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SARS-CoV-2 Vaccination: The Time Is Now

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March 2020 marked the beginning of unprecedented times. Pandemic-related lockdowns, government shutdowns, outbreaks, overloaded health care systems, and the resultant debates regarding masking, social distancing, political divides, and outright madness has become the hallmark of the past year and a half. Vaccination and the elusive "herd immunity" was a glowing point on the horizon, signaling the return to normalcy. However, for many, the promise of a vaccine preventing transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the development of severe coronavirus disease 2019 (COVID-19) have fallen short. Immunocompromised individuals, including transplant recipients on immunosuppressive medications, have been found to have significantly lower rates of SARS-CoV-2 spike protein antibody positivity than the general population after receiving a vaccination of any of the available products (1–5). Additionally, those who do have a positive response tend to have much lower antibody titers compared with the general population.

In this issue, Kolb and colleagues describe their experience with mRNA vaccine responses in kidney transplant recipients (KTRs) and patients with ESKD on dialysis compared with controls. Similar to previous reports, they found significantly reduced SARS-CoV-2 spike S1–specific IgG titers in KTRs compared with an immunocompetent comparator (6,7). Interestingly, the patients with ESKD also had significantly improved responses over KTRs, despite their perceived degree of functional immunosuppression. To better characterize the humoral immune response to vaccination, the group also measured the neutralization capacity. Unsurprisingly, the neutralizing responses were significantly lower in KTRs than in patients with ESKD on dialysis, or controls. The authors point specifically to reduced immune response when mycophenolate was used in the immunosuppressive regimen, as has been previously reported, highlighting the role of iatrogenic immunosuppression in blunted responses.

Lower SARS-CoV-2 spike S1-specific IgG titers seen in transplant recipients has led to an inquiry into the utility of additional doses to boost titers and theoretically increase the likelihood of protective immunity. Several recent reports have shown significant increases in antibody titers after a booster dose in transplant recipients (8–11). These reports have prompted regulatory bodies in the Unites States, Germany, and France to recommend a third dose of either the BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) vaccine in patients who are immunocompromised (12,13). Unfortunately, the findings of these studies did show that individuals who did not have detectable antibodies after a two-dose vaccine series had fairly low rates of seroconversion, with 50%–75% of patients remaining seronegative 4 weeks after their third dose. Given this potential lack of additional efficacy, the European Medical Agency does not suggest a booster dose to this population at this time, and cites inadequate data to make this recommendation. Additionally, the World Health Organization also does not endorse this practice given disparities in health care access, with the intent to shift additional vaccine supply to poorer countries with lower vaccination rates to improve global protection, before offering additional vaccines to those who have received two doses without adequate response (14).

But is it appropriate to begin ethical debates regarding additional doses when we cannot really define protection in the first place? Despite quantification of antibodies against the spike protein, there are no established thresholds for protective immunity. There are a multitude of commercial assays with various methodologies and capabilities of quantification, and therefore it can be very difficult to interpret the results of antibody testing. Furthermore, assessing the humoral response does not tell the whole story; both memory B cell and T cell responses play a role in protective immunity. Assessing the humoral response alone may underestimate the vaccine efficacy, particularly in transplant recipients. That being said, in a recent report evaluating both humoral and cellular responses to SARS-CoV-2 vaccination, transplant recipients still demonstrated inferior response rates, with 35% developing neither humoral nor cellular responses after vaccination (15). There is a need for better guidance and a more standardized approach to testing vaccine response through both humoral and cellular immunity to more reliably understand the degree of protection inferred via vaccination, with or without additional booster doses.

The findings of Kolb and colleagues, along with previous research, emphasize the importance of SARS-CoV-2 vaccination on the waitlist. The potent immunosuppressive medications used in the transplant medication regimen have a more significant effect on immune response than any degree of

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functional immunosuppression. Therefore, it should be a requirement that all patients be vaccinated before kidney transplant. Allocation of a lifesaving organ transplant to an unvaccinated individual represents a significant risk to long-term patient and graft outcomes. The American Society of Transplantation recommends that patients complete a SARS-CoV-2 vaccine series ≥2 weeks before transplant (16). However, despite the clear evidence of a benefit of vaccination before transplant, vaccine hesitancy persists.

In addition to dedicating resources to evaluation of boosters, the efforts of the transplant community should turn to reducing hesitancy and increasing vaccination rates before transplant. The provider-patient relationship has been shown to be the most important tool to supersede malignant misinformation regarding risks and benefits of the SARS-CoV-2 vaccine. We have come so far since March 2020, learning how to manage our lives while minimizing the risks of exposure. Masks and social distancing have become the norm. Although the vaccine cannot confer 100% protection, it clearly reduces mortality related to COVID-19 and the need for hospitalization or ventilator support. Despite this proven benefit, only about 60% of the population in the United States and Europe have been vaccinated, and there are dozens of countries with vaccination rates in the single digits. This is the real problem with the vaccine, it does not work unless you get it, and it does not end the pandemic unless we are all vaccinated. Research continues to evaluate the degree of protective immunity elicited by vaccination, outcome drivers modifying these vaccine responses, and ways to improve these. However, in the meantime, encourage your patients, friends, families, and neighbors to get vaccinated now; it is the only way we are going to beat this.

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Author Contributions

J. J. Wiegel conceptualized the study, wrote the original draft, and reviewed and edited the manuscript.

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