

Coronavirus Disease 2019 Convalescent Plasma Outpatient Therapy to Prevent Outpatient Hospitalization: A Meta-Analysis of Individual Participant Data From 5 Randomized Trials

Adam C. Levine,¹ Yuriko Fukuta,² Moises A. Huaman,³ Jiangda Ou,⁴ Barry R. Meisenberg,⁵ Bela Patel,⁶ James H. Paxton,⁷ Daniel F. Hanley,⁴ Bart J. A. Rijnders,⁸ Arvind Gharbharan,⁸ Casper Rokx,⁸ Jaap Jan Zwaginga,^{9,10} Andrea Alemany,^{11,12} Oriol Mitjà,^{11,12,13} Dan Ouchi,^{11,12} Pere Millat-Martinez,¹⁴ Valerie Durkalski-Mauldin,¹⁵ Frederick K. Korley,¹⁶ Larry J. Dumont,^{17,18} Clifton W. Callaway,¹⁹ Romina Libster,^{20,21} Gonzalo Perez Marc,²⁰ Diego Wappner,²⁰ Ignacio Esteban,²⁰ Fernando Polack,^{20,21} and David J. Sullivan²²

¹Department of Emergency Medicine, Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA; ²Infectious Disease, Department of Medicine, Baylor College of Medicine, Houston, Texas, USA; ³Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA; ⁴Division of Brain Injury Outcomes, Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; ⁵Department of Hematology–Oncology, Anne Arundel Medical Center, Annapolis, Maryland, USA; ⁶Division of Critical Care Medicine, McGovern Medical School, University of Texas Health Science Center, Houston, Texas, USA; ⁷Department of Emergency Medicine, Wayne State University School of Medicine, Detroit, Michigan, USA; ⁸Department of Internal Medicine, Section of Infectious Diseases and Department of Medical Microbiology and Infectious Diseases, Erasmus University Medical Center, University Medical Center, Rotterdam, The Netherlands; ⁹Department of Haematology, Leiden University Medical Centre, Leiden, The Netherlands; ¹⁰Center for Clinical Transfusion Research, Sanquin Blood Supply, Amsterdam, The Netherlands; ¹¹Fight Infectious Diseases Foundation, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; ¹²Infectious Diseases Department, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; ¹³Lihir Medical Centre, International SOS, Lihir Island, Papua New Guinea; ¹⁴ISGlobal, Department of Infectious Diseases, Hospital Clinic, Universitat de Barcelona, Barcelona, Spain; ¹⁵Department of Public Health Sciences, Medical University of South Carolina, Charleston, South Carolina, USA; ¹⁶Department of Emergency Medicine, University of Michigan, Ann Arbor, Michigan, USA; ¹⁷Vitalant Research Institute, Research Department, Denver, Colorado, USA; ¹⁸Department of Pathology, University of Colorado School of Medicine, Aurora, Colorado, USA; ¹⁹Department of Emergency Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA; ²⁰Fundación INFANT, Buenos Aires, Argentina; ²¹Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, Tennessee, USA; and ²²Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

(See the Editorial Commentary by Shoham on pages 2087–9.)

Background. Outpatient monoclonal antibodies are no longer effective and antiviral treatments for coronavirus disease 2019 (COVID-19) disease remain largely unavailable in many countries worldwide. Although treatment with COVID-19 convalescent plasma (CCP) is promising, clinical trials among outpatients have shown mixed results.

Methods. We conducted an individual participant data meta-analysis from outpatient trials to assess the overall risk reduction for all-cause hospitalizations by day 28 in transfused participants. Relevant trials were identified by searching Medline, Embase, medRxiv, World Health Organization COVID-19 Research Database, Cochrane Library, and Web of Science from January 2020 to September 2022.

Results. Five included studies from 4 countries enrolled and transfused 2620 adult patients. Comorbidities were present in 1795 (69%). The virus neutralizing antibody dilutional titer levels ranged from 8 to 14 580 in diverse assays. One hundred sixty of 1315 (12.2%) control patients were hospitalized, versus 111 of 1305 (8.5%) CCP-treated patients, yielding a 3.7% (95% confidence interval [CI], 1.3%–6.0%; $P = .001$) absolute risk reduction and 30.1% relative risk reduction for all-cause hospitalization. The hospitalization reduction was greatest in those with both early transfusion and high titer with a 7.6% absolute risk reduction (95% CI, 4.0%–11.1%; $P = .0001$) accompanied by a 51.4% relative risk reduction. No significant reduction in hospitalization was seen with treatment >5 days after symptom onset or in those receiving CCP with antibody titers below the median titer.

Conclusions. Among outpatients with COVID-19, treatment with CCP reduced the rate of all-cause hospitalization and may be most effective when given within 5 days of symptom onset and when antibody titer is higher.

Keywords. SARS-CoV-2; COVID-19 convalescent plasma; hospitalization; therapy; COVID-19.

Received 26 October 2022; editorial decision 23 January 2023; published online 21 February 2023

Correspondence: D. Sullivan, Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Rm W4606, 615 N Wolfe St, Baltimore, MD 21205 (dsullivan7@jhmi.edu).

Clinical Infectious Diseases® 2023;76(12):2077–86

© The Author(s) 2023. Published by Oxford University Press on behalf of Infectious Diseases Society of America.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<https://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com <https://doi.org/10.1093/cid/ciad088>

The coronavirus disease 2019 (COVID-19) pandemic is responsible for an estimated 18 million excess deaths through 2021 including >1 million in the United States [1]. Despite widespread vaccination in high- and middle-income countries, new variant outbreaks, including the December 2022 outbreak in China, continue to fuel economic disruptions and increased hospitalizations [2]. Novel vaccines and treatments against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been developed, tested, and deployed in record time, yet most arrived too late to benefit the millions of people who died in the pandemic's first year [1]. Three years into the COVID-19 pandemic, it remains unclear how we can respond faster and more effectively to the next pandemic [3, 4].

Antibodies to the SARS-CoV-2 virus, whether induced by vaccination or infused as monoclonal antibodies (mAbs) or polyclonal convalescent plasma, have been shown to reduce the risk of COVID-19-related hospitalization and death, but only convalescent plasma is likely to be both available and affordable for the majority of the world in the early days of the next viral pandemic [5]. COVID-19 convalescent plasma (CCP) was first administered to a hospitalized patient in China in January 2020 [6] and in the United States in March 2020 [7]. Meanwhile, mAbs to prevent hospitalization [8, 9] and vaccines [10, 11] to prevent symptomatic infection, hospitalization, or death were not available until December 2020. By that time, more than 79 million cases of COVID-19 and 1.7 million deaths had been reported worldwide [12]. Effective oral drug therapy for outpatient use was not available until December 2021 [13]. While safe and effective oral agents against SARS-CoV-2 are ideal to prevent COVID-19 hospitalizations, this solution remains unavailable to many patients worldwide due to high costs [14, 15], with effectiveness threatened at any time by new resistant variants.

Escape spike protein mutations leading to acquired resistance during treatment with a single mAb have been repeatedly described in immunocompromised patients [16, 17]. The rapid rise of variants with spike protein mutations has created a dilemma in mAb development, as pharmaceutical companies weigh the high development cost against short-lived utility [18]. Now that all authorized mAbs are no longer effective against recent omicron variants like BQ.1.1 [19–21], CCP, which can be continuously updated from regionally circulating variants, remains an important therapeutic option, especially for severely immunocompromised and other high-risk patients [22, 23].

Most initial randomized controlled trials (RCTs) of CCP were conducted in patients already hospitalized with COVID-19, largely due to the convenience of conducting research in this population. Later in the pandemic, RCTs of CCP targeting outpatients were designed to determine whether early CCP treatment could prevent hospitalization, though few

had sufficient power on their own to measure this outcome. Our objective in this study was to conduct an individual patient meta-analysis of all available RCTs of CCP in adult COVID-19 outpatients to determine whether early CCP therapy reduces hospitalization.

METHODS

This study followed the guidelines provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [24].

Objectives

This review aimed to find, assess, and synthesize all RCTs that assessed the efficacy of CCP in preventing all-cause hospitalization among outpatients with confirmed symptomatic SARS-CoV-2 infection.

Eligibility, Search Strategy, RCT Selection, and Data Extraction and Quality

Our PICO (population, intervention, comparator, and outcome) included the following: population = adult (≥ 18 years) COVID-19 outpatients (not hospitalized at time of transfusion with CCP or placebo) regardless of risk factors; intervention = intravenous CCP transfusion, qualified by antibody titer; comparators = control (nonconvalescent plasma or normal saline); and outcome = all-cause hospitalization within 28 days of transfusion. We used a modified intention-to-treat (mITT) analysis, which included patients for whom transfusion with CCP or placebo was initiated (though not necessarily completed). For 1 study in Argentina, patients meeting prespecified hypoxic respiratory criteria were sometimes admitted to a specific unit within their long-term care facilities, which provided hospital-level care, to avoid overcrowding hospitals. For purposes of trial eligibility, we considered these admissions to be hospitalizations. Only English-language documents were reviewed.

A literature search was performed independently by 2 authors (Y. F., D. J. S.). The Medline, Embase, medRxiv, Cochrane Library, World Health Organization COVID-19 Research Database, and Web of Science were searched for all RCTs as of 30 September 2022. Search strategies were designed with terms related to CCP and COVID-19 (Supplementary Figure 1). All RCTs were included that met the eligibility criteria above. We contacted the corresponding authors for each of the included trials and asked them to contribute data and serve as coauthors for the prepared manuscript.

The investigators for each RCT provided the following data elements: trial design characteristics, descriptions of the intervention and control groups, baseline characteristics of the patients (including underlying comorbidities and days after symptom onset), CCP characteristics (eg, antibody titers), hospitalizations, enrollment period, target enrollment, number of

enrollments, number of transfusions, and trial locations. Data not provided in the published reports were collected from the authors.

A risk of bias assessment was independently performed by COVID-19 Network Meta-Analysis [25, 26].

Statistical Analysis

Primary and secondary analyses were done in the mITT population including all randomized participants who received the intervention (CCP or control). The primary outcome used for analysis was all-cause hospitalization within 28 days of transfusion, and the secondary outcome was all-cause hospitalization among those patients admitted to hospitals >24 hours after transfusion. Two subgroup analyses were performed: (1) the reduction in hospital admission for patients with ≤ 5 versus > 5 days of symptoms at the time of intervention; and (2) the reduction in hospitalizations for patients receiving CCP with antibody titers above the median SARS-CoV-2 antibody titer value for each individual RCT versus those receiving CCP not above the median.

Descriptive analysis included the country in which the study was conducted, patient demographics, days since symptom onset, plasma donor antibody levels, and high-risk comorbidities. Box plots were used for visualization and comparison of viral neutralization among studies. Treatment effect was determined using the absolute risk reduction (ARR), relative risk reduction (RRR), and number needed to treat (NNT). Odds ratio (OR), 95% confidence interval (CI), weight of each study (inverse of the variances), heterogeneity (I^2), between-study variance (τ^2), and significance levels were estimated using mixed random-effects models and displayed in forest plots. A funnel plot was used to estimate the risk of publication bias. The significance level for analyses was set at .05. All of the data manipulation and analyses were performed using Excel software and R software (version 4.2.0, R Foundation, Vienna, Austria) and its statistical packages “meta” (version 6.0-0) and “metafor” (version 3.8-1).

RESULTS

Trial Population

A total of 617 studies were identified by our primary search strategy. After screening and exclusion of ineligible studies, 5 RCTs were included (Figure 1). Two were conducted in the United States [27, 28], 2 in Europe [29, 30], and 1 in Argentina [31]. All of the trials were stopped early: 1 due to slow recruitment as COVID-19 cases in the trial region decreased considerably [31], 3 due to rapid uptake of vaccination resulting in substantial reduction in hospital admission rates [27, 29, 30], and 1 due to a finding of futility to detect the planned difference after the second planned interim analysis of the primary outcome analysis [28].

The 5 RCTs enrolled 2693 patients from June 2020 to October 2021 [27–31], and transfusion was initiated in 2620 patients (Table 1). Seventy-three patients were either hospitalized or withdrew from the study after randomization but before transfusion with CCP or placebo could be initiated. These 5 trials varied in terms of their demographic and clinical profiles, including median age, sex distribution, and the prevalence of major risk factors for COVID-19–related hospitalization (Table 1). The target study populations were all COVID-19 outpatient participants regardless of comorbidities (diabetes, cardiovascular, or lung disease) without contraindication to plasma transfusion. Studies also varied somewhat in the timing of the intervention, although 1562 patients (60%) were transfused within 5 days of symptom onset. Overall, only 159 (6%) of all patients were fully vaccinated (defined as 2 messenger RNA doses or 1 adenovirus-vectored dose). We found that the risk of bias was low for the 5 RCTs (Supplementary Table 1). Funnel plot analysis did not suggest a risk of publication bias (Supplementary Figure 2).

Convalescent Plasma

The included studies used diverse assays to qualify and characterize the CCP transfused in study subjects (Supplementary Table 2). There was insufficient residual donor plasma samples available to compare neutralization titers across the different studies using the same assay. Two studies qualified units with 50% viral neutralization dilutional plasma titers $> 1:160$. Two studies qualified with dilutional antibody binding greater than 1000 or 320, while the last measured Euroimmun immunoglobulin G was > 6.0 AU. Separate viral neutralization indices, depicted in Supplementary Figure 3, show that COVID-19 serologic studies consortium (CSSC-004) and COVID-19 convalescent plasma-Argentina (CCP-Argentina) had slightly lower viral neutralization metrics, albeit a different viral neutralization assay than clinical-trial of COVID-19 convalescent plasma in outpatients (C3PO), early convalescent plasma therapy (CoV-Early), and convalescent methylene blue treated (MBT) plasma for early treatment (CONV-ERT).

Primary Outcome: Hospitalization

Modified intention-to-treat analysis (Table 2) was performed on patients who received either CCP or control. CSSC-004 added 7 all-cause hospitalizations (4 CCP and 3 control plasma) above reported COVID-19–related hospitalizations and C3PO added 2 participants hospitalized after day 15 but before day 28. Overall, 160 (12.2%) subjects in the control group were hospitalized, compared to 111 (8.5%) in the CCP treatment group, yielding an ARR of 3.7% (95% CI, 1.3%–6.0%), NNT of 27, and RRR of 30.1% (95% CI, 12.0%–44.4%) for all-cause hospitalization (Table 2). The OR for hospitalization was 0.64 (95% CI, .45–.92) in the pooled meta-analysis, and trial heterogeneity was moderate, with an I^2 of 42% (Figure 2). A secondary analysis was conducted excluding those

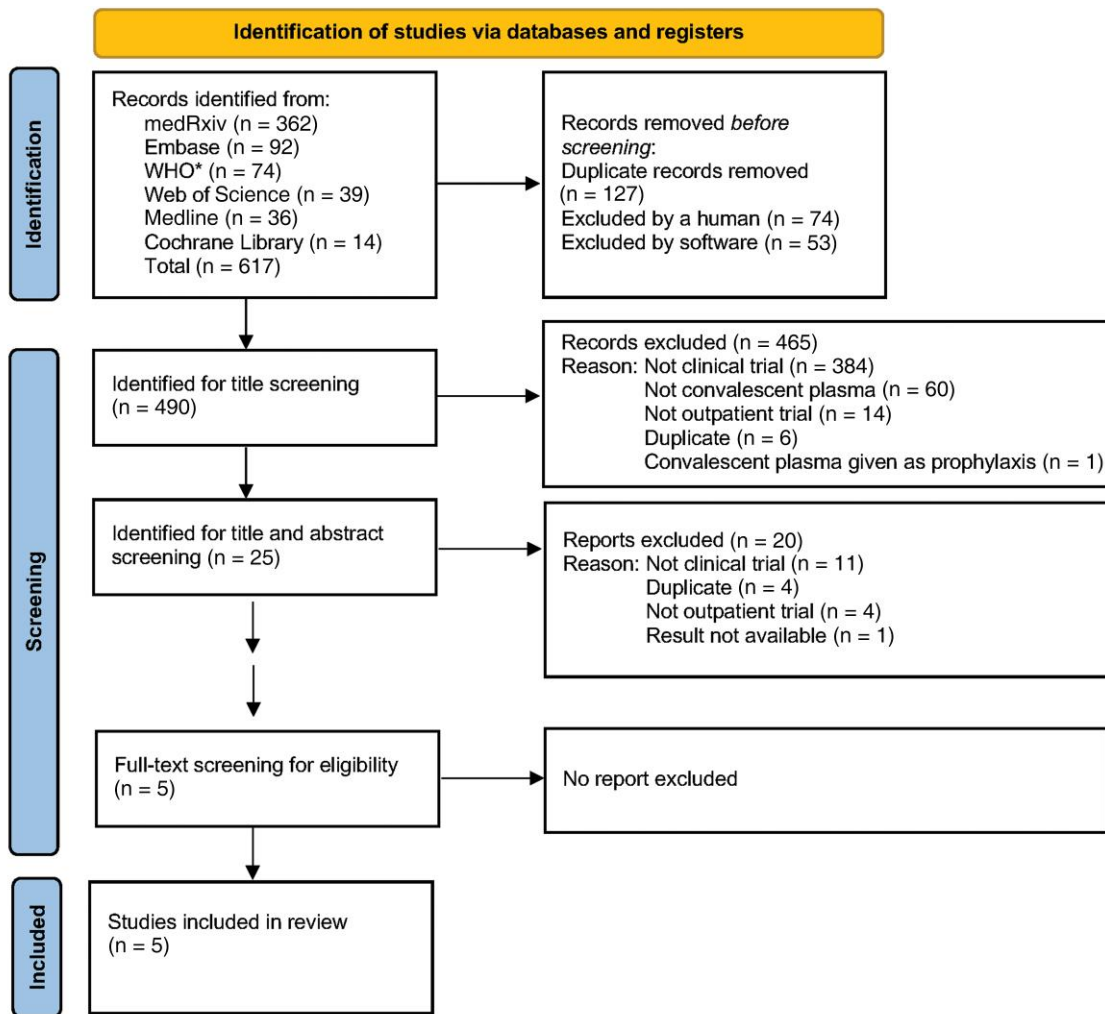


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart. The Medline, Embase, medRxiv, Cochrane Library, World Health Organization (WHO) COVID-19 Research Database, and Web of Science were searched for all randomized controlled trials as of 30 September 2022. Abbreviation: COVID-19, coronavirus disease 2019. *WHO COVID-19 global literature on coronavirus disease.

patients admitted to the hospital within 24 hours of CCP (25 patients) or control (13 patients) transfusion, yielding an ARR of 4.4% (95% CI, 2.2%–6.6%), NNT of 23, and RRR of 39.2% (95% CI, 21.7%–52.8%). The OR for hospitalization was 0.58 (95% CI, .41–.82), and trial heterogeneity was low in this secondary analysis, with an I^2 of 31% (Figure 2).

Subgroup Analyses

Subgroup analyses were performed based upon the timing of CCP transfusion and the SARS-CoV-2 antibody titer level in transfused CCP units. For subjects transfused within 5 days of symptom onset, pooled analysis among all 5 studies indicated an ARR of 5.8% (95% CI, 2.6%–9.0%), NNT of 17, and RRR of 39.5% (95% CI, 19.9%–54.3%) in hospitalizations when compared to control (Table 2 and Figure 3). Study subjects transfused with high antibody titer CCP (defined as equal to or greater than

the median neutralization titer for each individual study) had an ARR of 4.8% (95% CI, 2.2%–7.4%), NNT of 21, and RRR of 40.3% (95% CI, 18.8%–56.1%) in hospitalization compared with subjects given the control (Table 2 and Figure 4). Subjects transfused after 6 days of symptoms or with low antibody titer CCP did not show a significant decrease in hospitalization when compared with control (Table 2). The risk reduction in patients receiving high antibody titer CCP and within 5 days of symptom onset was higher for the combined studies at an ARR of 7.6% (95% CI, 4.0%–11.1%), NNT of 13, and RRR of 51.7% (95% CI, 28.3%–67.1%) (Table 2 and Figure 5).

Safety

Due to small numbers, we did not combine severe adverse events related to transfusion in a meta-analysis; however, they were collected for each trial. In CSSC-004, 1 subject experienced a

Table 1. Trial Characteristics

Characteristic	CSSC-004	CCP-Argentina	CONV-ERT	C3PO	CoV-Early	Total
Control arm	Plasma	Saline	Saline	Saline/MVC	Plasma	...
Enrollment period	June 2020 to Oct 2021	June 2020 to Oct 2020	Nov 2020 to July 2021	Aug 2020 to Feb 2021	Nov 2020 to July 2021	...
Trial duration, mo	16	5	9	7	9	46
Variants	614G, Alpha, Beta, Delta	WA-1, D614G	D614G, Alpha	D614G	D614G, Alpha	...
Geography	US	Argentina	Spain	US	Netherlands	...
Target enrollment, No.	1280	210	474	900	690	3554
Enrolled, No.	1225	160	376	511	421	2693
mITT (% of target enrollment)	1181 (92)	154 (73)	369 (78)	500 (55)	416 (60)	2620 (74)
Age, y, median (range)	43 (18–85)	77 (65 to ≥90)	56 (IQR, 52–62)	54 (18–93)	60 (IQR, 55–65)	...
≥1 medical high-risk condition for COVID-19 progression	470 (40)	131 (82)	278 (74)	511 (100)	416 (100)	1806 (68.6)
Enrollment symptom duration for inclusion, d	0–8	0–3	0–7	0–7	0–7	0–8
Symptoms ≤5 d	517 (44)	154 (100)	283 (77)	389 (78)	226 (54)	1569 (60)
Symptoms ≤3 d	168 (14)	154 (100)	101 (27)	240 (48)	52 (13)	715 (27)
Median/mean duration of symptoms, median (mean)	6	3	(4.4)	4	5	...
Total female	675 (57)	98 (64)	169 (46)	265 (53)	93 (22)	1300 (50)
Age >50 y	411 (35)	154 (100)	368 (100)	310 (61)	414 (100)	1657 (63)
Age >65 y	80 (7)	154 (100)	73 (20)	95 (19)	113 (27)	515 (20)
Diabetes	99 (8)	35 (23)	39 (10)	142 (28)	29 (7)	344 (13)
Hypertension	276 (23)	110 (71)	244 (66)	216 (42)	Not reported	846 (38) ^a
Obesity (BMI >30 kg/m ²)	444 (38)	11 (7)	95 (26)	302 (60)	126 (30)	978 (37)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; C3PO, clinical-trial of COVID-19 convalescent plasma in outpatients; CCP-Argentina, COVID-19 convalescent plasma-Argentina; CONV-ERT, convalescent methylene blue treated (MBT) plasma for early treatment; CoV-Early, early convalescent plasma therapy; CSSC-004, COVID-19 serologic studies consortium; COVID-19, coronavirus disease 2019; IQR, interquartile range; mITT, modified intention-to-treat (those transfused); MVC, multivitamin concentrate; US, United States.

^aOnly included 4 reported studies.

transfusion reaction that required cessation of the transfusion [27]. The CCP-Argentina trial did not report any instances of volume overload, allergic reactions, or vasovagal syndromes, but did report 1 case of thrombophlebitis in the control arm. The C3PO authors noted 3 serious transfusion reactions in the CCP arm resulting in steroid or epinephrine administration or hospitalization [28]. The CONV-ERT team communicated no severe adverse events related to transfusion, but 3 vasovagal reactions and mild allergic reactions in 12 of 188 (6.4%) subjects transfused with CCP [30]. A participant with pulmonary embolism was reported 7 days after transfusion. The CoV-Early investigators reported 3 severe adverse events possibly related to plasma transfusion (all with nonconvalescent plasma). Two developed an anaphylactic reaction shortly after receiving plasma for which no hospital admission was required, and 1 patient developed generalized urticaria requiring hospitalization.

DISCUSSION

This meta-analysis of all available RCTs found that early outpatient therapy with CCP in adult patients with COVID-19 was associated with a 30% all-cause hospitalization RRR (NNT,

27) and a 39% RRR (NNT, 23) when excluding patients admitted on the same day as treatment (Table 2). Early treatment with high antibody titer CCP demonstrated a 51% hospitalization RRR (NNT, 13) in all-cause hospitalization among adult patients with COVID-19. Despite differences in the demographics and clinical characteristics of the 5 study populations, overall study heterogeneity was low to moderate, suggesting the appropriateness of combining these studies in a single meta-analysis and broadly generalizing these results. While the effectiveness of early CCP treatment in reducing all-cause hospitalization was less than that of many mAb treatments [32, 33] and antiviral therapies [13, 34], this should be balanced against its increased availability and potential for activity against variant strains of SARS-CoV-2.

Two of the 5 RCTs included in this meta-analysis (CONV-ERT and C3PO) failed to demonstrate a reduction in all-cause hospitalization with CCP, while the other 3 trials (CCP-Argentina, CSSC-004, CoV-Early) all showed approximately 50% reductions in hospitalizations. One potential explanation for the lack of effectiveness for CCP in the CONV-ERT trial is that methylene blue photoinactivation was used for pathogen reduction in transfused units. This might have

Table 2. Overall Numbers and Percentage of Pooled Numbers for Hospitalization and Totals

Study	Total CCP Outcomes	Total CCP	Total Control Outcomes	Total Control	Totals	CCP, %	Control, %	ARR, % (95% CI)	RRR % (95% CI)	Significance Level, P Value	NNT Benefit
mITT (all-cause hospitalizations)	111	1305	160	1315	2620	8.5	12.2	3.7 (1.3–6.0)	30.1 (12.0–44.4)	.0011	27
mITT (hospitalizations after 24 h from transfusion)	88	1282	147	1302	2584	6.9	11.3	4.4 (2.2–6.6)	39.2 (21.7–52.8)	.0001	23
Onset ≤5 d	70	787	114	775	1562	8.9	14.7	5.8 (2.6–9.0)	39.5 (19.9–54.3)	.0002	17
Onset ≥6 d	41	518	46	540	1058	7.9	8.5	.6 (–2.7 to 3.9)	7.1 (–39.1 to 37.9)	.3605	166
Donor titer ≥ median	49	687	157	1315	2002	7.1	11.9	4.8 (2.2–7.4)	40.3 (18.8–56.1)	.0004	21
Donor titer below median	62	593	157	1315	1908	10.5	11.9	1.5 (–1.5 to 4.5)	12.4 (–15.6 to 33.7)	.1735	67
High titer AND onset ≤5 d	29	406	114	775	1181	7.1	14.7	7.6 (4.0–11.1)	51.4 (28.3–67.1)	.0001	13
Low titer and onset ≤5 d, high titer and onset >5 d, low titer and onset >5 d	75	836	160	1315	2151	9.0	12.2	3.2 (1.6–5.8)	26.3 (4.4–43.2)	.0105	31

Data are presented as No. unless otherwise indicated.

Abbreviations: ARR, absolute risk reduction; CCP, coronavirus disease 2019 convalescent plasma; CI, confidence interval; mITT, modified intention-to-treat; NNT, number needed to treat; RRR, relative risk reduction.

affected the constant regions of antibody function without interfering with the viral neutralization assay [35]. The C3PO trial, unlike the other RCTs, enrolled only patients presenting to the emergency department (ED) with COVID-19, which likely included a more severely ill patient population further along in the inflammatory phase of disease. Indeed, there are often less tangible factors signifying more severe illness that lead a patient to present to the ED rather than to their primary care doctor. This is evidenced by the much larger number of subjects in the C3PO trial (23% of all hospitalizations) who were admitted directly to the hospital from the ED on the same visit in which they were transfused. Eliminating these same-day admissions (as in our secondary analysis) bring the C3PO results in line with those from the other studies and greatly reduces heterogeneity among the 5 studies.

Antibody levels for the transfused CCP used across these 5 trials varied substantially, despite the fact that donors had been selected based upon a minimum antibody level cutoff in each trial. However, different cutoffs were used as well as different antibody tests. Our observation that the reduction in hospital admission was limited to patients receiving CCP with titers above the median concentration level in each of the trials suggests that the CCP selection process was suboptimal. It is likely that more stringent antibody titer criteria for CCP units may further improve the effectiveness of this intervention [36].

Plasma transfusion, unlike the use of antiviral and mAb agents, presents a risk of transfusion reactions, which may vary from easily treatable conditions (eg, urticaria) to life-threatening reactions such as anaphylaxis. Rates of severe adverse reactions, however, appeared to be low in these outpatient trials.

This study does have several important limitations. While CSSC-004 enrolled both COVID-19-vaccinated and unvaccinated individuals, the other RCTs primarily included unvaccinated patients, which limits our ability to analyze the effectiveness of CCP for reducing COVID-19 hospitalization in a primarily vaccinated population. The NNT with CCP may be much higher in a primarily vaccinated population, although this difference may be mitigated by the rise of mutant variants that undermine the effectiveness of vaccines and mAbs. All 5 included studies also ended before meeting their transfusion goals, reducing their individual power to detect a difference in hospitalizations between treatment and control groups, and therefore increasing the need for this meta-analysis.

Our meta-analysis chose to use an mITT analysis, excluding 73 patients who were randomized to a given treatment but did not receive it due to hospitalization or withdrawal prior to transfusion, which could introduce bias. However, this represents <3% of enrolled patients and would be unlikely to significantly affect our results. More importantly, patients and providers did not know of their randomization assignment,

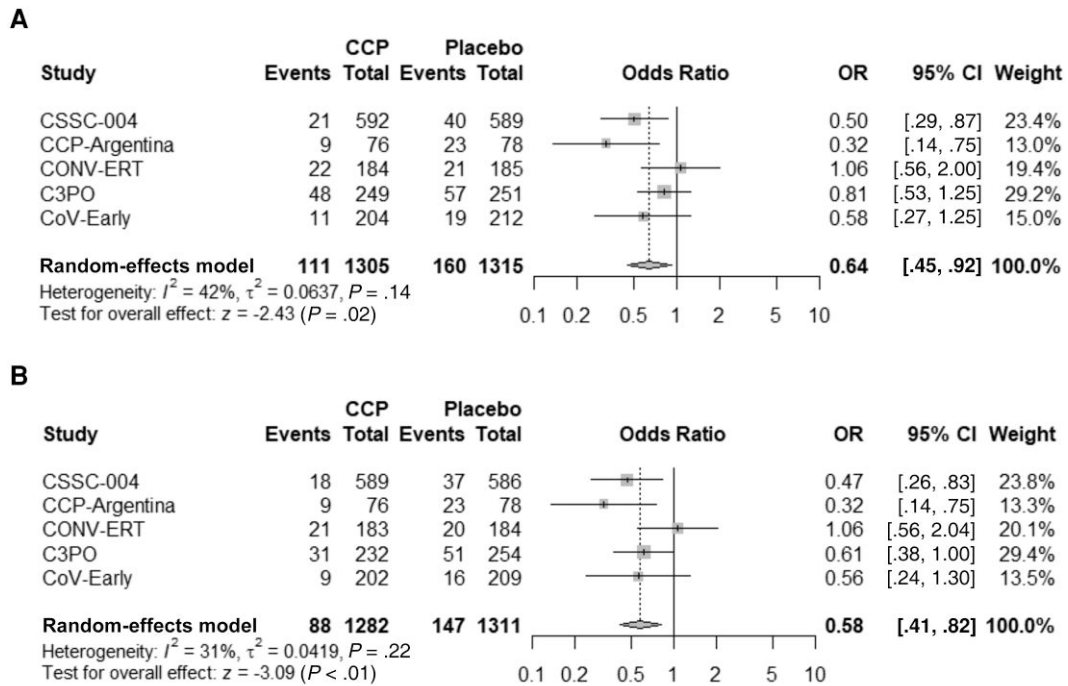


Figure 2. Forest plot of modified intention-to-treat (mITT) analysis (A) and of mITT analysis excluding same-day hospital admissions on transfusion day (B). Abbreviations: C3PO, clinical-trial of COVID-19 convalescent plasma in outpatients; CCP, coronavirus disease 2019 convalescent plasma; CCP-Argentina, COVID-19 convalescent plasma-Argentina; CI, confidence interval; CONV-ERT, convalescent methylene blue treated (MBT) plasma for early treatment; CoV-Early, early convalescent plasma therapy; CSSC-004, COVID-19 serologic studies consortium; OR, odds ratio.

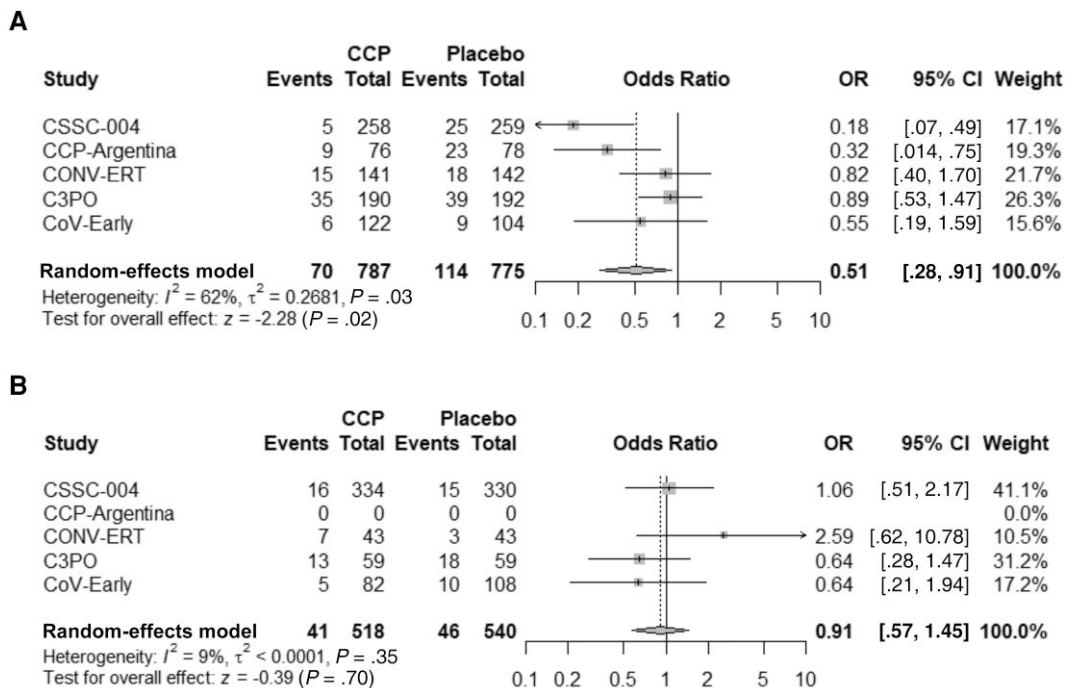


Figure 3. Forest plots of transfusion within 5 days (A) or >5 days (B). Abbreviations: C3PO, clinical-trial of COVID-19 convalescent plasma in outpatients; CCP, coronavirus disease 2019 convalescent plasma; CCP-Argentina, COVID-19 convalescent plasma-Argentina; CI, confidence interval; CONV-ERT, convalescent methylene blue treated (-MBT) plasma for early treatment; CoV-Early, early convalescent plasma therapy; CSSC-004, COVID-19 serologic studies consortium; OR, odds ratio.

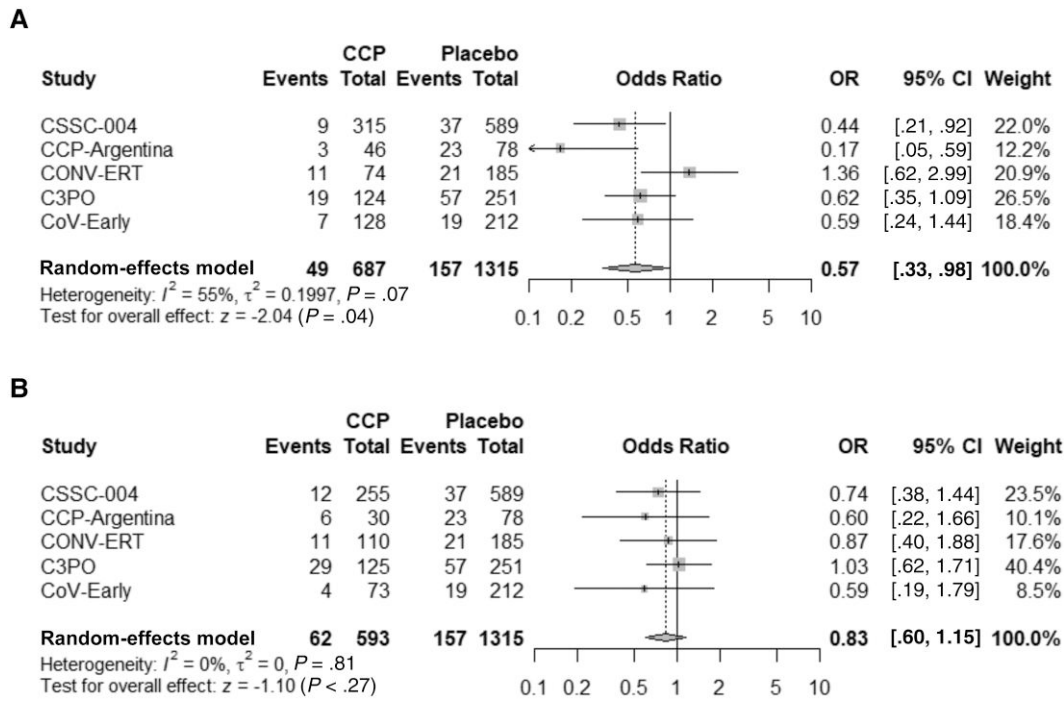


Figure 4. Forest plots of plasma donor antibody levels at or above median titer (A) or less than median titer (B). Abbreviations: C3PO, clinical-trial of COVID-19 convalescent plasma in outpatients; CCP, coronavirus disease 2019 convalescent plasma; CCP-Argentina, COVID-19 convalescent plasma-Argentina; CI, confidence interval; CONV-ERT, convalescent methylene blue treated (MBT) plasma for early treatment; CoV-Early, early convalescent plasma therapy; CSSC-004, COVID-19 serologic studies consortium; OR, odds ratio.

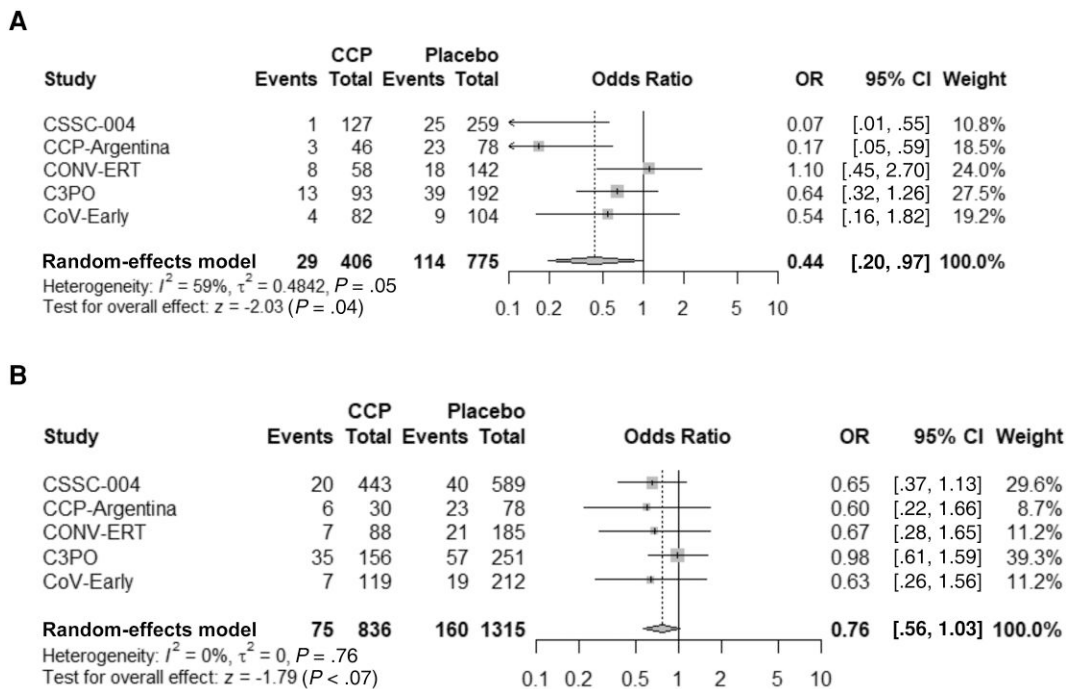


Figure 5. Forest plots of plasma donor antibody levels and early treatment at or above median titer AND transfusion within 5 days (A) or total of low titer and onset ≤ 5 days, high titer and onset over 5 days, low titer and onset over 5 days (B). Abbreviations: C3PO, clinical-trial of COVID-19 convalescent plasma in outpatients; CCP, coronavirus disease 2019 convalescent plasma; CCP-Argentina, COVID-19 convalescent plasma-Argentina; CI, confidence interval; CONV-ERT, convalescent methylene blue treated (-MBT) plasma for early treatment; CoV-Early, early convalescent plasma therapy; CSSC-004, COVID-19 serologic studies consortium; OR, odds ratio.

so the risk of bias due to our analysis methodology is low. In the CCP-Argentina study, some patients not actually admitted to a hospital were considered to meet the primary outcome, but these patients did meet standard hospital admission criteria (ie, hypoxia/respiratory distress) and were instead provided with hospital-level care within their long-term care unit. As described above, the actual donor antibody titer levels varied across the 5 RCTs, and the studies used varying assays to measure antibody titer, making it difficult to compare absolute antibody titers across studies. Consequently, we chose to look at median antibody titers within the individual studies as a means of comparing the CCP used in the various RCTs.

Although there are several implementation considerations that could affect the real-world efficacy and sustainability of CCP transfusion programs [37], our pooled meta-analysis including 5 large, rigorously conducted RCTs suggests that high-titer CCP administered early to adult outpatients with COVID-19 significantly reduces the risk of all-cause hospitalizations across a diverse range of demographic and clinical profiles, geographic locations, and transfusion settings. We believe that CCP should be considered as an outpatient treatment option (especially for patients at high-risk for poor outcomes) in settings where mAbs or antivirals are not currently accessible, or when new variants arise that undermine the effectiveness of these interventions. Pandemic preparedness should also incorporate flexible antibody neutralization assay systems for model organisms. Future research should focus on defining the optimal antibody titer and dosage for CCP and evaluating its effectiveness among immunocompromised vaccinated patients. Despite its limitations, CCP has the potential to be an effective, readily available, and highly adaptable intervention for use in both this and future pandemics.

Supplementary Data

[Supplementary materials](#) are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. A. C. L. and D. J. S. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: D. J. S., D. F. H., A. C. L. Acquisition, analysis, or interpretation of data: A. C. L., Y. F., M. A. H., J. O., B. R. M., B. P., J. H. P., D. F. H., B. J. A. R., A. G., C. R., J. J. Z., A. A., O. M., V. D.-M., L. J. D., F. K. K., C. W. C., R. L., D. J. S. Drafting of the manuscript: D. J. S., A. C. L., Y. F., M. A. H., J. O., B. R. M., B. P., J. H. P. Critical revision of the manuscript for important intellectual content: A. C. L., Y. F., M. A. H., J. O., B. R. M., B. P., J. H. P., D. F. H., B. J. A. R., A. G., A. A., O. M., V. D.-M., F. K. K., C. W. C., R. L., D. J. S., C. R., J. J. P., P. M.-M. Statistical analysis: J. O., D. J. S., A. C. L. Obtained funding: D. J. S., B. J. A. R., O. M., C. W. C., F. P. Administrative, technical, or material support: C. R., J. J. Z., P. M.-M. Supervision: D. J. S., A. G., A. A., C. W. C., R. L.

Acknowledgments. The authors thank the patients who participated, all of the plasma donors, and the study nurses involved at the study sites. The authors also thank the 5 separate consortiums that performed the trials.

Data sharing. Data are available from individual authors upon request.

Disclaimer. The funders had no role in the collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Financial support. This work was supported principally by the US Department of Defense (DOD) Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense, in collaboration with the Defense Health Agency (contract number W911QY2090012), with additional support from Bloomberg Philanthropies, the State of Maryland, the National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID; grant number 3R01AI152078-01S1), NIH National Center for Advancing Translational Sciences (cooperative agreement number U24TR001609), Division of Intramural Research of the NIAID/NIH, Mental Wellness Foundation, Moriah Fund, Octapharma, HealthNetwork Foundation, and the Shear Family Foundation. CoV-Early was supported by ZonMw, the Netherlands (grant number 10430062010001). Sanquin Blood Supply provided convalescent plasma free of charge for study sites in the Netherlands. CONV-ERT was sponsored by the Fight AIDS and Infectious Diseases Foundation (Badalona, Spain) with funding from the pharmaceutical company Grifols Worldwide Operations (Dublin, Ireland) and the crowd-funding campaign YoMeCorono. The study received support from the Hospital Universitari Germans Trias i Pujol and Banc de Sang i Teixits de Catalunya. CCP-Argentina was supported by the Bill & Melinda Gates Foundation and by the Fundación INFANT Pandemic Fund, which received contributions from Laboratorio Roemmers, Bodega Vistalba, Swiss Medical Group, Laboratorios Bago, Laboratorio Raffo, Laboratorios Monserrat y Clair, Tuteur Sacifia, TASA Logistica, Fundación Inversiones y Representaciones, Puerto Asís Investments, and Fundación Hematológica Sarmiento and individual contributions from Alec Oxenford, Carlos Kulish and family, Renato Montefiore and family, Irene Gorodisch, Alejandro Gorodisch, the Braun family, Agustín Otero-Monsegur, and Luis R. Otero. C3PO was supported by awards (1OT2HL156812-01, U24NS100659, and U24NS100655) from the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute of Neurological Disorders and Stroke of the NIH and by a contract (number 75A50120C00094) with the Biomedical Advanced Research and Development Authority (BARDA) through the Department of Health and Human Services and the Operation Warp Speed interagency program. Support included funding and material support in the form of plasma and testing supplies.

Potential conflicts of interest. R. L. has received fees from Pfizer for serving as subinvestigator of a COVID vaccine trial. F. P. has received fees from Pfizer for serving as a principal investigator for a COVID vaccine trial. D. J. S. is a founder and board member of AliquantumRx with stock options; Hemex Health malaria diagnostics consulting; royalties for malaria diagnostic test control standards from Alere (Binax Inc/D/B/A Inverness Medical); consulting fees for legal malaria case from Mabrey Firm (2019); the following grants or contracts: NIH/NIAID R01AI150763, NIH R21TR001737, NIH R01AI111962, DOD TB210115 (CDMRP Tick-Borne Disease Research Program); the following patents: USP 9642865 (issued 9 May 2017, New angiogenesis inhibitors), USP 7270948 (issued 18 September 2007, Detection of malaria parasites by laser desorption mass spectrometry), Salts and polymorphs of cethromycin for the treatment of disease (pending, application 20210163522), and Macrolide compounds and their use in liver stage malaria and related disease (pending, application PCT/US2015/046665); and participation on 2018 NIAID Safety Monitoring Committee/Independent Safety Monitor Intramural, all outside the submitted work. B. J. A. R. reports advisory board membership for Roche and AstraZeneca on a COVID-19 therapy; membership on a data and safety monitoring board (DSMB) for Exevir; consulting fees from Roche and AstraZeneca; grants or contracts and payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing, or educational events from Gilead Sciences; and support for attending meetings

and/or travel from Pfizer. J. J. Z. reports consulting fees from City of Hope; cell therapy consultant; participation on DSMB for the PACER trial; DSMB for the Tolerant trial; and advisory boards for Sanofi and Sobi. L. J. D. reports the following grants or contracts: 75A50120C00094 (BARDA), Collection, testing, and provision of COVID-19 convalescent plasma for NHLBI/NIH (C3PO) through America's Blood Centers; US Veterans Health Administration, Pittsburgh (contract number 36C24E20D0027, VA CURES-1); and Vanderbilt University (Collection, testing, and provision of COVID-19 convalescent plasma for Association of Convalescent Plasma Treatment with Mortality and Clinical Trajectory in Patients Hospitalized with COVID-19 in the Community Setting). B. P. reports the following grants or contracts: COVID Trials, Incyte, Parexel, Novartis Pharmaceuticals, Partner Therapeutics, Fulcrum Therapeutics (to University Health Science Center), and Pulmonary Hypertension Trials, United Therapeutics, GlaxoSmithKline, Inmed, Merck Sharp & Dohme (to University of Texas Health Center). C. W. C. reports consulting honorarium for participation on NHLBI ACTIV4 CONNECTS Steering Committee. I. E. reports support for attending meetings and/or travel for 50 Congreso Argentino de Medicina Respiratoria 2022, Abstract Scholarship, American Thoracic Society, International Conference in Philadelphia, 2020 Assembly on Pediatrics. G. P. M. reports grants or contracts from Pfizer, Moderna, Medicago, and Merck for clinical research (as principal investigator), and payment for presentations from Moderna. D. O. reports consulting fees paid to author from the Fight Infectious Diseases Foundation and the Infectious Diseases Department, Hospital Universitari Germans Trias i Pujol. B. R. M. reports the following grants or contracts: NIH/NIAID R01AI150763, NIH R21TR001737, NIH R01AI111962, and DOD TB210115 (CDMRP Tick-Borne Disease Research Program). D. W. reports payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing, or educational events from AstraZeneca, and support for attending meetings and/or travel from Laboratorios Raffo. C. R. reports grants or contracts from Gilead Sciences, ViiV Healthcare, Janssen-Cilag, AIDSfonds, and Health~Holland; participation on a DSMB or advisory board as well as support for attending meetings and/or travel from Gilead Sciences and ViiV Healthcare; and gifts for the #awarehivukraine foundation. M. A. H. reports grants or contracts from Gilead, Inmed, and AN2 Therapeutics, as well as participation on the AIDS Clinical Trials Group Tuberculosis Transformative Science Group Study Monitoring Committee. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

- COVID-19 Excess Mortality Collaborators. Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020–21. *Lancet* **2022**; 399:1513–36.
- Paredes MI, Lunn SM, Famulare M, et al. Associations between SARS-CoV-2 variants and risk of COVID-19 hospitalization among confirmed cases in Washington state: a retrospective cohort study. medRxiv [Preprint]. Posted online 16 February 2022. <https://doi.org/10.1101/2021.09.29.21264272>
- Newland M, Durham D, Asher J, et al. Improving pandemic preparedness through better, faster influenza vaccines. *Expert Rev Vaccines* **2021**; 20:235–42.
- Kachali H, Haavisto I, Leskela RL, Valja A, Nuutinen M. Are preparedness indices reflective of pandemic preparedness? A COVID-19 reality check. *Int J Disaster Risk Reduct* **2022**; 77:103074.
- Ramachandran R, Ross JS, Miller JE. Access to COVID-19 vaccines in high-, middle-, and low-income countries hosting clinical trials. *JAMA Netw Open* **2021**; 4:e2134233.
- Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA* **2020**; 323:1582–9.
- Salazar E, Christensen PA, Graviss EA, et al. Treatment of coronavirus disease 2019 patients with convalescent plasma reveals a signal of significantly decreased mortality. *Am J Pathol* **2020**; 190:2290–303.
- Chen P, Nirula A, Heller B, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. *N Engl J Med* **2021**; 384:229–37.
- Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. *N Engl J Med* **2021**; 384:238–51.
- Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* **2020**; 383:2603–15.
- Anderson EJ, Roupael NG, Widge AT, et al. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. *N Engl J Med* **2020**; 383:2427–38.
- World Health Organization (WHO). Weekly epidemiological update—29 December 2020. Geneva, Switzerland: WHO, **2020**.
- Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. *N Engl J Med* **2022**; 386:1397–408.
- Plata GG. The black market for covid-19 antiviral drugs. *BMJ* **2022**; 377:o1282.
- Hill A, Ellis L, Wang J, Pepperrell T. Prices versus costs of production for molnupiravir as a COVID-19 treatment. Research Square [Preprint]. Posted online 15 December 2021. <https://doi.org/10.21203/rs.3.rs-1169509/v1>
- Huygens S, Munnink BO, Gharbharan A, Koopmans M, Rijnders B. Sotrovimab resistance and viral persistence after treatment of immunocompromised patients infected with the SARS-CoV-2 Omicron variant. *Clin Infect Dis* **2023**; 76:e507–9.
- Birnie E, Biemond JJ, Appelman B, et al. Development of resistance-associated mutations after sotrovimab administration in high-risk individuals infected with the SARS-CoV-2 Omicron variant. *JAMA* **2022**; 328:1104–7.
- Hernandez AV, Piscoya A, Pasupuleti V, et al. Beneficial and harmful effects of monoclonal antibodies for the treatment and prophylaxis of COVID-19: a systematic review and meta-analysis of randomized controlled trials. *Am J Med* **2022**; 135:1349–61.e18.
- Wang Q, Iketani S, Li Z, et al. Alarming antibody evasion properties of rising SARS-CoV-2 BQ and XBB subvariants. *Cell* **2023**; 186:279–86.e8.
- Arora P, Kempf A, Nehlmeier I, et al. Omicron sublineage BQ.1.1 resistance to monoclonal antibodies. *Lancet Infect Dis* **2023**; 23:22–3.
- Planas D, Bruel T, Staropoli I, et al. Resistance of Omicron subvariants BA.2.75.2, BA.4.6 and BQ.1.1 to neutralizing antibodies. *Nat Commun* **2023**; 14:824.
- Malah SRK, Hoek RAS, Dalm V, et al. Clinical characteristics and outcome of immunocompromised patients with COVID-19 caused by the Omicron variant: a prospective observational study. *Clin Infect Dis* **2023**; 76:e172–8.
- Bhimraj AMR, Shumaker AH, Baden L, et al. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. Available at: <https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/>. Accessed 30 September 2022.
- Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* **2021**; 372:n71.
- Boutron I, Chaimani A, Meerpohl JJ, et al. The COVID-NMA project: building an evidence ecosystem for the COVID-19 pandemic. *Ann Intern Med* **2020**; 173:1015–7.
- Nguyen TV, Ferrand G, Cohen-Boulakia S, et al. RCT studies on preventive measures and treatments for COVID-19. Zenodo [Preprint]. Posted online 1 April 2020. <https://doi.org/10.5281/zenodo.4266529>
- Sullivan DJ, Gebo KA, Shoham S, et al. Early outpatient treatment for Covid-19 with convalescent plasma. *N Engl J Med* **2022**; 386:1700–11.
- Korley FK, Durkalski-Mauldin V, Yeatts SD, et al. Early convalescent plasma for high-risk outpatients with Covid-19. *N Engl J Med* **2021**; 385:1951–60.
- Gharbharan A, Jordans C, Zwaginga L, et al. Outpatient convalescent plasma therapy for high-risk patients with early COVID-19. A randomized placebo-controlled trial. *Clin Microbiol Infect* **2023**; 29:208–14.
- Aleman A, Millat-Martinez P, Corbacho-Monne M, et al. High-titre methylene blue-treated convalescent plasma as an early treatment for outpatients with COVID-19: a randomised, placebo-controlled trial. *Lancet Respir Med* **2022**; 10:278–88.
- Libster R, Perez Marc G, Wappner D, et al. Early high-titer plasma therapy to prevent severe covid-19 in older adults. *N Engl J Med* **2021**; 384:610–8.
- Verderese JP, Stepanova M, Lam B, et al. Neutralizing monoclonal antibody treatment reduces hospitalization for mild and moderate coronavirus disease 2019 (COVID-19): a real-world experience. *Clin Infect Dis* **2022**; 74:1063–9.
- Jenks JD, Aslam S, Horton LE, et al. Early monoclonal antibody administration can reduce both hospitalizations and mortality in high-risk outpatients with coronavirus disease 2019 (COVID-19). *Clin Infect Dis* **2022**; 74:752–3.
- Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of covid-19 in nonhospitalized patients. *N Engl J Med* **2022**; 386:509–20.
- Ross V. Photodynamic action of methylene blue on diphtheric antitoxin. *J Immunol* **1938**; 35:371–7.
- Rijnders BJA, Huygens S, Mitjà O. Evidence-based dosing of convalescent plasma for COVID-19 in future trials. *Clin Microbiol Infect* **2022**; 28:667–71.
- Bloch EM, Tobian AAR, Shoham S, et al. How do I implement an outpatient program for the administration of convalescent plasma for COVID-19? *Transfusion* **2022**; 62:933–41.