

Antibody Response to a Fourth Dose of a SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series

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The antibody response after 2 doses of an mRNA severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine is excellent in the general population but less robust in transplant patients.¹ Severe breakthrough infections in solid organ transplant recipients (SOTRs) have prompted debate on how to protect these individuals.^{2,3} We previously reported improved antibody responses in ~50% of SOTRs after a third dose (D3) of vaccine.⁴ In this series, we studied antibody responses to a fourth dose (D4) of SARS-CoV-2 vaccine in 18 SOTRs from April 24, 2021, through June 16, 2021.

Participants were enrolled in an observational study of SARS-CoV-2 vaccination outcomes in SOTRs.¹ Eighteen received a D4 of a coronavirus disease 2019 (COVID-19)

vaccine and had no known history of COVID-19 infection. Semiquantitative antispike antibody testing was performed using the Roche Elecsys anti-SARS-CoV-2 S or the EUROIMMUN immunoglobulin G enzyme immunoassays 2–6 wk post-D4. We categorized titers as negative, low-positive, and high-positive; low-positive titers were >0.8 U/mL but <50 U/mL (Roche), or >1.1 but <4 AU (EUROIMMUN). High-positive titers were ≥50 U/mL (Roche) or ≥4 AU (EUROIMMUN). This study was approved by the Johns Hopkins Institutional Review Board and participants provided informed consent electronically.

The median age was 58 y (interquartile range [IQR], 50–65). The median time from transplant was 7.1 y (IQR, 2.3–16.2). The median time from D3 to D4 was 28 d (IQR, 21–30). Eleven (61.1%) participants received kidney transplants. Sixteen (88.9%) were on mycophenolate mofetil at the time of vaccination. Pre-D4, there were 6 participants with negative titers, 2 with low-positive, and 10 with high-positive. Post-D4, 5 of 8 (63%) participants with negative or low-positive titers showed boosting to high-positive titers (Table 1). Additionally, among 11 SOTRs serially tested on similar assays, post-D4 titers rose in 7 (63%). Most participants with high-positive pre-D4 titers showed further boosting. The 3 participants with persistently negative titers post-D4 were kidney transplant recipients <5 y posttransplant taking tacrolimus and mycophenolate mofetil, and 2 of 3 were additionally taking corticosteroids. Eleven of 16 participants (69%) receiving antiproliferative agents showed antibody boosting.

To our knowledge, this is the first series describing the antibody response among SOTRs after 4 doses of vaccine against COVID-19. Given neutralizing antibody level may be the best correlate of vaccine-associated immunoprotection to date, it is encouraging that 50% of participants with negative and all with low-positive titers pre-D4 showed boosting to high-positive titers post-D4.⁵ This echoes previous findings that one-third of negative and all low-positive patients after 2 doses were boosted to high-positive titers after receiving a D3 of vaccine.⁴ These findings suggest that immunogenic potential exists for these poor responders.

Limitations include small sample size, lack of formal neutralizing antibody, B-cell or T-cell assays, durability of antibody levels, or safety information regarding the D4 given limited time to follow-up. We also lacked CD4 counts or hypogammaglobulinemia information in persistent suboptimal responders.

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TABLE 1.
Antibody titers after each vaccine

Age, y	Sex	Organ(s)	Time since transplant, y	Antimetabolite	Initial vaccine series	Post-D2 titer	D3	Post-D3 titer	Post-D3 titer	D4	Post-D4 titer	Post-D4 titer
44	F	Kidney	4	Yes	Moderna	Negative	Pfizer	Negative	0.22 E	Pfizer	Negative	0.92 E
65	F	Kidney	0.5	Yes	Moderna	Negative	Moderna	Negative	0.06 E	Moderna	Negative	0.06 E
44	M	Kidney	3	Yes	Pfizer	Negative	Pfizer	Negative	0.09 E	J&J	Negative	0.4 R
63	M	Liver	11	Yes	Pfizer	Negative	J&J	Negative	0.46 R	Pfizer	High	54.9 R
57	M	Kidney	15	Yes	J&J	Negative	Moderna	Negative	0.97 E	Moderna	High	286.9 R
53	M	Kidney	21	Yes	Pfizer	Negative	Pfizer	Negative	(self-report)	J&J	High	343 R
61	F	Kidney	8	Yes	Pfizer	Negative	Moderna	Low	2.75 R	Moderna	High	>2500 R
49	F	Kidney	1	Yes	Moderna	Negative	Pfizer	Low	7.3 R	Pfizer	High	82.9 R
52	F	Kidney-Pancreas	20	Yes	Moderna	Negative	Pfizer	High	504.4 R	Pfizer	High	845 R
54	M	Liver	1	Yes	Pfizer	Low	Moderna	High	125.7 R	Moderna	High	>2500 R
69	M	Heart	16	Yes	Pfizer	Negative	Moderna	High	8.37 E	Moderna	High	>2500 R
68	M	Heart	2	Yes	Pfizer	Negative	Moderna	High	>250 R	Moderna	High	402.9 R
43	F	Pancreas	1	Yes	Pfizer	Negative	Moderna	High	4.72 E	Moderna	High	5.27 E
58	M	Kidney	3	Yes	Moderna	Low	Moderna	High	6.93 E	Moderna	High	4.16 E
42	F	Liver	5	No	Moderna	Negative	Pfizer	High	11.39 E	Pfizer	High	8.75 E
73	F	Kidney-Liver	18	Yes	Pfizer	Low	Moderna	High	4.45 E	Moderna	High	1691 R
67	F	Kidney	11	Yes	Moderna	Low	Pfizer	High	9.19 E	Pfizer	High	>2500 R
64	M	Liver	21	No	Moderna	Low	Pfizer	High	7.21 E	Pfizer	High	>2500 R

D, dose; E, EUROIMMUN assay (parameters: low-positive, ≥ 1.1 and < 4 ; high-positive, ≥ 4 AU); F, female; J&J, Johnson & Johnson; M, male; R, Roche assay (parameters: low-positive, ≥ 0.8 and < 50 ; high-positive, ≥ 50 U/mL).

Though some patients may require additional measures such as immunosuppression modulation to achieve immunity, these data support continued exploration of subsequent vaccine doses in SOTRs.

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