AST Statement about Vaccine Efficacy in Organ Transplant Recipients.

The recent reports of some transplant patients' failure to develop an antibody response to SARS-CoV-2 after vaccination has resulted in considerable concern and confusion within the transplant community. Our transplant societies are aware that clinical studies are evolving and therefore we are updating this guidance.

Community spread of SARS-CoV-2 is waning in some parts of the world, especially in those areas with greater vaccine acceptance, while activity is increasing in other parts of the world due to the Delta variant. Information about COVID-19 vaccine responses in transplantation is rapidly evolving. The impact of more easily transmissible variants is unknown but is likely to be less where greater numbers of individuals are vaccinated. Because vaccines are critical to containing further spread of the pandemic, there has been interest in optimizing vaccine responses in vulnerable populations, including solid organ transplant (SOT) recipients. To date, we have learned the following:

- Antibody responses to COVID-19 vaccines in transplant recipients are diminished compared with the general population (1-16). However;
    - The level of protective antibody has yet to be defined. Based on data derived from trials in the general population, there is a correlation between the level of neutralizing antibody to SARS-CoV-2 spike protein and symptomatic disease.
    - The threshold for protection against severe COVID-19 is significantly lower than that required to prevent viral infection (17).
    - Determination of protective levels of antibody is confounded by the wide variety of antibody tests that are commercially available, with no direct means to compare results from the different tests.
- The protective components of Cellular (T cell and NK T cells) and humoral responses (IgG/IgM vs IgA) may not be linked in individual SOT recipients; it is possible to have an active acquired or innate immune response in the absence of antibody and vice versa (3,6, 9,10, 11, 16). However, the clinical consequence of this divergence is not known nor measurable.
- Even in the absence of "protective antibody titers," there is likely some protection against more severe disease after vaccination (18-20).
- Clinical effectiveness studies in the setting of SOT are lacking.
- While the level of immunosuppression, specifically the use of antiproliferative agents, has been implicated as a factor in poor antibody response after vaccination, there is no reliable guide to immunosuppression management in anticipation of vaccine responses.
- Current data suggest that providing a third dose of mRNA vaccine to SOT recipients that have previously received two doses of mRNA vaccine can increase antibody titers to SARS-CoV-2 (21-25); in a recent, double-blind, randomized placebo-controlled trial, a third dose mRNA vaccine provided at an interval of two months after the second dose significantly increased antibody titers, neutralizing antibody, and cellular immune response to SARS-CoV-2 compared to third dose placebo (11).
- The published data to date suggest that additional doses are safe and reasonably well-tolerated with no evidence of an increased risk of rejection attributable to vaccine, although sample sizes are generally small.
- Many of the reports to date focus on kidney transplant recipients, but it does appear that other organ recipients experience similar responses to additional vaccine doses. Despite 3 doses of mRNA vaccine, there are still patients that have poor response and we do not know what interventions, if any, might be indicated. Whether altering the vaccine used for the additional dose (e.g. giving adenovirus vector following mRNA or vice versa) is unknown.

RECOMMENDATIONS:

Based on the above information, we strongly recommend the following until further data are available:

- All solid organ transplant recipients should be vaccinated against SARS-CoV-2, using locally approved vaccines.
- All eligible household and close contacts of SOT recipients should be vaccinated against SARS-CoV-2 to minimize risks to the recipient.
- Whenever possible, vaccination should occur prior to transplantation (ideally with completion of vaccine series a minimum of 2 weeks prior to transplant).
    - We support the development of institutional policies regarding pre-transplant vaccination as we believe that this is in the best interest of the transplant candidate, optimizing their chances of being safely transplanted, especially at times of greater infection prevalence.
- Routine antibody testing following vaccination is not recommended by the FDA. Considerations include:
    - Most commercially available tests do not examine neutralizing antibody to the spike protein receptor binding domain (RBD).
    - Many commercially available tests are qualitative.
    - The analytical cut-off values for antibody detection are not necessarily the same as clinically relevant values.
    - There is no commonly agreed upon titer that has been defined as protective against SARS-CoV-2 infection.
    - Cellular responses may occur in the absence of measurable antibody
- However, individual physicians and patients may decide that antibody testing is desirable following a discussion regarding the interpretation of the test results and the consequences/risks of acquiring COVID-19 infection. There are many additional issues relevant to the patient, such as local prevalence of SARS-CoV-2 and its variants, personal situations relating to immunosuppression and transplant infections and the vaccination level in the household.
- Based on current evidence, we recommend providing a third dose of mRNA vaccine for SOT recipients that have previously completed a 2-dose mRNA vaccine series if local regulations allow; The use of a third dose should, until further evidence is available, be based on individual patients' unique situation and must depend on local availability of vaccines and local regulations.

  Clinical effectiveness of this approach is pending. There is insufficient data to recommend the use of antibody testing to guide decision-making about additional doses. The effect of additional vaccine doses for vector-based and other vaccines is not clear. Monitoring of long-term responses and adverse effects is important to clarify existing clinical uncertainties. There are no data currently to support adjustment of immunosuppression in anticipation of additional doses of vaccination. We strongly encourage participation in clinical studies to determine the effects of additional doses or other strategies to improve vaccine responses. We strongly encourage people to follow the evolving clinical evidence and the local regulatory guidance regarding vaccine use/availability including the option for additional vaccine doses
    - Administration of an additional dose of vaccine after completion of the vaccine series has been authorized by the EUA in the US as of August 12, 2021. International regulations regarding additional dosing may vary. We strongly encourage people to follow the evolving clinical evidence and the local regulatory guidance regarding vaccine use/availability including the option for additional vaccine doses.
- It is suggested that recipients who are concerned about their ongoing Covid risks after full vaccination discuss with their transplant physicians re: continued level of precautionary behavior to mitigate disease transmission/acquisition, testing and any new information about additional vaccine doses or

booster vaccination. Information about viral variants, vaccine effectiveness and perceived/real risk is changing rapidly and it is important to address the concerns of transplant recipients.

- It is strongly recommended that all health care providers be vaccinated against SARS-CoV-2 to foster a safer environment for our patients.
- While COVID-19 variants continue to circulate in the community and the extent of protection is still unknown in transplant recipients, it is recommended that SOT candidates and recipients continue to adhere to protective measures including masking in public spaces, social distancing, frequent hand washing, and avoiding indoor crowds. These measures should be followed regardless of whether the patient has received additional doses of vaccine.
- We recommend ongoing monitoring of the regulatory and health department websites to obtain up to date COVID-19 prevalence and vaccine updates.
- We strongly urge funding agencies to invest in research evaluating vaccine immunogenicity, vaccine effectiveness, and strategies to enhance vaccine responses in vulnerable populations, including SOT candidates and recipients, who may fuel the perpetuation of the pandemic.

AST AMERICAN SOCIETY OF TRANSPLANTATION

THE INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION

A Society that Includes Basic Science, the Failing Heart and Advanced Lung Disease.

References

1. Boyarsky BJ, Werbel WA, Avery RA, Tobian AAR, Massie AB, Segev DL, Garonzik-Wang JM: Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients. JAMA 2021.Benotmane I, Gautier-Vargas G, Cognard N, Olagne J, Heibel F, Braun-Parvez L et al. Weak anti-SARS-CoV-2 antibody response after the first injection of an mRNA COVID-19 vaccine in kidney transplant recipients. Kidney Int 2021.
2. Sattler A SE, Weber U, Potekhin A, Bachmann F, Budde K, Storz E, Proß V, Bergmann Y, Thole L, Tizian C, Hölsken O, Diefenbach A, Schrezenmeier H, Jahrsdörfer B, Zemojtel T, Jechow K, Conrad C, Lukassen S, Stauch D, Lachmann N, Choi M, Halleck F, Kotsch K. MedRxv. doi: https://doi.org/10.1101/2021.04.06.21254963. Accessed 4/19/2021. Impaired Humoral and Cellular Immunity after SARS-CoV2 BNT162b2 (Tozinameran) Prime-Boost Vaccination in Kidney Transplant Recipients. Available from:
3. Yi SG, Knight RJ, Graviss EA, Nguyen DT, Ghobrial RM, Gaber AO et al. Kidney Transplant Recipients Rarely Show an Early Antibody Response Following the First COVID-19 Vaccine Administration. Transplantation 2021.
4. Peled Y RE, Lavee J, Sternik L, Segev A, Wieder-Finesod A, Mandelboim M, Indenbaum V, Levy I, Raanani E, Lustig Y, Rahav G. BNT162b2 vaccination in heart transplant recipients: clinical experience and antibody response. J Heart Lung Transplant 2021.
5. Havlin J SM, Dvorackova E et al. Immunogenicity of BNT162b2 mRNA COVID19 Vaccine and SARS-CoV-2 Infection in Lung Transplant Recipients. Journal of Heart and Lung Transplantation 2021.
6. Narasimhan M ML, Clark AE, Usmani A, Cao J, Raj E, Torres F, Sarode R, Kaza V, Lacelle C, Muthukumar A. Serological Response in Lung Transplant Recipients after Two Doses of SARS-CoV-2 mRNA Vaccines. medRxiv 2021.
7. Shostak Y SN, Heching M, Rosengarten D, Shtraichman O, Shitenberg D, Amor SM, Yahav D, Zvi HB, Pertzov B, Kramer MR. Early humoral response among lung transplant recipients vaccinated with BNT162b2 vaccine. The Lancet Resp Med 2021.

8. Miele M, Busa R, Russelli G, Sorrentino MC, Di Bella M, Timoneri F et al. Impaired anti-SARS-CoV-2 Humoral and Cellular Immune Response induced by Pfizer-BioNTech BNT162b2 mRNA Vaccine in Solid Organ Transplanted Patients. Am J Transplant 2021.
9. Cucchiari D, Egri N, Bodro M, Herrera S, Del Risco-Zevallos J, Casals-Urquiza J et al. Cellular and humoral response after mRNA-1273 SARS-CoV-2 vaccine in kidney transplant recipients. Am J Transplant 2021.
10. Rozen-Zvi B, Yahav D, Agur T, Zingerman B, Ben-Zvi H, Atamna A et al. Antibody response to SARS-CoV-2 mRNA vaccine among kidney transplant recipients: a prospective cohort study. Clin Microbiol Infect 2021.
11. Hall, VG, Ferreira, VH, Ierullo, M, et al. Humoral and cellular immune response and safety of two-dose SARS-CoV-2 mRNA-1273 vaccine in solid organ transplant recipients. *Am J Transplant*. 2021; 00: 1– 10. https://doi.org/10.1111/ajt.16766
12. Rabinowich L, Grupper A, Baruch R, Ben-Yehoyada M, Halperin T, Turner D et al. Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients. J Hepatol 2021.
13. Grupper A, Rabinowich L, Schwartz D, Schwartz IF, Ben-Yehoyada M, Shashar M et al. Reduced humoral response to mRNA SARS-Cov-2 BNT162b2 vaccine in kidney transplant recipients without prior exposure to the virus. Am J Transplant 2021.
14. Itzhaki Ben Zadok O, Shaul AA, Ben-Avraham B, Yaari V, Ben Zvi H, Shostak Y et al. Immunogenicity of the BNT162b2 mRNA vaccine in heart transplant recipients - a prospective cohort study. Eur J Heart Fail 2021CHC Inc. (n.d.).
15. Khoury, D. S., Cromer, D., Reynaldi, A., Schlub, T. E., Wheatley, A. K., Juno, J. A., Subbarao, K., Kent, S. J., Triccas, J. A., & Davenport, M. P. (2021). Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nature Medicine*. https://doi.org/10.1038/s41591-021-01377-8
16. Herrera S, Colmenero J, Pascal M, Escobedo M, Castel MA, Sole-González E, Palou E, Egri N, Ruiz P, Mosquera M, Moreno A, Juan M, Vilella A, Soriano A, Farrero M, Bodro M. Cellular and humoral immune response after mRNA-1273 SARS-CoV-2 vaccine in liver and heart transplant recipients. Am J Transplant. 2021 Jul 22. doi: 10.1111/ajt.16768. Epub ahead of print. PMID: 34291552.
17. Basic-Jukic N, Jelicic I. SARS-CoV-2 infection after two doses of mRNA vaccine in renal transplant recipients. Transpl Infect Dis 2021:e13628.
18. Tsalouchos A, Rossolini GM, Magg L, Mazzoni A, Annunziato F, Dattolo PC. COVID-19 in a kidney transplant recipient after mRNA-based SARS-CoV-2 vaccination. Transpl Infect Dis 2021:e13649.
19. Tau N, Yahav D, Schneider S, Rozen-Zvi B, Abu Sneineh M, Rahamimov R. Severe consequences of COVID-19 infection among vaccinated kidney transplant recipients. Am J Transplant 2021.
20. *CDC Director Rochelle Walensky Talks Boosters, Masks and Health Equity*. Home - Community Health Center Presents Conversations on Health Care -. https://www.chcradio.com/episode/Rochelle-Walensky/579.
21. U.S. Department of Health and Human Services. (2021, June 1). NIH clinical trial evaluating mixed COVID-19 vaccine schedules begins. National Institutes of Health. https://www.nih.gov/news-events/news-releases/nih-clinical-trial-evaluating-mixed-covid-19-vaccine-schedules-begins
22. Kamar, N., Abravanel, F., Marion, O., Couat, C., Izopet, J., & Del Bello, A. (2021). Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients. *New England Journal of Medicine*. https://doi.org/10.1056/nejmc2108861
23. Werbel, W. A., Boyarsky, B. J., Ou, M. T., Massie, A. B., Tobian, A. A. R., Garonzik-Wang, J. M., & Segev, D. L. (2021). Safety and Immunogenicity of a Third Dose of SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series. *Annals of Internal Medicine*. https://doi.org/10.7326/l21-0282

24. Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients. N Engl J Med. 2021 Jun 23:NEJMc2108861. doi: 10.1056/NEJMc2108861. Epub ahead of print. PMID: 34161700; PMCID: PMC8262620.
25. Stumpf, Julian MD[1,2]; Tonnus, Wulf[1]; Paliege, Alexander MD[1,2]; Rettig, Ronny MD[1]; Steglich, Anne Dr[1]; Gembardt, Florian Dr.[1]; Kessel, Friederike[1]; Kroöger, Hannah[1]; Arndt, Patrick[1]; Sradnick, Jan Dr.[1]; Frank, Kerstin[3]; Tonn, Torsten Prof[4,5]; Hugo, Christian Prof[1,2] Cellular And Humoral Immune Responses after Three Doses of BNT162b2 mRNA SARS-Cov-2 Vaccine in Kidney Transplant, Transplantation: July 22, 2021 - Volume - Issue - doi: 10.1097/TP.0000000000003903