Special Considerations in Solid Organ Transplant, Hematopoietic Stem Cell Transplant, and Cellular Immunotherapy Candidates, Donors, and Recipients

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<table>
<thead>
<tr>
<th>Summary Recommendations</th>
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<tbody>
<tr>
<td><strong>Vaccination for COVID-19</strong></td>
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<tr>
<td>• COVID-19 vaccination remains the most effective way to prevent SARS-CoV-2 infection and should be considered the first line of prevention. Given the effectiveness of COVID-19 vaccines in the general population and the increased risk of worse clinical outcomes of COVID-19 in transplant and cellular immunotherapy candidates and recipients, the COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination for these patients (AIII).</td>
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<td>• Because vaccine response rates may be lower in moderately or severely immunocompromised patients, specific guidance on administering vaccines to these individuals is provided by the Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices. The Panel recommends following the current COVID-19 vaccination schedule for these patients.</td>
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<td>• Vaccinating household members, close contacts, and health care providers who provide care to transplant and cellular immunotherapy candidates and recipients is important to protect these patients from infection. All close contacts are strongly encouraged to get vaccinated against COVID-19 as soon as possible (AIII).</td>
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<td>• All potential organ and stem cell donors are encouraged to get vaccinated against COVID-19 (AI).</td>
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<td><strong>Pre-Exposure Prophylaxis</strong></td>
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<td>• Some transplant candidates or recipients cannot or may not mount an adequate protective response to COVID-19 vaccines. These patients are eligible to receive the anti-SARS-CoV-2 monoclonal antibodies tixagevimab plus cilgavimab (Evusheld) as pre-exposure prophylaxis (PrEP). See Prevention of SARS-CoV-2 Infection for more information.</td>
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<td><strong>Potential Transplant and Cellular Immunotherapy Candidates</strong></td>
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<td>• The Panel recommends performing diagnostic molecular or antigen testing for SARS-CoV-2 for all potential solid organ transplant, hematopoietic stem cell transplant (HCT), and cellular immunotherapy candidates with signs and symptoms that suggest acute COVID-19 (AIII).</td>
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<td>• The Panel recommends following the guidance from medical professional organizations that specialize in providing care for solid organ transplant, HCT, or cellular immunotherapy recipients when performing diagnostic molecular or antigen testing for SARS-CoV-2 in these patients (AIII).</td>
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<td>• If SARS-CoV-2 is detected or if infection is strongly suspected, transplantation should be deferred, if possible (BIII).</td>
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<td>• The Panel recommends assessing all potential solid organ transplant and HCT donors for signs and symptoms of COVID-19 according to guidance from medical professional organizations (AIII).</td>
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<td><strong>Transplant and Cellular Immunotherapy Recipients With COVID-19</strong></td>
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<td>• Clinicians should follow the guidelines for evaluating and managing COVID-19 in nontransplant patients when treating transplant and cellular immunotherapy recipients (AIII). See Therapeutic Management of Hospitalized Adults With COVID-19 and Therapeutic Management of Nonhospitalized Adults With COVID-19 for more information.</td>
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<tr>
<td>• Immunocompromised patients with mild to moderate COVID-19 are at high risk of progressing to severe disease and should receive anti-SARS-CoV-2 therapies for treatment.</td>
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</table>
Clinicians who are treating COVID-19 in transplant and cellular immunotherapy patients should consult a transplant specialist before adjusting immunosuppressive medications (AIII). When treating COVID-19, clinicians should pay careful attention to potential overlapping toxicities and drug-drug interactions between drugs that are used to treat COVID-19 (e.g., ritonavir-boosted nirmatrelvir [Paxlovid]) and immunosuppressants, prophylactic antimicrobials, or other medications (AIII).

Rating of Recommendations: A = Strong; B = Moderate; C = Weak
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Introduction

Treating COVID-19 in solid organ transplant, hematopoietic stem 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 the host’s 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 (AST), the American Society for Transplantation and Cellular Therapy (ASTCT), and the European Society for Blood and Marrow Transplantation (EBMT) 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 that is used to treat COVID-19 may be different for transplant patients and nontransplant patients.

COVID-19 Vaccination in Solid Organ Transplant, Hematopoietic Stem Cell Transplant, and Cellular Immunotherapy Candidates, Donors, and Recipients

The clinical trials that evaluated the safety and efficacy of the COVID-19 vaccines excluded severely immunocompromised patients. The Center for Disease Control and Prevention’s (CDC) Advisory Committee on Immunization Practices notes that the currently authorized or approved COVID-19 vaccines are not live vaccines; therefore, they can be safely administered to immunocompromised people. 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.

Given the effectiveness of COVID-19 vaccines in the general population and the increased risk of worse
clinical outcomes of COVID-19 in transplant and cellular immunotherapy recipients, the COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination for potential transplant and cellular immunotherapy candidates and recipients (AIII). See the CDC website COVID-19 Vaccines for People Who Are Moderately or Severely Immunocompromised for the current COVID-19 vaccination schedule for all populations, including 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 are awaiting transplant.
- In general, vaccination should be completed at least 2 weeks prior to a solid organ transplant or started 1 month after a solid organ transplant.
- In certain situations, it may be appropriate to delay vaccination until 3 months after a solid organ transplant, such as when T cell- or B cell-ablative therapy (with antithymocyte globulin or rituximab) is used at the time of transplant.9
- At this time, reducing the dose of immunosuppressants and withholding immunosuppressants prior to 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 efficacy of the vaccines may be reduced compared to the efficacy observed in the general population.10-12 Patients who are scheduled to receive cytotoxic or B cell-depleting therapies should complete their COVID-19 vaccination prior to initiation or between cycles of cytotoxic or B cell-depleting therapies, if possible.
- After completing COVID-19 vaccination, immunocompromised persons 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, maintain a distance of 6 feet from others, and avoid crowds and poorly ventilated spaces).13

There is insufficient evidence for the Panel to recommend either for or against the use of SARS-CoV-2 serologic testing to assess for immunity or to guide clinical decisions about using COVID-19 vaccines. It is currently unknown whether revaccination offers a clinical benefit for people who received COVID-19 vaccines during treatment with immunosuppressive drugs.

Vaccinating household members, close contacts, and health care providers who provide care to transplant and cellular immunotherapy candidates and recipients is important to protect these patients from infection. All close contacts are strongly encouraged to get vaccinated against COVID-19 as soon as possible (AIII). There is evidence that vaccinated individuals who are infected with SARS-CoV-2 have lower viral loads than unvaccinated individuals14,15 and that COVID-19 vaccines reduce the incidence of SARS-CoV-2 infections not only among vaccinated individuals but also among their household contacts.16-18 All potential organ and stem cell donors are encouraged to get vaccinated against COVID-19 (AII).

**Pre-Exposure Prophylaxis**

Vaccination remains the most effective way to prevent SARS-CoV-2 infection and should be considered the first line of prevention. However, some individuals, including some transplant candidates and recipients, cannot or may not mount an adequate protective response to COVID-19 vaccines. These patients are at high risk of progressing to severe COVID-19 and may be eligible to receive the anti-SARS-CoV-2 monoclonal antibodies (mAbs) tixagevimab plus cilgavimab (Evusheld) as pre-exposure

**Assessing SARS-CoV-2 Infection in Transplant and Cellular Immunotherapy Candidates and Donors**

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 for all potential solid organ transplant candidates with signs and symptoms that suggest acute COVID-19 (AIII). All potential solid organ transplant candidates should be assessed for exposure to COVID-19 and clinical symptoms that are compatible with COVID-19 before they are called in for transplantation and should undergo diagnostic molecular testing for SARS-CoV-2 shortly before a solid organ transplant (AIII).

Clinicians should perform diagnostic testing for SARS-CoV-2 in all HCT and cellular immunotherapy candidates who exhibit symptoms. All candidates should also undergo diagnostic molecular testing for SARS-CoV-2 shortly before HCT or cellular immunotherapy (AIII).

**Assessing Donors**

Living solid organ donors should be counseled on strategies to prevent infection and be monitored for exposures and symptoms in the 14 days prior to a scheduled transplant. Living donors should undergo SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) testing with a sample collected from the respiratory tract within 3 days of donation. Deceased donors should be tested for SARS-CoV-2 infection using an RT-PCR assay of a sample taken from the upper respiratory tract within 72 hours of death; ideally, the test should be performed as close to organ recovery as possible. Deceased donors can be considered for donation if the results are negative. Lower respiratory sampling for COVID-19 testing is required for potential lung transplant donors by the United Network for Organ Sharing.

The Panel recommends following the guidance from medical professional organizations and assessing all potential HCT donors for exposure to COVID-19 and clinical symptoms that are compatible with COVID-19 before donation (AIII). HCT donors should practice good hygiene and avoid crowded places and large gatherings during the 28 days prior to donation. Recommendations for screening HCT donors are outlined in the ASTCT and EBMT guidelines.

**If SARS-CoV-2 Infection Is Detected or Strongly Suspected**

If SARS-CoV-2 is detected or if infection is strongly suspected in a potential solid organ transplant candidate, transplant should be deferred, if possible. The optimal disease-free interval before transplantation is not known. When deciding on the appropriate timing for the transplant, clinicians should consider both the risk of viral transmission and the risks to the candidate if the transplant is deferred, such as the potential progression of the underlying disease and the risk of death. This decision should be continually reassessed as conditions evolve.

Current guidelines recommend deferring transplants or immunotherapy procedures, including peripheral blood stem cell mobilization, bone marrow harvest, T cell collection, and conditioning/lymphodepletion, in HCT and cellular immunotherapy candidates who test positive for SARS-CoV-2 or who have clinical symptoms that are consistent with infection. Final decisions should be made on a case-by-case basis while weighing the risks of delaying or altering therapy for the underlying disease.
**Transplant Recipients With COVID-19**

Solid organ transplant recipients who are receiving immunosuppressive therapy should be considered to be at increased risk for severe COVID-19. A national survey of 88 U.S. transplant centers conducted between March 24 and 31, 2020, reported that 148 solid organ transplant recipients received a diagnosis of SARS-CoV-2 infection (69.6% were kidney recipients, 15.5% were liver recipients, 8.8% were heart recipients, and 6.1% were lung recipients). COVID-19 was mild in 54% of recipients and moderate in 21% of recipients, and 25% of recipients were critically ill. Initial reports of transplant recipients who were hospitalized with COVID-19 suggest mortality rates of up to 28%.

**Risk of Graft Rejection**

There are concerns that COVID-19 itself may increase the risk for acute rejection. Acute cellular rejection should not be presumed in solid organ transplant recipients without biopsy confirmation, regardless of whether the individual has COVID-19. Similarly, immunosuppressive therapy should be initiated in recipients with or without COVID-19 who have rejection confirmed by a biopsy.

There are limited data on the incidence and clinical characteristics of SARS-CoV-2 infection in HCT and cellular immunotherapy recipients. Recent data from the Center for International Blood and Marrow Transplant Research demonstrated a mortality rate of approximately 30% within a month of COVID-19 diagnosis among a cohort of 318 HCT recipients. This mortality rate 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 a slightly lower mortality rate 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. 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**

Currently, remdesivir is the only antiviral drug that is approved by the Food and Drug Administration for the treatment of COVID-19 in both nonhospitalized and hospitalized patients. Outpatient transplant recipients who are immunosuppressed or who have certain underlying comorbidities are candidates for several other therapeutic agents that are available through Emergency Use Authorizations (EUAs). See Therapeutic Management of Nonhospitalized Adults With COVID-19 for more information.

When treating hospitalized patients with mild to moderate, symptomatic COVID-19, clinicians should consider administering the therapeutics used in nonhospitalized patients with similar disease severity. 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 in hospitalized people with severe COVID-19 who were mechanically ventilated or who required supplemental oxygen. Tocilizumab or baricitinib used in combination with dexamethasone is recommended for some patients with severe or critical COVID-19 who exhibit rapid respiratory decompensation (see Therapeutic Management of Hospitalized Adults With COVID-19). Because dexamethasone, tocilizumab, and baricitinib 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 to treat COVID-19. Clinicians should follow hospital protocols for managing anticoagulation in patients with thrombocytopenia.

The Panel’s recommendations for the use of remdesivir, dexamethasone, tocilizumab, baricitinib, and anticoagulation in hospitalized patients with COVID-19 can be found in Therapeutic Management of Hospitalized Adults With COVID-19.

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 that are used to prevent allograft rejection, antimicrobials that are used to prevent opportunistic infections, and other medications. Dose modifications may be necessary for drugs that are 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 who are treating COVID-19 in transplant patients should consult a transplant specialist before adjusting immunosuppressive medications (AIII).

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 a narrow therapeutic index. 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.

A 5-day course of ritonavir-boosted nirmatrelvir (Paxlovid) is 1 of the preferred therapies for treating mild to moderate COVID-19 in nonhospitalized patients who are at risk for disease progression. However, this regimen has the potential for significant and complex drug-drug interactions with concomitant medications, primarily due to the ritonavir component of the combination. 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 and sometimes life-threatening drug toxicities.

For nonhospitalized transplant patients who are receiving calcineurin or mTOR inhibitors as part of their antirejection regimen, AST recommends either an anti-SARS-CoV-2 mAb or remdesivir as the first-line therapy. If these drugs are not available or feasible to use, ritonavir-boosted nirmatrelvir may be used with caution. Ritonavir-boosted nirmatrelvir should only be used when close monitoring of the patient is possible, and clinicians should consult with transplant specialists during the treatment course. 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 (if possible) during and after the treatment course of ritonavir-boosted nirmatrelvir.

Some small case series have reported real-life success in using these recommendations to manage
patients; however, cases of significant toxicities due to supratherapeutic tacrolimus concentrations have also been reported.\textsuperscript{43} The reintroduction or dose modification of calcineurin and mTOR inhibitors in patients who have completed a course of ritonavir-boosted nirmatrelvir should be guided by therapeutic drug monitoring. 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 EUA fact sheet 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.

Among the drugs that are 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, anti-SARS-CoV-2 antibody products, and immune-based therapies for COVID-19 are noted in Tables 4d, 5c, and 6g.

References


