May 9, 2022

Dear NIH Research Committee,

We thank you for your efforts to continuously analyze rapidly evolving data on COVID-19 therapeutics to offer the best advice to the medical community on the care of patients with COVID-19. We are pleased to see the most recent update on COVID-19 convalescent plasma (CCP) from the NIH Research Committee and agree that evaluating the efficacy of therapies against rapidly emerging SARS-CoV-2 variants is a challenge. Nevertheless, we would like to respond to several points in the most recent NIH guidelines and to request consideration of additional changes.

We agree that "*The use of CCP should be limited to high-titer products. Products that are not labeled "high titer" should not be used*". This recommendation reflects both historical experience with passive immunization and the findings of two key studies that assessed the effect of high versus lower titer CCP. Libster *et al.* showed, in a randomized trial of CCP in high-risk outpatients, that efficacy in preventing disease progression increased from 48% to 73% when using high titer CCP (1) and Joyner *et al.* documented a dose-response relationship of antibody titer to mortality in non-ventilated hospitalized patients (2). Testing methodologies currently available identify CCP with nearly 100% likelihood of antiviral efficacy against circulating Omicron variants (3).

Timing of treatment is also a key driver of CCP efficacy in non-immunocompromised patients. This is underscored by historical data (4), numerous observational time to infusion studies (2, 5), and recently, the results of a large RCT (6). In the latter study, CCP, in a trial of almost 1200 participants, found that high levels of antibody given within 9 days of symptom onset reduced hospitalizations by more than half, and, if treatment was initiated within 5 days of symptom onset, reduced hospitalizations by more than 80% (6). Thus, there is now substantial evidence that CCP reduces progression to severe COVID-19 when a high titer product is given early.

The emergence and dominance of Omicron variants presents a challenge to passive antibody therapeutics. Given that the activity of monoclonal antibodies (mAbs) depends on a single determinant, mAbs are particularly susceptible to the emergence of new variants and some previously useful mAbs are no longer effective against circulating variants. This contrasts with vaccine-elicited antibody responses and CCP, which contain polyclonal antibodies to multiple epitopes, making them less susceptible to escape by new SARS-CoV-2 variants. Real world evidence shows that vaccination with ancestral SARS-CoV-2 WA-1 spike protein-based vaccines confers protection against severe disease with subsequent variants, including Omicron. As the NIH panel has indicated, high titer, vaccine-elicited polyclonal antibodies from donors with and without prior COVID-19, are active against mismatched virus strains.

Following the FDA's Dec 28, 2021, EUA revision, which extended CCP use to immunodeficient outpatients with COVID-19, the Red Cross and other blood collectors resumed or increased CCP collections in early March 2022. These new units, which meet the revised FDA criteria for high titer include plasma from predominantly vaccinated, convalescent persons, many of whom are likely to have recovered from infections with Omicron variants. In addition, there is a wealth of laboratory data on viral recognition by non-Omicron CCP, which supports its predicted therapeutic efficacy (see (3) for a representative study). As the prevalence of new variants increases, the polyclonal nature of CCP is likely to be an important hedge against future variants.

We have four concerns with the guidelines:

1. Recommendations for antibody therapy are not internally consistent. The update recommends bebtelovimab when ritonavir-boosted nirmatrelvir (Paxlovid) and remdesivir are not available, infeasible to use, or clinically inappropriate based on in vitro binding neutralization data for the omicron variant. This recommendation was made despite absence of robust clinical evidence for outpatient bebtelovimab effectiveness. The single RCT with this agent reported 2 hospitalizations in each arm of a study of 250 low risk patients. Since there are considerable clinical efficacy data for pre-Omicron CCP (7) and in vitro evidence for activity of EUA qualified CCP against Omicron variants (3), a similar recommendation for CCP would be consistent, particularly because both agents have the same active ingredient, namely specific antibody to SARS-CoV-2. Since the revised NIH panel guidelines combined clinical data from randomized trials using earlier mAbs with in vitro data from a newer agent (bebtelovimab), the same approach should be applied to CCP meeting FDA EUA standards.

2. The guidelines emphasize negative CCP studies. The section discussing hospitalized patients, mentions three negative RCTs from other countries - RECOVERY, CONCOR-1, and REMAP-CAP20 - each of which tested CCP in late disease. However, each of the four US RCTs in hospitalized patients reported to date (8-11) reported a reduction in mortality that was statistically significant (9, 10). Furthermore, aggregated data from the COMPILE real-time meta-analysis of 8 international RCTs found a signature of efficacy in patients with early disease who did not require supplemental oxygen and those with certain conditions, and these patients could be identified with a predictive algorithm (12). A reduction in mortality in US hospitalized patients was also observed in a large real-world study of CCP use in the USA (13) and in epidemiological data from the first year of the epidemic(14).

3. The guidelines compare studies that are not comparable. In the section discussing CCP for non-hospitalized, immunocompetent patients, the guidelines juxtapose the two positive RCTs (1, 6) with two negative RCTs (15, 16). However, this comparison is flawed because of major differences in the design of the negative RCTs. The C3PO RCT was performed in patients in emergency rooms not outpatients, indicating that some of the patients were already in an advanced state of disease. Although this trial is negative if one focuses strictly on trial design and outcome, its design allowed cases who were admitted to hospital on the index visit to be counted. In so doing, the trial tested CCP in a phase of COVID-19 when it was biologically implausible to be effective, since one cannot expect an antibody infusion to mediate its protective effects the very day it was given. On the other hand, if the data are analyzed by omitting patients admitted on the day of treatment and limiting the analysis to those who left the ER after treatment and were subsequently admitted to the hospital with COVID-19, a statistically significant treatment effect of about 30% is apparent. This is more consistent with the two other outpatient trials - Libster (1)and Sullivan (6) – that examined patients before they had progressive disease requiring medical attention. We have posted a detailed critique of the C3PO trial at ccpp19.org. The other outpatient trial - CONV-ERT - is seriously flawed because it used methylene-blue inactivated CCP. This unusual procedure, designed to inactivate microbial agents, has been shown to damage antibodies, and likely reduced the efficacy of CCP (17). Methylene blue is known to react with sugar moieties and damage to immunoglobulin glycosylation may inactivate critical Fc functions even if in vitro neutralization is maintained (18). Methylene blue is not used in the United States, which makes the comparison to CONV-ERT even less relevant.

4. The adverse effects listed are unlikely to be representative of the experience with CCP. There has been no evidence of CCP-mediated antibody-dependent enhancement (ADE). ADE is a theoretical possibility that has not been demonstrated. The reference to the CONCOR-1 trial subgroup associated with worse outcomes only emerged in a flawed multivariate analysis (see

discussion of this trial on the CCPP19 website) and is most likely a false positive finding since no other study has corroborated it (19). This concern is not relevant since there is no evidence to support the use of CCP in advanced disease. In contrast, data from multiple RCTs has shown that CCP is extremely safe.

We request that the NIH Research Committee revisit the guidelines to address these four concerns. In addition, in the interest of providing a more accurate and consistent representation of the available information, we request that the guidelines:

1. State that available evidence shows high titer plasma, benchmarked by FDA criteria for use as per the December 28, 2021, EUA, neutralizes SARS-CoV-2 variants in vitro no matter when it was collected.

2. Recommend the use of qualified high titer CCP in immunosuppressed persons and those on immunosuppressive therapies as recommended by the current EUA for CCP considering the removal of many mAbs from clinical use because of variant neutralization escape.

We close this request by noting that CCP has no pharmaceutical support. It is made from altruistic donors, and has been studied by clinicians and academic researchers, and has no profit, no intellectual property, and lacks pharmaceutical representatives and lobbyists to defend its merits. As CCP is the only antibody therapy for COVID-19 available in many low to mid income countries and is the only therapy that keeps pace with new variants in real time, it is very important to consider its efficacy, benefits, and hazards carefully. We are sure that the committee understands this important responsibility.

Finally, we note that both the IDSA and AABB Guideline Committees recommend CCP for certain groups and that the European Conference on Infections in Leukaemia (ECIL 9) has given it a BIII recommendation for use in immunosuppressed patients (20). The IDSA-CDC COVID-19 treatment roadmap prominently stresses the use of CCP. We are hopeful that you will consider our concerns and arguments and further revise your recommendations for CCP.

Sincerely,

The U.S. Convalescent Plasma Project leadership team (ccpp19.org)
Arturo Casadevall MD, PhD (CCPP19.org Chair)
Chair, Molecular Microbiology & Immunology
Alfred & Jill Sommer Professor and Chair
Bloomberg Distinguished Professor
Professor, Department of Molecular Microbiology and Medicine
Johns Hopkins School of Public Health and School of Medicine

Michael J Joyner M.D.
Caywood Professor of Anesthesiology
Vice Chair (Research) Department of Anesthesiology & Perioperative Medicine
Mayo Clinic

Brenda J. Grossman MD, MPH
Professor, Pathology & Immunology
Professor of Medicine
Medical Director, Transfusion Medicine Services

Jeffrey P. Henderson MD, PhD
Associate Professor of Medicine and Molecular Microbiology
Division of Infectious Diseases
Washington University

Nigel Paneth MD MPH
University Distinguished Professor, Emeritus
Departments of Epidemiology & Biostatistics and Pediatrics & Human Development
Michigan State University

Liise-anne Pirofski MD
Selma and Dr. Jacques Mitrani Chair in Biomedical Research
Professor, Medicine, Microbiology, and Immunology
Chief, Division of Infectious Diseases
Albert Einstein College of Medicine and Montefiore Medical Center

Shmuel Shoham MD
Professor
Department of Medicine
Johns Hopkins School of Medicine

Other Signatories

Jennifer Alexander-Brett, MD, PhD
Associate Professor of Medicine
Division of Pulmonary and Critical Care Medicine
Washington University, USA

Paul G. Auwaerter, MD
Sherrilyn and Ken Fisher Professor of Medicine
Clinical Director, Division of Infectious Diseases
Johns Hopkins University School of Medicine
Baltimore, Maryland USA

Elliott Marshall Antman, M.D.
Professor, Brigham and Women's Hospital, Division of Cardiovascular Medicine
Harvard Medical School

Katherine Bar, MD
Attending Physician, Infectious Diseases, Hospital of the University of Pennsylvania
Physician, International Travel Medicine Clinic, Perelman Center for Advanced Medicine
Director, Penn CFAR Viral and Molecular Core

Rachel Bartash, M.D.
Assistant Professor
Division of Infectious Diseases
Albert Einstein College of Medicine and Montefiore Medical Center

Todd Fehniger, MD, PhD
Professor of Medicine
Division of Oncology

Washington University, USA

Neil Gaffin MD
Ridgewood Infectious Disease Associates
947 Linwood Avenue
Ridgewood, NJ

Kelly Anne Gebo, M.D., M.P.H.
Professor, Division of Infectious Diseases
Johns Hopkins School of Medicine

Inessa Gendlina, M.D., Ph.D.
Assistant Professor
Director, East Campus Clinical Infectious Diseases Services
Albert Einstein College of Medicine and Montefiore Medical Center

Amita Gupta, M.D., M.H.S.
Chief, Division of Infectious Diseases,
Professor of Medicine
Johns Hopkins School of Medicine

Robert Grossberg, M.D.
Medical Director, Center for Positive Living/ID Clinic
Associate Professor of Medicine, Albert Einstein College of Medicine

Christopher James Hoffmann, M.D., M.P.H., M.Sc.
Associate Professor of Medicine
Johns Hopkins School of Medicine

Brian Koffman, MDCM (retired), DCFP, FCFP, DABFP, MSEd
Co-Founder
Executive Vice President
Chief Medical Officer
Board Member at Large
Chronic Lymphocytic Leukemia Society

Vadim S Koshkin, MD
Assistant Professor of Medicine
Division of Oncology
University of California San Francisco, USA

Megan Morales, MD
Medical Director, Transplant Infectious Diseases
Assistant Professor of Medicine
Virginia Commonwealth University

C. Fred LeMaistre, MD, FASTCT
Pronouns: he, him, his
Senior Vice President, Market Operations
Physician-in-Chief, Hematology

James M. Musser, MD, PhD
Chair, Department of Pathology & Genomic Medicine
Fondren Presidential Distinguished Chair, Research Institute
Professor of Pathology and Genomic Medicine, Academic Institute
Director, Center for Molecular & Translational Human Infectious Diseases Research
Houston Methodist

Mila B. Ortigoza, M.D., Ph.D.
Assistant Professor
Department of Medicine, Division of Infectious Diseases
Department of Microbiology
NYU Langone Health

Eva Petkova, Ph.D.
Professor
NYU School of Medicine
Department of Population Health
Division of Biostatistics
Department of Child and Adolescent Psychiatry
NYU Langone Health

Monika Paroder, M.D., Ph.D.
Assistant Professor
Department of Pathology
Albert Einstein College of Medicine and Montefiore Medical Center

James R. Stubbs MD
Consultant, Transfusion Medicine
Mayo Clinic, Rochester MN

David Sullivan MD
Professor
Departments of Molecular Microbiology and Immunology and Medicine
Johns Hopkins School of Public Health

Aaron A. R. Tobian, M.D., Ph.D.
Director, Transfusion Medicine Division
Professor of Pathology

Michael Thompson, MD, PhD
VP of Clinical Partnerships
Tempus Labs, USA

Andrea C. Troxel, Sc.D.
Director, Division of Biostatistics
Professor, Department of Population Health
NYU Langone Health

Amit K. Verma, MBBS
Professor, Medical Oncology, Oncology and Hematology,
Director, Division of Hemato-Oncology, Montefiore Department of Oncology

May 9, 2022

Albert Einstein College of Medicine and Montefiore Medical Center

Barry Zingman, M.D.
Clinical Director, Infectious Diseases, Moses Division
Professor of Medicine, Albert Einstein College of Medicine

Jeremy L. Warner MD, MS, FAMIA, FASCO
Associate Professor of Medicine (Hematology/Oncology) and Biomedical Informatics
Director, COVID-19 and Cancer Consortium (CCC19) Research Coordinating Center
Vanderbilt University, USA

R. Scott Wright MD
Professor
Director, Mayo Clinic Human Research Protection Program and Senior Chair, Mayo Clinic Institutional Review Board

Hyunah Yoon, M.D.
Assistant Professor
Division of Infectious Diseases
Albert Einstein College of Medicine and Montefiore Medical Center

References:

1. Libster R, Perez Marc G, Wappner D, Coviello S, Bianchi A, Braem V, Esteban I, Caballero MT, Wood C, Berrueta M, et al. Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults. *The New England journal of medicine.* 2021;384(7):610-8.
2. Joyner MJ, Carter RE, Senefeld JW, Klassen SA, Mills JR, Johnson PW, Theel ES, Wiggins CC, Bruno KA, Klompas AM, et al. Convalescent Plasma Antibody Levels and the Risk of Death from Covid-19. *The New England journal of medicine.* 2021;384(11):1015-27.
3. Li M, Beck EJ, Laeyendecker O, Eby Y, Tobian AA, Caturegli P, Wouters C, Chiklis GR, Block W, McKie RO, et al. Convalescent plasma with a high level of virus-specific antibody effectively neutralizes SARS-CoV-2 variants of concern. *Blood advances.* 2022.
4. Casadevall A, Pirofski LA, and Joyner MJ. The Principles of Antibody Therapy for Infectious Diseases with Relevance for COVID-19. *mBio.* 2021;12(2).
5. Salazar E, Christensen PA, Graviss EA, Nguyen DT, Castillo B, Chen J, Lopez BV, Eagar TN, Yi X, Zhao P, et al. Significantly decreased mortality in a large cohort of COVID-19 patients transfused early with convalescent plasma containing high titer anti-SARS-CoV-2 spike protein IgG. *The American journal of pathology.* 2020.
6. Sullivan DJ, Gebo KA, Shoham S, Bloch EM, Lau B, Shenoy AG, Mosnaim GS, Gniadek TJ, Fukuta Y, Patel B, et al. Early Outpatient Treatment for Covid-19 with Convalescent Plasma. *The New England journal of medicine.* 2022.
7. Focosi D, Franchini M, Pirofski LA, Burnouf T, Paneth N, Joyner MJ, and Casadevall A. COVID-19 Convalescent Plasma and Clinical Trials: Understanding Conflicting Outcomes. *Clin Microbiol Rev.* 2022:e0020021.
8. Bennett-Guerrero E, Romeiser JL, Talbot LR, Ahmed T, Mamone LJ, Singh SM, Hearing JC, Salman H, Holiprosad DD, Freedenberg AT, et al. Severe Acute Respiratory Syndrome Coronavirus 2 Convalescent Plasma Versus Standard Plasma in Coronavirus Disease 2019 Infected Hospitalized Patients in New York: A Double-Blind Randomized Trial. *Crit Care Med.* 2021.
9. O'Donnell MR, Grinsztejn B, Cummings MJ, Justman JE, Lamb MR, Eckhardt CM, Philip NM, Cheung YK, Gupta V, João E, et al. A randomized double-blind controlled trial of convalescent plasma in adults with severe COVID-19. *The Journal of clinical investigation.* 2021.
10. Bar KJ, Shaw PA, Choi GH, Aqui N, Fesnak A, Yang JB, Soto-Calderon H, Grajales L, Starr J, Andronov M, et al. A randomized controlled study of convalescent plasma for individuals hospitalized with COVID-19 pneumonia. *The Journal of clinical investigation.* 2021.
11. Ortigoza MB, Yoon H, Goldfeld KS, Troxel AB, Daily JP, Wu Y, Li Y, Wu D, Cobb GF, Baptiste G, et al. Efficacy and Safety of COVID-19 Convalescent Plasma in Hospitalized Patients: A Randomized Clinical Trial. *JAMA internal medicine.* 2021.
12. Park H, Tarpey T, Liu M, Goldfeld K, Wu Y, Wu D, Li Y, Zhang J, Ganguly D, Ray Y, et al. Development and Validation of a Treatment Benefit Index to Identify Hospitalized Patients With COVID-19 Who May Benefit From Convalescent Plasma. *JAMA network open.* 2022;5(1):e2147375.

13. Arnold Egloff SA, Junglen A, Restivo JS, Wongskhaluang M, Martin C, Doshi P, Schlauch D, Fromell G, Sears LE, Correll M, et al. Convalescent plasma associates with reduced mortality and improved clinical trajectory in patients hospitalized with COVID-19. *The Journal of clinical investigation.* 2021;131(20).
14. Casadevall A, Dragotakes Q, Johnson PW, Senefeld JW, Klassen SA, Wright RS, Joyner MJ, Paneth N, and Carter RE. Convalescent plasma use in the United States was inversely correlated with COVID-19 mortality. *Elife.* 2021;10(
15. Alemany A, Millat-Martinez P, Corbacho-Monné M, Malchair P, Ouchi D, Ruiz-Comellas A, Ramírez-Morros A, Rodríguez Codina J, Amado Simon R, Videla S, et al. High-titre methylene blue-treated convalescent plasma as an early treatment for outpatients with COVID-19: a randomised, placebo-controlled trial. *The Lancet Respiratory medicine.* 2022;10(3):278-88.
16. Korley FK, Durkalski-Mauldin V, Yeatts SD, Schulman K, Davenport RD, Dumont LJ, El Kassar N, Foster LD, Hah JM, Jaiswal S, et al. Early Convalescent Plasma for High-Risk Outpatients with Covid-19. *The New England journal of medicine.* 2021;385(21):1951-60.
17. Ross V. Photodynamic action of methylene blue on antipneumococcal serum. *The Journal of Immunology.* 1938;35(5):351-69.
18. Focosi D, and Casadevall A. Convalescent plasma in outpatients with COVID-19. *The Lancet Respiratory medicine.* 2022;10(3):226-8.
19. Joyner MJ, Paneth NS, Senefeld JW, Fairweather D, Bruno KA, Wright RS, Carter RE, and Casadevall A. Concerns about estimating relative risk of death associated with convalescent plasma for COVID-19. *Nature medicine.* 2022;28(1):51-2.
20. Cesaro S, Ljungman P, Mikulska M, Hirsch HH, von Lilienfeld-Toal M, Cordonnier C, Meylan S, Mehra V, Styczynski J, Marchesi F, et al. Recommendations for the management of COVID-19 in patients with haematological malignancies or haematopoietic cell transplantation, from the 2021 European Conference on Infections in Leukaemia (ECIL 9). *Leukemia.* 2022.