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COVID-19 Prevention in Solid Organ Transplant Recipients: Current State of the Evidence

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KEYWORDS

• COVID-19 • SARS-CoV-2 • Solid organ transplant • mRNA vaccine • Antibody • T-cell

KEY POINTS

- COVID-19 vaccine responses in solid organ transplant (SOT) are poor.
- Three or greater vaccine doses result in superior antibody responses compared to two doses, but some people do not respond, especially those who are older, who have been vaccinated within a year of SOT, who are receiving mycophenolate, or who have received BNT162b2.
- Vaccine effectiveness in SOT is suboptimal but improved by boosters.
- Safety and efficacy of immunosuppression reduction around vaccination warrant further study.
- Monoclonal antibody pre-exposure prophylaxis with tixagevimab–cilgavimab may be protective but is no longer authorized for use in the United States as of January 26, 2023, due to the increased prevalence of variants with reduced in vitro susceptibility to tixagevimab–cilgavimab.

INTRODUCTION

Solid organ transplant (SOT) recipients are at risk for poor COVID-19-related outcomes due to the use of immunosuppressive medications and the presence of comorbidities.[1] Although the advent of direct-acting antivirals such as monoclonal antibodies (none of which are currently authorized in the United States due to the dominance of resistant variants), remdesivir, nirmatrelvir-ritonavir, and molnupiravir

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appears to have ameliorated COVID-19 outcomes after transplantation,[2–5] it remains critical to optimize preventing Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, particularly in vulnerable populations. Unfortunately, although COVID-19 vaccines after SOT are safe, SOT recipients have generally not reaped the benefits of COVID-19 vaccination, with multiple studies establishing that they exhibit extremely attenuated humoral and cellular immune responses compared to their non-immunocompromised counterparts. Exacerbating this problem is the remarkable plasticity of SARS-CoV-2, whereby novel variants—particularly Omicron—are capable of escaping antibody-inducted neutralization.[6] Although novel variants do not appear to evade T-cell-mediated responses elicited by ancestral variants,[7] all these variables have contributed to the high rates of COVID-19 hospitalizations experienced by immunocompromised patients, including SOT recipients.[8] Here, we review the evidence regarding COVID-19 prevention in SOT recipients to date. We discuss humoral and T-cell responses to existing COVID-19 vaccines, as well as clinical effectiveness. We also review the preliminary data on the safety and efficacy of immunosuppression modulation around the time of vaccination, as well as monoclonal antibody pre-exposure prophylaxis and current US Centers for Disease Control and Prevention (CDC) and Food and Drug Administration (FDA) recommendations for COVID-19 prevention. Although we briefly discuss adenovirus vector vaccines, we focus our review on homologous vaccination with monovalent messenger RNA (mRNA) vaccines, as most studies thus far have evaluated these vaccination modalities. We do not discuss bivalent or protein subunit vaccines, as there are currently no data on SOT recipients.

HUMORAL IMMUNE RESPONSES

First mRNA Vaccine Dose

In the first published study of humoral immune responses to COVID-19 vaccines among SOT recipients, Boyarsky and colleagues[9] demonstrated that only 17% of patients had a detectable anti-Spike IgG antibody level after a single dose of either the BNT162b2 or mRNA-1273 vaccine. The extremely low seropositivity starkly contrasted with the results of early mRNA vaccine trials among healthy individuals, which showed 100% seroconversion after a single mRNA-1273 or BNT162b2 dose.[10,11] Other studies evaluating antibody responses after a single mRNA vaccine dose demonstrated similarly poor responses, with only 4% to 10% of SOT developing anti-Spike IgG antibodies, and with almost negligible in vitro neutralization of SARS-CoV-2.[12,13] Importantly, these early studies also identified certain risk factors associated with poor antibody responses, such as the use of anti-metabolites, advanced age, vaccination within 1 year of SOT, and the use of BNT162b2 as opposed to mRNA-1273.[9,12]

Second mRNA Vaccine Dose

Humoral responses after a second mRNA vaccine dose, which for a limited time constituted the primary vaccination series in SOT recipients, are also blunted compared to those of non-immunocompromised individuals, with 0% to 64% of SOT recipients becoming seropositive.[14–21]Several longitudinal studies have followed patients after one then two mRNA vaccine doses. Two small studies showed an increase in the seropositive proportion of transplant patients from approximately 5% to only around 35% after the first and then second mRNA vaccine dose, with comparable increases in neutralization titers.[22,23] By contrast, in a study of 50 heart transplant recipients, 90% of patients had no humoral response after both the first and second mRNA vaccine dose; the second dose also failed to meaningfully increase neutralizing anti-SARS-

CoV2 antibody titers.[13] In a prospective cohort study of 658 solid SOT recipients that longitudinally tracked antibody responses after mRNA vaccination, 15% had a detectable antibody response after dose 1 and dose 2, 46% had no antibody response after dose 1 or dose 2, and 39% had no antibody response after dose 1 but subsequently developed an antibody response after dose 2. Use of anti-metabolites, vaccination with BNT162b2, advanced age, and vaccination within 1 year of SOT were among the variables associated with poor responses.[24] In another prospective observational study which compared humoral responses to two doses of BNT162b2 or mRNA-1273 among over 1200 immunocompromised versus non-immunocompromised individuals, SOT recipients exhibited the lowest seropositivity, with only 30.7% of participants developing a positive anti-Spike IgG response, compared to 92.4% of non-immunocompromised individuals, 50% of patients with hematologic malignancies, and approximately 80% of patients with autoimmune conditions, HIV infection, or solid tumors.[21] In this study, age > 45 years, vaccination with BNT162b2 versus mRNA-1273, vaccination within 1 year of SOT, administration of $\geq$ 2 immunosuppressive medications, and non-liver transplant status were among the variables associated with lower odds of seropositivity.[21] Lung transplant recipients had particularly poor vaccine responses.[21] Similar predictors of an attenuated humoral response to vaccines have also been reported in other studies, with anti-metabolites such as mycophenolate emerging as a potentially modifiable risk factor.[25] Of note, the underlying etiologies for the superior antibody responses observed with mRNA-1273 compared to BNT162b2 are thought to be related to the higher mRNA dose in the mRNA-1273 vaccine, the longer interval between doses, or other unknown reasons.

Data regarding the durability of antibody responses after two mRNA vaccine doses in transplant patients are more mixed. For instance, 3 months after administration of the second mRNA vaccine, antibody titers decreased in 35% of patients, increased in 43%, and remained stable in 21%.[26] However, 4% of patients with detectable antibodies at 1 month became seronegative by 3 months, while 19% of patients with high-positive titers at 1 month had low-positive titers at 3 months.[26] Another study found that at 6 months after the second mRNA vaccine dose, anti-Spike IgG antibody titers increased in 27% of patients, decrease in 12%, and remained stable in 61%.[27]

Third mRNA Vaccine Dose

As of the writing of this manuscript, three monovalent mRNA vaccine doses are considered to be part of the primary vaccine series for all immunocompromised individuals, including SOT recipients (see the section on CDC and FDA recommendations).[28] In general, metrics of humoral immune responses improve with a third dose, with similar findings for both the mRNA-1273 and BNT162b2 vaccines. In a randomized, placebo-controlled trial of 120 SOT recipients who received either a third mRNA-1273 vaccine dose or placebo, there was a significantly greater proportion of patients with detectable anti-receptor binding domain (RBD) antibodies in the mRNA-1273 vaccine group compared to the placebo group (55% vs 18%, respectively).[29] Similarly, viral neutralization ability was significantly higher in the mRNA-1273 group versus the placebo group (median 71% vs 13%, respectively).[29] The antibody level after the second dose also appears to predict humoral responses after the third dose. For instance, in an observational study of two versus three mRNA-1273 doses, SOT recipients who had a low-positive response after the second dose were more likely to develop an antibody response after the third dose compared with those without an antibody response.[30]

Multiple observational studies have sought to evaluate risk factors for poor humoral responses. In a prospective study of 101 SOT recipients (most of whom were kidney

transplant recipients), seropositivity increased from 40% after the second dose to 68% after the third dose, with advanced age, higher degree of immunosuppression, and lower glomerular filtration rate (GFR) being associated with an inability to mount an antibody response.[31] A study of 96 heart transplant recipients, which demonstrated that a third BNT162b2 dose resulted in a nine-fold increase in SARS-CoV-2 neutralization antibody titers, also identified that the use of mycophenolate and lower GFR predicted a reduced likelihood of developing a humoral immune response.[32]

Unfortunately, waning antibody responses and the emergence of novel viral variants capable of immune escape can limit the protection conferred by a third mRNA vaccine dose. For instance, in a prospective study of 103 heart transplant recipients, a third BNT162b2 vaccine dose resulted in significantly greater neutralization titers against wild-type SARS-CoV-2 compared to Delta, with minimal neutralization against Omicron.[33] Neutralizing activity substantially declined at 6 months but was still high versus the wild-type virus and the Delta variant. By contrast, neutralization activity was essentially negligible against the Omicron variant.[33] These observations provided the rationale for additional vaccine doses ("boosters") in immunocompromised patients, as discussed further in the next section. By comparison, among the general population, neutralizing antibodies against Omicron continue to be detected at 6 months, although they are up to six-fold lower than those of other variants and appear to decline more quickly.[34]

Fourth and Fifth mRNA Vaccine Doses

Before the bivalent mRNA vaccine recommendations that were released in the fall of 2022, the US CDC had recommended that all immunocompromised patients, including SOT recipients, receive two additional or booster monovalent mRNA vaccine doses after their three-dose primary mRNA vaccination series.[28] However, practical experience with these boosters remains limited, with less robust adherence to these booster recommendations than was seen with the primary two- then three-dose mRNA vaccine series[28] Nonetheless, a few studies have evaluated metrics of humoral immunity after four or five mRNA vaccine doses. In a study of kidney transplant recipients 19.1%, 29.4%, 55.6%, and 57.5% of patients became seropositive after a second, third, fourth, and fifth mRNA vaccine dose, respectively.[35] Factors associated with an improved response after the fourth dose were baseline low-positive anti-SARS-Cov2-S-protein IgG titers, younger age, and greater time elapsed since transplant, while factors associated with a reduced response were treatment with belatacept or higher mycophenolate doses.[35]

In another study with 25 SOTs, a fourth dose of mRNA-1273 resulted in higher antibody titers and improved neutralizing activity against all variants except Omicron.[36] Indeed, median neutralization activity after the fourth dose increased for the Alpha, Beta, Gamma, and Delta variants, but paradoxically decreased for the Omicron variant.[36] In one small study assessing a fifth vaccine dose, all 17 SOT recipients who were seropositive before the fifth dose exhibited an increase in antibody titers following the fifth dose (some to antibody levels mirroring those of the general population). However, one patient who was receiving high-dose mycophenolate and was seronegative at baseline remained seronegative after the fifth dose.[37] Thus, it is evident that even after up to 4 or 5 mRNA vaccine doses, some SOT recipients will fail to mount any humoral responses to vaccination.

Adenovirus Vaccines

Limited studies have been published evaluating humoral responses after administration of adenovirus vaccines in SOT recipients. However, the results overall appear to

mirror those of mRNA vaccines. In a study of 25 kidney transplant recipients without humoral responses after two doses of BNT162b2, administration of a third dose of either heterologous ChAdOx1 (adenovirus vector vaccine) or homologous BNT162b2 resulted in 36% of patients seroconverting at day 27 after vaccination.[38] In a study with 99 heart transplant recipients who received ChAdOx1, 24% of patients had detectable antibody levels after the first dose, which increased to 34.8% after the second dose.[39] As has been demonstrated with mRNA vaccines, risk factors associated with a lack of response included the use of mycophenolate and chronic kidney disease.[39]

Clinical Utility of Antibody Level Measurements

Anti-SARS-CoV-2 Spike IgG levels appear to positively correlate with viral neutralization,[21] with high antibody levels being associated with more potent in vitro neutralization. Thus, there has been interest in the use of anti-SARS-CoV-2 antibody levels to determine the level of protection against COVID-19; indeed, the availability of such a biomarker would have drastic implications on clinical care and would allow clinicians to provide individualized counseling to their patients about how well-protected they are against SARS-CoV-2 infection. However, as indicated above, the neutralizing activity of SARS-CoV-2 antibodies is a "moving target" that is influenced by the dominant variant of concern, making it difficult if not impossible to identify a fixed and accurate immune correlate of protection. For instance, a given anti-SARS-CoV-2 Spike IgG assay result may be associated with robust neutralization against an ancestral variant such as D614G but negligible neutralization against emerging variants such as the Omicron subvariants. As a result, a simple antibody-based biomarker that accurately and consistently estimates the degree of protection does not currently exist. Furthermore, existing anti-Spike or anti-RBD IgG assays cannot distinguish between antibodies elicited by vaccines or circulating antibody levels detected as a result of prior monoclonal antibody administration (as all monoclonal antibodies to date target the Spike protein),[40,41] including tixagevimab–cilgavimab, which may continue to be detected for over 6 months after injection. Any antibody-based correlates of protection should be focused on neutralizing antibody titers and should be updated as new variants come along.[42] At this stage, both the FDA and the American Society of Transplantation recommend against routine measurements of anti-SARS-CoV-2 antibody levels for clinical care,[43,44] because currently authorized SARS-CoV-2 antibody tests are not validated to evaluate specific immunity or protection from SARS-CoV-2 infection.

T-CELL RESPONSES

The proportion of SOT recipients with a detectable T-cell response after COVID-19 vaccination has varied from approximately 50% to 79% after two mRNA vaccine doses,[20,45] and approximately 47.9% to 78% after three doses.[29,32] Not surprisingly, SOT recipients also have diminished T-cell responses compared to the general population. For instance, T-cell reactivity (measured by an interferon-γ release assay) was diminished in cardiothoracic transplant recipients compared to non-immunocompromised individuals after two BNT162b2 vaccine doses.[13] Similarly, kidney transplant recipients were found to have reduced T helper cell responses compared to immunocompetent individuals after BNT162b2 vaccination, as well as impairments in effector cytokine production, memory differentiation, and activation-related signatures.[16] Variables associated with the absence of cellular immunity included advanced age, diabetes, receiving lymphocyte depletion with anti-thymocyte

globulin within the past year, lymphopenia, vaccination within 1 year of transplant, and lower eGFR.[45]

Interestingly, in certain SOT recipients, T-cell responses are present even in the absence of a humoral response,[13,46] suggesting that some SOT recipients may potentially remain protected against severe COVID-19 despite mounting no meaningful antibody response. In one study, 10% of SOT recipients who did not develop a humoral response developed a T-cell response after two doses of the BNT162b2 vaccine.[25] None of the clinical risk factors associated with absence of humoral responses were associated with the absence of T-cell responses; however, the presence of lower anti-RBD antibody titers was associated with a lack of T-cell responses.[25] Furthermore, in a randomized trial comparing a third mRNA-1273 vaccine dose to a placebo, 46.2% of SOT recipients with a negative anti-RBD IgG titer still had a positive CD4+ T-cell response.[23] A study of heart transplant recipients showed that a T-cell response was present in a small subset of individuals with absent serum neutralization; there was no correlation between the SARS-CoV-2-specific T-cell response and neutralization.[32] However, the correlation between T-cell responses and vaccine clinical effectiveness is not currently known.

Cellular immune responses appear to persist longer than humoral responses.[46] A third dose of BNT162b2 administered to heart transplant recipients induced a T-cell response which persisted through 6 months, in contrast with the levels of neutralizing antibodies, which rapidly declined.[33] Finally, although immune evasion of T-cell immunity with novel variants has not emerged as a major phenomenon in the general population, it remains unknown whether this holds true for SOT recipients. Thus, although the FDA has authorized the use of certain SARS-CoV-2 T-cell reactivity assays,[47] the utility of these assays and how they correlate with protection against SARS-CoV-2 infection is unknown. Therefore, the routine use of these T-cell assays to guide clinical care cannot be recommended at this time.

CLINICAL EFFECTIVENESS

The low immunogenicity of COVID-19 vaccines in SOT recipients has expectedly resulted in poor clinical effectiveness. In a cohort of transplant patients who received either one or two doses of BNT162b2 or mRNA-1273, 0.6% of patients developed a breakthrough infection, which is over ten-fold higher than the rate of 0.05% reported in the general population.[48,49] SOT recipients with breakthrough infection also had undetectable or low-positive anti-Spike antibodies, and their clinical course was similar to that of unvaccinated SOT recipients with COVID-19.[48] In a follow-up multicenter study of SOT recipients who were vaccinated during the two-mRNA vaccine dose era, 0.83% of patients developed breakthrough infection, a rate that was 82-fold higher than that of healthy adults.[50] Furthermore, 0.48% of patients were hospitalized and 0.077% died after breakthrough COVID-19, representing a 485-fold higher risk of breakthrough infection with associated hospitalization and death compared to the general population. However, the authors noted that the incidence of both infection and death was lower than that reported in unvaccinated SOTs in the literature (approximately 5% and 20.5% at the time, respectively).[51,52] By contrast, another study found that SOT recipients who developed medically attended COVID-19 following one- or two-dose mRNA vaccination experienced similar disease severity to unvaccinated SOT recipients with COVID-19, supporting recommendations for additional vaccine doses in these patients.[53] However, it is encouraging that vaccine effectiveness against infection in SOT recipients appears to increase with additional vaccine doses. In a population-based study from Canada which included data for the BNT162b2,

mRNA-1273, and ChAdOx1 vaccines, vaccine effectiveness against any SARS-CoV-2 infection was 31%, 46%, and 72% after one, two, and three doses, respectively.[54] Importantly, vaccine effectiveness against hospitalization or death also incrementally increased with one, two, and then three vaccine doses (38%, 54% and 67%, respectively).[54]

IMMUNOSUPPRESSION MODULATION TO IMPROVE VACCINE RESPONSES

Antimetabolite immunosuppression has been associated with a reduced likelihood of developing a humoral response to COVID-19 vaccines.[9,24,32,35] Additionally, studies in patients with autoimmune and rheumatologic conditions have shown that temporary discontinuation of mycophenolate is safe and is associated with improved vaccine responses.[55] These observations have led to the hypothesis that temporary antimetabolite cessation around the time of vaccination might augment humoral response to vaccines in SOT recipients. However, in transplant patients, there is a concern that temporary discontinuation of anti-rejection therapy may precipitate allograft rejection.

Nonetheless, a few observational studies have begun to shed light on the safety and effectiveness of this approach. In a study of kidney transplant recipients who failed to mount a humoral immune response after three mRNA vaccine doses, stopping mycophenolate or azathioprine for 5 weeks led to seroconversion with neutralizing activity in over 70% of patients, accompanied by robust increases in other metrics of SARS-CoV-2 immunity, including T-cell responses.[56] Reassuringly, no de novo human leukocyte antigen (HLA) antibodies developed, and biomarkers for subclinical allograft rejection did not increase.[56] In another study of kidney transplant recipients, stopping mycophenolate and adding 5 mg of prednisone before the fourth vaccine dose and maintaining this low net-state of immunosuppression for 4 to 8 weeks resulted in an increase in serological response rates of 75% compared to no dose adjustment (52% response) or mycophenolate dose reduction without cessation (46% response).[35] Among patients in whom mycophenolate was held, only 1% each developed de novo donor-specific antibodies or T-cell mediated rejection; these patients required additional immunosuppressive therapy.[35] Although these results are reassuring, they require validation in randomized trials. Furthermore, whether these findings are generalizable to other SOT recipients, particularly lung transplant recipients who are at a greater risk for acute rejection, requires further evaluation. An ongoing, multicenter randomized trial is being conducted to determine the safety and efficacy of immunosuppression reduction around the time of COVID-19 vaccination in kidney transplant and liver transplant recipients (NCT05077254).

MONOCLONAL ANTIBODIES

Passive administration of monoclonal antibodies with neutralizing activity against SARS-CoV-2 may confer rapid protection against COVID-19 among high-risk individuals who do not respond to or cannot tolerate vaccines.[57] The monoclonal antibody combination tixagevimab–cilgavimab, has been shown to prevent COVID-19.[57] In a randomized trial that did not include SOT recipients, tixagevimab–cilgavimab was associated with a 76.7% relative risk reduction of developing COVID-19.[57] Several "real world" studies have since shown clinical effectiveness of tixagevimab–cilgavimab in immunocompromised patients. In a preprint of a retrospective study of over 1800 patients from the Veterans Affairs database (over 92% of whom were immunocompromised), patients receiving tixagevimab–cilgavimab had a lower incidence of COVID-19, hospitalization, and all-cause mortality.[58] In another retrospective cohort study evaluating 444 SOT recipients, tixagevimab–cilgavimab was associated

with a lower incidence of breakthrough infection, especially in kidney transplant and lung transplant recipients.[59] Tixagevimab–cilgavimab conferred protection regardless of vaccination history and number of vaccine doses, but was not associated with a reduced incidence of COVID-19 among previously infected SOT recipients.[59]

Despite these promising findings, new SARS-CoV-2 variants with reduced susceptibility to tixagevimab–cilgavimab have emerged, as was the case for therapeutic monoclonal antibodies. Tixagevimab–cilgavimab seems to maintain its neutralizing activity against Omicron BA.2,[60] while partially neutralizing BA.1.[61] However, new emerging Omicron subvariants, including BQ.1, BQ.1.1, BA.4.6, BF.7, and BA.2.75.2 exhibit reduced susceptibility and even resistance to tixagevimab–cilgavimab in vitro.[62] Thus, as of January 26, 2023, the US FDA has paused its authorization of tixagevimab–cilgavimab because the national prevalence of SARS-CoV-2 variants with reduced susceptibility to this drug is now greater than 90%.[63] As a result, tixagevimab–cilgavimab is no longer available in the United States, as it was only authorized for use when the combined frequency of non-susceptible variants is less than or equal to 90%.[62] A clinical trial evaluating the safety and efficacy of a new next-generation long-acting monoclonal antibody (AZD3153) as pre-exposure prophylaxis of COVID-19 among immunocompromised individuals is currently underway.[64] This monoclonal antibody is thought to have broad neutralizing activity against multiple SARS-CoV-2 variants, including those that are resistant to neutralization by tixagevimab–cilgavimab.

POST-EXPOSURE PROPHYLAXIS

Post-exposure prophylaxis of COVID-19 was shown to be effective with the monoclonal antibody casirivimab-imdevimab.[65] However, this strategy was only briefly implemented in the United States because the authorization of this monoclonal antibody was revoked due to the rapid emergence of variants with reduced susceptibility to casirivimab-imdevimab.[66] In contrast, post-exposure prophylaxis using nirmatrelvir-ritonavir[67] was not effective. Given the poor immune responses of SOT recipients to COVID-19 vaccines and the pause of the authorization of tixagevimab–cilgavimab for pre-exposure prophylaxis, post-exposure prophylaxis is a potential option to protect these vulnerable individuals from COVID-19. As no agent is currently authorized for this indication, future trials should re-evaluate the efficacy of novel monoclonal antibodies or antivirals for post-exposure prophylaxis of COVID-19, with a focus on SOT recipients and other immunocompromised individuals.

CENTERS FOR DISEASE CONTROL AND PREVENTION AND FOOD AND DRUG ADMINISTRATION RECOMMENDATIONS (AS OF JANUARY 31, 2023)

CDC recommendations (current as of January 31, 2023) for COVID-19 vaccination in immunocompromised patients, including SOT recipients, are found in **Table 1**.[68] Prior to the withdrawal of tixagevimab–cilgavimab's authorization, the CDC had recommended that it be administered every 6 months for pre-exposure prophylaxis, and at least 2 weeks after a COVID-19 vaccine.[69] However, as outlined in **Table 1**, tixagevimab–cilgavimab is no longer authorized in the United States at this time. Because of the rapidly evolving landscape of COVID-19 prevention recommendations, the reader is encouraged to review the CDC website for the most up to date vaccine and prophylaxis guidelines.

FUTURE DIRECTIONS

In the coming years, ongoing data collection is needed to define humoral and cellular immune responses to vaccines targeting novel variants, such as the bivalent mRNA

Table 1
Fall 2022 US Centers for Disease Control COVID-19 vaccine/prophylaxis recommendations in immunocompromised patients

	Primary Vaccine Series							
Strategy	**Dose 1**	**Interval**	**Dose 2**	**Interval**	**Dose 3**	**Interval**	**Booster**	**Tixagevimab–Cilgavimab**
Option 1	mRNA: BNT162b2 (Pfizer, ages 5 or greater) or mRNA-1273 (Moderna, ages 6 or greater)	3 weeks if BNT162b2; 4 weeks if mRNA-1273	mRNA (preferably the same)	At least 4 weeks	mRNA (preferably the same)	At least 2 months	Any age-appropriate bivalent mRNA vaccine[a], irrespective of prior number of boosters	Not currently authorized (as of January 26, 2023). Prior to January 26, 2023, the recommendation was: "*at least 2 weeks after any COVID-19 vaccine dose; once tixagevimab–cilgavimab given, no minimum interval for next vaccine.*"
Option 2 (12 years and older)	Protein subunit (NVX-CoV2373, Novavax)	3 weeks	Protein subunit (NVX-CoV2373, Novavax)	NA	NA			
Option 3 (18 years and older)	Ad26.COV2.S (Janssen, only brand available in the United States)	At least 4 weeks	Additional mRNA vaccine (any brand)	NA	NA			

Abbreviation: NA, not applicable.

[a] Pfizer bivalent booster authorized for ages 5 and greater; Moderna bivalent booster authorized for ages 6 and greater. Table up to date as of January 31, 2023.

Data from Refs.[62,63,68,69]

vaccines, as well as the clinical effectiveness of these vaccines. Determining whether temporary discontinuation of immunosuppressive drugs will bolster immune responses without precipitating allograft rejection is an unmet need; randomized clinical trial data across the different SOT types are needed to truly determine the safety and efficacy of this approach. Newer generation prophylactic monoclonal antibodies will also be expected to add an extra layer of protection to SOT recipients.[64] Finally, post-exposure prophylaxis should continue to be evaluated in trials.

CLINICS CARE POINTS

- COVID-19 vaccines in SOT recipients are safe
- SOT recipients exhibit poor humoral and cellular immune responses to COVID-19 vaccines
- A three-dose primary mRNA vaccine series results in better immune responses than one or two-dose mRNA vaccination, but a substantial proportion of SOT recipients remains seronegative even after three doses
- mRNA vaccine boosters improve antibody responses, though some patients, especially those who are highly immunosuppressed, remain seronegative
- Risk factors for poor humoral immune responses include advanced age, degree of immunosuppression, mycophenolate use, chronic kidney disease, vaccination within 1 year of transplant, and use of BNT162b2 instead of mRNA-1273
- Although T-cell responses in SOT recipients are worse than those of immunocompetent individuals, some SOT recipients exhibit T-cell responses without humoral responses
- Immune correlates of protection after vaccination are not defined; routine measurement of antibody levels of T-cell reactivity is therefore not currently recommended
- Clinical effectiveness of mRNA vaccines in SOT recipients is significantly worse than the general population (for infection, hospitalization, and death). However, clinical effectiveness is improved by booster vaccine doses
- Immunosuppression reduction around the time of vaccination may improve immune responses, but additional studies of efficacy and safety (particularly as it relates to rejection) are needed
- The monoclonal antibody combination tixagevimab–cilgavimab appears to protect SOT recipients from COVID-19, but it is no longer available for use in the United States (as of January 26, 2023) due to the increased prevalence (>90%) of variants with reduced susceptibility to this agent
- No drugs are currently authorized for post-exposure prophylaxis of COVID-19
- CDC COVID-19 vaccine recommendations (current as of January 31, 2023) for SOT recipients include a three-dose primary mRNA vaccine series, or a two-dose primary protein subunit, or a one-dose adenovirus vector vaccine followed by one mRNA vaccine dose, all followed at least 2 months later by a bivalent mRNA vaccine booster. These recommendations are updated periodically.

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CONFLICT OF INTEREST/DISCLOSURES

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