Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the editor

The feasibility of multiple units of convalescent plasma in mechanically ventilated patients with COVID-19: A pilot study

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To the Editor:

A renewed interest in convalescent plasma (CP) was triggered by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. Based on the historical use of CP during prior viral outbreaks, a small number of case series and observational studies were conducted early in the pandemic to evaluate the therapeutic role of CP in coronavirus disease 2019 (COVID-19) [1]. Though the results were mixed, in April 2020, the Mayo Clinic received permission from the US Food and Drug Administration (FDA) to start an Expanded Access Program (EAP) for the use of CP as treatment for COVID-19. The EAP increased access to CP and facilitated investigation of its safety and efficacy [2]. In August of 2020, the FDA granted an emergency use authorization (EUA) for CP [3]. When the EUA was granted, the efficacy of CP in COVID-19 was still unknown, and important questions about timing of treatment, patient selection, dosing, and antibody testing remained unanswered. There is now a better understanding of the serological response to SARS-CoV-2, "high-titer" thresholds for different anti-SARS-CoV-2 antibody assays have been defined [3], and a large cohort study suggests that "high-titer" CP may be effective in reducing progression of COVID-19 in some hospitalized patients [2].

Early in the pandemic, we were interested in strategies that would increase a patient's chances of receiving the quantity (i.e.; titer) and type (i.e.; neutralizing) of antibodies needed to suppress SARS-CoV-2 viral injury. We anticipated this could be done safely via serial transfusions of CP given the low risk of plasma transfusion [4]. Based on this premise, we conducted a pilot study to evaluate the feasibility of repeated dosing of anti-SARS-CoV-2 CP in critically ill mechanically ventilated patients. Key parameters included access to CP and provider willingness to transfuse multiple units of CP to profoundly hypoxemic, mechanically ventilated patients. Additional areas of interest included the antibody content of the transfused CP and measures of safety.

In this single-arm, open-label, pilot study conducted at two academic medical centers (NCT04353206), 10 hypoxemic ($PaO_2/FiO_2 < 300$) mechanically ventilated adults (age > 18 years) with acute respiratory failure due to COVID-19 were enrolled within 72 h of intubation. Patients were transfused with up to six units of CP (2 units of CP on day 0, 3, and 6), or until significant clinical improvement ($PaO_2/FiO_2 > 300$), extubation, futility (i.e., as determined by the treating physician), or death (whichever occurred first). Plasma transfused to enrolled patients at Cedars Sinai was sourced from donors via the Blood Donor Service of the Cedars Sinai Transfusion Medicine Program. These units were then screened using a lateral flow assay to detect the presence or absence anti-SARS-CoV-2 antibodies (Haelgen COVID-19 IgG/IgM Rapid Test). By contrast, at Johns Hopkins, CP was sourced via an expanded access resource to which individuals donate after recovery from COVID-19, but no assessments for antibody presence were made before use. Vital signs, laboratory studies, and assessment of clinical status (including ventilatory requirements) were performed on days 0, 3, and 6 of plasma administration. Additional follow-up was performed on days 14, 28, and 60, which included assessments of respiratory and overall clinical status. Antibody levels of the transfused units of CP were measured retrospectively at both sites using commercially available enzyme-linked immunosorbent assays (ELISAs).

The baseline demographics and clinical outcomes of the 10 patients are reported in Table 1. The median age was 59 years; 7 patients were male, and 8 met criteria for obesity (BMI > 30). The median time between date of onset of respiratory symptoms and mechanical ventilation and first CP infusion was 11 and 12.5 days, respectively. All patients received concomitant SARS-COVID-2 therapy with remdesivir and dexamethasone. Six patients were extubated by day 60. Among the eight patients who were discharged alive, the median time on mechanical ventilation was 22.5 days. The median length of stay for these survivors was 35 days. Two patients died before discharge. Neither death was attributed to the use of CP. In fact, none of the 10 patients in the pilot had any adverse events attributable to CP.

Table 2 shows severity of disease based on APACHE II and SOFA Scores [5,6]. The median APACHE II score was 22 on day 0, which correlates to an approximated 40% likelihood of in-hospital death [5]. The median SOFA score on day 0 was 9, and for those who remained alive and in hospital at day 28 (n = 5), the median SOFA score was 8.

Table 3 displays the antibody content of each plasma unit administered to the 10 patients enrolled at the two sites. Antibodies were measured using the Abbott Architect or the Euroimmun anti-SARS-CoV-2 IgG assays at site 1 (patients 1 – 6; Cedars Sinai) and site 2 (patients

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Table 1
Baseline demographics and clinical outcomes of enrolled patients with COVID-19 who received multiple doses of CP.

Patient Number	1	2	3	4	5	6	7	8	9	10
Age (years)	51	65	69	49	40	33	74	53	70	72
Sex (M/F)	F	M	M	M	M	M	M	M	F	F
Race/ Ethnicity	Hispanic	African-American	Caucasian	Hispanic	Hispanic	Caucasian	Caucasian	Hispanic	African-American	African-American
BMI	38	33	33	36	28	30	28	38	40	46
Comorbidity	Obesity, HLD, pre-diabetes	CAD, DM, CKD, HLD, HTN, Obesity	CAD, HTN, Obesity	Obesity	None	HIV/AIDS, Obesity	HLD, HTN, OSA	DM, HLD, HTN	DM, GERD, HTN, Obesity, OSA	Asthma, CKD, Obesity
Time to MV	1	15	12	16	11	3	21	11	5	9
Time to CP	2	16	13	18	13	5	24	12	6	9
Other Therapy	Dex, Remdesivir	Dex, Remdesivir	Azithro, Dex, Remdesivir	Dex, Remdesivir	Dex, Remdesivir	Dex, Remdesivir	Azithro, Dex, Remdesivir, Vit C	Dex, Remdesivir	Dex, Remdesivir	Dex, Remdesivir
Extubated	N	Y	Y	N	Y	Y	N	Y	N	Y
MV Days	7	32	18	21	27	4	64	3	67	5
Adverse Events	0	0	0	0	0	0	0	0	0	0
Discharged Alive	N	Y	Y	N	Y	Y	Y	Y	Y	Y
Hospital Days	8	44	35	23	71	13	64 *	10	80	22

Azithro = Azithromycin, BMI = body mass index, CAD = coronary artery disease, CKD = chronic kidney disease, CP = convalescent plasma, Dex = Dexamethasone, DM = diabetes mellites, GERD = gastroesophageal reflux disease, HLD = hyperlipidemia, HTN = hypertension, MV = mechanical ventilation, OSA = obstructive sleep apnea, Vit C = Vitamin. *Discharged alive to vent rehabilitation unit

Table 2
Severity of disease based on APACHE II and Modified SOFA.

Patient number	1	2	3	4	5	6	7	8	9	10
APACHE II										
Day 0 mSOFA	19	41	34	24	16	24	28	20	18	18
Day 0	8	13	11	7	10	7	10	8	7	10
Day 3	9	12	10	8	11	3	11	3	6	8
Day 6	N/A	17	9	8	8	3	8	2	7	4
Day 14	N/A	12	7	9	4	2	12	DC	6	2
Day 28	N/A	8	1	N/A	6	DC	9	DC	9	DC

Note: Patient 4 expired by Day 28. Patient 6 did not follow-up on Day 28.
DC: patient discharged alive and SOFA not calculated.

7−10; Johns Hopkins), respectively [7,8]. Antibodies were measured in the plasma of all but one donor; one patient did not receive CP on day 3, and four patients did not did not receive CP on day 6. Based on the EUA-defined thresholds for high-titer using the Abbott Architect assay (specimen/calibrator [S/C] > 4.5) or Euroimmun assay (Arbitrary Unit [AC] > 3.5), all patients at Cedars Sinai and one patient at Johns Hopkins received at least 1 unit of high-titer CP. Overall, 20 of the 50 (40%) CP units administered met criteria for high-titer. Notably, review of transfusion records demonstrated that some patients received more than one unit of CP from the same donor (e.g. units 1–2 in patient 2, units 1, 3, and 5 in patient 7). This had the potential to provide serial doses of high-titer CP to some patients (patient 2), while in others it resulted in serial transfusions of non-high-titer CP (patient 7). Moreover, 53% of units administered at Cedars Sinai met criteria for high-titer CP compared to only 11% of units at Johns Hopkins. Indeed, it appears that the practice at Cedars Sinai of using a lateral flow assay to identify units as having some detectable anti-SARS-CoV-2 antibodies was of value in identifying units with a higher likelihood of being high-titer. Notably, lateral flow assays are easy to use, portable, provide a rapid result, and do not require the laboratory infrastructure and technical expertise necessary to conduct ELISA assays [9].

Our study also suggests that administering multiple units of CP is feasible. Among patients receiving units pre-screened with a lateral flow assay, the cumulative antibody delivered overall was much greater than had a single unit been transfused. CP was readily accessible and clinical providers were supportive of a multi-dosing strategy, whereby concerns related to volume overload and the potential for transfusion associated

Table 3
Abbott and Euroimmun anti-SARS-CoV-2 IgG Serum/Calibrator per unit of plasma administered.

IgG S/C	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Assay	Abbott	Abbott	Abbott	Abbott	Abbott	Abbott	Euroimmun	Euroimmun	Euroimmun	Euroimmun
Day 0										
Unit 1	4.63	7.38	5.26	3.07	7.18	4.33	0.2	0.19	0.84	1.03
Unit 2	2.46	7.38	Not tested	9.17	6.26	7.5	0.32	1.6	1.06	3.59
Day 3										
Unit 1	0.61	5.26	7.74	4.2	7.03	1.66	0.2	N/A	0.84	3.17
Unit 2	2.63	7.95	0.57	2.81	2	1.66	0.32	N/A	1.06	8.37
Day 6										
Unit 1	N/A	7.74	6.88	6.88	7.46	N/A	0.2	N/A	0.38	N/A
Unit 2	N/A	0.57	6.88	3.11	8.03	N/A	0.32	N/A	0.38	N/A
Sum of Titer	10.33	36.28	> 27.33	29.24	37.76	15.55	1.56	1.79	4.56	16.16

S/C = specimen/calibrator
Note: EUA-defined high-titer CP is an index (S/C) > 4.5 for the Abbott assay & > 3.5 for Euroimmun
N/A = Not applicable because not transfused on this day

lung injury did not impact enrollment. Further, no adverse events were attributed to CP infusion.

There are limitations of this study. First, while we did not observe any transfusion associated adverse events, the small sample size and non-randomized design limit this observation. Second, we did not measure pre- and post-infusion anti-SARS-CoV-2 endogenous antibody titers, so whether the infusion of the convalescent plasma changed antibody levels in the recipients is unknown.

In conclusion, a strategy that employs a qualitative assay and transfusion of multiple units can be used to increase the amount of antigen specific antibody transfused overall. This strategy may be especially valuable in resource-limited settings where ELISA assays and monoclonal antibodies are scarce. We encourage continued enrollment into clinical trials to better understand CP as treatment, both for COVID-19 as well as to inform the response to emerging infectious diseases.

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Noah M. Merin[a], Alexis A. LeVee[b], Christian A. Merlo[a,c], Kellie Spector[b], Hannah Coleman[d], Ellen Klapper[e], Chelsea Hayes[e], Rachel Zabner[f], John F. McDyer[g], Yolanda J. Eby[h], David J. Sullivan[i], Aaron A. R. Tobian[h], Evan M. Bloch[h], David N. Hager[c,*]

[a] *Department of Internal Medicine, Division of Hematology, Cedars-Sinai Medical Center, Los Angeles, USA*
[b] *Department of Internal Medicine, Cedars-Sinai Medical Center, Los Angeles, USA*
[c] *Department of Medicine, Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, USA*
[d] *Cedars-Sinai Medical Center, Los Angeles, USA*
[e] *Department of Pathology, Division of Transfusion Medicine, Cedars-Sinai Medical Center, Los Angeles, USA*
[f] *Department of Medicine, Division of Infectious Diseases, Cedars-Sinai Medical Center, Los Angeles, USA*
[g] *Department of Medicine, Division of Pulmonary, Allergy, and Critical Care Medicine, University of Pittsburgh, Pittsburgh, USA*
[h] *Department of Pathology, Division of Transfusion Medicine, Johns Hopkins University School of Medicine, Baltimore, USA*
[i] *Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA*

[*] Corresponding author.
E-mail address: dhager1@jhmi.edu (D.N. Hager).