COVID-19 Vaccination

• COVID-19 vaccination remains the most effective way to prevent serious outcomes and death from SARS-CoV-2 infection. The COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination for everyone who is eligible, including transplant and cellular immunotherapy candidates and recipients, according to the Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices (AI).

• See the Centers for Disease Control and Prevention webpage COVID-19 Vaccines for People Who Are Moderately or Severely Immunocompromised for the current COVID-19 vaccination schedule for transplant and cellular immunotherapy recipients.

• Clinicians should strongly encourage all household members, close contacts, and health care providers who provide care to transplant and cellular immunotherapy candidates and recipients to be vaccinated against COVID-19 (AI).

• Clinicians should strongly encourage all potential organ and hematopoietic cell donors to get vaccinated against COVID-19 (AI).

Potential Transplant and Cellular Immunotherapy Candidates

• The Panel recommends performing diagnostic molecular or antigen testing for SARS-CoV-2 in all potential solid organ transplant, hematopoietic cell transplant, and cellular immunotherapy candidates with signs and symptoms that suggest acute COVID-19 (AIII). Additional guidance is available from medical professional organizations. See the text below for more information.

• If SARS-CoV-2 is detected or infection is strongly suspected in a potential transplant or cellular immunotherapy candidate, transplantation or immunotherapy should be deferred, if possible (BIII).

• The optimal management and therapeutic approach to COVID-19 in these populations is unknown. At this time, the procedures for evaluating and managing COVID-19 in transplant candidates are the same as those for nontransplant patients (AII).

Potential Transplant Donors

• The Panel recommends performing diagnostic molecular testing for SARS-CoV-2 and assessing for symptoms of COVID-19 in all potential solid organ transplant and hematopoietic cell transplant donors prior to donation (AIII). Additional guidance is available from medical professional organizations. See the text below for more information.

Transplant and Cellular Immunotherapy Recipients With COVID-19

• For transplant and cellular immunotherapy recipients with COVID-19, clinicians should follow COVID-19 evaluation and management guidelines for nontransplant patients. See Therapeutic Management of Hospitalized Adults With COVID-19, Therapeutic Management of Nonhospitalized Adults With COVID-19, and Special Considerations in People Who Are Immunocompromised for more information.

• For nonhospitalized patients with mild to moderate COVID-19 who are transplant or cellular immunotherapy recipients, the Panel recommends prompt treatment with antiviral drugs at the doses and durations recommended for the general population (AII).

• Clinicians should consult with a transplant specialist when making decisions about stopping or adjusting the doses of immunosuppressive drugs in transplant or cellular immunotherapy recipients with COVID-19.

• Clinicians should pay special attention to the potential for drug-drug interactions and overlapping toxicities between treatments for COVID-19 and concomitant medications, such as immunosuppressants used to prevent or treat allograft rejection and antimicrobials used to prevent or treat opportunistic infections.

Each recommendation in the Guidelines receives a rating for the strength of the recommendation (A, B, or C) and a rating for the evidence that supports it (I, IIa, IIb, or III). See Guidelines Development for more information.
Introduction

Treating COVID-19 in solid organ transplant, hematopoietic cell transplant (HCT), and cellular immunotherapy recipients can be challenging due to the presence of coexisting medical conditions, the potential for transplant-related cytopenias, and the need for chronic immunosuppressive therapy to prevent graft rejection and graft-versus-host disease. Transplant recipients may also have a higher risk of exposure to SARS-CoV-2 given their frequent contact with the health care system. Since immunosuppressive agents modulate several aspects of immune response, the severity of COVID-19 could potentially be affected by the type and intensity of the immunosuppressive effect of the agent, as well as by specific combinations of immunosuppressive agents. Some transplant recipients have medical comorbidities that have been associated with more severe cases of COVID-19 and a greater risk of mortality, which makes the impact of transplantation on disease severity difficult to assess.

The International Society for Heart and Lung Transplantation, the American Society of Transplantation, the American Society for Transplantation and Cellular Therapy, and the European Society for Blood and Marrow Transplantation provide guidance for clinicians who are caring for transplant recipients with COVID-19 and guidance on screening potential donors and transplant or cellular immunotherapy candidates. In addition, the American Society of Hematology offers guidance regarding COVID-19 vaccination for transplant and cellular immunotherapy recipients.

This section of the COVID-19 Treatment Guidelines complements these sources and focuses on considerations for managing COVID-19 in solid organ transplant, HCT, and cellular immunotherapy recipients. The optimal management and therapeutic approach to COVID-19 in these populations is unknown. At this time, the procedures for evaluating and managing COVID-19 in transplant recipients are the same as those for nontransplant patients (AIII). See Therapeutic Management of Hospitalized Adults With COVID-19 and Therapeutic Management of Nonhospitalized Adults With COVID-19 for more information. The risks and benefits of each medication used to treat COVID-19 may be different for transplant patients and nontransplant patients.

COVID-19 Vaccination

The clinical trials that evaluated the safety and efficacy of the COVID-19 vaccines excluded patients who were severely immunocompromised.1,2 Authorized and approved COVID-19 vaccines in the United States are not live-virus vaccines and can be safely administered to patients who are immunocompromised. However, solid organ transplant recipients have reduced immunological antibody responses following a primary 2-dose or 3-dose series of the mRNA COVID-19 vaccines.3-6

COVID-19 vaccination remains the most effective way to prevent serious outcomes and death from SARS-CoV-2 infection. The COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination for everyone who is eligible, including transplant and cellular immunotherapy candidates and recipients, according to the Centers for Disease Control and Prevention’s (CDC) Advisory Committee on Immunization Practices (AI). See the CDC webpage COVID-19 Vaccines for People Who Are Moderately or Severely Immunocompromised for the current COVID-19 vaccination schedule for transplant and cellular immunotherapy recipients.

When determining the timing of COVID-19 vaccination in solid organ transplant, HCT, and cellular immunotherapy recipients, clinicians should consider the following factors:

- Ideally, solid organ transplant candidates should receive COVID-19 vaccines while they wait for transplant.
- In general, vaccination should be completed at least 2 weeks before a solid organ transplant, or vaccination should be started 1 month after a solid organ transplant.
• In certain situations, such as when T cell– or B cell–ablative therapy (with antithymocyte globulin or rituximab) is used at the time of transplant, delaying vaccination until 3 months after a solid organ transplant may be appropriate.\textsuperscript{7}

• Reducing the dose of immunosuppressants and withholding immunosuppressants before vaccination are not recommended.

• COVID-19 vaccines can be offered as early as 3 months after a patient receives HCT or chimeric antigen receptor T cell therapy, although the vaccines may be less effective in these patients than in the general population.\textsuperscript{8-10}

• If possible, patients who are scheduled to receive cytotoxic or B cell–depleting therapies should receive their COVID-19 vaccination before initiating these therapies or between cycles of these therapies. The suggested interval before resuming vaccination is about 6 months after completion of the B cell–depleting therapy.\textsuperscript{11}

• Graft-versus-host disease symptoms may flare after COVID-19 vaccination.\textsuperscript{12}

• After receiving a vaccination, people who are immunocompromised should be advised to continue to exercise precautions to reduce their risk of SARS-CoV-2 exposure and infection (e.g., they should wear a mask and avoid crowds and poorly ventilated spaces).\textsuperscript{8}

Currently, antibody tests are not recommended for assessing SARS-CoV-2 immunity following COVID-19 vaccination or for assessing the need for vaccination in a person who is unvaccinated. For people who received COVID-19 vaccines during treatment with immunosuppressive drugs, it is currently unknown whether revaccination offers a clinical benefit.

Clinicians should strongly encourage all household members, close contacts, and health care providers who provide care to transplant and cellular immunotherapy candidates and recipients to be vaccinated against COVID-19 (AI). There is evidence that vaccinated individuals who are infected with SARS-CoV-2 have lower viral loads than unvaccinated individuals\textsuperscript{13,14} and that COVID-19 vaccines reduce the incidence of SARS-CoV-2 infections not only among vaccinated individuals but also among their household contacts.\textsuperscript{15-17} Clinicians should strongly encourage all potential organ and hematopoietic cell donors to get vaccinated against COVID-19 (AI).

Assessing SARS-CoV-2 Infection

The risk of transmission of SARS-CoV-2 from donors to candidates is unknown. The probability that a donor or candidate may have SARS-CoV-2 infection can be estimated by considering the epidemiologic risk, obtaining a clinical history, and testing with molecular techniques. No current testing strategy is sensitive enough or specific enough to totally exclude active infection.

Assessing Transplant and Cellular Immunotherapy Candidates

The Panel recommends performing diagnostic molecular or antigen testing for SARS-CoV-2 in all potential solid organ transplant, HCT, and cellular immunotherapy candidates with signs and symptoms that suggest acute COVID-19 (AIII). The CDC testing algorithm recommends performing additional confirmatory testing with a laboratory-based nucleic acid amplification test (NAAT) when a person who is strongly suspected of having SARS-CoV-2 infection (i.e., a person who is symptomatic) receives a negative result on an antigen test.\textsuperscript{18} Shortly before solid organ transplant, HCT, or cellular immunotherapy, all candidates should undergo diagnostic molecular testing for SARS-CoV-2 and assessment for symptoms of COVID-19 (AIII).
Assessing Donors

The Panel recommends performing diagnostic molecular testing for SARS-CoV-2 and assessing for symptoms of COVID-19 in all potential solid organ transplant and HCT donors prior to donation (AIII). Additional guidance is available from medical professional organizations, such as the Organ Procurement and Transplantation Network and the American Society of Transplantation.

Living donors should undergo a SARS-CoV-2 NAAT using a specimen collected from the respiratory tract within 3 days of donation. Deceased donors should be tested for SARS-CoV-2 infection using a NAAT with a specimen taken from the upper respiratory tract within 72 hours of death; ideally, the test should be performed as close to organ recovery as possible. Lower respiratory sampling for COVID-19 testing is required for potential lung transplant donors by the United Network for Organ Sharing.\textsuperscript{19} The Organ Procurement and Transplantation Network and American Society of Transplantation provide information to help guide the decision-making process when managing solid organ transplant donors with a history of COVID-19.

If SARS-CoV-2 Infection Is Detected or Strongly Suspected in Transplant and Cellular Immunotherapy Candidates

If SARS-CoV-2 is detected or infection is strongly suspected in a potential transplant or cellular immunotherapy candidate, transplantation or immunotherapy should be deferred, if possible (BIII). The optimal disease-free interval before transplantation or immunotherapy is not known. In this situation, decisions about the appropriate timing for transplantation or cellular immunotherapy should be made on a case-by-case basis. Clinicians should consider both the risk of viral transmission and the risks of delaying or altering therapy, which may include progression of the underlying disease or death.

Transplant Recipients With COVID-19

Solid organ transplant recipients receiving immunosuppressive therapy should be considered at increased risk of severe COVID-19.\textsuperscript{20,21} Initial reports of transplant recipients hospitalized with COVID-19 suggested mortality of up to 28\%.\textsuperscript{22-26} However, COVID-19 vaccines and better treatments have improved clinical outcomes.

Risk of Graft Rejection

There are concerns that COVID-19 itself may increase the risk of acute rejection. In solid organ transplant recipients with or without COVID-19, acute cellular rejection should not be presumed without biopsy confirmation.\textsuperscript{20} Similarly, in recipients with or without COVID-19 who have had rejection confirmed by a biopsy, immunosuppressive therapy should be initiated.

Data on the incidence and clinical characteristics of SARS-CoV-2 infection in HCT\textsuperscript{27} and cellular immunotherapy recipients are limited.\textsuperscript{28} Data from the Center for International Blood and Marrow Transplant Research demonstrated that approximately 30\% of a cohort of 318 HCT recipients died within 30 days of COVID-19 diagnosis.\textsuperscript{21} This probability of mortality was observed in both allogeneic and autologous recipients. Older age (≥50 years), male sex, and receipt of a COVID-19 diagnosis within 12 months of transplantation were associated with a higher risk of mortality among allogeneic recipients. In autologous recipients, patients with lymphoma had a higher risk of mortality than patients who had plasma cell disorder or myeloma.

A smaller study demonstrated slightly lower mortality among HCT and cellular immunotherapy recipients than earlier reports. This study found that the number of comorbidities, the presence of infiltrates on initial chest imaging, and neutropenia were predictors for increased disease severity.\textsuperscript{19} Additional factors that have been used to determine the clinical severity of other respiratory viral
infections include the degree of cytopenia, the intensity of the conditioning regimen, the graft source, the degree of mismatch, and the need for further immunosuppression to manage graft-versus-host disease. Prolonged viral shedding has been described in solid organ transplant and HCT recipients; this can have implications for preventing infection and for the timing of therapeutic interventions.

**Treating COVID-19 in Transplant Recipients**


For nonhospitalized patients with mild to moderate COVID-19 who are transplant or cellular immunotherapy recipients, the Panel recommends prompt treatment with antiviral drugs at the doses and durations recommended for the general population (AIII). In hospitalized people with severe COVID-19 who required supplemental oxygen or mechanical ventilation, data from a large randomized controlled trial found that a short course of dexamethasone (6 mg once daily for up to 10 days) improved survival. A second immunomodulator (e.g., baricitinib, tocilizumab, abatacept, infliximab) used in combination with dexamethasone is recommended for some patients with severe or critical COVID-19. Because dexamethasone and the other immunomodulators are immunosuppressive agents, patients who receive these medications should be closely monitored for secondary infections.

Therapeutic anticoagulation for transplant recipients who are hospitalized for COVID-19 should be managed similarly to anticoagulation for other hospitalized patients. Patients with platelet counts <50,000 cells/µL should not receive therapeutic anticoagulation for COVID-19. Clinicians should follow hospital protocols for managing anticoagulation in patients with thrombocytopenia.

The Panel’s recommendations for the treatment of COVID-19 in hospitalized patients with COVID-19 can be found in [Therapeutic Management of Hospitalized Adults With COVID-19](https://www.covid19treatmentguidelines.nih.gov/).

**Concomitant Medications**

Clinicians should pay special attention to the potential for drug-drug interactions and overlapping toxicities between treatments for COVID-19 and concomitant medications, such as immunosuppressants used to prevent or treat allograft rejection and antimicrobials used to prevent or treat opportunistic infections. Dose modifications may be necessary for drugs used to treat COVID-19 in transplant recipients with pre-existing organ dysfunction. Adjustments to the immunosuppressive regimen should be individualized based on disease severity, the specific immunosuppressants used, the type of transplant, the time since transplantation, the drug concentration, and the risk of graft rejection. Clinicians should consult with a transplant specialist when making decisions about stopping or adjusting the doses of immunosuppressive drugs in transplant or cellular immunotherapy recipients with COVID-19.

**Drug-Drug Interactions**

Calcineurin inhibitors (e.g., cyclosporine, tacrolimus) and mammalian target of rapamycin (mTOR) inhibitors (e.g., everolimus, sirolimus), which are commonly used to prevent allograft rejection, have narrow therapeutic indices. Medications that inhibit or induce cytochrome P450 (CYP) enzymes or P-glycoprotein may put patients who receive these drugs at risk of clinically significant drug-drug interactions, increasing the need for therapeutic drug monitoring and the need to assess for signs of toxicity or rejection.
Some clinicians prefer to administer a 3-day course of intravenous remdesivir to nonhospitalized transplant recipients who are receiving immunosuppressive therapy to avoid significant drug-drug interactions. If remdesivir is not available or feasible to use, a 5-day course of ritonavir-boosted nirmatrelvir (Paxlovid) may be used with caution and only when close therapeutic drug monitoring of the antirejection therapy is possible. Clinicians should consult with transplant specialists throughout the treatment. Boosting with ritonavir, a strong CYP3A inhibitor, is required to increase the exposure of nirmatrelvir to a concentration that is effective against SARS-CoV-2. Ritonavir may also increase concentrations of certain concomitant medications, including calcineurin and mTOR inhibitors, during the treatment course and for ≥3 days after ritonavir is discontinued. Significant increases in the concentrations of these drugs may lead to serious or life-threatening drug toxicities.

General guidance for coadministering ritonavir-boosted nirmatrelvir with concomitant medications includes temporarily withholding certain immunosuppressive agents (e.g., tacrolimus, everolimus, sirolimus) or reducing the dosage of certain immunosuppressive agents (e.g., cyclosporine), monitoring the patient closely for toxicities, and performing therapeutic drug monitoring during and after the 5-day treatment course of ritonavir-boosted nirmatrelvir.36,37

Some small case series have reported success using these recommendations to manage patients.38,39 However, cases of significant toxicities due to supratherapeutic tacrolimus concentrations have also been reported.40 Therapeutic drug monitoring should be used to guide the process of reintroducing or modifying the doses of calcineurin and mTOR inhibitors in patients who have completed a course of ritonavir-boosted nirmatrelvir. Clinicians should also consult with a specialist who has experience with dose management. Clinicians should take additional precautions when treating transplant recipients who are also receiving other concomitant medications (e.g., certain triazole antifungals) that may interact with ritonavir, the immunosuppressants, or both. The extent and significance of multiple drug-drug interactions are much more complex and unpredictable.

Clinicians should refer to resources such as the Liverpool COVID-19 Drug Interactions website, Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications, and the Food and Drug Administration prescribing information for ritonavir-boosted nirmatrelvir for guidance on identifying and managing potential drug-drug interactions. If significant interactions prohibit the concomitant use of ritonavir-boosted nirmatrelvir, another COVID-19 treatment option should be used (see Therapeutic Management of Nonhospitalized Adults With COVID-19).

Among the drugs commonly used to treat hospitalized patients with COVID-19, dexamethasone is a moderate inducer of CYP3A4, and interleukin-6 inhibitors may lead to increased metabolism of CYP substrates. Clinicians should closely monitor the serum concentrations of calcineurin and mTOR inhibitors when these drugs are used.

Additional details about the adverse effects and drug-drug interactions of antiviral medications and immune-based therapies for COVID-19 are noted in Tables 4e and 5e.

References


