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VIEWPOINT

SARS-CoV-2 antibody testing for transplant recipients: A tool to personalize protection versus COVID-19

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Anti-spike antibody testing has emerged as a powerful tool to assess SARS-CoV-2 vaccine response in solid organ transplant (SOT) recipients, many of whom remain at risk for COVID-19 despite vaccination. Neither the US Food and Drug Administration nor major transplant societies recommend testing antibody responses after vaccination, or its general incorporation into COVID-19 risk stratification. Notably, in December 2021, the American Society of Transplantation recognized anti-spike seronegativity as a consideration for use of monoclonal antibody pre-exposure prophylaxis. In this viewpoint, we narrate the evolving rationale for anti-spike antibody testing and ultimately recommend that all SOT recipients be tested for anti-spike antibody after vaccination. This result should then be used to personalize efforts to improve protection versus COVID-19 for the most vulnerable, such as additional vaccination strategies and consideration of passive immunoprophylaxis.

1 | ANTIBODY RESPONSE TO COVID-19 VACCINES IN SOLID ORGAN TRANSPLANT RECIPIENTS

In March 2021 our research group reported that anti-spike/receptor binding domain antibody responses (hereafter "anti-spike antibodies") to the otherwise extremely immunogenic mRNA COVID-19 vaccines were significantly diminished in many solid organ transplant (SOT) recipients.[1] This work used two clinical assays designed to detect exposure to SARS-CoV-2, later validated as associated with neutralizing activity at higher levels in convalescent persons.[2,3] Many groups corroborated and expanded upon these findings, establishing phenotypes associated with poor sero-response: older persons, non-liver recipients, persons closer to transplant, and those receiving certain immunosuppressives such as antimetabolite therapies (mycophenolate) and belatacept.[4–6] The deleterious impact of other biologics and cellular therapies, such as B cell–depleting agents, was also confirmed.[7]

The significance of poor antibody response was uncertain, but there was suspicion that this would connote higher risk of infection by SARS-CoV-2 and might associate with serious disease given transplant patients reside at the intersection of multimorbidity associated with poor COVID-19 outcomes (diabetes, obesity, cardiovascular disease)[8] and multifactorial transplant immunosuppression. Hesitance to use anti-spike antibody levels as a marker for either vulnerability to or protection from COVID-19 was, in part, due to flooding of the commercial market with antibody assays with varying operating characteristics, including those that targeted the nucleocapsid (N)

Abbreviations: CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019; FDA, Food and Drug Administration; mAb, monoclonal antibody; mRNA, messenger ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOT, solid organ transplant.

protein, which is not contained in the COVID-19 vaccines and is not a marker of vaccine response. This, as well as a general data vacuum regarding direct association between antibody level and real-world protection, prompted the US FDA to strongly recommend against assessing antibody level to measure vaccine response (fda.gov, press release May 16, 2021). Transplant societies also remained cautious to endorse any form of antibody testing after vaccination. For example, in August 2021 The Transplantation Society (TTS) stated they "do not recommend checking antibody responses to the vaccine"[9] and in November 2021 the American Society of Transplantation (AST) stated that they "do not recommend routinely checking antibody responses after any dose and do not recommend its use to determine need for additional vaccine doses".[10]

Accumulating research did demonstrate that anti-spike assays were well correlated with neutralizing antibody after vaccination, which in turn emerged as the best correlate of protection after vaccination in the general population.[11–13] For example, vaccine trial participants with lower anti-spike antibody levels and neutralizing capacity experienced higher rates of infection after vaccination (so-called "breakthrough"). Additionally, exogenous administration of monoclonal neutralizing anti-spike antibody (mAb) was shown to prevent COVID-19[14] and reduce mortality specifically among seronegative persons.[15]

Large-scale data directly linking antibody level to outcomes in SOT recipients were (and remain) limited, due to multiple factors including lack of broad testing or prospective studies. Several case series in spring and summer 2021 suggested a strong relationship between anti-spike level and breakthrough COVID-19,[16–18] with 82% (47/57) of tested SOT recipients showing nil anti-spike antibody predominately following a two-dose mRNA series. A striking association between SOT status and severe breakthrough infections was reinforced through multicenter studies, even higher than other immunocompromised persons, although antibody testing was not reported.[19,20] Synthesized data by the CDC demonstrated that seroconversion rates were lowest among SOT recipients as compared to other immunocompromised populations, supporting a link between these outcomes.[21]

2 | IMPACT OF ADDITIONAL VACCINATIONS

Spurred by reports of poor sero-response and serious COVID-19 outcomes after vaccination, research teams and SOT recipients alike called for urgent investigation into methods to improve protection versus COVID-19. Once vaccine access increased in the United States, many transplant recipients began to independently obtain additional doses in late spring and summer of 2021. This approach was also adopted in several European countries with routine administration of a third vaccine dose in immunocompromised persons, often with preceding testing of anti-spike antibody.

Impressively, in many SOT recipients with low but detectable antibody, an additional dose did boost anti-spike antibody levels to those seen in the general population after two mRNA doses.[22,23] This also laid the groundwork for a key clinical trial that formally tested this hypothesis and confirmed that, indeed, additional vaccine doses boosted humoral responses for a number of SOT recipients.[24] This mounting evidence was heavily cited by the FDA and CDC in their authorization of an additional mRNA vaccine dose for moderately-to-severely immunocompromised persons.

Disappointingly, a significant subset of transplant recipients who were seronegative after two mRNA vaccine doses remain seronegative after a third, or even fourth vaccine dose.[25,26] Among these persons, seroconversion to additional doses was typically 20%–40%, to lower peak levels, and with very little associated neutralizing capacity particularly versus variants of concern.[27] In the absence of routine antibody testing, many patients and their providers remained unaware of potential extreme susceptibility to infection despite vaccination. For example, we have recently cared for several SOT recipients admitted with critical COVID-19 who were discovered on admission to be seronegative despite three-dose mRNA vaccination.

3 | SEEKING A CORRELATE OF PROTECTION

Much of the remaining controversy surrounding antibody testing relates to (1) the quest for an antibody threshold associated with protection in patients taking longitudinal immunosuppression and (2) the potential for protective cellular responses in the absence of robust antibody response. In the general population, multiple studies have attempted to either directly measure or model thresholds associated with high vaccine effectiveness, primarily based on anti-spike antibody response and associated neutralizing capacity, demonstrating correlation with protection on a continuous scale.[12,13,28] An absolute threshold of protection is a very lofty goal for respiratory viruses, and one that has not truly been achieved in the general population, let alone in the transplant population with impaired cellular compartments and potential for sluggish immune responses versus SARS-CoV-2. Furthermore, the goalposts are constantly moving, as evidenced by the rise of the Omicron variant, which demonstrates significant immune evasion and need for potentially >20-fold higher antibody levels to neutralize.[29] Thus, although this goal is important, it should not be the all-encompassing focus in the setting of an ongoing public health emergency. We can expect that SOT recipients will need to mount at least a level of anti-spike antibody associated with putative protection in the general population,[12,13] potentially significantly higher given a lack of other innate and adaptive immune "cavalry" as a result of immunosuppressive medications as well as the immune evasion of SARS-CoV-2 variants of concern.

4 | DISCORDANCE BETWEEN CELLULAR AND HUMORAL RESPONSES

Several studies have indicated a subset of vaccinated SOT recipients show T cell reactivity versus the spike protein via cytokine release

assays in the absence of detectable anti-spike antibody response (0%–50% discordance, varying widely depending upon population, vaccine type, and assay used).[30–34] This finding is encouraging that a degree of protection versus severe disease may be present despite a lack of humoral response, though the significance and real-world applicability are uncertain for the SOT population. In particular, to our knowledge, there has been no correlative study between T cell responses and protection versus COVID-19 in any vaccinated population, let alone in transplant recipients taking anti-rejection medications specifically designed to impair T cell function. This is compounded by a lack of standardization among assays, including testing with different T cell subtypes, cytokine profiling, and stimulation procedures. Importantly, there is no clinically available assay to test spike-specific T cell responses and few research labs have capacity to perform these in a relevant time frame. These features all contrast with the accessibility, utility, and data supporting anti-spike antibody as a bedside test with significant clinical consequence. This, however, does not discount the important role for cellular responses, particularly SARS-CoV-2-specific CD8+ T cells, in painting the full landscape of vaccine-associated immune response to COVID-19 vaccination, particularly if interrogated using epitope-specific assays such as MHC-multimer staining or T cell receptor sequencing.

5 | STRATEGIES TO IMPROVE PROTECTION VERSUS COVID-19

The above lines of reasoning bring us directly to discussion of the role for anti-spike antibody testing as an important means to risk-stratify patients and direct them toward interventions to improve protection against COVID-19. Although not an all-encompassing immune assessment, data and biology support that transplant patients with negative or low anti-spike antibody levels are at high risk for infection, which in turn is the sine qua non for downstream severe disease in a subset of these patients. This likely reflects that antibody level is not only a measure of circulating proteins with neutralizing capacity but is a biomarker for the cellular machinery that permits vaccine response (i.e., functional B cells) and frequently correlates with other aspects of immune response (particularly CD4+ T cells).[35] Thus, we believe that the transplant community should be active in pursuing approaches to improve vaccine response and protection, and that benefit/risk calculus is best informed by anti-spike antibody levels. This starts with vaccination strategies, given demonstration in millions of persons that these vaccines are very safe and if optimized they have the potential to generate both humoral and cellular protection (the latter providing key cross-variant activity and memory).[36] For example, we have partnered with the NIH to launch a multicenter clinical trial investigating the role for temporary peri-vaccination reduction of immunosuppression in seronegative SOT recipients deemed to be of low clinical alloimmune risk (NCT05077254). Several other groups are pursuing similar studies (NCT04961229; NCT0506099). Additionally, we are invested in rigorously studying differences in immunogenicity of mixed platform vaccinations (e.g., adenoviral vector, mRNA, adjuvanted peptide, and variant-specific boosters), which have shown encouraging antibody and cellular responses.[30,37] This is important given the current carte blanche for receipt of any vaccine as a booster dose amid ongoing equipoise.

Very relevantly, there is interest in the use of combinations of monoclonal antibodies (mAbs) for passive immunoprophylaxis of high-risk, immunocompromised individuals, such as SOT recipients. This is based on evidence that early treatment (or post-exposure prophylaxis) with mAb, especially among those who are seronegative, significantly reduced serious COVID-19 in the general population.[14,15] Most recently, the anti-spike mAb combination tixagevimab plus cilgavimab (AstraZeneca, EVUsheld®) was authorized by the FDA as pre-exposure prophylaxis after demonstrating effectiveness against symptomatic COVID-19 (https://www.fda.gov/media/154701/download). mAbs hold potential to reduce severe COVID-19 in SOT recipients, yet there is concern that many of these formulations may be evaded by the Omicron variant, including potentially tixagevimab plus cilgavimab,[29,38] although sotrovimab (Vir/GSK, Xevudy®) appears to maintain high activity.[39]

So, how should we select which transplant recipients should be prioritized for alternative vaccination strategies or mAb? Discussion should start with a combination of well-established clinical factors for severe disease (age, obesity, diabetes, chronic kidney disease, etc.), coupled with assessment for risk of poor humoral vaccine response. Observational data have partially established this phenotype, but given wide availability of commercial antibody assays and the potential for variability in sero-response, we should simply test for anti-spike antibody. It is encouraging that the AST recently acknowledged anti-spike seronegativity as high-risk feature warranting prioritization for pre-exposure immunoprophylaxis,[40] yet clear guidance from our transplant societies is needed in choosing among assays, optimizing timing of antibody assessment, and ultimate interpretation of results. We recognize that antibody testing may not be immediately available at each transplant center and that it is important to ensure equity in access to this biomarker if it is to be used for allocation of scarce resources such as mAb. Public recognition by government agencies of anti-spike antibody testing as integral to clinical care may incentivize use and help reduce inequities in access including insurance coverage of these tests. Experience, thus far, supports the use of an FDA authorized semi or fully quantitative anti-spike assay[41] validated in vaccinated, immunocompromised persons via neutralization testing (preferably live virus).[27,42,43] Reporting anti-spike values in binding antibody units (BAU), normalized to the WHO international standard would also help reduce heterogeneity and confusion among assays (https://www.who.int/publications/m/item/WHO-BS-2020.2403). Several clinical platforms have established conversion factors to BAU, which can either be directly used or correlated to other assays if binding the same target.[44]

6 | CONCLUSIONS

We are facing yet another COVID-19 wave driven by a transmissible variant of concern resistant to neutralization, but this time we have a

paradigm and tools, particularly anti-spike antibody testing, to mitigate risk and personalize efforts to maximize protection for the most vulnerable. We do not agree with recommending against antibody testing under the narrow premise that the biomarker is imperfect or that a threshold of protection is not definitely established: we frequent use cutting-edge testing in transplant medicine that requires clinical experience and guidelines to maximize benefit.

Although all transplant patients irrespective of antibody level should maintain physical distancing, masking, and avoidance of indoor crowded environments during periods of high SARS-CoV-2 circulation, the recognition of extreme susceptibility to infection in the setting of minimal antibody response after vaccination may factor in to an individual's risk calculus. Furthermore, this may provide additional incentive for family members, coworkers, and employers to maximize critical ring protection by undergoing booster vaccinations or observing other behavioral measures to protect the vulnerable recipient. Antibody testing by well-informed providers using appropriate assays will be key to identifying which SOT recipients remain at highest risk for disease after vaccination, and for whom we should target progressive vaccination and immunoprophylactic therapies. Explicit guidance from our transplant societies on how best to integrate antibody testing into clinical practice would help raise awareness and foster the responsible use of the practice, potentially saving lives as the pandemic continues.

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DATA AVAILABILITY STATEMENT

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