

UC Irvine

UC Irvine Previously Published Works

Title

Early Outpatient Treatment for Covid-19 with Convalescent Plasma

Permalink

<https://escholarship.org/uc/item/95w5c09s>

Journal

New England Journal of Medicine, 386(18)

ISSN

0028-4793

Authors

Sullivan, David J
Gebo, Kelly A
Shoham, Shmuel
[et al.](#)

Publication Date

2022-05-05

DOI

10.1056/nejmoa2119657

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

ORIGINAL ARTICLE

Early Outpatient Treatment for Covid-19 with Convalescent Plasma

D.J. Sullivan, K.A. Gebo, S. Shoham, E.M. Bloch, B. Lau, A.G. Shenoy, G.S. Mosnaim, T.J. Gniadek, Y. Fukuta, B. Patel, S.L. Heath, A.C. Levine, B.R. Meisenberg, E.S. Spivak, S. Anjan, M.A. Huaman, J.E. Blair, J.S. Currier, J.H. Paxton, J.M. Gerber, J.R. Petrini, P.B. Broderick, W. Rausch, M.-E. Cordisco, J. Hammel, B. Greenblatt, V.C. Cluzet, D. Cruser, K. Oei, M. Abinante, L.L. Hammitt, C.G. Sutcliffe, D.N. Forthal, M.S. Zand, E.R. Cachay, J.S. Raval, S.G. Kassaye, E.C. Foster, M. Roth, C.E. Marshall, A. Yarava, K. Lane, N.A. McBee, A.L. Gawad, N. Karlen, A. Singh, D.E. Ford, D.A. Jabs, L.J. Appel, D.M. Shade, S. Ehrhardt, S.N. Baksh, O. Laeyendecker, A. Pekosz, S.L. Klein, A. Casadevall, A.A.R. Tobian, and D.F. Hanley

ABSTRACT

BACKGROUND

Polyclonal convalescent plasma may be obtained from donors who have recovered from coronavirus disease 2019 (Covid-19). The efficacy of this plasma in preventing serious complications in outpatients with recent-onset Covid-19 is uncertain.

METHODS

In this multicenter, double-blind, randomized, controlled trial, we evaluated the efficacy and safety of Covid-19 convalescent plasma, as compared with control plasma, in symptomatic adults (≥ 18 years of age) who had tested positive for severe acute respiratory syndrome coronavirus 2, regardless of their risk factors for disease progression or vaccination status. Participants were enrolled within 8 days after symptom onset and received a transfusion within 1 day after randomization. The primary outcome was Covid-19–related hospitalization within 28 days after transfusion.

RESULTS

Participants were enrolled from June 3, 2020, through October 1, 2021. A total of 1225 participants underwent randomization, and 1181 received a transfusion. In the prespecified modified intention-to-treat analysis that included only participants who received a transfusion, the primary outcome occurred in 17 of 592 participants (2.9%) who received convalescent plasma and 37 of 589 participants (6.3%) who received control plasma (absolute risk reduction, 3.4 percentage points; 95% confidence interval, 1.0 to 5.8; $P=0.005$), which corresponded to a relative risk reduction of 54%. Evidence of efficacy in vaccinated participants cannot be inferred from these data because 53 of the 54 participants with Covid-19 who were hospitalized were unvaccinated and 1 participant was partially vaccinated. A total of 16 grade 3 or 4 adverse events (7 in the convalescent-plasma group and 9 in the control-plasma group) occurred in participants who were not hospitalized.

CONCLUSIONS

In participants with Covid-19, most of whom were unvaccinated, the administration of convalescent plasma within 9 days after the onset of symptoms reduced the risk of disease progression leading to hospitalization. (Funded by the Department of Defense and others; CSSC-004 ClinicalTrials.gov number, NCT04373460.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Sullivan can be contacted at dsullivan7@jhmi.edu or at Rm. W4606, Johns Hopkins Bloomberg School of Public Health, Department of Molecular Microbiology and Immunology, 615 N. Wolfe St., Baltimore, MD 21205.

Drs. Sullivan, Gebo, Casadevall, Tobian, and Hanley contributed equally to this article.

This article was published on March 30, 2022, at NEJM.org.

DOI: 10.1056/NEJMoa2119657

Copyright © 2022 Massachusetts Medical Society.

IN THE UNITED STATES, APPROXIMATELY 8% of persons are hospitalized after infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (Covid-19). Most therapies for Covid-19 have targeted disease progression or death in hospitalized patients. However, the Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for three monoclonal-antibody therapies for outpatients after data showed decreases in the incidences of disease progression and hospitalization when these therapies were administered within 5 to 7 days after the onset of Covid-19.¹⁻³ Alternative outpatient therapies are needed, particularly in settings where monoclonal-antibody therapy is either unavailable (e.g., in low-income and middle-income countries),⁴ scarce, or ineffective (i.e., because of monoclonal antibody-resistant variants).⁵

Safety concerns about Covid-19 convalescent plasma have not been identified in hospitalized populations.^{6,7} In one study, high-titer Covid-19 convalescent plasma administered soon after hospitalization reduced the incidence of death from Covid-19 by 50%,⁸ but data from randomized clinical trials have not shown a consistent benefit in hospitalized patients.⁹ Some heterogeneity exists with respect to hospitalized participants, with some studies that show efficacy in reducing the incidence of death^{10,11} and others that do not show these findings.¹²⁻¹⁵ In general, improved outcomes are associated with the provision of high-titer plasma within days after the onset of symptoms.¹⁶

Data from randomized trials involving outpatients with Covid-19 are limited.¹⁷ In a trial conducted in Argentina, the use of Covid-19 convalescent plasma in outpatients was associated with a relative risk reduction of 48% in progression to severe disease (absolute risk reduction, 15 percentage points) when it was administered within 72 hours after the onset of mild Covid-19 symptoms.¹⁸ However, in a trial of Covid-19 convalescent plasma that was administered to patients in the emergency department who were at high risk for progression of Covid-19, enrollment was halted owing to futility.¹⁹

In the Convalescent Plasma to Limit SARS-CoV-2 Associated Complications (CSSC-004) Study, we sought to determine whether a transfusion of Covid-19 convalescent plasma (containing >1:320 SARS-CoV-2 anti-spike protein antibody levels)

within 9 days after the onset of symptoms would be effective in preventing disease progression leading to hospitalization. Our trial population consisted of adults who were 18 years of age or older, and participants were included in the trial regardless of their coexisting conditions and vaccination status.

METHODS

TRIAL DESIGN AND OVERSIGHT

In this double-blind, randomized, controlled trial, we compared qualified Covid-19 convalescent plasma with control plasma. The FDA approved the trial protocol (available with the full text of this article at NEJM.org) in the investigational new drug application (IND 19725), sponsored by Johns Hopkins University. The enrollment sites and investigators are listed in the Supplementary Appendix, available at NEJM.org.

Data were collected by the investigators and personnel at the blood bank at each participating site. The trial leadership and investigators from the clinical coordination center and data coordination center designed the trial, analyzed the data, and vouch for the accuracy and completeness of the data and the adherence of the trial to the protocol. No prespecified confidentiality agreements were in place between the sponsors and authors. The trial sponsors did not contribute to the trial design, to the collection, analysis, and interpretation of data, or to the decision to submit the manuscript for publication.

The institutional review board of Johns Hopkins University served as the single institutional review board. For the Center for American Indian Health sites, the protocol was independently reviewed and approved by the Navajo Nation Human Research Review Board and the Indian Health Service National Institutional Review Board. The protocol was also approved by the Human Research Protection Office of the Department of Defense. An independent medical monitor who was unaware of the trial-group assignments reviewed all serious adverse events, and an independent panel of three physicians who were unaware of the trial-group assignments adjudicated Covid-19-related hospitalizations and severity. An independent data and safety monitoring board provided interim safety and efficacy reviews. The trial was conducted in accordance with the principles of the Declaration of Helsinki, the Good

Clinical Practice guidelines of the International Council for Harmonisation, and all applicable regulatory requirements.

PARTICIPANTS

At 23 trial sites in the United States, we assigned SARS-CoV-2–positive participants (≥ 18 years of age) within 8 days after the onset of Covid-19 symptoms to receive a transfusion by day 9. Participants were recruited with the use of clinic-based lists of SARS-CoV-2–positive outpatients, physician referrals, or participant referrals, or by paid media advertisements that were augmented by earned media stories, directing participants to a call center or website managed by a marketing communications agency and consulting firm. Paid media advertisements were geographically focused near clinical trial sites. Advertisements were placed in search engines, social-media sites, high-volume Covid-19 testing sites, and local media outlets. Trial personnel and investigators confirmed that each participant could be safely treated on an outpatient basis.

Exclusion criteria included previous Covid-19–related hospitalization or planned hospitalization within 24 hours after enrollment, previous reactions to blood-product transfusions, an inability to adhere to the protocol, or receipt of monoclonal antibodies before enrollment. Pregnant persons as well as those who had received a Covid-19 vaccine before or during follow-up and those who had received glucocorticoids were eligible. All the trial participants provided written informed consent.

RANDOMIZATION AND INTERVENTION

After screening, participants from all the sites were randomly assigned in a 1:1 ratio with the use of a central Web-based system and a permuted-block sequence to receive either Covid-19 convalescent plasma or control plasma (each administered in a single dose at a volume of approximately 250 ml). Randomization was stratified according to trial site and participant age (< 65 years or ≥ 65 years). Both investigational products were matched for ABO compatibility, and the existing labels were covered with labels that read “Thawed plasma (volume), store at 1–6°C; new drug limited by federal (or U.S.) law to investigational use” in order to preserve verification codes. Convalescent plasma or control plasma was transfused over a period of approximately 1 hour within 24 hours

after enrollment, followed by an observation period of 30 minutes.

The presence of SARS-CoV-2 antibodies was confirmed in eligible donors after a 1:320 plasma dilution was positive on one of three validated spike-protein enzyme-linked immunosorbent assays (ELISAs), including the Anti-SARS-CoV-2 ELISA (IgG) (Euroimmun), the Vitros Covid-19 IgG Assay (Ortho Clinical Diagnostics), and the Covid-19 ELISA IgG Antibody Test (Mount Sinai Laboratory), in a laboratory certified by the Clinical Laboratory Improvement Amendments process. After the donor convalescent plasma was qualified for use, the antibody levels were characterized in research laboratories by full-length ancestral spike end-point titers, live-virus growth neutralization assays, and arbitrary units on the Euroimmun IgG assay according to the assay manufacturer’s recommended dilution of 1:101.²⁰ After July 2021, transfusions were restricted to units of plasma with arbitrary units of greater than 3.5 at a 1:101 dilution on the Euroimmun IgG assay, in accordance with the March 9, 2021, FDA EUA²¹ for high-titer convalescent plasma for hospitalized patients. Units of control plasma were either donated in 2019 or obtained from persons who tested seronegative for SARS-CoV-2 after December 2019.

OUTCOMES

The primary outcome was Covid-19–related hospitalization within 28 days after transfusion, assessed as the cumulative incidence in the convalescent-plasma group as compared with the control-plasma group. The decision to hospitalize patients was at the discretion of local providers. Although death before hospitalization was part of the protocol-specified primary outcome, it did not occur in the trial. Hence, the primary outcome is equivalent to Covid-19–related hospitalization. Covid-19–related hospitalizations and disease severity in hospitalized patients were adjudicated by a panel of three physicians who were unaware of the trial-group assignments.

No prespecified secondary outcomes are reported here. In the subgroup analysis, all the subgroups (e.g., the time from symptom onset to the transfusion of plasma) were prespecified.

SAFETY ASSESSMENTS

Adverse events were graded according to the Common Terminology Criteria for Adverse Events, ver-

sion 5.0. Safety outcomes that were monitored throughout the trial included transfusion-related serious adverse events that manifested as the following: severe transfusion reactions, acute respiratory distress syndrome, or adverse events of grade 3 or 4. An independent medical monitor who was unaware of the trial-group assignments evaluated adverse events, serious adverse events, and changes from baseline in safety laboratory values.

STATISTICAL ANALYSIS

The statistical analysis plan, included with the trial protocol at NEJM.org, was finalized before database lock and unblinding. We initially estimated that a sample size of 1280 participants would provide the trial with 80% power to detect a between-group difference of at least 25% in the relative risk of hospitalization, assuming an estimated 22% risk of hospitalization in the control-plasma group, at a one-sided significance level of 0.05. This sample size was increased to 1344 to allow for potential loss to follow-up.

We calculated the risk difference and the restricted mean survival time (the expected mean time to hospitalization or death by 28 days) in a modified intention-to-treat analysis that excluded participants who did not receive transfusion of convalescent plasma or control plasma. We estimated the cumulative incidence using the doubly robust estimator based on a targeted minimum loss–based estimator.²² In order to increase the precision of estimates and to account for potential dependent censoring, the analyses were adjusted for baseline variables that were potentially related to the primary outcome.²² In order to determine which prespecified candidate variables to include, we conducted variable selection using the random survival forest method in the entire sample while we were unaware of the trial-group assignments (see the Supplementary Appendix). We used imputation for missing values in an algorithm to select covariates for inclusion in a targeted minimum loss–based estimation model. A time-to-event analysis was based on the period from the time of transfusion until an outcome occurred. A two-sided test with a type I error of 0.05 was used to determine statistical significance. Full details of the trial conduct are provided in the protocol.

RESULTS

TRIAL POPULATION

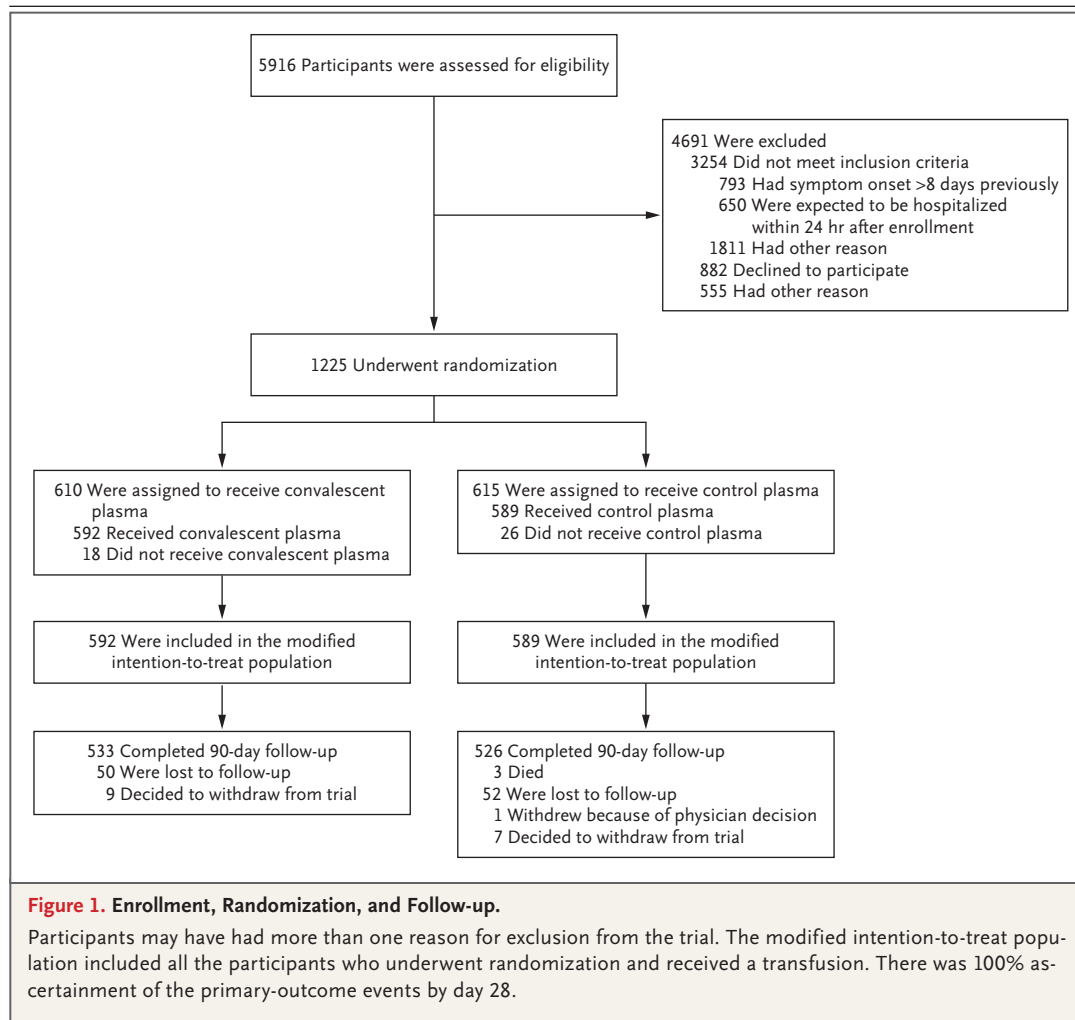
From June 3, 2020, through October 1, 2021, a total of 1225 participants at 23 sites who had tested positive for SARS-CoV-2 (87% by RNA detection and 13% by antigen detection) underwent randomization; of these participants, 592 received convalescent plasma and 589 received control plasma, for a total of 1181 participants who were included in the modified intention-to-treat analysis (Fig. 1). Owing to sharply declining numbers of hospitalizations after the first 1000 participants were enrolled, the trial enrollment was halted by the trial leadership (whose members were unaware of the trial-group assignments) after more than 90% of the initial enrollment target was reached.

There were no obvious imbalances between the trial groups with respect to baseline characteristics, including coexisting conditions, Covid-19 vaccination status, vital signs, and clinical laboratory results (Table 1, and Table S1 in the Supplementary Appendix). The median age was 43 years; 80 participants (7%) were 65 years of age or older, and 411 participants (35%) were 50 years of age or older. Black participants (163 persons) and Hispanic or Latino participants (170 persons) each accounted for more than 10% of the participants, whereas 21 participants (2%) were American Indians or Alaska Natives or Native Hawaiians or other Pacific Islanders. Women, including 3 who were pregnant, made up 57% of the participants. The median time from symptom onset to transfusion was 6 days.

The proportion of Black participants in the trial was similar to that in the general U.S. population, but the proportion of Hispanic participants was lower. In addition, in the trial population, participants who were 65 years of age or older and men were less frequently represented than younger participants and women (Table S2).

CONVALESCENT PLASMA

A total of 333 units of Covid-19 convalescent plasma that had been obtained from unique donors were transfused into 592 participants. Many identical aliquots of plasma that had been obtained from large-volume single donations were administered to 2 to 4 recipients. Of the 333 units of



convalescent plasma, 300 (90%) were donated between April and December 2020, and the remaining 33 were donated between January and April 2021. Serologic analysis with the use of assays developed at the Johns Hopkins University research laboratory²⁰ revealed that 80% of all the units had SARS-CoV-2 spike protein antibody titers of at least 1:4860 (the end-point titer equivalent to 105 spike-binding international arbitrary units per milliliter), virus 2- to 3-day culture neutralization of at least 8 international units per milliliter, and greater than 3.5 arbitrary units on the Euroimmun IgG assay (Fig. S1). The Euroimmun benchmark met the 2021 FDA definition of high-titer convalescent plasma.²¹

PRIMARY OUTCOME: HOSPITALIZATION

In the prespecified modified intention-to-treat trial population that excluded participants who

did not receive a transfusion, the outcome of Covid-19–related hospitalization within 28 days occurred in 17 of 592 participants (2.9%) who received Covid-19 convalescent plasma and in 37 of 589 participants (6.3%) who received control plasma (absolute risk reduction, 3.4 percentage points; 95% confidence interval [CI], 1.0 to 5.8; $P=0.005$) (Fig. 2 and Table 2). The relative risk reduction was 54%.

The results of a prespecified, adjusted, targeted minimum loss–based estimation analysis were similar to those of the unadjusted analysis (Table 2) because the cumulative incidences were similar. The results were similar in prespecified subgroups defined according to sex, body-mass index, age, vaccination status, and status with respect to hypertension and diabetes (Fig. 3). The results suggest that point-estimate outcomes were better in participants who received a transfusion

Table 1. Baseline Characteristics of the Participants in the Modified Intention-to-Treat Population.*

Characteristic	Convalescent Plasma (N=592)	Control Plasma (N=589)
Median age (IQR) — yr	42 (32–54)	44 (33–55)
Age category — no. (%)		
18–34 yr	190 (32.1)	165 (28.0)
35–49 yr	207 (35.0)	208 (35.3)
50–64 yr	155 (26.2)	176 (29.9)
≥65 yr	40 (6.8)	40 (6.8)
Female sex — no. (%)	323 (54.6)	352 (59.8)
Race or ethnic group — no. (%)†		
Asian	22 (3.7)	22 (3.7)
Black	92 (15.5)	71 (12.1)
American Indian or Alaska Native	8 (1.4)	9 (1.5)
Native Hawaiian or other Pacific Islander	2 (0.3)	2 (0.3)
White	459 (77.5)	475 (80.6)
Hispanic or Latino	80 (13.5)	90 (15.3)
BMI — no. (%)‡		
≥30	210 (35.5)	234 (39.7)
≥35	97 (16.4)	107 (18.2)
Coexisting conditions — no. (%)		
Hypertension	140 (23.6)	136 (23.1)
Diabetes	49 (8.3)	50 (8.5)
Asthma	59 (10.0)	73 (12.4)
HIV infection	13 (2.2)	12 (2.0)
Pregnancy	2 (0.3)	1 (0.2)
Median time from symptom onset to transfusion (IQR) — days	6 (4–7)	6 (4–7)
Vaccination status — no. (%)		
Unvaccinated	493 (83.3)	481 (81.7)
Partially vaccinated	27 (4.6)	31 (5.3)
Fully vaccinated	72 (12.2)	77 (13.1)

* The corresponding percentages for age, sex, and race or ethnic group in persons with coronavirus disease 2019 (Covid-19) in the U.S. population are provided in Table S2. HIV denotes human immunodeficiency virus, and IQR interquartile range.

† Race or ethnic group was reported by the participants.

‡ The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

within 5 days after the onset of symptoms than in those who received a transfusion later (Fig. 3).

Most participants who were hospitalized were unvaccinated (53 of 54 participants). The baseline demographic and clinical characteristics of the hospitalized participants were similar to those

of participants who were not hospitalized. The antibody levels in the units of transfused Covid-19 convalescent plasma were similar in hospitalized and nonhospitalized participants (Fig S1). The mean duration of hospitalization was the same (6 days in both trial groups) after exclusion of the three deaths in the control-plasma group. The interval from plasma donation to transfusion was similar in the recipients of convalescent plasma who were hospitalized and those who were not hospitalized (Fig. S2).

DISEASE SEVERITY

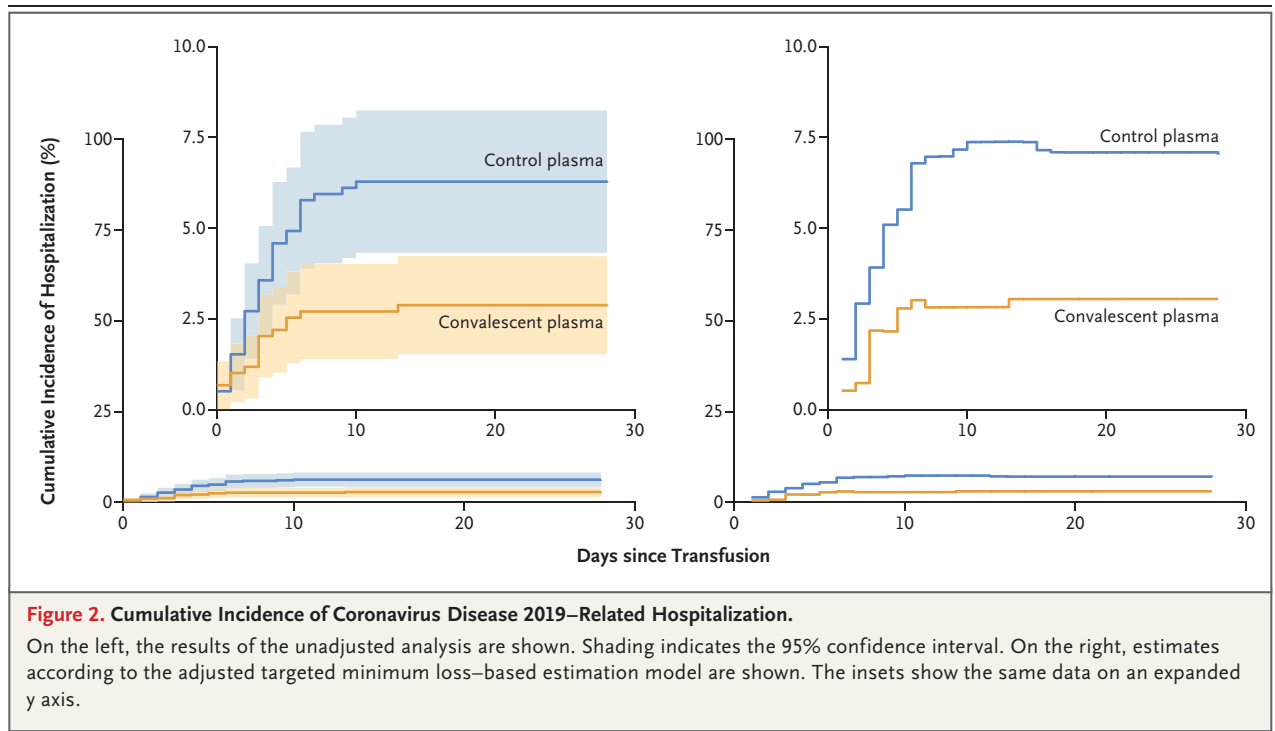
In the modified intention-to-treat population, 12 participants in the convalescent-plasma group and 26 participants in the control-plasma group had disease progression leading to the use of oxygen in the hospital (Table 2). All three deaths after hospitalization occurred in the control-plasma group.

OTHER TRIAL ANALYSES

Before unblinding of the trial data, 7 hospitalizations were adjudicated as being unrelated to Covid-19 (Supplementary Appendix). In an analysis that included 61 hospitalizations for any cause within 28 days after transfusion, hospitalizations occurred in 21 of 592 participants (3.5%) who received Covid-19 convalescent plasma and in 40 of 589 participants (6.8%) who received control plasma (absolute risk reduction, 3.3 percentage points; 95% CI, 0.7 to 5.8), with a relative risk reduction of 47%. All 1181 participants who had received a transfusion had confirmed hospital status by day 28.

SAFETY

A total of 89 adverse events of grade 3 or 4 were reported (34 in the convalescent-plasma group and 55 in the control-plasma group) (Table S3). The 44 cases of pneumonia that were classified as adverse events (14 in the convalescent-plasma group and 30 in the control-plasma group) were also trial outcomes. A total of 16 grade 3 or 4 adverse events (7 in the convalescent-plasma group and 9 in the control-plasma group) occurred in participants who were not hospitalized (Table S4). One transfusion was stopped after 2 to 3 ml had been administered, when diffuse erythema and nausea developed in the participant; that participant was evaluated in the emergency department and was discharged (Table S5). One participant



in the control-plasma group had disease progression to acute respiratory distress syndrome that was adjudicated to be caused by Covid-19 (Table S6); that participant received mechanical ventilation and died.

DISCUSSION

In this randomized trial involving outpatients with recent SARS-CoV-2 infection, the administration of Covid-19 convalescent plasma decreased the incidence of hospitalization. The number needed to treat to avert one hospitalization was 29.4. Immune serum or plasma has been used safely to treat infectious diseases for more than 100 years.¹⁷ Mixed results with these treatments in previous outbreaks of infectious diseases may have been due to a lack of modern study designs, small sample sizes, a differential viral response to passive antibodies, the inclusion of units with low antibody titers, or administration too long after the onset of disease.²³ The results of our blinded, multisite trial are consistent with those of previous trials of antibody-based therapies. These trials have shown that effectiveness is associated with early administration of sufficient amounts of pathogen-specific antibodies to mediate an antiviral effect.²³ Recent clinical data provide support

for the observation that both polyclonal plasma and monoclonal antibodies lead to a reduced risk of disease progression when administered early (i.e., in the first week or within 5 days after symptom onset) and in high doses in both outpatients and seronegative inpatients.

Our trial builds on the findings of an Argentinian trial involving 160 older adult outpatients with Covid-19 who were randomly assigned to receive convalescent plasma or control plasma within 72 hours after symptom onset. That study showed a relative risk reduction of 48% for hypoxemia or tachypnea.¹⁸ In contrast, in our trial, participants who were 18 to 84 years of age received a transfusion within 9 days after the onset of symptoms, and 44% of these participants received a transfusion within 5 days; because of potential delays in diagnostic testing, this later transfusion may be more practical than transfusion within 72 hours. Our trial results contrast with those of another trial of Covid-19 convalescent plasma.¹⁹ In that trial, which was conducted at 48 emergency departments, the participants who were enrolled at presentation to the emergency department possibly represented a population at increased risk for hospitalization. A quarter of the hospitalized participants had a primary-outcome event during randomization and the

Table 2. Covid-19–Related Hospitalization or Death before Day 28 in Participants Who Received Convalescent Plasma or Control Plasma.*

Variable	Convalescent Plasma (N=592)	Control Plasma (N=589)	P Value†
Primary outcome: participants with Covid-19–related hospitalization (no.)	17	37	0.005‡
Participants with hospitalization unrelated to Covid-19 (no.)§	4	3	
Disease severity in hospitalized participants (no.)			
Death¶	0	3	
Mechanical ventilation, ICU hospitalization, or both due to Covid-19	3	4	
Non-ICU hospitalization due to Covid-19, with supplemental oxygen	12	26	
Non-ICU hospitalization due to Covid-19, without supplemental oxygen	2	4	
A stay of >24 hr for observation in an emergency department, field hospital, or other health care unit or receipt of oxygen for >24 hr outside of hospital	0	0	
Expected time free of hospitalization (days)	27.26	26.27	
Difference (days)	0.99±0.28		0.004**
Probability of remaining free of hospitalization (%)	97	93	
Risk difference (percentage points)	4±1		0.006††

* Plus–minus values are means ±SE. A total of 610 participants were randomly assigned to the convalescent-plasma group, and 615 participants were randomly assigned to the control-plasma group. Included here are persons in the modified intention-to-treat population, which included only participants who received a transfusion. ICU denotes intensive care unit.

† The P values shown are two-sided.

‡ Fisher's exact test was used for calculations with the Cochran–Mantel–Haenszel test. The one-sided P value specified in the statistical analysis plan is 0.004 (unadjusted risk difference, 3.4 percentage points).

§ The numbers of first hospitalizations that were adjudicated to be unrelated to Covid-19 are shown. In the convalescent-plasma group, the reasons for these hospitalizations were attempted suicide, hallucinations in a participant who had stopped receiving medication, complex migraines, and constipation. In the control-plasma group, the reasons for these hospitalizations were epigastric pain, complex migraines, and focal bacterial pneumonia.

¶ Clinical details are described in the Supplementary Appendix.

|| The restricted mean survival time was adjusted for age; BMI; baseline levels of albumin, bicarbonate, C-reactive protein, glucose, and potassium; and baseline abnormal findings on physical examination of the head, eyes, ears, nose, and throat, as specified from a random survival forest analysis of baseline characteristics. The data set for the primary analysis was restricted by principal component analysis, and the data set was reduced to 990 participants (496 who received convalescent plasma and 494 who received control plasma).

** The one-sided P value specified as the level of significance in the statistical analysis plan is 0.002.

†† The one-sided P value specified as the level of significance in the statistical analysis plan is 0.003.

initial visit in the emergency department, so there was limited time for the Covid-19 convalescent plasma to exert an effect. In addition, in that trial, patients in the convalescent-plasma group and those in the control group had an equal number of return visits to the emergency department or urgent care clinic.

Our findings are similar to those of a trial that evaluated the efficacy of monoclonal antibodies against SARS-CoV-2, including the magnitude of effect. In the full analysis set in that trial, the likelihood of future medically attended visits was 49% lower in the combined monoclonal-antibody group than in the control group, and in the SARS-CoV-2 antibody–negative subgroup, the likelihood of future medically attended visits was 59% lower in the combined monoclonal-antibody group than in the control group.¹

Our population included participants who had had symptoms for up to 8 days, whereas a trial of sotrovimab included participants who had had symptoms for 5 days or less,² and a trial of bamlanivimab plus etesevimab was limited to infusion within 3 days after a diagnosis of SARS-CoV-2 infection.³ In a subgroup analysis in our trial, early transfusion (administration ≤5 days after symptom onset) appeared to be associated with a greater reduction in the risk of hospitalization.

Although monoclonal antibodies are available in high-income countries, they are expensive to produce, require time for new drug approval, and may not be widely available during Covid-19 surge conditions. In contrast, Covid-19 convalescent plasma is available in low-income and middle-income countries, has no patent limitations, and

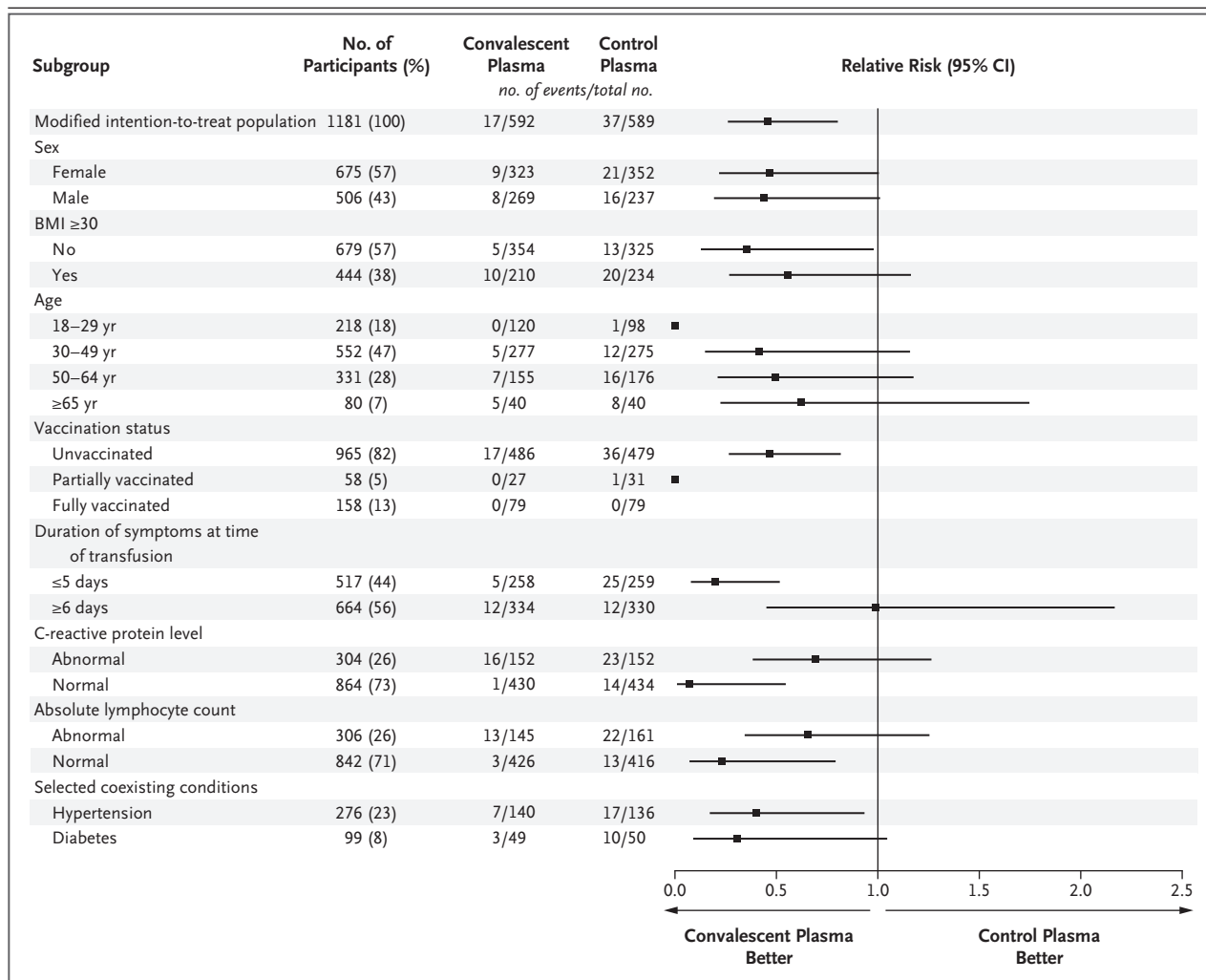


Figure 3. Subgroup Analyses.

Subgroup analyses suggested that participants who received a transfusion within 5 days after symptom onset had a greater reduction in the risk of hospitalization than those who received a transfusion later. These subgroup point estimates are considered to be hypothesis generating. The statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for other outcomes, so the results are reported as point estimates for relative risk and corresponding 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for these outcomes. The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

is relatively inexpensive to produce, since many single donors can provide multiple units, as was evident from this trial. Because it provides a diverse mix of antibodies with different specificities and functions, Covid-19 convalescent plasma should be less vulnerable to the emergence of antibody resistance. In fact, this plasma has been used for rescue therapy in immunocompromised patients who were infected with monoclonal antibody-resistant SARS-CoV-2 variants.⁵ Any person who recovers from infection with a SARS-

CoV-2 variant has antibodies against that variant, so Covid-19 convalescent plasma is an antibody-based therapy that in theory should keep up with locally circulating variants.²⁴ Hence, if a system is developed to qualify units of convalescent plasma, it may be a potential therapeutic option for Covid-19.

In our trial, the most common reason for hospitalization was symptomatic hypoxemia that resulted from pulmonary inflammation in response to SARS-CoV-2 infection. Plasma antibodies me-

diate several antiviral activities, including direct virus neutralization, complement activation, viral particle phagocytosis, and antibody-dependent cellular cytotoxicity.²⁵ We hypothesize that a normal C-reactive protein level and a normal absolute lymphocyte count at baseline among hospitalized persons suggest a role for Covid-19 convalescent plasma in decreasing subsequent host inflammation.

Our trial faced important challenges. First, standards of care and available therapies changed throughout the trial period. Anti-SARS-CoV-2 monoclonal antibodies became available in late November 2020, so the number of persons who were eligible to receive Covid-19 convalescent plasma steadily decreased. Second, as the use of vaccines increased, the frequency of hospitalizations in our trial decreased. Third, variants of concern became more prevalent during the trial period, first with the alpha (B.1.1.7) variant and then with the delta (B.1.617.2) variant in the summer of 2021. The trial plasma was largely obtained in 2020 from donors who had recovered from infection with ancestral forms of SARS-CoV-2. Fourth, the trial logistics involved multiple blood banks that could provide plasma for all blood types at 23 sites during a pandemic when many health care systems were working at limited, fluctuating capacity. However, routine blood-banking standards were able to support proper supply logistics with remote coordination. Finally, because of the risk of SARS-CoV-2 infection, appropriate infection-prevention measures were warranted in the outpatient sites, which were often specially constructed and separated from hospital populations.

In addition to challenges, our trial has limitations. First, for practical purposes, the trial outcome was Covid-19–related hospitalization, not death. The three deaths occurred in the control-plasma group. Second, the incidence of hospitalization in the control-plasma group was 6.3%, which is lower than the incidence of hospitalization among persons with Covid-19 in the United States (approximately 8%). Third, only 35% of the participants who received a transfusion were 50 years of age or older. Fourth, the trial was not large enough for definitive subgroup analyses according to medical coexisting conditions or pregnancy. Finally, measured antibody levels are only modestly predictive of virus neutralization activity.

The strengths of this randomized, controlled trial include a large, diverse trial population of participants who were enrolled at more than 23 sites throughout the United States. The trial included participants who were 18 to 84 years of age. In addition, our trial involved a double-blind intervention with control plasma, and a high percentage of participants received a transfusion and underwent follow-up. Finally, the decision by the institutional review board to include pregnant women in the trial was based on previous studies showing an acceptable safety profile of plasma when administered to pregnant women with other conditions, as well as on emerging data on the safety of convalescent plasma in nonpregnant hospitalized adults. This population of pregnant participants who are at high risk for progression of Covid-19 had been excluded from previous trials of treatment for Covid-19.

Our trial has important public health implications, especially in resource-constrained areas with imbalances in vaccine distribution. Covid-19 convalescent plasma can be considered for initial use in patients with Covid-19 and for use in future pandemics while monoclonal therapies and vaccines are being developed. The establishment of infusion centers that can rapidly administer Covid-19 convalescent plasma for outpatients during pandemics may be a consideration for future health care systems. Even in the current pandemic, the continued propagation of SARS-CoV-2 variants with evolving resistance to currently available monoclonal antibodies indicates the potential usefulness of developing capacity for the availability and distribution of Covid-19 convalescent plasma, especially because locally sourced, recently obtained plasma should include antibodies to circulating strains.²⁶ Antibody levels are heterogeneous among donors,²⁰ and in future pandemics, only the use of therapeutic plasma with antibody levels in the upper deciles should be considered.

Supported by a contract (W911QY2090012, to Dr. Sullivan) with the Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense of the Department of Defense, in collaboration with the Defense Health Agency; Bloomberg Philanthropies; the State of Maryland; a grant (3R01AI152078-01S1, to Dr. Casadevall) from the National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID); a grant (U24TR001609-S3, to Dr. Hanley) from the NIH National Center for Advancing Translational Sciences; a grant (1K23HL151826NIH, to Dr. Bloch) from the National Heart, Lung, and Blood Institute; the Division of Intramural Research, NIAID, NIH; the Mental Wellness Foundation;

the Moriah Fund; Octapharma; the Healthnetwork Foundation; and the Shear Family Foundation.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the trial participants who generously gave of their time and donated biologic specimens.

APPENDIX

The authors' full names and academic degrees are as follows: David J. Sullivan, M.D., Kelly A. Gebo, M.D., M.P.H., Shmuel Shoham, M.D., Evan M. Bloch, M.B., Ch.B., Bryan Lau, Ph.D., Aarthi G. Shenoy, M.D., Giselle S. Mosnaim, M.D., Thomas J. Gniadek, M.D., Ph.D., Yuriko Fukuta, M.D., Ph.D., Bela Patel, M.D., Sonya L. Heath, M.D., Adam C. Levine, M.D., M.P.H., Barry R. Meisenberg, M.D., Emily S. Spivak, M.D., Shweta Anjan, M.D., Moises A. Huaman, M.D., Janis E. Blair, M.D., Judith S. Currier, M.D., James H. Paxton, M.D., Jonathan M. Gerber, M.D., Joann R. Petrini, Ph.D., M.P.H., Patrick B. Broderick, M.D., William Rausch, Sc.B., C.I.P., Marie-Elena Cordisco, M.A., Jean Hammel, M.D., Benjamin Greenblatt, M.D., Valerie C. Cluzet, M.D., Daniel Crusier, M.D., Kevin Oei, D.O., Matthew Abinante, D.O., M.P.H., Laura L. Hammitt, M.D., Catherine G. Sutcliffe, Ph.D., Donald N. Forthal, M.D., Martin S. Zand, M.D., Edward R. Cachay, M.D., Jay S. Raval, M.D., Seble G. Kassaye, M.D., E. Colin Foster, Michael Roth, Christi E. Marshall, Anusha Yarava, Pharm.D., Karen Lane, C.C.R.P., Nichol A. McBee, M.P.H., Amy L. Gawad, M.P.H., Nicky Karlen, Atika Singh, M.S.P.H., Daniel E. Ford, M.D., Ph.D., Douglas A. Jabs, M.D., M.B.A., Lawrence J. Appel, M.D., M.P.H., David M. Shade, J.D., Stephan Ehrhardt, M.D., M.P.H., Sheriza N. Baksh, Ph.D., M.P.H., Oliver Laeyendecker, Ph.D., M.B.A., Andrew Pekosz, Ph.D., Sabra L. Klein, Ph.D., Arturo Casadevall, M.D., Ph.D., Aaron A.R. Tobian, M.D., Ph.D., and Daniel F. Hanley, M.D.

The authors' affiliations are as follows: the Department of Medicine, Division of Infectious Diseases (K.A.G., S.S.), the Department of Pathology (E.M.B., C.E.M., A.A.R.T.), the Department of Neurology, Brain Injury Outcomes Division (A.Y., K.L., N.A.M., A.L.G., N.K., D.F.H.), the Department of Ophthalmology (D.A.J.), the Welch Center for Prevention, Epidemiology and Clinical Research (L.J.A.), and the Institute for Clinical and Translational Research (D.E.F.), Johns Hopkins School of Medicine, and the Departments of Molecular Microbiology and Immunology (D.J.S., A.S., A.P., S.L.K., A.C.), International Health (L.L.H., C.G.S.), and Epidemiology (B.L., D.M.S., S.E., S.N.B.), Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University, Baltimore, the Division of Intramural Research, National Institute of Allergy and Infectious Diseases, Bethesda (O.L.), and Luminis Health, Annapolis (B.R.M.) — all in Maryland; the Department of Medicine, Division of Hematology and Oncology, MedStar Washington Hospital Center (A.G.S.), and the Department of Medicine, Division of Infectious Diseases, Georgetown University Medical Center (S.G.K.) — both in Washington, DC; the Division of Allergy and Immunology, Department of Medicine (G.S.M.), and the Department of Pathology (T.J.G.), North-Shore University Health System, Evanston, IL; the Department of Medicine, Section of Infectious Diseases, Baylor College of Medicine (Y.F.), the Department of Medicine, Division of Pulmonary and Critical Care Medicine, University of Texas Health Science Center (A.G.S.), Houston, and The Next Practices Group, Austin (E.C.F.) — all in Texas; the Department of Medicine, Division of Infectious Diseases, University of Alabama at Birmingham, Birmingham (S.L.H.); the Department of Emergency Medicine, Rhode Island Hospital, Brown University, Providence, RI (A.C.L.); the Department of Medicine, Division of Infectious Diseases, University of Utah School of Medicine, Salt Lake City (E.S.S.); the Department of Medicine, Division of Infectious Diseases, University of Miami Miller School of Medicine, Miami (S.A.); the Department of Medicine, Division of Infectious Diseases, University of Cincinnati, Cincinnati (M.A.H.); the Department of Medicine, Division of Infectious Diseases, Mayo Clinic Hospital, Phoenix, AZ (J.E.B.); the Department of Medicine, Division of Infectious Diseases, University of California, Los Angeles (J.S.C.), Ascada Research (K.O., M.A.), the Department of Medicine, Division of Infectious Diseases, University of California, Irvine (D.N.F.), and the Department of Medicine, Division of Infectious Diseases, University of California, San Diego (E.R.C.) — all in California; the Department of Emergency Medicine, Wayne State University, Detroit (J.H.P.); the Department of Medicine, Division of Hematology and Oncology, University of Massachusetts Chan Medical School, Worcester (J.M.G.); Nuance Health (J.R.P., W.R., M.-E.C.), and Nuance Health Danbury Hospital (P.B.B.), Danbury, and Nuance Health Norwalk Hospital, Norwalk (J.H., B.G.) — all in Connecticut; Nuance Health Vassar Brothers Medical Center, Poughkeepsie (V.C.C., D.C.), the Department of Medicine, University of Rochester Medical Center, Rochester (M.S.Z.), and the Bliss Group, New York (M.R.) — all in New York; and the Department of Pathology, University of New Mexico School of Medicine, Albuquerque, NM (J.S.R.).

REFERENCES

- 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.
- Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early treatment for Covid-19 with SARS-CoV-2 neutralizing antibody sotrovimab. *N Engl J Med* 2021;385:1941-50.
- Dougan M, Nirula A, Azizad M, et al. Bamlanivimab plus etesevimab in mild or moderate Covid-19. *N Engl J Med* 2021;385:1382-92.
- Bloch EM, Goel R, Montemayor C, Cohn C, Tobian AAR. Promoting access to COVID-19 convalescent plasma in low- and middle-income countries. *Transfus Apher Sci* 2021;60:102957.
- Pommeret F, Colomba J, Bigenwald C, et al. Bamlanivimab + etesevimab therapy induces SARS-CoV-2 immune escape mutations and secondary clinical deterioration in COVID-19 patients with B-cell malignancies. *Ann Oncol* 2021;32:1445-7.
- Joyner MJ, Wright RS, Fairweather D, et al. Early safety indicators of COVID-19 convalescent plasma in 5000 patients. *J Clin Invest* 2020;130:4791-7.
- Joyner MJ, Bruno KA, Klassen SA, et al. Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients. *Mayo Clin Proc* 2020;95:1888-97.
- Liu STH, Lin HM, Baine I, et al. Convalescent plasma treatment of severe COVID-19: a propensity score-matched control study. *Nat Med* 2020;26:1708-13.
- 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.
- 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;131:150646.
- Rasheed AM, Fatak DF, Hashim HA, et al. The therapeutic potential of convalescent plasma therapy on treating critically-ill COVID-19 patients residing in respiratory care units in hospitals in Baghdad, Iraq. *Infez Med* 2020;28:357-66.
- Agarwal A, Mukherjee A, Kumar G, et al. 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.
- RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a

- randomised controlled, open-label, platform trial. *Lancet* 2021;397:2049-59.
14. 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;324:460-70.
15. Bégin P, Callum J, Jamula E, et al. Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial. *Nat Med* 2021; 27:2012-24.
16. Tobian A, Cohn CS, Shaz B. COVID-19 convalescent plasma. *Blood* 2021 October 25 (Epub ahead of print).
17. Bloch EM, Shoham S, Casadevall A, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. *J Clin Invest* 2020;130:2757-65.
18. Libster R, Pérez 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.
19. 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.
20. 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;130:6141-50.
21. Verdun N. EUA 26382 — emergency use authorization of COVID-19 convalescent plasma, reissued on March 9, 2021, under Section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360bbb-3) — amendment to allow use of a new test as an acceptable test for use in the manufacture of high titer COVID-19 convalescent plasma. Silver Spring, MD: Food and Drug Administration. June 2, 2021 (<https://www.fda.gov/media/149803/download>).
22. Díaz I, Colantuoni E, Hanley DF, Rosenblum M. Improved precision in the analysis of randomized trials with survival outcomes, without assuming proportional hazards. *Lifetime Data Anal* 2019;25:439-68.
23. Casadevall A, Pirofski LA, Joyner MJ. The principles of antibody therapy for infectious diseases with relevance for COVID-19. *mBio* 2021;12(2):e03372-20.
24. Casadevall A, Henderson JP, Joyner MJ, Pirofski LA. SARS-CoV-2 variants and convalescent plasma: reality, fallacies, and opportunities. *J Clin Invest* 2021;131(7):e148832.
25. Natarajan H, Crowley AR, Butler SE, et al. Markers of polyfunctional SARS-CoV-2 antibodies in convalescent plasma. *mBio* 2021;12(2):e00765-21.
26. Kunze KL, Johnson PW, van Helmond N, et al. Mortality in individuals treated with COVID-19 convalescent plasma varies with the geographic provenance of donors. *Nat Commun* 2021;12:4864.

Copyright © 2022 Massachusetts Medical Society.