these include changes in therapies and availability of highly effective vaccines. In addition, there was duplication of RCT results for late stages of disease and limited data available for early disease when CCP is most effective. Limited data are available on the role of CCP in the vaccinated population. The applicability of these guidelines may also vary depending on the disease severity of each VOC. However, CCP likely has the most potential with the current VOCs for persons with preexisting immunosuppression who do not respond well to vaccination.

In comparison with other CCP guidelines, the recommendations and authorizations from other societies and government agencies vary often by the timing of their most recent evaluation. In December 2021, the WHO issued 2 strong recommendations against CCP use for either patients with nonsevere COVID-19 or patients with severe COVID-19 (69). The WHO only recommends CCP use in the context of clinical trials. In April 2022, the National Institutes of Health COVID-19 Treatment Guidelines Panel recommended against CCP for immunocompetent hospitalized patients and stated that there is insufficient evidence to recommend either for or against CCP for outpatients or immunosuppressed hospitalized patients (70). In March 2022, the Infectious Diseases Society of America issued a strong recommendation against CCP for hospitalized patients with COVID-19 (71). However, the Infectious Diseases Society of America has a conditional recommendation to transfuse CCP for ambulatory patients with mild to moderate COVID-19 who are at high risk for progression and without other treatment options. In December 2021, the FDA revised the emergency use authorization to limit the use of high-titer CCP for patients with COVID-19 who are immunosuppressed (61). The AABB recommendations for those without antibodies or who are immunosuppressed are consistent with the FDA but may differ from the other societies because AABB specifically focused on targeted hospital patient populations who could receive CCP rather than unselected groups, many later in their

disease course. The AABB's recommendations for CCP use in outpatients at high risk for disease progression and against CCP use in unselected hospitalized patients with severe disease are consistent with other organizations.

There are several areas of uncertainty that would benefit from additional clinical trials. Although the AABB suggests that CCP should be provided for immunosuppressed patients with COVID-19, the committee strongly encourages additional research in this area. Additional data are also needed about the role of CCP in combination with other antiviral therapies. In addition, there are limited data on the safety and efficacy of CCP in pediatric patients and pregnant women.

In conclusion, the data about optimal use of CCP has dramatically advanced in the past 2 years. Similar to the historical data for use of CP in other viral outbreaks (1–4), randomized trial data have shown that CCP is most beneficial when the units contain high levels of neutralizing antibodies and are transfused early after infection. The AABB's recommendations are biologically consistent in supporting CCP transfusion for patients without antibodies. Coronavirus disease 2019 CP is relatively easy to obtain and often one of the first therapeutics available for emerging infections. These key principles will be important to incorporate during the current evolving pandemic and future epidemics.

From NHS Blood and Transplant and Radcliffe Department of Medicine, University of Oxford, United Kingdom (L.J.E.); University of Minnesota, Department of Laboratory Medicine and Pathology, Minneapolis, Minnesota (C.S.C.); University of Washington, Department of Laboratory Medicine and Pathology, Seattle, Washington (M.B.P.); Evidence-based Oncology, Department of Internal Medicine, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany (C.I., N.K., N.S.); University of California San Diego, Department of Pathology, La Jolla, California (E.S.A.); The Johns Hopkins University School of Medicine, Department of Pathology, Baltimore, Maryland (E.M.B., R.G., A.A.R.T.); Minneapolis, Minnesota (G.B.); The Johns Hopkins University School of Public Health, Department of Molecular Microbiology and Immunology, Baltimore, Maryland (A.C.); Canadian Blood Services, Vancouver, British Columbia, Canada (D.V.D.); University Health Network, Ted Rogers Centre for Heart Research, Toronto, and Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada (F.F.); NorthShore University Health System, Department of Pathology and Laboratory Medicine, Evanston, Illinois (T.J.G.); Innovative Blood Resources, Division of New York Blood Center Enterprises, St. Paul, Minnesota (J.G.); Washington University in St. Louis School of Medicine, Department of Pathology and Immunology, St. Louis, Missouri (B.J.G.); Mayo Clinic, Department of Anesthesiology and Perioperative Medicine, Rochester, Minnesota (M.J.J.); University of Utah, Department of Pathology, Salt Lake City, Utah (R.A.M.); University of New Mexico, Department of Pathology, Albuquerque, New Mexico (J.S.R.); Vanderbilt University Medical Center, Division of Allergy, Pulmonary, and Critical Care Medicine, Nashville, Tennessee (T.W.R.); Duke University, Department of Pathology, Durham, North Carolina (B.H.S.); Vitalant, Medical Affairs, Scottsdale, Arizona (R.R.V.); and Mayo Clinic, Department of Laboratory Medicine and Pathology, Rochester, Minnesota (J.L.W.).

Acknowledgment: The authors thank the trial participants, the Cochrane Group, and Imani Burgess and Sharon Carayiannis for administrative support.

Financial Support: By AABB.

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M22-1079.

Corresponding Author: Aaron A.R. Tobian, MD, PhD, Department of Pathology, School of Medicine, Johns Hopkins University, Carnegie 437, 600 North Wolfe Street, Baltimore, MD 21287; e-mail, atobian1@jhmi.edu.

Previous Posting: The guidelines were initially posted on the AABB website.

Author contributions are available at Annals.org.

References

1. Tobian A, Cohn CS, Shaz B. COVID-19 convalescent plasma. *Blood*. 2021. [PMID: 34695186] doi:10.1182/blood.2021012248
2. Casadevall A, Pirofski LA. The convalescent sera option for containing COVID-19. *J Clin Invest*. 2020;130:1545-1548. [PMID: 32167489] doi:10.1172/JCI138003
3. Luke TC, Kilbane EM, Jackson JL, et al. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment. *Ann Intern Med*. 2006;145:599-609. [PMID: 16940336]
4. Bloch EM, Shoham S, Casadevall A, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. *J Clin Invest*. 2020;130:2757-2765. [PMID: 32254064] doi:10.1172/JCI138745
5. Busch MP, Bloch EM, Kleinman S. Prevention of transfusion-transmitted infections. *Blood*. 2019;133:1854-1864. [PMID: 30808637] doi:10.1182/blood-2018-11-833996
6. Cohn CS, Estcourt L, Grossman BJ, et al. COVID-19 convalescent plasma: interim recommendations from the AABB. *Transfusion*. 2021;61:1313-1323. [PMID: 33586160] doi:10.1111/trf.16328
7. Joyner MJ, Bruno KA, Klassen SA, et al. Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients. *Mayo Clin Proc*. 2020;95:1888-1897. [PMID: 32861333] doi:10.1016/j.mayocp.2020.06.028
8. Carson JL, Guyatt G, Heddle NM, et al. Clinical practice guidelines from the AABB: red blood cell transfusion thresholds and storage. *JAMA*. 2016;316:2025-2035. [PMID: 27732721] doi:10.1001/jama.2016.9185
9. Kaufman RM, Djulbegovic B, Gernsheimer T, et al; AABB. Platelet transfusion: a clinical practice guideline from the AABB. *Ann Intern Med*. 2015;162:205-13. [PMID: 25383671] doi:10.7326/M14-1589
10. Association for the Advancement of Blood & Biotherapies. AABB conflicts of interest disclosure form. Accessed at www.aabb.org/membership/governance/committees/Pages/AABB-Conflicts-of-Interest-Disclosure-Form.aspx on 27 June 2022.
11. Piechotta V, Iannizzi C, Chai KL, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. *Cochrane Database Syst Rev*. 2021;5:CD013600. [PMID: 34013969] doi:10.1002/14651858.CD013600.pub4
12. Valk SJ, Piechotta V, Kimber C, et al. Convalescent plasma and hyperimmune immunoglobulin to prevent infection with SARS-CoV-2. *Cochrane Database Syst Rev*. 2020;12:CD013802. doi:10.1002/14651858.CD013802
13. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0. The Cochrane Collaboration; 2011. Accessed at <https://handbook-5-1.cochrane.org/> on 27 June 2022.
14. Higgins JPT, Thomas J, Chandler J, et al, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 6.0. The Cochrane Collaboration; 2019. Accessed at <https://training.cochrane.org/handbook/archive/v6> on 27 June 2022.
15. The Cochrane Collaboration. RevMan Web. Accessed at revman.cochrane.org on 27 June 2022.
16. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924-6. [PMID: 18436948] doi:10.1136/bmj.39489.470347.AD
17. Atkins D, Best D, Briss PA, et al; GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ*. 2004;328:1490. [PMID: 15205295]
18. Alonso-Coello P, Schünemann HJ, Moher J, et al; GRADE Working Group. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. *BMJ*. 2016;353:i2016. [PMID: 27353417] doi:10.1136/bmj.i2016
19. Schandelmaier S, Briel M, Varadhan R, et al. Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses. *CMAJ*. 2020;192:E901-E906. [PMID: 32778601] doi:10.1503/cmaj.200077
20. Sullivan DJ, Gebo KA, Shoham S, et al. Early outpatient treatment for Covid-19 with convalescent plasma. *N Engl J Med*. 2022;386:1700-1711. [PMID: 35353960] doi:10.1056/NEJMoa2119657
21. Libster R, Pérez Marc G, Wappner D, et al; Fundación INFANT-COVID-19 Group. Early high-titer plasma therapy to prevent severe covid-19 in older adults. *N Engl J Med*. 2021;384:610-618. [PMID: 33406353] doi:10.1056/NEJMoa2033700
22. Millat-Martinez P, Gharbharan A, Alemany A, et al; CoV-Early study group. Prospective individual patient data meta-analysis of two randomized trials on convalescent plasma for COVID-19 outpatients. *Nat Commun*. 2022;13:2583. [PMID: 35546145] doi:10.1038/s41467-022-29911-3
23. Ross V. Photodynamic action of methylene blue on antipneumococcal serum. *J Immunol*. 1938;35:351-69.
24. Siemieniuk RA, Bartoszko JJ, Díaz Martínez JP, et al. Antibody and cellular therapies for treatment of Covid-19: a living systematic review and network meta-analysis. *BMJ*. 2021;374:n2231. [PMID: 34556486] doi:10.1136/bmj.n2231
25. RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. *Lancet*. 2021;397:2049-2059. [PMID: 34000257] doi:10.1016/S0140-6736(21)00897-7
26. Bégin P, Callum J, Jamula E, et al; CONCOR-1 Study Group. Author correction: convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial. *Nat Med*. 2022;28:212. [PMID: 35022578] doi:10.1038/s41591-021-01667-1
27. Avendaño-Solá C, Ramos-Martínez A, Muñoz-Rubio E, et al; ConPlas-19 Study Group. A multicenter randomized open-label clinical trial for convalescent plasma in patients hospitalized with COVID-19 pneumonia. *J Clin Invest*. 2021;131. [PMID: 34473652] doi:10.1172/JCI152740
28. Bar KJ, Shaw PA, Choi GH, et al. A randomized controlled study of convalescent plasma for individuals hospitalized with COVID-19 pneumonia. *J Clin Invest*. 2021;131. [PMID: 34788233] doi:10.1172/JCI155114
29. Agarwal A, Mukherjee A, Kumar G, et al; PLACID Trial Collaborators. 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:m3939. [PMID: 33093056] doi:10.1136/bmj.m3939

30. Ortigoza MB, Yoon H, Goldfeld KS, et al; **CONTAIN COVID-19 Consortium for the CONTAIN COVID-19 Study Group**. Efficacy and safety of COVID-19 convalescent plasma in hospitalized patients: a randomized clinical trial. *JAMA Intern Med*. 2022;182:115-126. [PMID: 34901997] doi:10.1001/jamainternmed.2021.6850
31. De Santis GC, Oliveira LC, Garibaldi PMM, et al. High-dose convalescent plasma for treatment of severe COVID-19. *Emerg Infect Dis*. 2022;28:548-555. [PMID: 35081022] doi:10.3201/eid2803.212299
32. Korley FK, Durkalski-Mauldin V, Yeatts SD, et al; **SIREN-C3PO Investigators**. Early convalescent plasma for high-risk outpatients with Covid-19. *N Engl J Med*. 2021;385:1951-1960. [PMID: 34407339] doi:10.1056/NEJMoa2103784
33. AlQahtani M, Abdulrahman A, Almadani A, et al. Randomized controlled trial of convalescent plasma therapy against standard therapy in patients with severe COVID-19 disease. *Sci Rep*. 2021;11:9927. [PMID: 33976287] doi:10.1038/s41598-021-89444-5
34. Devos T, Van Thillo Q, Compemolle V, et al; **DAWn-plasma investigators**. Early high antibody titre convalescent plasma for hospitalised COVID-19 patients: DAWn-plasma. *Eur Respir J*. 2022;59. [PMID: 34446469] doi:10.1183/13993003.01724-2021
35. Holm K, Lundgren MN, Kjeldsen-Kragh J, et al. Convalescence plasma treatment of COVID-19: results from a prematurely terminated randomized controlled open-label study in Southern Sweden. *BMC Res Notes*. 2021;14:440. [PMID: 34863304] doi:10.1186/s13104-021-05847-7
36. Kirenga B, Byakika-Kibwika P, Muttamba W, et al. Efficacy of convalescent plasma for treatment of COVID-19 in Uganda. *BMJ Open Respir Res*. 2021;8. [PMID: 34376401] doi:10.1136/bmjresp-2021-001017
37. Menichetti F, Popoli P, Puopolo M, et al; **TSUNAMI Study group**. 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 Netw Open*. 2021;4:e2136246. [PMID: 34842924] doi:10.1001/jamanetworkopen.2021.36246
38. Simonovich VA, Burgos Pratz LD, Scibona P, et al; **PlasmAr Study Group**. A randomized trial of convalescent plasma in Covid-19 severe pneumonia. *N Engl J Med*. 2021;384:619-629. [PMID: 33232588] doi:10.1056/NEJMoa2031304
39. Pouladzadeh M, Safdarian M, Eshghi P, et al. A randomized clinical trial evaluating the immunomodulatory effect of convalescent plasma on COVID-19-related cytokine storm. *Intern Emerg Med*. 2021;16:2181-2191. [PMID: 33837906] doi:10.1007/s11739-021-02734-8
40. Ray Y, Paul SR, Bandopadhyay P, et al. A phase 2 single center open label randomised control trial for convalescent plasma therapy in patients with severe COVID-19. *Nat Commun*. 2022;13:383. [PMID: 35046397] doi:10.1038/s41467-022-28064-7
41. Sekine L, Arns B, Fabro BR, et al; **PLACOVID Study Group**. Convalescent plasma for COVID-19 in hospitalised patients: an open-label, randomised clinical trial. *Eur Respir J*. 2022;59. [PMID: 34244316] doi:10.1183/13993003.01471-2021
42. O'Donnell MR, Grinsztejn B, Cummings MJ, et al. A randomized double-blind controlled trial of convalescent plasma in adults with severe COVID-19. *J Clin Invest*. 2021;131:e150646. [PMID: 33974559] doi:10.1172/JCI150646
43. Li L, Zhang W, Hu Y, 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;324:460-470. [PMID: 32492084] doi:10.1001/jama.2020.10044
44. Baldeón ME, Maldonado A, Ochoa-Andrade M, et al. Effect of convalescent plasma as complementary treatment in patients with moderate COVID-19 infection. *Transfus Med*. 2022;32:153-161. [PMID: 35001439] doi:10.1111/tme.12851
45. Bennett-Guerrero E, Romeiser JL, Talbot LR, et al; **Stony Brook Medicine COVID Plasma Trial Group**. 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;49:1015-1025. [PMID: 33870923] doi:10.1097/CCM.0000000000005066
46. Gharbharan A, Jordans CCE, GeurtsvanKessel C, et al. Effects of potent neutralizing antibodies from convalescent plasma in patients hospitalized for severe SARS-CoV-2 infection. *Nat Commun*. 2021;12:3189. [PMID: 34045486] doi:10.1038/s41467-021-23469-2
47. Hamdy Salman O, Ail Mohamed HS. Efficacy and safety of transfusing plasma from COVID-19 survivors to COVID-19 victims with severe illness: a double-blinded controlled preliminary study. *Egypt J Anaesth*. 2020;36:264-72. doi:10.1080/11101849.2020.1842087
48. Bajpai M, Kumar S, Maheshwari A, et al. Efficacy of convalescent plasma therapy compared to fresh frozen plasma in severely ill COVID-19 patients: a pilot randomized controlled trial. *medRxiv*. Preprint posted online 27 October 2020. doi:10.1101/2020.10.25.20219337
49. Gonzalez JLB, González Gámez M, Mendoza Enciso EA, et al. Efficacy and safety of convalescent plasma and intravenous immunoglobulin in critically ill COVID-19 patients: a controlled clinical trial. *medRxiv*. Preprint posted online 31 March 2021. doi:10.1101/2021.03.28.21254507
50. Körper S, Weiss M, Zickler D, et al; **CAPSID Clinical Trial Group**. Results of the CAPSID randomized trial for high-dose convalescent plasma in patients with severe COVID-19. *J Clin Invest*. 2021;131. [PMID: 34464358] doi:10.1172/JCI152264
51. Effects of COVID-19 Convalescent Plasma (CCP) on Coronavirus-associated Complications in Hospitalized Patients (CAPRI) [clinical trial]. Accessed at <https://clinicaltrials.gov/ct2/show/NCT04421404> on 30 March 2022.
52. Estcourt LJ, Turgeon AF, McQuilten ZK, et al; **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;326:1690-1702. [PMID: 34606578] doi:10.1001/jama.2021.18178
53. Benner SE, Patel EU, Laeyendecker O, et al. SARS-CoV-2 antibody avidity responses in COVID-19 patients and convalescent plasma donors. *J Infect Dis*. 2020;222:1974-1984. [PMID: 32910175] doi:10.1093/infdis/jiaa581
54. Joyner MJ, Carter RE, Senefeld JW, et al. Convalescent plasma antibody levels and the risk of death from Covid-19. *N Engl J Med*. 2021;384:1015-1027. [PMID: 33523609] doi:10.1056/NEJMoa2031893
55. Arnold Egloff SA, Junglen A, Restivo JS, et al. Convalescent plasma associates with reduced mortality and improved clinical trajectory in patients hospitalized with COVID-19. *J Clin Invest*. 2021;131:e151788. [PMID: 34464352] doi:10.1172/JCI151788
56. Boyarsky BJ, Werbel WA, Avery RK, et al. Antibody response to 2-dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. *JAMA*. 2021;325:2204-2206. [PMID: 33950155] doi:10.1001/jama.2021.7489
57. Garibaldi BT, Fiksel J, Muschelli J, et al. Patient trajectories among persons hospitalized for COVID-19. A cohort study. *Ann Intern Med*. 2021;174:33-41. [PMID: 32960645] doi:10.7326/M20-3905
58. Shoham S, Bloch EM, Casadevall A, et al. Transfusing convalescent plasma as post-exposure prophylaxis against SARS-CoV-2 infection: a double-blinded, phase 2 randomized, controlled trial. *Clin Infect Dis*. 2022. [PMID: 35579509] doi:10.1093/cid/ciac372
59. O'Brien MP, Forleo-Neto E, Musser BJ, et al; **Covid-19 Phase 3 Prevention Trial Team**. Subcutaneous REGEN-COV antibody combination to prevent Covid-19. *N Engl J Med*. 2021;385:1184-1195. [PMID: 34347950] doi:10.1056/NEJMoa2109682
60. Salazar E, Christensen PA, Graviss EA, et al. Significantly decreased mortality in a large cohort of coronavirus disease 2019 (COVID-19) patients transfused early with convalescent plasma containing high-titer anti-severe acute respiratory syndrome coronavirus

- 2 (SARS-CoV-2) spike protein IgG. *Am J Pathol.* 2021;191:90-107. [PMID: 33157066] doi:10.1016/j.ajpath.2020.10.008
61. **U.S. Food and Drug Administration.** Fact sheet for health care providers: emergency use authorization (EUA) of COVID-19 convalescent plasma for treatment of coronavirus disease 2019 (COVID-19). Accessed at www.fda.gov/media/141478/download on 27 June 2022.
62. Bloch EM, Crowe EP, Tobian AAR. Coronavirus disease 2019 convalescent plasma and the severe acute respiratory syndrome coronavirus 2 neutralizing titer. *J Infect Dis.* 2021;223:740-742. [PMID: 33411937] doi:10.1093/infdis/jiab008
63. Klein SL, Pekosz A, Park HS, et al. Sex, age, and hospitalization drive antibody responses in a COVID-19 convalescent plasma donor population. *J Clin Invest.* 2020;130:6141-6150. [PMID: 32764200] doi:10.1172/JCI142004
64. Natarajan H, Crowley AR, Butler SE, et al. Markers of polyfunctional SARS-CoV-2 antibodies in convalescent plasma. *m. Bio.* 2021;12. [PMID: 33879585] doi:10.1128/mBio.00765-21
65. Bonny TS, Patel EU, Zhu X, et al. Cytokine and chemokine levels in coronavirus disease 2019 convalescent plasma. *Open Forum Infect Dis.* 2021;8:ofaa574. [PMID: 33553467] doi:10.1093/ofid/ofaa574
66. Schmidt F, Muecksch F, Weisblum Y, et al. Plasma neutralization properties of the SARS-CoV-2 Omicron variant [Preprint]. *medRxiv.* 2021. [PMID: 34931199] doi:10.1101/2021.12.12.21267646
67. Li M, Beck EJ, Laeyendecker O, et al. Convalescent plasma with a high level of virus-specific antibody effectively neutralizes SARS-CoV-2 variants of concern. *Blood Adv.* 2022;6:3678-3683. [PMID: 35443020] doi:10.1182/bloodadvances.2022007410
68. Iketani S, Liu L, Guo Y, et al. Antibody evasion properties of SARS-CoV-2 Omicron sublineages. *bioRxiv.* Preprint posted online 9 February 2022. doi:10.1101/2022.02.07.479306
69. **World Health Organization.** Therapeutics and COVID-19: living guideline. Accessed at www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.3 on 27 June 2022.
70. **National Institutes of Health.** Coronavirus disease 2019 (COVID-19) treatment guidelines. Accessed at www.covid19treatmentguidelines.nih.gov/ on 27 June 2022.
71. Bhimraj A, Morgan RL, Shumaker AH, et al. IDSA guidelines on the treatment and management of patients with COVID-19. Accessed at www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/ on 27 June 2022.

Author Contributions: Conception and design: C.S. Cohn, L.J. Estcourt, F. Foroutan, M.J. Joyner, T.W. Rice, B.H. Shaz, A.A.R. Tobian, R.R. Vassallo, J.L. Winters.

Analysis and interpretation of the data: E.S. Allen, E.M. Bloch, A. Casadevall, C.S. Cohn, D.V. Devine, L.J. Estcourt, F. Foroutan, T. J. Gniadek, R. Goel, J. Gorlin, B.J. Grossman, N. Kreuzberger, R. A. Metcalf, M.B. Pagano, J.S. Raval, T.W. Rice, B.H. Shaz, N. Skoetz, A.A.R. Tobian, R.R. Vassallo, J.L. Winters.

Drafting of the article: E.M. Bloch, A. Casadevall, C.S. Cohn, L.J. Estcourt, R. Goel, N. Skoetz, A.A.R. Tobian, J.L. Winters.

Critical revision of the article for important intellectual content: E.S. Allen, C.S. Cohn, L.J. Estcourt, F. Foroutan, T.J. Gniadek, R. Goel, J. Gorlin, B.J. Grossman, M.J. Joyner, R.A. Metcalf, M.B. Pagano, J.S. Raval, T.W. Rice, B.H. Shaz, A.A.R. Tobian, R.R. Vassallo, J.L. Winters.

Final approval of the article: E.S. Allen, G. Beaudoin, E.M. Bloch, A. Casadevall, C.S. Cohn, D.V. Devine, L.J. Estcourt, F. Foroutan, T.J. Gniadek, R. Goel, J. Gorlin, B.J. Grossman, C. Iannizzi, M.J. Joyner, N. Kreuzberger, R.A. Metcalf, M.B. Pagano, J.S. Raval, T.W. Rice, B.H. Shaz, N. Skoetz, A.A.R. Tobian, R.R. Vassallo, J.L. Winters.

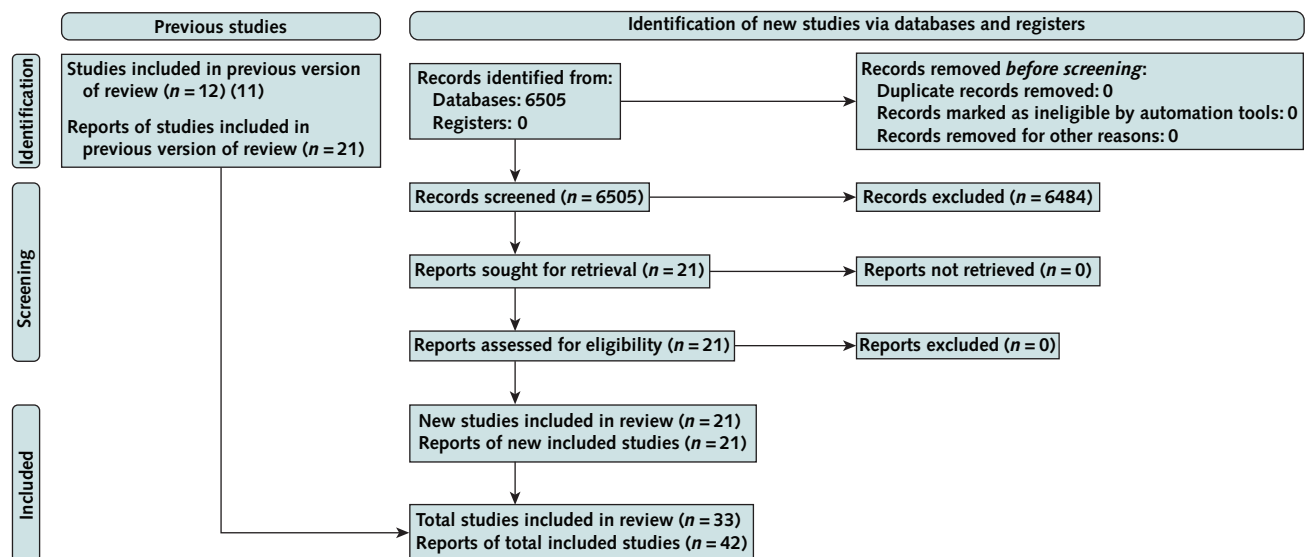
Provision of study materials or patients: G. Beaudoin.

Statistical expertise: L.J. Estcourt, F. Foroutan, N. Skoetz.

Administrative, technical, or logistic support: C.S. Cohn, T.W. Rice, A.A.R. Tobian.

Collection and assembly of data: L.J. Estcourt, C. Iannizzi, N. Kreuzberger, N. Skoetz.

Appendix Figure. PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram.



Modeled using Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. [PMID: 33782057] doi:10.1136/bmj.n71.