Authors: Ajit P Limaye, MD, FACP, FIDSA, Karen Hardinger, PharmD, BCPS
Section Editors: Daniel C Brennan, MD, FACP, Emily A Blumberg, MD
Deputy Editors: Albert Q Lam, MD, Sheila Bond, MD

Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Apr 2020. | **This topic last updated:** May 13, 2020.

INTRODUCTION

Solid organ transplant recipients may be at increased risk for COVID-19 because they are immunosuppressed and have frequent contact with the health care system. There is also a theoretical risk of transmission of SARS-CoV-2 (the virus that causes COVID-19) with organ transplantation, although no cases of organ transplant-transmitted infection have been described to date.

This topic reviews aspects of COVID-19 that are specific to solid organ transplantation, including screening prior to transplantation, distinct clinical features, managing immunosuppression, and important drug interactions. Other aspects of COVID-19 care are discussed separately:

- (See "Coronavirus disease 2019 (COVID-19): Epidemiology, virology, clinical features, diagnosis, and prevention".)
- (See "Coronavirus disease 2019 (COVID-19): Management in hospitalized adults".)
- (See "Coronavirus disease 2019 (COVID-19): Critical care and airway management issues".)
- (See "Coronavirus disease 2019 (COVID-19): Issues related to kidney disease and hypertension".)
- (See "Coronavirus disease 2019 (COVID-19): Pregnancy issues".)

- (See "Coronavirus disease 2019 (COVID-19): Arrhythmias and conduction system disease".)
- (See "Coronavirus disease 2019 (COVID-19): Anesthetic concerns, including airway management and infection control".)

RISK OF TRANSMISSION

Potential for donor-derived infection — The risk of transmitting SARS-CoV-2 from an organ donor to a recipient is theoretical and based upon the detection of viral RNA in organs that can be transplanted (eg, lung, heart, kidney, intestine) and in other sites (ie, blood, urine) [1-4]. While it is clear that viable infectious virus can be cultured from the lung and other parts of the respiratory and gastrointestinal (GI) tracts, additional study is needed to determine whether SARS-CoV-2 detected at extra-respiratory sites is intact, replication competent, and therefore transmissible by non-lung organ transplantation.

To date, no organ donor-derived infections have been reported. Similarly, bloodborne transmission has not been reported and is not expected; both the frequency of SARS-CoV-2 viremia and its magnitude are low [1,4-6]. (See "Blood donor screening: Medical history", section on 'SARS-CoV-2 (no evidence of transfusion-transmitted infection)'.)

Posttransplantation risk — It is not known whether solid organ transplant recipients are at higher risk for acquiring SARS-CoV-2 infection than the general population. However, chronic immunosuppression may lower the infectious dose needed to cause COVID-19 and impair adequate immune control once infection is established. Organ transplant recipients also have frequent contact with the health care system and are therefore potentially more likely to be exposed to the virus.

Like other immunosuppressed persons, solid organ transplant recipients may shed greater amounts of virus for longer durations than otherwise healthy hosts. Thus, they may be more likely to spread infection to others. Further data is needed to confirm these theories and to quantify viral dynamics and transmission risks in the solid organ transplant population.

DEFERRAL OF NONURGENT TRANSPLANTATION

To minimize the risk of infection and conserve hospital resources, elective transplantation (eg, living-donor kidney transplantation) and nonurgent, deceased-donor transplantation are being deferred at some transplant centers where the community prevalence of COVID-19 is high and/or where

resources (personnel, hospital or intensive care unit [ICU] beds, operating rooms, other equipment) are limited [7].

Life-saving transplantation continues to be performed, and the Centers for Medicare & Medicaid Services have classified organ transplantation as a tier 3b activity: Do not delay, on the basis of assessment of the potential risks compared with known benefits [8].

PRETRANSPLANTATION SCREENING

All organ donors and potential recipients should be screened for COVID-19 prior to organ procurement. This is necessary to prevent initiation of potent induction immunosuppression in the context of active infection and for the safety of the organ transplant recipients (who are typically potently immunosuppressed in the immediate posttransplant period) and the organ procurement team.

Reverse-transcriptase polymerase chain reaction (RT-PCR; primarily used to detect active infection) is the main assay used for screening. The utility of serology (primarily used to detect past infection) for pretransplant screening has not been established. However, once the performance characteristics of serology are more well established among solid organ transplant recipients, serologies may become a helpful adjunct assay. (See "Coronavirus disease 2019 (COVID-19): Epidemiology, virology, clinical features, diagnosis, and prevention", section on 'Microbiologic diagnosis'.)

Donor screening — All donors should be screened for COVID-19 [9]. We generally perform a careful history, obtain chest imaging, and perform microbiologic testing. In all cases the decision to proceed to transplantation should take into account the urgency of the transplant and the risk and benefits in each individual. As general principles:

- Donors with known or suspected active COVID-19 based on exposure, symptoms, or chest imaging should generally be declined or deferred.
- Donors with known or suspected COVID-19 within the past 28 days should generally be declined or deferred.
- Donors who have been exposed to individuals with known or suspected COVID-19 in the recent past (eg, within the past 21 days) should generally be declined or deferred. However, if such a donor tests negative for COVID-19, transplantation can be considered in selected cases (eg, if transplantation is urgently life-saving).

- Donors should also be tested for SARS-CoV-2 infection by RT-PCR performed on respiratory tract samples. The approach to screening varies among institutions and by the organ to be transplanted:

  - For deceased organ donors (especially lung donors), it is recommended to sample both the upper respiratory tract (eg, nasopharyngeal swab) and the lower respiratory tract (eg, bronchoalveolar lavage) when screening, based upon data suggesting increased sensitivity of lower tract (ie, sputum, bronchoalveolar lavage) specimens compared with upper tract specimens.

  - For other donors, screening for COVID-19 should be performed on a single upper respiratory tract sample, at a minimum. The need to obtain serial samples and/or lower respiratory tract samples varies among centers and is often individualized.

For living donors who test positive for COVID-19 or for deceased donors who have recovered from COVID-19, the optimal deferral period is not known. Based upon the mean duration of viral shedding (20 days) [10], the American Society of Transplantation (AST) suggests waiting at least 28 days from the time of diagnosis and complete resolution of symptoms (if living donor) before organ donation/procurement be considered [9]. As knowledge of COVID-19 accumulates, screening recommendations are expected to evolve.

Candidate screening — All potential organ transplant recipients should be screened for COVID-19 by history, chest imaging, and microbiologic testing prior to transplantation. Although data is lacking, COVID-19 can be asymptomatic, and there is concern that the intense immunosuppression given at the time of transplantation could result in rapidly progressive and potentially fatal COVID-19:

- All potential organ recipients should be screened for COVID-19 prior to transplantation. At most transplant centers this includes RT-PCR of an upper respiratory tract specimen (eg, nasopharyngeal swab), a thorough symptom and exposure history, and chest imaging. A chest radiograph is usually sufficient for patients who lack respiratory symptoms, however, for those with respiratory symptoms (even if minor), computed tomography (CT) of the chest is appropriate.

- Candidates with active COVID-19 and/or signs or symptoms of other respiratory illnesses should generally be deferred for transplantation.

For patients with active COVID-19 and patients who screen positive, the optimal deferral period is not known. The AST suggests waiting until all symptoms have resolved and at least two RT-PCRs for SARS-CoV-2 have been negative [9]. As with any transplantation, the risk of transplantation must be balanced with the risk of not transplanting a patient with acute or recent COVID-19.

PREVENTION

Preventive measures for organ transplant recipients are similar to those defined for the general population (eg, social distancing, careful hand and respiratory hygiene). (See "Coronavirus disease 2019 (COVID-19): Epidemiology, virology, clinical features, diagnosis, and prevention", section on 'Prevention'.)

One additional consideration is that solid organ transplant recipients who have COVID-19 may shed greater amounts of virus for longer durations than nonimmunosuppressed patients. Thus, a longer duration of isolation and/or testing to document viral clearance to help reduce the likelihood of spreading the infection to others may be needed. (See "Coronavirus disease 2019 (COVID-19): Infection control in health care and home settings", section on 'Infection control in the home setting' and "Coronavirus disease 2019 (COVID-19): Infection control in health care and home settings", section on 'Discontinuation of precautions'.)

ACTIVE COVID-19 IN SOLID ORGAN TRANSPLANT RECIPIENTS

Clinical presentation

Clinical features — Clinical features of COVID-19 among solid organ transplant recipients are variable and similar to those in nonimmunocompromised patients. However, fever appears to be less common, possibly as a consequence of the effects of immunosuppressive therapy on the systemic inflammatory response [11-13]. As an example, in two case series of solid organ transplant recipients in New York City, fever was a presenting symptom in only 58 to 70 percent [12,13]. Lymphopenia is also common and may be more profound than in nontransplant patients with COVID-19 [13]. (See "Coronavirus disease 2019 (COVID-19): Epidemiology, virology, clinical features, diagnosis, and prevention", section on 'Clinical features'.)

Severity of illness — It is unclear if solid organ transplant recipients have a higher risk of severe disease compared with nontransplant patients if infected with SARS-CoV-2. Many solid organ transplant recipients have medical comorbidities (eg, hypertension, diabetes mellitus, chronic kidney disease, cardiovascular disease) that have been associated with more severe COVID-19 disease and mortality, which makes the attributable impact of solid organ transplantation on disease severity difficult to assess.

Limited data suggest that solid organ transplant recipients with COVID-19 infection may have severe disease, similar to that described in non-solid organ transplant patients with serious underlying comorbidities [12,13]. As an example, in the study of 90 solid organ transplant recipients

cited above, 24 percent had mild disease (outpatient care only), 46 percent had moderate disease (admitted to general inpatient floor), and 30 percent had severe disease (mechanical ventilation, admission to intensive care unit [ICU], or death) [12]. At a median of 20 days, the mortality rate was 18 percent. Compared with patients who had mild to moderate disease, those with severe disease were older and more likely to have hypertension or active cancer, but other comorbidities associated with severe disease in the general population were not significantly different between the groups. In addition, there were no significant differences between the groups in the types of organ transplant or the median time from transplant to COVID-19 diagnosis.

Risk factors for severe COVID-19 are discussed in detail elsewhere. (See "Coronavirus disease 2019 (COVID-19): Epidemiology, virology, clinical features, diagnosis, and prevention", section on 'Risk factors for severe illness'.)

Effect of immunosuppression — The impact of immunosuppression in the solid organ transplant population on COVID-19 disease severity remains unclear. The pathogenesis of COVID-19 appears to represent an interplay between direct virally mediated injury and the associated host response, with experimental data suggesting that a dysregulated and hyperintense immune response may mediate more severe disease [14]. Since immunosuppressive agents modulate several aspects of the host immune response, the severity of COVID-19 infection could potentially be affected by the type, combinations, and intensity of immunosuppression. As an example, certain immunosuppressive medications can either directly (eg, lymphocyte-depleting antibodies) or indirectly (eg, antimetabolites) cause lymphopenia, which is a reported risk factor for severe COVID-19 illness. Specific agents that have been independently associated with decreased immune responses to vaccines (eg, mammalian [mechanistic] target of rapamycin [mTOR] inhibitors, mycophenolate) could theoretically impair the ability to develop an adequate immune response to natural infection. Conversely, some experimental data suggest that mTOR inhibitors may have some biological activity against SARS-CoV-2 [15]. Additional studies are required to determine the impact of specific immunosuppressive agents on the course of COVID-19 infection.

Diagnosis — Criteria for testing for COVID-19 in solid organ transplant recipients are similar to those for the general population. However, clinicians should have a higher index of suspicion of infection, as is generally recommended for immunosuppressed individuals:

- For solid organ transplant recipients with suspected COVID-19 who are hospitalized, testing is recommended.
- For solid organ transplant recipients with mild symptoms, optimal practice is not defined. While some favor testing all such patients based upon the potential for rapid disease progression, others favor making a clinical diagnosis and monitoring the patient at home. Thus, the decision

is often individualized based upon local COVID-19 prevalence, available resources, and patient-provider preference.

- Routine screening of asymptomatic solid organ transplant recipients is not recommended.

Specific testing methods are discussed separately. (See "Coronavirus disease 2019 (COVID-19): Epidemiology, virology, clinical features, diagnosis, and prevention", section on 'Clinical suspicion and criteria for testing'.)

Management

General considerations — The approach to the management of acute COVID-19 infection in solid organ transplant recipients is similar to that for nontransplant patients. All specific antiviral agents being used for the treatment of COVID-19 are investigational. Use of these agents is generally limited to hospitalized patients who have or are at risk for severe disease. When possible, treatment should be given as part of a clinical trial.

These issues are discussed in more detail separately:

- (See "Coronavirus disease 2019 (COVID-19): Management in hospitalized adults".)
- (See "Coronavirus disease 2019 (COVID-19): Considerations in children".)
- (See "Coronavirus disease 2019 (COVID-19): Critical care and airway management issues".)

Adjusting immunosuppression — Adjustments to the immunosuppressive regimen are necessarily individualized, based upon disease severity, the specific regimen used, type of organ transplanted, time posttransplant, and the risk of acute allograft rejection [12].

Although the optimal approach is not defined, we usually reduce immunosuppression in patients with moderate to severe COVID-19 infection (eg, those requiring hospitalization):

- As a first step, we often reduce or hold the antimetabolite (eg, mycophenolate mofetil/sodium), particularly for patients with lymphopenia (eg, absolute lymphocyte count <700 cells/mL).
- We generally continue the calcineurin inhibitor (CNI) because CNIs inhibit interleukin (IL)-6 and IL-1 pathways, which may contribute to the development of the severe, dysregulated immune response seen in some patients with severe COVID-19.
- We typically avoid use of high-dose glucocorticoids as these agents have been associated with prolonged viral shedding and may predispose to poor outcomes, based on experience with other epidemic coronaviruses. (See "Coronavirus disease 2019 (COVID-19): Management in hospitalized adults", section on 'Limited role of glucocorticoids'.)

However, in all cases the decision to reduce immunosuppression must be carefully weighed against the risk for acute rejection, particularly in transplant recipients who generally require high levels of maintenance immunosuppression (eg, lung or heart recipients). The optimal management of immunosuppressive therapy in solid organ transplant recipients with COVID-19 infection is not known, and data are limited to case reports and series [12,13,16,17].

There are also concerns that COVID-19 infection itself may increase the risk for acute rejection and that an overly intense inflammatory host immune response might contribute to overall disease severity. Thus, attenuating the immune response by maintaining low-dose immunosuppression could theoretically be beneficial. In addition, experimental data suggest that certain immunosuppressive agents such as mTOR inhibitors may have some biological activity against SARS-CoV-2 [15]. Additional studies are required to confirm these findings.

Additional guidance on adjusting immunosuppression in transplant recipients with active infection can be found in the following topic reviews:

- (See "Kidney transplantation in adults: Maintenance immunosuppressive therapy", section on 'Patients who develop an infection'.)
- (See "Maintenance immunosuppression following lung transplantation", section on 'Monitoring and adjusting maintenance therapy'.)
- (See "Coronavirus disease 2019 (COVID-19): Myocardial injury", section on 'Issues for ventricular assist devices and cardiac transplantation'.)

Recommendations from specific medical societies are listed separately. (See 'Society guideline links' below.)

Drug-drug interactions — A number of experimental COVID-19 therapies have potential drug-drug interactions with medications that are commonly used among solid organ transplant recipients. In particular, medications that prolong the QT interval (eg, hydroxychloroquine, azithromycin) should be used with caution since many solid organ transplant recipients are taking a CNI, which may also prolong the QT interval. In addition, care should be taken with protease inhibitors (such as lopinavir and ritonavir), which can reduce the metabolism and significantly increase blood levels of CNIs (table 1).

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Coronavirus disease 2019 (COVID-

19) – International and government guidelines for general care" and "Society guideline links: Coronavirus disease 2019 (COVID-19) – Guidelines for specialty care" and "Society guideline links: Coronavirus disease 2019 (COVID-19) – Resources for patients".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Coronavirus disease 2019 (COVID-19) overview (The Basics)")

SUMMARY AND RECOMMENDATIONS

- COVID-19 poses new challenges for individual solid organ transplant candidates and recipients, as well as the process of organ transplantation. (See 'Introduction' above.)
- There is a theoretical risk of transmitting SARS-CoV-2 (the virus that causes COVID-19) from an organ donor to a recipient based upon the detection of viral RNA in organs that can be transplanted (eg, lung, heart, kidney, intestine), although donor-derived infections have not been reported to date. (See 'Potential for donor-derived infection' above.)
- Because of this risk and the potential for transmitting SARS-CoV-2 to health care providers, all solid organ donor and transplant candidates should be screened for COVID-19 by history, chest imaging, and microbiologic testing. (See 'Pretransplantation screening' above.)
- Posttransplantation, solid organ transplant recipients may be at increased risk for acquisition of COVID-19 because they are immunocompromised and have frequent contact with the health care system, although this association has not been studied. (See 'Posttransplantation risk' above.)

- The clinical manifestations of COVID-19 in solid organ transplant recipients are variable and similar to those observed in nonimmunocompromised patients. However, fever appears to be less common. Whether the disease course is more severe is not known. (See 'Clinical presentation' above and 'Severity of illness' above.)

- The approach to diagnosis is similar to that for the general population. Because signs and symptoms of COVID-19 may be subtle in transplant recipients and disease progression can be rapid, some clinicians have a lower threshold for evaluating and testing transplant recipients. (See 'Diagnosis' above.)

- The approach to management (eg, use of antivirals, supportive care) is also similar to that for the general population, although careful attention should be paid to potential drug-drug interactions and effects on the immunosuppressive regimen. (See 'General considerations' above and 'Drug-drug interactions' above.)

- Adjustments to the immunosuppressive regimen are necessarily individualized, based upon disease severity, the specific regimen used, type of organ transplant, time posttransplant, and the risk of acute allograft rejection. Some organ transplant recipients recover without reduction in immunosuppression, which carries the risk of rejection and immune reconstitution. Conversely, continued immunosuppression may enhance the risk of uncontrolled infection. (See 'Adjusting immunosuppression' above.)

REFERENCES

1. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. JAMA 2020.

2. Tavazzi G, Pellegrini C, Maurelli M, et al. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. Eur J Heart Fail 2020.

3. Bo Diao, Chenhui Wang, Rongshuai Wang, et al. Human Kidney is a Target for Novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection. medRxIv. This article is preprint and has not been peer-reviewed. https://doi.org/10.1101/2020.03.04.20031120.

4. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395:497.

5. Chang L, Yan Y, Wang L. Coronavirus Disease 2019: Coronaviruses and Blood Safety. Transfus Med Rev 2020.

6. Organ retrieval for transplantation in the COVID-19 era. American Society of Transplant Surgeons. https://asts.org/advocacy/covid-19-resources/asts-covid-19-strike-force/asts-covid-19-strike-force-organ-retrieval-guidance#.Xqb1BGhKiUl (Accessed on April 26, 2020).

7. Loupy A, Aubert O, Reese PP, et al. Organ procurement and transplantation during the COVID-19 pandemic. Lancet 2020.

8. Non-emergent, elective medical services, and treatment recommendations. Centers for Medicare & Medicaid Services. https://www.cms.gov/files/document/cms-non-emergent-elective-medical-recommendations.pdf (Accessed on April 26, 2020).

9. American Society for Transplantation. Information for transplant professionals and community members regarding 2019 novel coronavirus. https://www.myast.org/sites/default/files/1COVID19%20FAQ%20Tx%20Centers%2004.15.2020.pdf (Accessed on April 18, 2020).

10. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395:1054.

11. Guillen E, Pineiro GJ, Revuelta I, et al. Case report of COVID-19 in a kidney transplant recipient: Does immunosuppression alter the clinical presentation? Am J Transplant 2020.

12. Pereira MR, Mohan S, Cohen DJ, et al. COVID-19 in Solid Organ Transplant Recipients: Initial Report from the US Epicenter. Am J Transplant 2020.

13. Akalin E, Azzi Y, Bartash R, et al. Covid-19 and Kidney Transplantation. N Engl J Med 2020.

14. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest 2020; 130:2620.

15. Conti P, Ronconi G, Caraffa A, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. J Biol Regul Homeost Agents 2020; 34.

16. Zhong Z, Zhang Q, Xia H, et al. Clinical characteristics and immunosuppressant management of coronavirus disease 2019 in solid organ transplant recipients. Am J Transplant 2020.

17. Banerjee D, Popoola J, Shah S, et al. COVID-19 infection in kidney transplant recipients. Kidney Int 2020.

Topic 127582 Version 6.0