Summary Recommendations

Vaccination for COVID-19
- 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, potential donors, and recipients (AIII). See the text below for information on the appropriate timing for COVID-19 vaccination in these patients.
- A third dose of an mRNA vaccine (given at least 4 weeks after the second dose) is currently recommended by the Centers for Disease Control and Prevention for solid organ transplant recipients who are taking immunosuppressive medications and hematopoietic stem cell transplant (HCT) recipients who are within 2 years of transplantation or who are taking immunosuppressive medications.

Potential Transplant and Cellular Immunotherapy Candidates
- The Panel recommends diagnostic molecular testing for SARS-CoV-2 for all potential solid organ transplant, HCT, and cellular immunotherapy candidates with signs and symptoms that suggest acute COVID-19 (AIII).
- 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 testing for SARS-CoV-2 in these patients (AIII).
- If SARS-CoV-2 is detected or if infection is strongly suspected, transplantation 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 candidates (AIII).
- Additionally, many transplant candidates are at high risk of progressing to serious COVID-19, and they may be eligible to receive anti-SARS-CoV-2 monoclonal antibodies (mAbs) for treatment or post-exposure prophylaxis (PEP).

Potential Transplant Donors
- The Panel recommends assessing all potential solid organ transplant and HCT donors for signs and symptoms that are associated with COVID-19 according to guidance from medical professional organizations (AIII).
- The Panel recommends performing diagnostic molecular testing for SARS-CoV-2 if symptoms are present (AIII).
- If SARS-CoV-2 is detected or if infection is strongly suspected, donation should be deferred (BIII).

Transplant and Cellular Immunotherapy Recipients With COVID-19
- 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 for more information.
- Immunocompromised patients with mild to moderate COVID-19 are at high risk of progressing to serious disease, and they may be eligible to receive anti-SARS-CoV-2 mAbs for treatment or PEP.
- The Panel recommends that clinicians who are treating COVID-19 in transplant and cellular immunotherapy patients consult with a transplant specialist before adjusting immunosuppressive medications (AIII).
- When treating COVID-19, clinicians should pay careful attention to potential drug-drug interactions and overlapping toxicities with immunosuppressants, prophylactic antimicrobials, and other medications (AIII).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
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, transplant-related cytopenias, and the need for chronic immunosuppressive therapy to prevent graft rejection and graft-versus-host disease. Transplant recipients may also have increased 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 the 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 (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 for more information. The medications that are used to treat COVID-19 may present different risks and benefits to transplant patients and nontransplant patients.

Vaccination for COVID-19 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 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. Compared to healthy vaccine recipients, solid organ transplant recipients have a reduced antibody response following a primary two-dose vaccine series of mRNA vaccines. Among those who had no detectable antibody response to the initial two-dose vaccine series, 33% to 50% of patients developed an antibody response to an additional mRNA vaccine dose.

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, potential donors, and recipients (AIII). Currently, the Centers for Disease Control and Prevention recommends administering an additional dose of vaccine to moderately to severely immunocompromised people at least 28 days after a second dose of an mRNA vaccine. This includes people who have:

- Received a solid organ transplant and are taking immunosuppressive medications
- Received an HCT within the last 2 years or who are taking immunosuppressive medications
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.\[11\]
- At this time, reducing the dose of immunosuppressants and holding 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.\[12,14\] 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 continue wearing a mask, maintain a distance of 6 feet from others, and avoid crowds and poorly ventilated spaces).\[15\]

It remains unclear whether the immune responses to COVID-19 vaccines can increase the risk of graft-versus-host disease or other immune-related complications.\[14,16\] Outside of a clinical study, antibody testing is not recommended to assess immunity to SARS-CoV-2 following COVID-19 vaccination in transplant patients. It is currently unknown whether revaccination offers a clinical benefit for people who received COVID-19 vaccines during treatment with immunosuppressive drugs.

Vaccination of household members, close contacts, and health care providers who provide care for immunocompromised patients is imperative to protect immunocompromised patients from infection. All close contacts are strongly encouraged to get vaccinated as soon as possible.

**Post-Exposure Prophylaxis for Transplant and Cellular Immunotherapy Recipients**

The Food and Drug Administration (FDA) expanded the Emergency Use Authorization (EUA) indication for the anti-SARS-CoV-2 monoclonal antibodies (mAbs) bamlanivimab plus etesevimab and casirivimab plus imdevimab to allow them to be used as post-exposure prophylaxis (PEP) for selected individuals who are at high risk for disease progression. This includes immunocompromised individuals who are not expected to mount an adequate immune response to vaccination. See Prevention of SARS-CoV-2 Infection for more information.

**Assessment of 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.
**Assessment of Transplant and Cellular Immunotherapy Candidates**

Diagnostic molecular testing for SARS-CoV-2 is recommended 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 in accordance with guidance from medical professional organizations (AIII).

Clinicians should consider performing 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).

**Assessment of Donors**

Living solid organ donors should be counseled on strategies to prevent infection and monitored for exposures and symptoms in the 14 days prior to a scheduled transplant. Living donors should undergo respiratory tract SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) testing 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 (BIII).

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 group gatherings during the 28 days prior to donation. Recommendations for screening for HCT donors are outlined in the ASTCT and EBMT guidelines.

**If SARS-CoV-2 Infection Is Detected or Is 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 (BIII). The optimal disease-free interval before transplantation is not known. The risks of viral transmission should be balanced against the risks to the candidate, such as progression of the underlying disease and risk of mortality if the candidate does not receive the transplant. This decision should be continually reassessed as conditions evolve. Donors for solid organ transplants who test positive for SARS-CoV-2 are medically ineligible for donation. For HCT and cellular immunotherapy candidates, current guidelines recommend deferring transplants or immunotherapy procedures, including peripheral blood stem cell mobilization, bone marrow harvest, T cell collection, and conditioning/lymphodepletion in recipients 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, moderate in 21% of recipients, and 25% of recipients were critically ill. Management strategies varied widely across the transplant centers, including different ways of modifying immunosuppressive therapy and the use of
different investigational therapies to treat COVID-19. Initial reports of transplant recipients who were hospitalized with COVID-19 suggest mortality rates of up to 28%.\textsuperscript{24-28}

**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.\textsuperscript{21}

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.\textsuperscript{29} This mortality rate was observed in both allogeneic and autologous recipients. Older age (\(\geq 50\) 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.\textsuperscript{30} 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.\textsuperscript{31}

**Treatment of COVID-19 in Transplant Recipients**

Currently, the antiviral agent remdesivir is the only drug that is approved by the FDA for the treatment of COVID-19. Outpatient transplant recipients who are immunosuppressed or who have certain underlying comorbidities are candidates for the anti-SARS-CoV-2 mAbs that are available through EUAs (see Anti-SARS-CoV-2 Monoclonal Antibodies). Transplant recipients who are hospitalized for reasons other than COVID-19 are also eligible to receive mAb therapy. Transplant recipients who are hospitalized with mild to moderate COVID-19 may be considered for anti-SARS-CoV-2 mAbs that are available through expanded access programs.

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 patients with COVID-19 who were mechanically ventilated or who required supplemental oxygen.\textsuperscript{32} 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 Interleukin-6 Inhibitors).\textsuperscript{33-35} The risks and benefits of using dexamethasone in combination with tocilizumab or baricitinib in transplant recipients with COVID-19 who are receiving immunosuppressive therapy are unknown. Because dexamethasone, tocilizumab, and baricitinib are immunosuppressive agents, patients who receive these medications should be closely monitored for secondary infections.

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

A number of other investigational agents and drugs that are approved by the FDA for other indications

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are being evaluated for the treatment of COVID-19 (e.g., antiviral therapies, COVID-19 convalescent plasma) and its associated complications (e.g., immunomodulators, antithrombotic agents). In general, the considerations for treating COVID-19 in transplant recipients are the same as those for the general population. When possible, treatment should be given as part of a clinical trial. The safety and efficacy of investigational agents and drugs that have been approved by the FDA for other indications are not well-defined in transplant recipients. Moreover, it is unknown whether concomitant use of immunosuppressive agents to prevent allograft rejection in the setting of COVID-19 affects treatment outcomes.

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 (e.g., corticosteroids, mycophenolate, and calcineurin inhibitors such as tacrolimus and cyclosporine), 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 medication (AIII).

Certain therapeutics (e.g., remdesivir, tocilizumab, baricitinib) are associated with elevated levels of transaminases. For liver transplant recipients, the American Association for the Study of Liver Diseases does not consider abnormal liver biochemistries a contraindication to using remdesivir. Close monitoring of liver biochemistries is warranted in patients with COVID-19, especially when they are receiving agents with a known risk of hepatotoxicity.

Calcineurin inhibitors, 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 calcineurin inhibitors 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. Among the drugs that are commonly used to treat COVID-19, dexamethasone is a moderate inducer of CYP3A4, and interleukin-6 inhibitors may lead to increased metabolism of CYP substrates. Close monitoring of serum concentration of calcineurin inhibitors should be considered when these drugs are used.

Additional details about the adverse effects and drug interactions of antiviral medications and immune-based therapy for COVID-19 are noted in Tables 2e, 3e, and 4e.

References


