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 became well established in the human race by person-to-person transmission.

As of the present date (April 12, 2021), multiple SARS-CoV-2 variants are circulating globally. Several variants of concern were reported in the fall of 2020 including B.1.1.7 (UK), B.1.351 (South Africa) and P.1 (Brazil)(1). The variants appear to be more transmissible. However, the impact of these variants on clinical outcomes and effectiveness of the current vaccines and antibody therapies are still under evaluation.

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 via droplet spread from symptomatic individuals with COVID-19. 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, although this is much less common. 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; accordingly, 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 (2).

Healthcare transmissions of COVID-19 have occurred. Given the potential for greater infectivity, strict isolation precautions should be followed for anyone with suspected SARS-CoV-2 infection. Since asymptomatic individuals can spread the virus, CDC recommended on April 3, 2020 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 use masks as recommended by the CDC; of note all masks should have double layers, not be see through, and not have venting (3). Although double masking may further reduce the risk of COVID-19 transmission, current CDC guidance does not specify this practice.

Healthcare personnel should always wear a facemask 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 nasopharyngeal 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 accumulating. Mild infections are common in transplant recipients. However, our initial understanding suggests that infection, once acquired by immunosuppressed transplant recipients, may be of greater severity than in normal hosts. Experience with other viruses including prior outbreaks of coronaviruses, also suggests that severe infections can 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. More recent data suggests similar outcomes in transplant recipients when compared to other higher risk populations; although this may vary based on organ type (4).

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 continue to 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 necessary. 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. 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. They should avoid crowded places and reduce travel as much as possible to reduce risk of exposure to 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, although the prevalence of other respiratory viruses is extremely low in many areas with strict adherence to masking and social distancing. 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 (5). 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 the guidelines for infection control (6).

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?

It is important whenever a transplant patient has persistent fever or other symptoms of infection that they contact their transplant center for guidance. The CDC notes that the following adults of any age with the following conditions are at increased risk of severe COVID-19:

- Immunosuppressed after organ transplant
- Advanced age (over 60, but increasing with greater age)
- Hypertension
- Heart conditions, such as heart failure, coronary artery disease and cardiomyopathy
- Diabetes mellitus 2
- Obesity (BMI > 30)
- Cancer
- HIV infection
- Chronic kidney disease
- COPD
- Down syndrome
- Pregnancy
- Sickle cell disease
- Smoking

At this time, the risk factors for severe disease have been characterized by observational studies. An initial publication by Pereira, *et al* (7) 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* (8) reported age > 65, chronic lung disease, congestive heart failure, and
obesity were independently associated with poor outcomes of COVID-19 in SOT. Further study is needed to better characterize which transplant recipients are at the greatest risk for poor outcomes.

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 community surrounding the transplant center, 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 need to consider the risk of nosocomial transmission of SARS-CoV-2 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.

As infection rates decline regionally, centers have made individual decisions regarding the timing of less urgent transplantation. 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. Centers will need to continue to explore expansion of deceased donor transplants. 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). Given uncertainty surrounding the efficacy of vaccination in transplant recipients or the impact of antibodies to SARS-CoV-2, it is unclear what role these factors should play in transplant decisions.

10. Should transplant candidates be counseled about potential risks for COVID-19 infection if called in for organ transplant?

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 (at least two unexpected transmissions have been proven from lung donors (9, 10)). 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. Transplant professionals should be encouraged to get vaccinated to reduce the risk of nosocomial transmission.

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 waitlist 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?

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, candidates with active COVID-19 should be deferred from transplantation in most cases. Some patients continue to have positive PCR swabs for viral mRNA long after symptoms have resolved (over 60 days from diagnosis in some patients). It is not always clear if a persistently positive PCR test represents shedding of active virus or not. 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.

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%) (11). The positive impact of corticosteroids on mortality in critically ill patients has been confirmed in a WHO meta-analysis (12). 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 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.(13) 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 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. The drug was formally FDA approved October 22, 2020 (14). 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. While not recommended for use in patients with GFR<30 ml/min, emerging evidence suggests that remdesivir may be relatively safe in this group of patients (15). There is no transplant specific sub-analysis from this trial; data regarding the relative efficacy in SOT are pending.

C. Convalescent plasma:

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 (16-18). The FDA issued an EUA on August 23, 2020 to permit use of COVID-19
convalescent plasma (19). There are several randomized controlled trials for convalescent
plasma. A recent systematic review and meta-analysis of published and unpublished
randomized controlled trials showed that there was no significant benefit of convalescent
plasma on clinical outcomes (20). The current IDSA recommendation (21) is that this therapy
be limited to patients participating in a clinical trial. In more recent study that high-titer
antibody in convalescent plasma and early administration in course of illness may reduce
hospitalization in cohort of outpatient older adults; hence, suggesting that there may be a
benefit in using convalescent plasma in patients with mild COVID-19 (22). Based on results
of recent studies, the FDA updated the issued EUA for convalescent plasma limiting the use
of high-titer COVID-19 convalescent plasma for treatment of hospitalized patients early in
the disease course (23). Thus far, there is no significant evidence of rejection related to the
use of convalescent plasma.

D. Monoclonal Antibodies:

With the rise in viral variants, the use of single agent monoclonal antibody, such as
bamlanivimab alone, use is no longer recommended. The BLAZE-1 trial showed that
bamlanivimab-etesevimab, compared with placebo, was associated with a statistically
significant reduction in SARS-CoV-2 viral load at day 11; no significant difference in viral load
reduction was observed for bamlanivimab monotherapy (24). An EUA has been approved
for the combination of bamlanivimab-etesevimab on Feb 9, 2021.

The FDA has also issued an EUA for casirivimab and imdevimab administered together for
the treatment of mild to moderate COVID-19 in ambulatory adults and pediatric patients with
positive results of direct SARS-CoV-2 viral testing and who are at high risk for progressing
to severe COVID-19. This combination was shown to reduce COVID-19-related
hospitalization or emergency room visits in patients at high risk for disease progression within
28 days after treatment when compared to placebo (25). The safety and effectiveness of this
investigational therapy is under study. Casirivimab and imdevimab are not authorized for
patients who are hospitalized due to COVID-19 or require oxygen therapy due to COVID-19,
and may be associated with worse clinical outcomes when administered to hospitalized
patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

In early April 2021, NIH and IDSA guidelines recommended that bamlanivimab/etesevimab
and casirivimab/imdevimab can be used for outpatients within the first 10 days of symptom
onset that are at high-risk of progression.

E. 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* (26) 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 (27). Although one published study has shown modest benefit in terms of a combined endpoint of intubation or death with concomitant dexamethasone administration, and another report in preprint form suggested possible benefit in critically ill patients, it remains unclear whether this treatment provides additional benefit to dexamethasone alone, especially in immunocompromised patients (28, 29). The NIH and IDSA guidelines recommend that tocilizumab could be used in patients with severe COVID that are not responding to dexamethasone or are within 24 hours of ICU admission. Similarly, sarilumab, another IL-6 inhibitor, failed to meet clinical trial endpoints (30).

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.

**The following therapies are not recommended:**
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, 31). 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.

Other therapies suggested for COVID-19 including colchicine (32) and ivermectin (33), have not shown significant clinical impact in adequately powered, randomized-controlled studies, and also are not recommended at this time (21, 31).

**F. Management of immunosuppression.**

The impact of immunosuppression on COVID-19 is not currently known but decreasing immunosuppression may 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 (> 6 weeks) in many transplant recipients. Both false negative and presumably false positive (pre-liver patients) antibody testing may be observed (34). Seroconversion may be delayed. Chest radiographs will lag behind resolution of symptoms and viral shedding.

It is anticipated that transplant recipients may have a greater viral burden and shedding resulting in greater infectivity and potential spread to other individuals. A single case report documented positive viral cultures, confirming active viral replication, in a heart transplant patient by day 21 (35). In another report, positive SARS-CoV-2 PCR was reported positive until day 57 after first positive test in a kidney transplant recipient (36).

Patients with prior positive SARS-CoV-2 PCR 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 CDC currently recommends that for mild or asymptomatic disease, patients must isolate for at least 10 days from date of symptom onset or diagnosis. For severe infection or severe immunocompromise, CDC recommends extending isolation to 20 days. This recommendation is based on data that even for patients with severe illness, replication-competent virus was not detectable >20 days after onset of symptoms (37). However, there have been rare cases of prolonged infective virus (up to 119 days from infection onset) in a patient after CAR-T cell therapy for multiple myeloma (38) and a patient with lymphoma on B-cell directed therapy (39), as well as a report of relapsing and recurring COVID-19 in a patient with anti-phospholipid syndrome on rituximab and eculizumab (40).

For organ transplant recipients with mild/asymptomatic COVID-19, it may be reasonable to follow CDC guidelines. However, some experts recommend adhering to a 20-day isolation with testing of those individuals at higher risk for prolonged infection, including those who have recently received cytolytic therapies or rituximab. Local institutional infection prevention policies should take precedence in removing patients from isolation.
If an elective procedure is required for a patient recovering from COVID-19, it may be advisable to wait until the patient is cleared and pre-procedural testing PCR testing is negative. For urgent procedures, strict infection control guidelines should be followed to minimize the risk of SARS-CoV-2 transmission to procedure teams. Ultimately, further data are required. Public health and local hospital guidelines should be followed.

14. Is a transplant recipient with resolved COVID-19 at risk for reinfection?

Cases of reinfection with COVID-19 have been reported but appear to be rare (41-43). The degree of protective immunity following primary infection or after vaccination in immunosuppressed hosts remains to be determined, especially in view of the viral evolution with increasing strain variants. Hence, transplant recipients should continue to practice COVID-19 precautions (refer to #5).

15. 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

*Vaccines*

- American Society of Transplantation: COVID-19 Vaccine FAQ

*Drug-Drug interactions*

- [https://www.covid19-druginteractions.org](https://www.covid19-druginteractions.org)

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