2019-nCoV (Coronavirus): FAQs for Organ Transplantation

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The AST’s Infectious Disease Community of Practice has received queries from transplant colleagues regarding the novel coronavirus (2019-nCoV). The following FAQ was developed to relay information on the current state of knowledge. This document is subject to change as more information becomes available.


Please note, the organ donor resources previously included in this document are now in a separate document.

1. What is the origin of the novel coronavirus?

COVID-19 is the disease caused by the novel coronavirus named Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) that was first recognized in the Hubei province of China in December 2019 subsequently spreading worldwide, being declared a pandemic on March 11, 2020. While the first infections with SARS-CoV-2 likely came from a non-human host it is currently transmitted from person-to-person.

There are 7 coronaviruses known to infect humans. Four seasonal coronavirus strains normally circulate in humans. These are usually mild common cold viruses but on occasion can cause viral pneumonia in immunosuppressed persons and can be identified using multiplex respiratory virus panels. There is no PCR laboratory cross reactivity between the seasonal coronaviruses and SARS-CoV-2. Two previous outbreaks from more virulent coronaviruses have been caused by Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS CoV). There are published case reports of transplant patients acquiring SARS and MERS viruses, in some cases with fatal outcomes (1, 2).

2. How is SARS CoV-2 transmitted?

Infection is acquired from someone who is shedding virus. Person-to-person transmission was recognized early in the pandemic during close exposure (<6 feet) to a person infected with COVID-19, primarily via respiratory droplets produced when the infected person coughs or sneezes. Most frequently, transmission is presumed to be from symptomatic individuals with COVID-19 via droplet spread. However, shedding from asymptomatic and pre-symptomatic
individuals can also transmit infection. In addition, indirect transmission from fomites with infected particles is presumed to occur. While stool has tested positive for SARS-CoV-2 in some cases by nucleic acid testing (NAT), it is not clear whether this is infectious to others. SARS-CoV-2 has been recovered from aerosols and aerosol generating events may also spread the infection. The incubation period is usually between 2-14 days in the general population although longer incubations have been documented.

Healthcare transmissions of COVID-19 have occurred. Given the potential for greater infectivity, strict isolation precautions should be followed for anyone with suspected SARS-CoV2 infection. Studies show that asymptomatic individuals can spread the virus and therefore, on April 3, 2020, CDC recommended that people wear face coverings such as cloth masks when going out in public or in instances where social distancing may be challenging. The public has been encouraged to make MASKS recommended by the CDC; of note all masks should have double layers, not be see through, and not have venting.

All healthcare personnel should wear a facemask at all times while in the healthcare facility. Personal protective equipment should be used by all healthcare workers who enter the room of a patient with known or suspected COVID-19 or as specified by institutional policies. Surgical masks plus eye protection and an isolation gown are recommended. N95 masks or their equivalents should be used for procedures that are more likely to generate respiratory aerosolization (including bronchoscopy, intubation, and nasal swab procurement). In addition to facemask, eye protection (i.e. goggles or disposable face shield that covers the front and sides of the face) can be worn to protect from splashes and sprays of infectious materials from others. Local institutional guidelines should be followed for personal protective equipment (PPE).

3. Are transplant patients at higher risk for COVID-19?

Data on transplant recipients with COVID-19 are still limited but experience is accumulating. Mild infections are common in transplant recipients. However, preliminary experience suggests that infection, once acquired by immunosuppressed transplant recipients, may be of greater severity than in normal hosts after the initial incubation period. Experience with other viruses including prior outbreaks of coronaviruses, also suggests that severe infections will occur in some transplant recipients. The New York City experience revealed high rates of respiratory failure and mortality in transplant recipients but was likely impacted by the sudden and severe surge of infection that hit the city.

At this time, the risk factors for severe disease have been characterized by observational studies. Initial report by Pereira, et al (5) reported advanced age was associated with severe disease in their transplant cohort, which is not different from reports of non-immunocompromised host. Kates, et al (6) reported age > 65, chronic lung disease, congestive heart failure, and obesity were independently associated with poor outcomes of COVID-19 in SOT. It is anticipated that transplant recipients may have a greater viral burden and shedding resulting in greater infectivity and potential spread to other individuals.
case report demonstrated that positive viral cultures confirming active viral replication was documented in a heart transplant by day 21. (7) In another report, positive SARS-CoV-2 PCR was reported positive until day 57 after first positive test in a kidney transplant recipient. (8)

For healthcare centers with a significant burden of individuals with COVID-19, consideration should be given to postponing non-essential transplant clinic or laboratory visits to avoid exposing vulnerable populations.

4. **Are there any specific travel restrictions for transplant patients?**

The CDC has recommended to suspend all non-essential travel and restrictions continue to be in place in multiple locations.

We recommend that transplant patients not travel unless it is essential. Should transplant recipients need to travel, we recommend taking additional essential medicines with them, to ensure they have a sustainable supply in the event of an unexpected quarantine or travel delay. We also suggest that transplant patients’ immediate household contacts not travel unless absolutely essential. Regardless, the household contact should avoid travel to high-risk areas. Given the rapidly evolving epidemiology of COVID-19, all nonessential travel should be carefully evaluated.

The CDC and WHO maintain websites that are being updated as the outbreak evolves, and travel recommendations will likely change over time.

- CDC COVID Data Tracker
- World Health Organization COVID-19 Pandemic website
- Canada Public Health Website COVID-19

5. **Should transplant patients wear a mask or avoid public places?**

The CDC recommends all people wear masks or face coverings when in public. Frequent handwashing or hand sanitizer use helps prevent infection. Transplant patients should exercise caution about being in overcrowded situations and practice social distancing.

Transplant candidates, recipients, and potential living donors should be educated about the importance of performing frequent hand hygiene, avoidance of crowds, and applying social distancing. If SARS-CoV-2 is circulating in the recipient’s area, avoid public places including school, and stay at home as much as possible to reduce risk of exposure SARS-CoV-2.

6. **When should COVID-19 be considered in the differential diagnosis for transplant recipients?**
Transplant patients with symptoms of a flu-like illness may have infection with SARS-CoV-2 as well as other infections. Many symptoms of COVID-19 are typical of respiratory viral infections. Transplant patients should be instructed to call the transplant center or their local physician if they have symptoms including, but not limited to, fever, chills, rigors, cough, dyspnea, myalgias, headache, sore throat, diarrhea, or new loss of sense of taste and/or smell. They should tell the transplant center if they have had close contact with a person known to have COVID-19 infection. They should notify the transplant center or hospital before presenting for care if possible. If patients are instructed to present for medical evaluation at a clinical center, transplant patients should wear a mask during transit and immediately upon entering the building. If the transplant patient has a medical emergency (e.g., shortness of breath, chest pain, or stroke/weakness), they should call 911 and notify the dispatcher if they have been exposed to SARS-CoV-2 or have suggestive symptoms so that appropriate safety precautions can be taken.

There are many different causes for flu-like/respiratory symptoms. Each hospital should have protocols in place for transplant patients with flu-like/respiratory symptoms in the era of COVID-19; these may vary seasonally in your geographic area. Consult your local hospital practices for outpatient COVID-19 screening availability or visitor restrictions for transplant recipients as these will change over time.

COVID-19 also has many atypical clinical manifestations affecting the skin (vesicles, rashes), cardiovascular system (e.g., myocarditis, cardiomyopathy, infarction), central nervous system (stroke and syncope, anosmia, dysgeusia), pulmonary emboli and vascular thrombosis, and renal or hepatic dysfunction.(9) The clinician must consider testing for SARS-CoV-2 infection for individuals with these symptoms who are from areas where this infection is circulating.

Patients suspected of COVID-19 should wear a surgical mask, be placed in isolation and local infection control should be notified. CDC has updated guidelines for infection control. (10)

Specific testing for SARS-CoV-2 must be requested. Testing is done via a nucleic acid test or antigen detection assay (preferred test is RT-PCR on nasopharyngeal, nasal, mid-turbinate or oropharyngeal swab) either as a single test or as part of a panel of tests for respiratory viruses. Antibody testing can be used to look for prior infection only and at this time it is unknown the sensitivity of this test in transplant patients and the durability of antibody. Testing guidelines vary by institution and availability may be limited.

7. Are all transplant patients at greater risk for severe infection due to SARS-CoV-2?

Immunosuppressed transplant patients may be at risk for more severe infection due to SARS-CoV-2. It is important whenever a transplant patient has persistent fever or other symptoms of infection that they contact their transplant center for guidance. Many transplant patients have risk factors for more severe infection including:

- Immunosuppressive medications
- Advanced age (over 60, but increasing with greater age)
- Hypertension
- Heart Disease
- Diabetes
- Obesity
- Cancer therapy
- HIV infection.

8. What is the approach to transplant candidates and recipients coming for routine appointments?

Each transplant program needs to decide their own policy for new transplants and outpatient visits when COVID-19 is circulating in the region.

Elective ambulatory appointments may be moved to virtual visits (e.g., telemedicine) and telephone contacts. Likewise, the urgency for bloodwork at the center, or for nonurgent procedures such as bronchoalveolar lavage and surveillance biopsies should be reviewed. Laboratory testing may be performed at centers outside the hospital or in the home if data can be provided expeditiously to the Transplant Center. Organizational leadership will need to be involved in prioritization plans. Some institutions may require SARS-CoV-2 testing prior to performing procedures on patients in both in and outpatient settings.

9. Should we be transplanting now?

In general, if COVID-19 is circulating in the transplant center community, issues of resource availability need to be balanced against the need for an organ transplant. This should include evaluating availability of intensive care beds, ventilators, blood products, dialysis supplies, and hospital staffing. In addition, local centers with circulating virus need to consider the risk of nosocomial transmission to a new transplant recipient, living donor or to healthcare workers. Temporary suspension of elective living donor transplantation or non-urgent deceased donor transplants may be considered in areas with high rates of COVID-19.

On April 7, CMS released recommendations regarding elective surgeries and non-essential procedures that include transplantation. Transplants fall into Tier 3b, noting that they should not be postponed in “high acuity/unhealthy patients.” As infection rates decline regionally, centers have started to make individual decisions regarding the timing of less urgent transplantation and many centers are now conducting transplantation as per pre-COVID-19 standards to address the needs of patients in need of transplantation, although the virus is still circulating in most communities. Centers will need to continue to explore expansion of deceased donor transplants with organizational leadership as the situation evolves both locally and nationally. Issues impacting this decision should include the level of circulating infection in their areas and/or operational issues (e.g. testing availability, bed space, availability of basic supplies and equipment, including PPE).
10. Should transplant candidates be counseled about potential risks for COVID-19 infection?

At this time, with active circulation of SARS-CoV-2, it is appropriate to counsel all candidates about the risk for acquisition from the community, the hospital environment and theoretically from an organ donor, although definitive proof of donor transmission is still absent. Candidates should be educated about preventive strategies such as social distancing, masking when in proximity to non-household contacts, frequent hand washing, and avoid travel to high-risk areas.

The risk - benefit ratio of transplantation during the COVID-19 pandemic should be reviewed with each patient considering individual risks of progression of underlying disease while on the wait-list and local infection and transmission rates. In general, all deceased and live donors should be tested for COVID-19 based on local testing availability and sensitivity.

11. What is the approach to ill transplant candidates who are actively listed for transplant?

If available, all patients in regions where SARS-CoV-2 is circulating should be tested for virus prior to transplantation, even if asymptomatic. It is not known if patients with active or recent COVID-19 can be safely transplanted. It is anticipated that transplantation of these patients with active viral infection and need for immunosuppression could result in adverse outcomes. The risk of transplantation must always be balanced against the need for life-saving transplantation. Given the absence of definitive treatment or effective vaccination, candidates with active COVID-19 should be deferred from transplantation. Some patients continue to have positive PCR swabs for viral mRNA long after symptom have resolved (over 40 days from diagnosis in some patients). It is not known whether positive tests by PCR indicate shedding of active virus. Blood tests that demonstrate antibodies to SARS-CoV-2 are encouraging, but it is not yet known whether and how long the individual is protected against further infection or whether relapse could occur. There have been reports of reinfection in normal hosts. Also passive antibody from convalescent plasma treatment would lead to false positive result. As more is learned about serologic conversion, antibody testing may aid in the pre-transplant evaluation. Current SARS-CoV-2 diagnostic guidelines of Infectious Diseases Society of America (IDSA) recommended serologic testing in patients with high clinical suspicion for COVID-19 when molecular testing is negative and at least 2 weeks from onset of symptoms.(12)

The ideal disease-free interval is unknown. Based on currently available data it is recommended that a candidate have complete symptom resolution and have a negative SARS-CoV-2 PCR from the upper respiratory tract prior to transplantation. This will also help to protect the hospital environment and the healthcare team. Some transplant physicians recommend two negative PCR tests at least 24 hours apart due to the limited sensitivity (~70%) of each test; the optimal timing of multiple tests is unknown.
12. Are there any effective treatments for COVID-19?

A small number of therapeutic approaches appear to provide benefit for hospitalized patients with symptoms severe enough to require oxygen administration. However, supportive care remains an important component of patient care for both mild and severe disease.

Stable transplant patients with COVID-19 may be managed at home if they have social supports and access to medical care should the infection progress. In this setting, the main treatment is supportive care. Telephone or video visits are an ideal approach for clinical monitoring. Home visits for laboratory testing or use of home oxygen saturation monitoring may be beneficial for outpatient assessment and determination of need for hospitalization.

A. Corticosteroids. In patients requiring hospital admission with severe COVID-19 disease, the primary therapy with proven benefit in terms of mortality is corticosteroid therapy. In the RECOVERY trial, a controlled, open-label study from the UK, the incidence of death was lower in patients receiving dexamethasone (6mg daily for up to 10 days) compared with standard of care therapy in patients receiving mechanical ventilation (29.3% vs 41.4%), and to a lesser degree, in patients receiving oxygen therapy without mechanical ventilation (23.3% vs 26.2%).(13) The positive impact of corticosteroids on mortality in critically ill patients has been confirmed in a WHO metanalysis.(14) Information regarding inclusion or impact in transplant recipients has not been provided. As hyperinflammation does occur in transplant recipients, this therapy is also likely to provide benefit; there is concern, however, for promotion of secondary infections including bacterial and fungal pneumonias in immunocompromised patients.

B. Antiviral therapy. While some trial data are encouraging, available antiviral agents appear to shorten the symptomatic period rather than eradicating viral infection. Physicians are encouraged to follow new or emerging data. Following our experience with antiviral therapy for influenza, start of antiviral therapy early in disease is more likely to effective than administration later in the course of viral infection.

Remdesivir is an investigational antiviral that inhibits viral genome replication and has been studied in a randomized controlled clinical trial for severe and moderate COVID-19 cases. The Adaptive COVID-19 Treatment Trial (ACTT)-1 Study revealed that remdesivir shortens the time to recovery in adults hospitalized with COVID-19 pneumonia (median 11 days vs 15 days), although the mortality rate did not significant differ between groups.(15) The FDA issued an Emergency Use Authorization (EUA) for remdesivir on May 1, 2020 to permit the emergency use of the unapproved product intravenously for treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in adults and children hospitalized with severe disease, defined as those with oxygen saturation (SpO2) ≤ 94% on room air or requiring supplemental oxygen or mechanical ventilation or extracorporeal membrane oxygenation.(16) Dosing is 200 mg IV on day one followed by 100 mg IV daily for a total of five days and liver function tests should be monitored during administration. Remdesivir should not be used in patients with GFR < 30mL/min. There is no transplant specific sub-analysis from this trial; data regarding the relative efficacy in SOT are pending.
C. Convalescent plasma. Data from randomized controlled trials are lacking. There may be a theoretical benefit to the use of convalescent plasma collected from patients who have recovered from COVID-19 infection, which may contribute to neutralization of virus via antibody-mediated effects. A number of uncontrolled case series have been published which have demonstrated that this treatment is generally well-tolerated and may lessen mortality.(17-19) The FDA issued an EUA on August 23, 2020 to permit use of COVID-19 convalescent plasma.(20) The current IDSA recommendation is that this therapy be limited to patients participating in a clinical trial.(21) Thus far, there is no significant evidence of rejection related to the use of convalescent plasma.

D. Other approaches. Prospective trials are underway to examine the risks and benefits of other immunomodulatory therapies for the acute inflammatory state associated with severe COVID-19. As with corticosteroids, concerns exist for use of such therapies when coupled with transplant immunosuppression due to the potential risk for superimposed infection. More data are required before a recommendation can be made. Reactivations of viruses such as hepatitis B virus (HBV), hepatitis C virus (HCV), or herpesviruses (HSV, CMV, VZV) or of latent infections such as tuberculosis or Strongyloides (22) may occur in patients receiving steroids or immunomodulation.

Several agents including interferon-1β, leronlimab, and tocilizumab were evaluated for anti-inflammatory responses; published data on efficacy have been variable. Data on tocilizumab, an IL-6 monoclonal antibody, have been mixed, with randomized-controlled trials not meeting clinical endpoints of improved clinical status and mortality. (23) Similarly, sarilumab, another IL-6 inhibitor, failed to meet clinical trial endpoints. (24) A number of other immune modulators are under investigation including anti-GMCSF antibodies, kinase inhibitors, leronlimab, an CCR5 inhibitor, and interferon therapy. For all of these therapies, few data are available from transplant recipients. Caution is warranted given the potential for increased vulnerability to secondary infections in patients receiving immunosuppression inhibiting the cellular immune response such as calcineurin inhibitors and mycophenolate mofetil. Given previous reports of allograft rejection with interferon therapy, we would recommend careful consideration of potential risks and benefits before enrollment of transplant recipients in interferon-based therapy trials.

At this point in time, given negative data on the use of chloroquine and hydroxychloroquine, we do not recommend the use of these drugs, in accordance with National Institutes of Health (NIH) and IDSA guidelines. (21, 25) The FDA EUA has been removed for chloroquine and hydroxychloroquine and these agents should be used with caution given known side effects. Patients receiving hydroxychloroquine require careful monitoring of QTc interval and for drug interactions.

Drug-drug interactions with immunosuppressant medications need to be evaluated and managed, particularly with the HIV drug lopinavir/ritonavir which leads to marked elevations in the levels of calcineurin inhibitors and mTOR inhibitors due to profound CYP34A-mediated inhibition of their metabolism by ritonavir. We recommend against the use of lopinavir/ritonavir...
for first line therapy given early data that it lacks efficacy and the potential for severe drug-drug
interactions. A useful resource of drug-drug interactions can be found online at COVID-19
Drug Interactions (University of Liverpool).

The suggestion that continued ARB and ACE inhibitor therapy may be detrimental to COVID-
19 outcomes is not yet supported by data; there is no firm recommendation regarding
discontinuation of these medications.

E. Management of immunosuppression. The impact of immunosuppression on COVID-19 is
not currently known but decreasing immunosuppression should be considered for infected
recipients who have not had recent rejection episodes. Many providers have decreased or
discontinued cell cycle inhibitors or reduced calcineurin inhibitor levels, but comparative data
regarding these interventions are not yet available. The decision to reduce
immunosuppression should be based on severity of COVID-19 disease in comparison with
rejection risk. Patients receiving maintenance corticosteroids have generally been maintained
on these during therapy.

13. How do we approach clearance of transplant patients after COVID-19 infection for
removal of enhanced isolation in the hospital and return to outpatient clinics?

Patients with COVID-19 have variable clearance of clinical symptoms as well as in testing for
SARS-CoV-2 from nose, pharynx, lungs and other sites. It is unknown whether the virus
detected by sensitive PCR assays remains infectious and what risk remains of infection for
social contacts and healthcare providers and the community in general. It is also unknown
whether positive antibody testing (serology) is predictive of a protective immune response or of
reduced infectivity, although this may be the case.

Based on other viral infections in immunocompromised individuals, it is expected that viral
shedding in the respiratory tract as detected by nucleic acid testing (NAT) using molecular
amplification (PCR) will be prolonged (>4-6 weeks) in many transplant recipients. Both false
negative and false positive (pre-liver patients) antibody testing may be observed.
Seroconversion may be delayed. Chest radiographs will lag behind resolution of symptoms
and viral shedding.

Patients with prior positive SARS-CoV-2 assays should have resolution of symptoms, including
fever, before enhanced respiratory precautions are removed. The CDC no longer recommends
a test-based strategy to determine when an individual with a SARS-CoV-2 infection is no
longer infectious. The current recommendation for patients with severe to critical illness
or “severely” immunocompromised patients, is to wait up to 20 days after symptom onset to
discontinue Transmission-Based Precautions. This change in recommendation is based on
data that even for patients with severe illness, replication-competent virus was not detectable
>20 days after onset of symptoms.(26)
However, for procedures involving increase in immunosuppression, including transplantation, treatment for rejection, or initiation of chemotherapy, it is still reasonable to await two negative nasopharyngeal swab assays (PCR) at least 24-48 hours apart as a basis for removal of COVID-19 precautions as described under section 11 above. For patients with a clinical diagnosis of COVID-19 without positive tests, it is reasonable to await symptom resolution; further viral testing (sputum, tracheal aspirate, blood, stool) and serology have been utilized in some cases to assist in decision-making.

Further data are required. Public health and hospital guidelines should be followed.

14. Useful links:

Hygiene, physical distancing, masks, isolating, quarantining, what to do if you are sick:

- CDC: How to Protect Yourself/What to Do If you are Sick
- CDC: Printable Handouts for Patients

Treatment COVID-19 Guidelines

- NIH Treatment Guidelines
- IDSA Treatment Guidelines

References


