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Elevated Rate of HLA Antibodies in Male COVID-19 Convalescent Plasma Donors: A Risk Factor for Transfusion-Related Acute Lung Injury



To The Editor: The FDA-approved Expanded Access Program provided an exception to collect coronavirus disease-2019 (COVID-19) convalescent plasma (CCP) from recovered patients. Convalescent plasma has become a treatment for patients with severe or life-threatening severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection under the Expanded Access Program. To date, CCP has been reported to be as safe as standard plasma transfusion.¹

Unlike regular blood donors, CCP donors have recently recovered from a potentially serious viral

infection. Although transmission of coronaviruses has never been reported from transfusion, other plasma-borne factors related to recent coronavirus infection potentially could. Donor human leukocyte antigen antibodies (HLA-Ab) are a primary cause of transfusion-related acute lung injury (TRALI), which is one of the top causes of transfusion-related mortality. Although donor HLA-Ab are usually caused by previous pregnancies, transfusions, or transplantations, viral infections can also trigger the formation and rise of HLA-Ab.^{2,3} As part of national TRALI mitigation strategies, blood banks currently only use plasma from male donors, never pregnant female donors or previously pregnant female donors who screen negative for HLA-Ab.

Given that patients with severe or life-threatening SARS-CoV-2 infection already have significant acute lung injury, CCP recipients would be at a greater mortality risk

if TRALI occurred. Moreover, TRALI in CCP recipients could be misattributed to progression of the recipient's underlying SARS-CoV-2 infection. For all of these reasons, we implemented universal screening of all CCP donors for HLA-Ab, regardless of sex, at our institution.

All CCP donors collected from April 3, 2020, through July 31, 2020, were screened for HLA-Ab (LabScreen Mixed Class I & II, One Lambda, West Hills, California). Positive screening cutoff ratios were previously established at the +5 standard deviation threshold in a population of never-transfused male standard blood donors (class I ratio >30; class II ratio >18) so that <0.01% of male blood donors would screen positive.^{4,5} HLA-Ab specificities of positive screens were confirmed using a single-antigen bead (SAB) assay (LabScreen Single Antigen Class I or II). Additional testing with

TABLE. Demographic and HLA Antibody Results for 5 Male COVID-19 Convalescent Plasma Donors With Positive HLA Antibody Screens

Donor number	Sex	Age (years)	Days since reported COVID-19 symptom resolution	Mixed class I HLA antibody ratio	Mixed class II HLA antibody ratio	Single antigen HLA antibody specificity [mean fluorescence intensity]
1	M	47	51	0.16	18.52	DR8[1188], DR13[1072], DR17[1070], DR14 [966], DR11[716], DR18[635], DR12[309] DRw52[370] DQ6[534], DQ5[300]
2	M	49	41	31.42	3.36	A25 [513], A11[444], A80[409], A23[391], A43[345], A34[305] B61[813], B46[585], B60[543], B63[453], B75 [409], B54 [385], B64[378], B75[373], B41 [349], B77[340], B55[313], B78[312] Cw12[1137], Cw7[1039], Cw8[964], Cw5 [684], Cw17[665], Cw6[612], Cw9[590], Cw4[551], Cw10[551], Cw15[530], Cw16 [483], Cw14[474], Cw18[435], Cw1[415], Cw2[383]
3	M	52	116	56.96	11.85	A25[16404], A66[1339], A33[800]
4	M	53	83	34.53	6.32	B46[1349], B76[322]
5	M	32	108	31.08	0	B46[811], B60[459], B62[304]

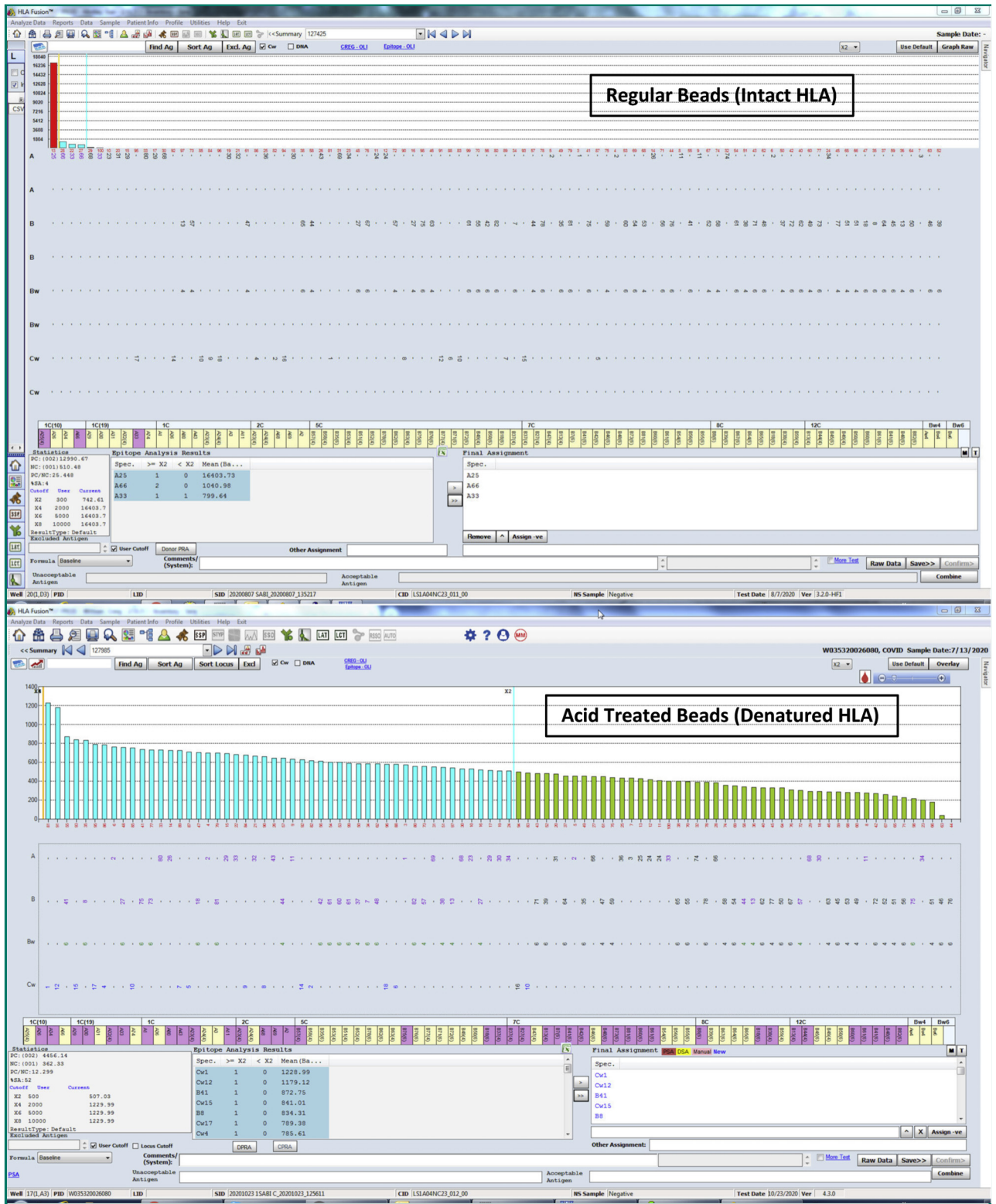


FIGURE. Donor #3 class I HLA antibody testing using native and acid-treated single-antigen beads.

acid-treated single antigen beads was also performed on those donors with class I HLA-Ab to confirm that the reactivity observed was to intact HLA.⁶

During the collection period, 157 unique CCP donors underwent HLA-Ab screening, and 16 CCP donors (10.1%) were deferred for a positive HLA-Ab screen. Of 69 unique male CCP donors, 5 screened positive for HLA-Ab (7.2%; Table); HLA-Ab specificities of all 5 male positive HLA antibody screens were confirmed and identified by SAB. Additional testing against acid-treated HLA beads for the 4 donors with class I HLA-Ab revealed that those with detected HLA-Ab essentially did not have reactivity against denatured HLA targets and are thus clinically relevant (Figure). None of these 5 male CCP donors had a history of transfusion, transplantation, or pregnancy. This male HLA-Ab screening positivity rate was significantly higher than expected for this donor population ($P < .0001$; χ^2 test). In all, male donors represented 31% of all CCP donors who have screened positive for HLA-Ab (5 of 16).

Given these findings in this unique donor population, further studies are needed to better understand the association of HLA-Ab with SARS-CoV-2 infection. Confirmation of these findings could have significant implications on CCP donor screening to help mitigate the risk of TRALI, especially now that use of CCP has broadened to any hospitalized patient with COVID-19 under an FDA Emergency-Use Authorization. Confirmation of these findings would also add to the growing body of literature on the role of viral infection in development

of HLA-Ab, which could have broader implications for persons prone to chronic infections (eg, patients with cystic fibrosis who need lung transplantation).

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1. Joyner MJ, Wright RS, Fairweather D, et al. Early safety indicators of COVID-19 convalescent plasma in 5000 patients. *J Clin Invest*. 2020;130(9):4791-4797.
2. D'Orsogna L, van den Heuvel H, van Kooten C, Heidt S, Claas FHJ. Infectious pathogens may trigger specific allo-HLA reactivity via multiple mechanisms. *Immunogenetics*. 2017;69(8-9):631-641.
3. Russell MR, Halnon NJ, Alejos JC, Salem MM, Reardon LC. COVID-19 in a pediatric heart transplant recipient: emergence of donor-specific antibodies. *J Heart Lung Transplant*. 2020;39(7):732-733.
4. Triulzi DJ, Kleinman S, Kakaiya RM, et al. The effect of previous pregnancy and transfusion on HLA alloimmunization in blood donors: implications for a transfusion-related acute lung injury risk reduction strategy. *Transfusion*. 2009;49(9):1825-1835.
5. Carrick DM, Norris PJ, Endres RO, et al. Establishing assay cutoffs for HLA antibody screening of apheresis donors. *Transfusion*. 2011;51(10):2092-2101.
6. Jacob EK, De Goey SR, Gandhi MJ. Positive virtual crossmatch with negative flow crossmatch results in two cases. *Transpl Immunol*. 2011;25(1):77-81.

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The Recalibration of
 Interventional
 Cardiology During
 COVID-19: An
 Opportunity for a
 Future Paradigm



A pessimist sees the difficulty in every opportunity; an optimist sees the opportunity in every difficulty.

Winston Churchill, 1938

To the Editor: As a consequence of the coronavirus disease 2019 (COVID-19) pandemic, hospitals have had to reconfigure the role for cardiac intensive care unit (CICU) staffing to meet the health care needs of their communities.¹ Interventional cardiologists (ICs), among other specialists, have been redeployed in the CICU to take care of a primary respiratory illness with multiorgan failure.^{1,2} These physicians are required to be skilled with ventilator management, end-organ injury, fluid and electrolyte balance, and end-of-life care. Even before the COVID-19 pandemic, the CICU had noted dramatic shifts in its landscape and started to resemble a medical intensive care unit population with a primary cardiac illness complicated by multiorgan involvement and intensive care needs.²⁻⁴ This contrast has been further amplified by the ongoing pandemic.

How then must the IC seek the opportunity within this difficulty? Interventional cardiology has increasingly become subspecialized with training programs for complex coronary, structural, and peripheral interventions. Increasingly, the IC has been required to serve as a leader of the acute cardiovascular team caring for patients with acute coronary syndrome, cardiogenic shock, cardiac arrest, and pulmonary embolism.^{2,4} In the catheterization laboratory, rapid decisions such as vascular access, hemodynamic evaluation, mechanical circulatory support, internal cooling, mechanical compression devices, and vasoactive medications are often made while performing diagnostic or therapeutic coronary interventions. In such circumstances, the training