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TRANSPLANTATION



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Joint 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.

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