COVID-19 Vaccination and Pre-Exposure Prophylaxis in Heart and Lung Transplant Candidates and Recipients

While the risk of severe disease and death may be higher in the solid organ transplant (SOT) population, the risk seems to be associated with the degree of immunosuppression.\textsuperscript{1,2} Although initially it was observed that the serologic response to vaccines in SOT patients was decreased, clinical trial data and observational studies are encouraging that additional doses can ameliorate this impact and provide clinical effectiveness. Additionally, pre-exposure prophylaxis strategies using monoclonal antibodies may be protective in SOT recipients.\textsuperscript{3}

**VACCINATION:**

**Safety:** The safety of the various COVID-19 vaccines (mRNA, viral vector, protein subunit) is similar to the general population with similar adverse event profile, and importantly, without excess risk of acute rejection.\textsuperscript{4–6}

**Antibody response:** SOT recipients are characterized by reduced antibody response following COVID-19 vaccines,\textsuperscript{7–11} which may lead to breakthrough infections,\textsuperscript{12,13} though disease severity of these events may be attenuated.\textsuperscript{14} In a systematic review of 96 studies, pooled rates of seroconversion were 49% (95% CI, 43-55%) in transplant recipients after the second dose of vaccine and 56% (95% CI, 49%-63%) after the third dose.\textsuperscript{15}

Risk factors for reduced antibody response include type of transplanted organ (liver recipients tend to have the highest antibody response and thoracic recipients the lowest), age at vaccination, time from transplant, type of vaccine (mRNA-based vaccines tend to have higher antibody response than adenovirus vector vaccines), interval between vaccine doses, and importantly, the type of immunosuppression (in particular use of mycophenolate and B-cell synthesis and function inhibitors such as belatacept).\textsuperscript{11,16–18}
While the level of immunosuppression, specifically the use of antiproliferative agents, has been associated with poor antibody response after vaccination, there is no validated guide for adjustment of immunosuppression to enhance vaccine responses. Recent data from European studies have demonstrated that the strategy of temporary immunosuppression reduction around the time of vaccination might be safe and effective among kidney transplant recipients who did not mount an antibody response to a third mRNA vaccine dose. A small case series suggested that such a strategy may be safely employed in selected lung transplant recipients as well.

The level of protective antibody is not clearly defined though there seems to be an inverse correlation between the level of neutralizing antibody to the SARS-CoV-2 spike protein and symptomatic disease. Determination of protective levels of antibody is confounded by the wide variety of antibody tests that are commercially available. Additionally, the neutralizing activity of SARS-CoV-2 antibodies is determined by the predominant variant of concern with increasing immune evasiveness of particular concern with the Omicron variant. Thus, booster doses, including those with variant specific targets, such as the bivalent Omicron-containing covid booster vaccines are needed.

Additional vaccine doses confer additional benefit, also because the serological response wanes over time. Booster doses are associated with improved rates of serum neutralization of SARS-CoV-2 variants in transplant recipients. Given the changing viral variants over time and the continuously updated vaccines targeting new variants for better immune coverage, it is reasonable to expect that “booster” or “seasonal” vaccine doses will be recommended for SOT recipients periodically.

**Cellular Response:** The protective components of Cellular (T cell and NK T cells) and humoral responses may not necessarily 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. However, the clinical consequence of this divergence is not known.
**Clinical Effectiveness:** The clinical effectiveness of COVID-19 vaccines against symptomatic infection, severe infection and death related to COVID-19 in SOT recipients has been demonstrated in multiple studies and for different vaccine types. These studies estimate clinical effectiveness against symptomatic infection between 46-81% for 2 doses and 72-77% for 3 doses of vaccine. Against death the protective effectiveness is 20% for viral vector vaccines and 76% for mRNA vaccines. Although the effect is lower than in the general population, effectiveness notably improves after successive vaccine doses.

**Timing of vaccination:** Pre-transplant vaccination for non-immunosuppressed waitlisted candidates shows similar serological response as the general population. Persistence of a vaccine-induced antibody response into the post-transplant periods has been demonstrated in heart and kidney transplant recipients. The response rate to COVID-19 vaccination is lower for patients in the first months after transplantation, especially for those who had received T or B cell-depleting agents as induction therapy or as treatment for rejection. As detailed earlier, steroids and high doses of mycophenolate mofetil and belatacept in maintenance regimens have also been associated with a lower rate of vaccine response. Recent studies in the general population demonstrate reduced risk of COVID-19 reinfection among people that complete their primary series of vaccination following recovery from a first episode of COVID-19. It seems reasonable extrapolate this finding to non-immunosuppressed patients who are wait-listed for SOT.

**Heterologous prime/ boost vaccination schedules:** In a prospective study comparing different vaccine regimens for immunocompromised adults including SOT recipients, vaccination with mRNA-1273 resulted in higher antibody levels than the adenovirus vaccine and BNT 162b2. The difference was significant even after adjusting for time from vaccination, age, and underlying condition. In kidney transplant recipients fully vaccinated with CoronaVac (whole inactivated virus vaccine), a third dose with an mRNA vaccine produced a higher seroconversion rate and antibody titers than a third homologous dose.
PRE-EXPOSURE PROPHYLAXIS

In a randomized controlled trial, long-acting monoclonal antibodies were shown to be as effective as pre-exposure prophylaxis in patients with increased risk of inadequate vaccine response for various reasons and/or increased risk of exposure to SARS-CoV-19 virus.49 There is recent data showing risk reduction in immunocompromised patients in general as well as SOT recipients specifically.

In a large healthcare system "real world" study from Israel consisting of almost 5000 immunocompromised patients (including 33% SOT), receipt of tixagevimab/cilgavimab led to 3.5% of the treated patients becoming infected compared to 7.2% in the untreated group. This risk reduction remained true for those on anti-CD20 inhibitors and those with SOT in subgroup analyses. There was also significant reduction in the risk of severe disease and zero deaths in the intervention group compared to 0.9% in the untreated patients.50 Other studies also demonstrate that tixagevimab/cilgavimab is effective in reducing the risk of COVID-19 among transplant recipients that failed to mount an effective antibody response after vaccination. 3,50-52 Pre-exposure prophylactic monoclonal antibody strategies may change over time due to emerging variants for which current agents have decreased coverage. With the emergence of omicron BA.1, the dose of tixagevimab/cilgavimab was increased from 150/150 mg to 300/300 mg with improved effectiveness.3 Maintained susceptibility to newer Omicron variants, including BA.5 and BA.2, to tixagevimab/cilgavimab may reduce the need for dose-escalation, however, repeated administrations over time may be necessary to confer sufficient protection. Adverse events have been reported in 4% of SOT recipients and are mostly mild.3

RECOMMENDATIONS:

- We recommend that all eligible children and adult transplant candidates and recipients be vaccinated with a COVID-19 vaccine that is approved or authorized in their region. At this time, initial three vaccine doses are considered the primary series for immunocompromised individuals and additional vaccines are considered as boosters.
RECOMMENDATIONS (Continued):

- If possible, mRNA-based vaccines are preferred as these confer the highest clinical effectiveness against symptomatic infection, severe infection and death related to COVID-19 in SOT recipients.

- Whenever possible, vaccination should occur prior to transplantation (ideally with completion of vaccine series a minimum of two weeks prior to transplant).

- We recommend the development of institutional policies supporting pre-transplant vaccination for listing purposes. We believe that this is in the best interest of the transplant candidates to optimize immune protection and limit severe COVID-19 in the perioperative and post-transplant periods, especially at times of greater infection prevalence. Centers must be transparent regarding listing requirements and must provide accurate, understandable, and culturally appropriate information about vaccination. Centers that require candidate vaccination must ensure that patients have ready access to the necessary vaccine doses.

- Administration of a COVID-19 vaccine within the first three months after transplantation or lymphocyte depleting therapies has limited efficacy, and it is advisable to postpone vaccination until after this period. Currently, the use of pre-exposure monoclonal antibody therapy should be strongly considered if available in this situation.

- Patients that have received viral vector/inactivated virus/protein subunits vaccines, will probably benefit from an mRNA vaccine booster dose if available.

- We recommend variant specific vaccine boosters as they become available.

- There is currently limited data to support adjustment of immunosuppression in anticipation of additional doses of vaccination in cardiothoracic transplant recipients and we suggest pursuing this strategy within clinical trials.
RECOMMENDATIONS (Continued):

• We do not recommend routine antibody testing as a measure of vaccine effectiveness or as a decision-making tool for further vaccine doses.

• If available, we recommend routine use of tixagevimab/cilgavimab for transplant recipients, in addition to vaccination, to further reduce the risk of COVID-19 related mortality.

• All eligible household and close contacts of SOT recipients should be vaccinated against SARS-CoV-2 to minimize risks to the recipient.

• We recommend that all health care providers be vaccinated against SARS-CoV-2 to foster a safer environment for our patients and maintain a skilled workforce.

• While COVID-19 variants continue to evolve and circulate in the community, we recommend that SOT candidates and recipients continue to adhere to any locally recommended protective measures including adequate protective face masks in confined public spaces.

• We encourage participation in clinical studies to determine the effects of additional doses or other strategies to improve vaccine responses. 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.
References


