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SARS-CoV-2 anti–spike antibodies after vaccination in pediatric heart transplantation: A first report

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KEYWORDS:

pediatric heart transplant;
SARS-CoV-2

BACKGROUND: BACKGROUND: There is a paucity of data regarding the antibody response to SARS-CoV-2 vaccination in children after solid organ transplant.

METHODS: We retrospectively reviewed the SARS-CoV-2 Anti–Spike IgG antibodies measured following SARS-CoV-2 vaccination at our pediatric heart transplant (HTx) center.

RESULTS: Among patients (median age 17.1 years) in whom antibody testing was performed (median 118 days post-vaccine completion), a SARS-CoV-2 Anti–Spike IgG antibody was detected in 28 of 40 (70%) post-HTx recipients (median antibody level 10.9 AU/ml). Neutropenia, diabetes mellitus, and previous use of rituximab were associated with absence of a detectable antibody. All 7 post-HTx patients with a known pre-vaccination SARS-CoV-2 viral infection had a detectable SARS-CoV-2 Anti–Spike IgG. All 12 vaccinated pre-HTx patients had a detectable antibody (median antibody level 11.6 AU/ml) including 5 patients that maintained detectable antibodies post-HTx. There were no cases of myocarditis among the total of 17 pre-HTx and 81 post-HTx patients that underwent SARS-CoV-2 vaccination.

CONCLUSION: Our data suggest that a significant proportion of pediatric HTx recipients have no detectable antibody response after SARS-CoV-2 vaccination and support the recommendation to complete the vaccination series prior to HTx in those pediatric patients waiting for HTx.

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On August 12, 2021, the United States Food and Drug Administration modified the Emergency Use Authorizations (EUAs) for SARS-CoV-2 messenger RNA (mRNA)

vaccines to allow for administration of a third dose for certain immune-compromised people.¹ Thereafter, the Centers for Disease Control and Prevention's Advisory Committee

Abbreviations: ACIP, Advisory Committee on Immunization Practices; AST, American Society of Transplantation; EUA, Emergency Use Authorization; HTx, Heart Transplant; ISHLT, International Society for Heart and Lung Transplantation; IQR, interquartile range; mRNA, messenger RNA; SOT, solid organ transplant

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on Immunization Practices (ACIP) made a recommendation for use of an additional dose of the Pfizer–BioNTech BNT162b2 (Pfizer) vaccine for persons aged ≥ 12 years or of the Moderna mRNA-1273 (Moderna) vaccine for persons aged ≥ 18 years for moderately to severely immunocompromised people.² The American Society of Transplantation (AST) and International Society for Heart and Lung Transplantation (ISHLT) then released a joint statement recommending a third dose of mRNA vaccine for recipients of a solid organ transplant (SOT) that have previously completed a 2-dose mRNA vaccine series based on the individual patients' unique situation and local regulations and vaccine availability.³

These recommendations are based in part on recent findings that a significant proportion of adult heart transplant (HTx) recipients who received Pfizer vaccine⁴ and adult SOT recipients who received either Pfizer or Moderna vaccine⁵ did not have measurable post-vaccine antibodies. There are now data that a third mRNA vaccine dose in adult SOT recipients significantly improves the immunogenicity of the mRNA vaccine in this population.^{6,7} In light of the recent recommendations from the ACIP² and AST/ISHLT,^{2,3} the paucity of data in pediatric SOT, and increasing spread of the SARS-CoV-2 Delta variant, it is imperative to study the antibody response to SARS-CoV-2 vaccination among pediatric SOT recipients.

At our pediatric hospital, we undertook a proactive strategy to vaccinate pediatric HTx recipients (and patients wait-listed for HTx) eligible to receive a SARS-CoV-2 vaccine. This is a retrospective, single-institutional experience aiming to describe the clinical characteristics and antibody responses of those vaccinated and in whom antibody testing was performed. Post-vaccination SARS-CoV-2 Anti–Spike IgG antibody testing was performed at outpatient clinic appointments or surveillance cardiac biopsy. This protocol was approved by the Baylor College of Medicine Institutional Review Board. SARS-CoV-2 Anti–Spike IgG antibodies were quantitated using the FDA-EUA approved Vitros 5600 immunoassay.⁸ The proportion of patients with detectable antibodies (>1.0 AU/ml) was assessed with an exact binomial confidence interval. The Fisher exact test (categorical variables) and Kruskal-Wallis test (continuous variables) were used as appropriate. All tests were 2-sided with $\alpha = 0.05$. Analyses were performed using SPSS (IBM Corporation, New York City, NY).

Ninety patients received a 2-dose Pfizer vaccine series, 6 patients received a 2-dose Moderna vaccine series, and 2 patients received a single Johnson & Johnson/Janssen (J&J) Ad26.COV2.S vaccine. Vaccine-induced antibodies were assessed in 40 post-HTx patients (median age 17.1 years; interquartile range [IQR] 15.7–18.4) at a median 118 (IQR 57–152) days after mRNA vaccine dose 2 or single J&J vaccine. SARS-CoV-2 Anti–Spike IgG was detected in 28 (70%) of these patients (Figure 1). Among those with a detectable antibody, the median antibody level was 10.9 (IQR 5.5–15.2) AU/ml. The previous use of rituximab within 6 months of vaccine dose 1, an absolute neutrophil count $< 1,500/\text{mm}^3$, and diabetes mellitus were associated with absence of a detectable antibody response (Table 1).

SARS-CoV-2 Anti-Spike Antibody Levels in Pediatric Heart Transplant Recipients

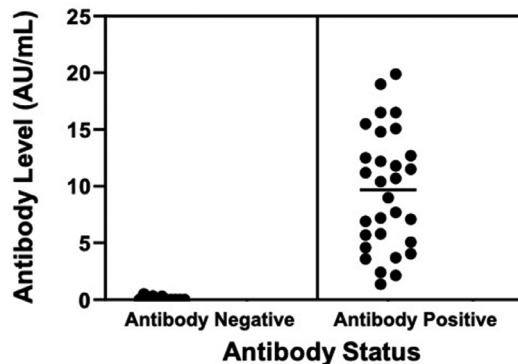


Figure 1 SARS-CoV-2 Anti–Spike Antibody Levels in Pediatric Heart Transplant Recipients. Comparison of SARS-CoV-2 Anti–Spike Antibody (IgG) levels between antibody “negative” (left panel) and antibody “positive” patients (right panel).

There were no detectable antibodies in the 2 patients that received a J&J vaccine. All 7 patients with known pre-vaccination SARS-CoV-2 viral infection (diagnosed by RT-PCR) had a detectable SARS-CoV-2 Anti–Spike IgG. The use of mycophenolate and use of sirolimus were not associated with vaccine response (Table 1).

SARS-CoV-2 Anti–Spike IgG was detected in all 12 pre-HTx patients (median age 16.5 years; IQR 15.7–17.1) in whom antibody testing was performed (median antibody level 11.6 AU/ml; IQR 8.3–13.9). Five patients underwent HTx after completion of the SARS-CoV-2 vaccine series; all 5 had detectable antibodies post-HTx (median 41 days post-HTx; IQR 14–76) despite enhanced immunosuppression.

After a median of 229 (IQR 145–248) days of follow-up after completion of SARS-CoV-2 vaccination (2-dose mRNA series or single J&J dose), there have been no cases of myocarditis among the 17 pre-HTx, and 81 post-HTx patients. Two patients experienced antibody mediated rejection (diagnosed 5 days and 104 days post-second vaccine); both patients had sub-therapeutic immunosuppressive drug levels and prior history of medication non-adherence and rejection. Three patients (3.1%) had symptomatic COVID-19 and tested positive for SARS-CoV-2 viral infection (nasopharyngeal RT-PCR) after completion of their 2-dose mRNA SARS-CoV-2 vaccination series; there were no detectable post-vaccination antibodies in the 1 patient in whom post-vaccination antibodies were assessed before infection.

Our data suggest that a significant proportion of pediatric HTx recipients (30%) have no detectable antibody response after completion of SARS-CoV-2 vaccination (2-dose mRNA series or single J&J dose). This may be an underestimation because pre-vaccination antibodies were not assessed and at least 7 of 40 post-HTx patients had known pre-vaccination infection. Since no antibody threshold has been established for protective immunity, it is possible that many patients with a detectable antibody response still have a reduced humoral response. It is important to note, however,

Table 1 Post-Vaccination SARS-CoV-2 Anti-Spike Antibody after Pediatric Heart Transplantation

Characteristic	Antibody absent (n = 12)	Antibody present (n = 28)	p-value
Sex			0.15
Female	6	7	
Male	6	21	
Race/Ethnicity			0.90
Hispanic	6	14	
Non-Hispanic Black	2	3	
Non-Hispanic White	4	11	
Age at HTx (years) ^a	9.6 (1.0 - 14.2)	10.8 (5.3 - 13.7)	0.9
Age at Vaccine #1 (years) ^a	16.9 (15.7 - 18.4)	17.3 (15.7 - 18.3)	0.94
Age at Vaccine #1 (years) by group			0.91
12 - 15	4	11	
16 - 17	3	8	
≥ 18	5	9	
Time to antibody testing (days) ^a	123.0 (66.5 - 148.0)	117 (55.5 - 152.0)	0.95
Vaccine			0.052
J&J/J Ad26.COV2.S	2	0	
Moderna mRNA-1273	0	4	
Pfizer-BioNTech BNT162b2	10	24	
SARS-CoV-2 infection pre-vaccine	0	7	0.08
ALC < 1,000/mm ³	3	3	0.34
ANC < 1,500/mm ³	3	0	0.02
Immunosuppression			
Use of mycophenolate	6	11	0.73
Use of prednisone	5	9	0.72
Use of sirolimus	6	10	0.49
Use of tacrolimus	9	25	0.34
Recent use of ATG ^b	2	1	0.21
Recent use of rituximab ^b	3	0	0.02
Recent use of IVIG ^c	3	3	0.34
Chronic Kidney Disease	6	6	0.13
Diabetes Mellitus	5	3	0.04
BMI category (kg/m ²)			1
<25	8	18	
25-29.9 (overweight)	2	4	
>30 (obese)	2	6	

Abbreviations: ALC, absolute lymphocyte count; ANC, absolute neutrophil count; ATG, anti-thymocyte globulin; BMI, Body Mass Index; HTx: Heart Transplant; IVIG, intravenous immune globulin; J&J, Johnson & Johnson/Janssen.

^adata expressed as median (interquartile range)

^bwithin 6 months

^cwithin 3 months

that the antibody response observed in the post-HTx patients with measurable antibody was equivalent to a neutralizing antibody titer of >1:80. At our center, most healthy pediatric individuals have a response from >1:80 to 1:320 (unpublished). The magnitude of the T-cell response in this patient population is unknown at this time.

Limitations of this study include a small sample size and retrospective nature. Pre-vaccination antibodies were not assessed and there was not enough follow-up time to determine post-vaccine SARS-CoV-2 infection rate or waning of antibodies. Antibody levels are not ideal surrogates for protective immunity, and memory B-cell and cell-mediated immunity were not assessed. Cell-mediated immunity and clinical endpoints including breakthrough infection, subsequent hospitalizations, and rates of rejection after SARS-CoV-2 vaccination should be assessed in future studies. It

is unclear if these findings are representative of other pediatric immunosuppressed populations.

In light of the recently modified EUA, data from studies in immunosuppressed adults, lack of known protective antibody thresholds, and increasing spread of the SARS-CoV-2 Delta variant, our data support consideration of an additional dose of SARS-CoV-2 mRNA vaccine among recipients of pediatric heart transplantation to achieve an initial antibody response. Our data also support the AST/ISHLT recommendation³ to complete the vaccination series before transplantation in those pediatric patients on the wait-list if possible. All pre-HTx patients in whom antibody testing was performed had detectable SARS CoV-2 Anti-Spike antibodies, and the 5 patients who underwent HTx after vaccination maintained detectable antibodies at a time of peak immunosuppression. While safety, clinical efficacy,

and immunologic response studies (including assessment of cell-mediated immunity) are ongoing among adult SOT recipients, it is also imperative that these studies be carefully planned and performed in children as well, as pediatric clinicians begin to consider and administer a third SARS-CoV-2 mRNA vaccine dose to pediatric solid organ transplant recipients.

Disclosure statement

The authors have no conflicts of interest to declare. None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript. F. Munoz is a local PI for the pediatric Pfizer SARS-CoV-2 vaccination trials. She is also a member of Data Safety Monitoring Boards for Moderna and Pfizer. C. Bocchini is a local sub-I for the pediatric Pfizer SARS-CoV-2 vaccination trials.

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