

**COVID-19:
FAQs for Organ Transplantation**

Updated: January 29, 2022

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.

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. COVID-19 was declared a pandemic on March 11, 2020. While the first infections with SARS-CoV-2 likely came from a non-human host, it quickly became well established in humans by person-to-person transmission.

As of January 19, 2022, multiple [SARS-CoV-2 variants](#) because of viral mutations, have circulated in the United States and globally. Variants of concern include B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.617.2 (Delta), and B.1.1.529 (Omicron) (1). Omicron variant appears to be more transmissible (20-50% increased transmission) and reduce efficacy of vaccines and effectiveness of monoclonal antibodies.

2. How is SARS-CoV-2 transmitted?

There are 3 major ways the virus is spread: (1) inhalation of air carrying very small particles of infectious virus, (2) droplets of virus deposited onto exposed mucous membranes such as with being coughed on, (3) touching mucous membranes with hands that are contaminated with infected respiratory fluids.

Most frequently, transmission is presumed to be via droplet and aerosol spread from symptomatic individuals with COVID-19. However, shedding from asymptomatic or pre-symptomatic individuals can transmit infection. The risk for exposure by breathing in the virus is felt to be highest when a person is within 3-6 feet of an infected individual. The incubation period is between 2-14 days in the general population although longer incubations have been documented (2).

Since asymptomatic individuals can spread the virus, the CDC recommends that unvaccinated people wear well-fitting face masks that cover the nose and mouth when going out in public or in instances where social distancing may be challenging. Single layer cloth masks are not

recommended; double layer cloth masks, disposable surgical masks or KN95 or N95 masks are all acceptable options, assuming they fit snugly without gaps. Given the data showing that vaccinated people can also spread the virus if infected, the CDC has now recommended that vaccinated people also wear masks indoors in public, especially if they are in an area with a high and substantial incidence of infection or if they are at high risk for complications from COVID-19, such as transplant recipients(3). Masks with exhalation valves or vents are not recommended as the hole in the material may allow escape of respiratory droplets (3).

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. Healthcare personnel should all be vaccinated. In addition, regardless of vaccination status they should always wear a face mask 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. N95 or an equivalent mask plus eye protection and an isolation gown are recommended. Local institutional guidelines should be followed for personal protective equipment (PPE).

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

Data on transplant recipients with COVID-19 suggests that although mild infections are common in transplant recipients, many have reported that infection, once acquired by immunosuppressed transplant recipients, may be of greater severity than in normal hosts. 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 (4, 5). Data from other centers suggested similar outcomes in transplant recipients when compared to other higher risk populations when outcome analysis are corrected for comorbidities such as diabetes and hypertension, although this may vary based on organ transplant type (6-8).

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

Risk factors for severe disease in transplant recipients include advanced age and the presence of other co-morbidities noted in the above list. (5) (9)

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

The CDC recommends that travel be delayed unless fully vaccinated. However, vaccinated SOT recipients often do not mount as robust an immune response to vaccine when compared to the general population. We continue to recommend that transplant patients delay travel unless it is essential. This is both to avoid risks of transportation in non-private vehicles as well as risk of exposure in settings where COVID-19 rates might be higher. 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. For household members of SOT recipients, we recommend that they read the most up to date guidance on domestic and international travel during COVID-19 at the CDC website (10, 11)

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 has recently updated the guidance on masks for fully vaccinated individuals (3). Those with **immunocompromising conditions** are advised to continue safety precautions (i.e., mask wearing, frequent hand hygiene, and physical distancing), regardless of vaccinated status. They should avoid crowded places and reduce travel to areas of high SARS-CoV-2 prevalence as much as possible to reduce risk of exposure.

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 decreased dramatically with strict adherence to masking and social distancing, these illnesses are beginning to re-emerge with unmasking and decreased 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 (12). The clinician must consider testing for SARS-CoV-2 infection for individuals with these symptoms especially during periods of increased viral circulation.

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 (13).

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, anterior nasal, mid-turbinate, or oropharyngeal swab) either as a single test or as part of a panel of tests for respiratory viruses. Testing guidelines vary by institution.

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

Each transplant program has their own policy for new transplants and outpatient visits in the context of COVID-19.

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.

Some institutions may require SARS-CoV-2 testing prior to performing procedures on patients in both in and outpatient settings.

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

Currently, it is appropriate to counsel all candidates about the risk for acquisition of COVID-19 from the community, the hospital environment and theoretically from an organ donor. Transplant

candidates should be counseled on and encouraged to use preventive strategies (e.g., masking, physical distancing, frequent hand washing). Transplant candidates, professionals and household members should be vaccinated to reduce the risk of infection and 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. All deceased and living donors are tested for SARS-CoV-2 infection.

9. What is the approach to 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, regardless of vaccination status. 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 be balanced against the need for life-saving transplantation. Given the potential for disease progression with initiation of immunosuppression, candidates with active COVID-19 should be deferred from transplantation, in most cases. Some patients continue to have positive PCR test for viral RNA long after symptoms have resolved (over 60 days from diagnosis in some patients). It is not clear if a persistently positive PCR test represents shedding of active virus or not. Reinfection or breakthrough infection after vaccination can occur in normal and immunosuppressed hosts.

The ideal disease-free interval before transplantation is unknown. The COVIDSurg Collaborative Group did attempt to answer ideal timing of surgery following SARS-CoV-2 infection (14). An international, multicenter, prospective cohort study evaluated the optimal duration of planned delay before any type of surgery in patients who had SARS-CoV-2 infection. Mortality was increased in patients having surgery within 0–2 weeks, 3–4 weeks and 5–6 weeks of the SARS-CoV-2 diagnosis (odds ratio (95%CI) 4.1 (3.3–4.8), 3.9 (2.6–5.1) and 3.6 (2.0–5.2), respectively). Surgery performed ≥ 7 weeks after SARS-CoV-2 diagnosis was associated with similar mortality risk compared to those without previous SARS-CoV-2 infection. Patients with ongoing symptoms ≥ 7 weeks had higher mortality than patients with resolved symptoms or asymptomatic.

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 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. Likewise, the decision to proceed with transplant when disease-free but still with a positive test must be made on an individual basis weighing the likelihood of true active shedding versus death while awaiting another organ offer.

10. Are there any effective treatments for COVID-19?

For hospitalized patients with severe symptoms, a number of therapeutic approaches appear to provide benefit.

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. Monoclonal antibody therapy or outpatient remdesivir can be considered soon after symptom onset. Low risk patients or those without access to medical therapy may be managed with supportive care plus close monitoring only. Recently, two oral antiviral agents have received emergency use authorization for treatment of COVID-19 in individuals with mild to moderate infection who are at high risk of disease progression but may pose challenges pertaining to drug-drug interaction with calcineurin inhibitors as discussed below.

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. Monoclonal Antibodies:

Since December 2021, the B.1.1.529 variant (Omicron) has become the dominant circulating variant in the United States. This variant has numerous mutations within the spike protein which result in reduced susceptibility of this variant to bamlanivimab/etesevimab and casirivimab/imdevimab. Only sotrovimab is anticipated to retain activity against the Omicron variant. The NIH no longer recommends use of bamlanivimab/etesevimab or casirivimab/imdevimab as first line therapy given concern for diminished effectiveness against the currently circulating Omicron variant (15).

Given the current dominance of the Omicron variant, sotrovimab is the preferred monoclonal antibody for treatment of patients with mild to moderate COVID-19 who are at risk for progression to severe COVID-19 (16). Emergency use authorization was based on interim analysis from a double-blind, placebo-controlled trial (COMET-ICE) in which an 85% reduction in hospitalization or death was observed in patients who received sotrovimab compared with placebo (17). This monoclonal in addition is likely to provide protection against emerging viral variants, as it targets a highly conserved epitope in the receptor binding domain of the SARS-CoV-2 spike protein. Sotrovimab is given as a single IV infusion and should be administered within 10 days of symptom onset.

Recently, tixagevimab/cilgavimab (Evusheld™, AZD7442) received an emergency use authorization for the prevention of COVID-19 in adults and children age ≥ 12 years who are immunocompromised or have a medical contraindication to COVID-19 vaccination. This monoclonal antibody has a longer half-life compared to other monoclonal antibodies. The EUA was based on data from the PROVENT trial which showed a 77% reduction in infection risk among patients randomized to receive AZD7442 in comparison to placebo over a 6-month follow-up period. It is important to note that this monoclonal antibody is NOT indicated for treatment of COVID-19. Given anticipated scarcity of this prophylaxis, the [AST has](#)

[suggested an approach for patient risk stratification](#). Because administration of monoclonal antibodies may blunt vaccine responses, it is recommended that COVID-19 vaccine be updated prior to administration of prophylactic monoclonal antibody.

B. 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%) (18). The positive impact of corticosteroids on mortality in critically ill patients has been confirmed in a WHO meta-analysis as well as a meta-analysis of randomized-controlled trials (19, 20). Although specific information regarding inclusion or impact in transplant recipients has not been provided in these trials, this approach has now been used routinely in critically ill transplant recipients with COVID-19 where it appears to provide similar benefit as non-immunocompromised hosts. As hyperinflammation does occur in transplant recipients, the benefit of this therapy is not surprising; there remains concern, however, for promotion of secondary infections including bacterial and fungal pneumonias in immunocompromised patients.

C. 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 be effective than administration later in the course of viral infection.

Remdesivir

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 significantly differ between groups (21). 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) \leq 94% on room air or requiring supplemental oxygen or mechanical ventilation or extracorporeal membrane oxygenation. The drug was formally FDA approved October 22, 2020 (22). The SOLIDARITY multicenter trial of repurposed antiviral agents also failed to show demonstrated impact on mortality in patients receiving remdesivir (23). This study, however, did not include immunocompromised patients, where the impact of antiviral therapy may be more likely to provide benefit in the setting of impaired immune

response. 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 (24). There is no transplant specific sub-analysis from this trial; data regarding the relative efficacy in SOT remain unavailable, although there does not seem to be increased toxicity in the setting of immunosuppressive drug use. In addition, additional case-control studies have demonstrated safety in terms of liver function elevations and acute kidney injury even in patients with impaired renal function (24).

Remdesivir was recently studied in outpatients with mild to moderate COVID-19 at high risk of progressing to severe disease. The PINETREE trial (25) demonstrated that a 3-day course of IV remdesivir administered once daily reduced the risk of hospitalization or death by 87% compared to placebo among patients with mild symptoms for less than 7 days. Based on results of this study, remdesivir can be considered for outpatient treatment, however, because an IV infusion is required, there could be logistical challenges to administering remdesivir in the outpatient setting. As of January 21, 2022, the US FDA expanded the EUA for outpatient mild to moderate COVID-19 for ages ≥ 12 years who weight at least 40 kg (26).

Oral Antivirals

In December 2021 the FDA granted EUAs for two oral antivirals (nirmatrelvir/ritonavir (Paxlovid™, Pfizer) and molnupiravir (Lagevrio™, Merck). The availability of a safe and effective oral antiviral therapy that could be delivered early in infection in the outpatient setting would be extremely valuable for immunosuppressed patients at risk for progression to severe COVID-19 infection, Although the concept of effective oral treatment for COVID-19 is extremely attractive, both drugs have significant drawbacks as described in detail in an [AST guidance document published in January 2022](#). Nirmatrelvir/ritonavir (Paxlovid™) is predicted to have significant drug-drug interactions with calcineurin inhibitors mTOR inhibitors, azole antifungals, and many anticoagulants because ritonavir is a potent inhibitor of CYP3A. Patients not taking any of these medications, such as those with an immunosuppression regimen based on belatacept may be considered for nirmatrelvir/ritonavir therapy. The mechanism of action of molnupiravir is to induce mutations in the virus, and studies of molnupiravir have demonstrated relatively low efficacy, making this drug also not an attractive option for immunocompromised patients.

D. 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), and analysis of data from the RECOVERY trial similarly failed to demonstrate benefit in terms of decrease in mortality (27). The current IDSA recommendation (28) is that this therapy be limited to patients participating in a clinical trial.

High-titer antibody in convalescent plasma and early administration in course of illness may reduce hospitalization in cohort of outpatient older adults; hence, there may be a benefit in using convalescent plasma in patients with mild COVID-19 (29). 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 (30). In addition, a placebo-controlled study of early outpatient use of high-titer convalescent plasma therapy demonstrated a reduced risk of hospitalization (31). How convalescent plasma collected after vaccination or after natural infection with Omicron might impact the course of Omicron infection in transplant patients remains unknown. Thus far, there is no significant evidence of rejection or other safety signal related to the use of convalescent plasma(32, 33), although data remain limited in transplant recipients.

E. Tocilizumab:

Data on tocilizumab, an anti-IL-6 receptor monoclonal antibody, have been mixed, with initial randomized-controlled trials not meeting clinical endpoints of improved clinical status and mortality (34). However, analysis of two large multicenter trials, RECOVERY and REMAP-CAP, as well as additional randomized controlled trials, did demonstrate decreased mortality and lower risk of clinical deterioration when administered early in the hospital course in patients with rapidly progressive disease requiring mechanical ventilation or high flow nasal canula, in combination with dexamethasone (35-37). It remains unclear whether this treatment provides additional benefit, or poses additional risk, when administered to immunocompromised patients, especially in combination with dexamethasone, although case series describing its use do exist (38, 39). The NIH and IDSA guidelines recommend that tocilizumab should be used in patients with severe COVID who have elevated markers of systemic inflammation, in addition to standard of care that are not responding to dexamethasone or are within 72 hours of hospital admission and 24 hours of ICU admission and are requiring ventilation or high flow nasal canula therapy. NIH guidelines recommend that tocilizumab administration be avoided “in patients who are significantly immunosuppressed, particularly in those with recent use of other biologic immunomodulating drugs (40).”

F. Baricitinib

Baricitinib is an immunomodulatory agent that belongs to the Janus kinase inhibitor family. These inhibitors can block signals leading to immune activation and inflammation. Several trials have shown improved outcomes in hospitalized patients with COVID-19. The first, ACTT-2, evaluated baricitinib in combination with remdesivir in hospitalized patients with COVID-19 requiring supplemental oxygen (41). Patients randomized to baricitinib experienced a shorter time to recovery and had increased odds of improvement by day 15, with the greatest improvements seen among the subgroup of patients receiving high-flow oxygen or non-invasive ventilation. A limitation of this study is that corticosteroids were not administered to study participants and thus the effect of baricitinib in addition to corticosteroids was not known. The COV-BARRIER trial enrolled patients with severe COVID-19 (requiring supplemental oxygen but not invasive mechanical ventilation) and randomized them to baricitinib or placebo (42). Most patients were receiving systemic corticosteroids (79%). There was a 38% reduction in 28-day mortality in the group receiving baricitinib with the greatest reduction in mortality seen among individuals requiring high flow nasal cannula. Baricitinib is given as a 4mg daily dose which is reduced to 2mg in individuals

with eGFR between 30 and 59 mL/min. It is not recommended for patients with eGFR <15 mL/min.

G. Other approaches:

Prospective trials have been performed to examine the risks and benefits of other immunomodulatory therapies for the acute inflammatory state associated with severe COVID-19. As with corticosteroids and tocilizumab, 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* (43) may occur in patients receiving steroids or immunomodulation.

Several agents including interferon-1 β , leronlimab, kinase inhibitors, and anti-GMCSF antibodies were evaluated for anti-inflammatory responses; published data on efficacy have been variable. Sarilumab, another IL-6 inhibitor, failed to meet clinical trial endpoints, so there is insufficient data to recommend its use (44).

For all these immune modulating 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.

Finally, NIH guidelines additionally updated guidance on anticoagulation to prevent venous thromboembolism associated with COVID 19 (45). Prophylactic-dose heparin for hospitalized ICU patient (including those receiving high flow oxygen) and therapeutic-dose heparin for those with elevated D-dimer above the upper limit normal and require low flow oxygen were recommended.

H. 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 (28, 40). 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.

Fluvoxamine, a selective serotonin reuptake inhibitor (SSRI), has been shown to reduce inflammatory cytokine production in murine sepsis model (46) and similarly, reduced expression of inflammatory gene of human endothelial cells and macrophages in vitro(47). It also can stimulate the sigma- 1 receptors on surface of endothelium reticulum which may result in reduced SARS-CoV-2 replication. Two randomized controlled studies evaluated

fluvoxamine in treatment of non-hospitalized COVID-19 patients. STOP COVID, a double blind RCT, enrolled non-hospitalized patients with positive SARS-CoV-2 within 7 days of symptoms(48). Clinical deterioration (i.e., dyspnea, O2 sat < 92% on ambient air or hospitalization) in the fluvoxamine arm was 0% compared to 8.3% of placebo arm (absolute difference 8.7%; 95% CI 1.8%-16.4%). Four patients in placebo arm were hospitalized compared to none in fluvoxamine arm. The study has several limitations including the small sample size (n=152) with short follow-up period, and 24% of patients included in analysis stopped responding prior to day 15 of assessment (49). The other study, TOGETHER is a double blind, adaptive RCT which enrolled non-hospitalized patients with SARS-CoV-2 infection within 7 days of symptoms (n=1497) (50). Primary outcome was a composite of either emergency setting observation for >6 hours or hospitalization due to COVID-19 progression within 28 days of randomization. Individuals randomized to fluvoxamine had a lower risk of the primary composite outcome in comparison to the placebo group (11% vs. 16%, RR 0.68; 95% CI 0.52-0.88). Although there was no statistically significant difference in secondary outcomes such as need for hospitalization or time to symptom resolution, a secondary per-protocol analysis found a lower mortality in those receiving fluvoxamine vs. placebo (<1% vs 2%, OR 0.09; 95%CI 0.01-0.47). Despite this data, there are limitations to this study notably the clinical relevance of emergency department observation as an endpoint and biases related to per-protocol analyses of secondary outcomes. As a result, NIH and IDSA guidelines have not recommended routine use of fluvoxamine for treatment of COVID-19 based on strength of evidence (15, 28).

Other therapies suggested for COVID-19 including colchicine (51) and ivermectin (52), HIV protease inhibitor, Interferon beta 1-a, IL-1 inhibitor have not shown significant clinical impact in adequately powered, randomized-controlled studies, and are not recommended at this time (28, 40).

I. 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.

Table 1. Summary of COVID-19 Therapeutics

Therapy	Mild disease, outpatient	Mild disease, hospitalized (no O2)	Moderate disease, hospitalized	Severe disease, hospitalized
Corticosteroids	-	-	+	+++
Tocilizumab	-	-	+/-	+/-
Baricitinib			+/-	+/-
Convalescent plasma	+/-	+/-	-	-
Remdesivir	+	+	+	+
Bamlanivimab/ etesevimab Casirivimab/ imdevimab	-	-	-	-
Sotrovimab	+	+	-	-
Nirmatrelvir/ritonavir (Paxlovid™)	+/- ^a	-	-	-
Molnupiravir (Lagevrio™)	+/- ^b	-	-	-

^a Given concern for drug-drug interactions, would not routinely recommend nirmatrelvir/ritonavir (Paxlovid™) for patients on calcineurin or mTOR inhibitors.

^b Would not recommend molnupiravir (Lagevrio™) for immunocompromised patients given poor efficacy and concern regarding mechanism of action.

See full discussion in the AST guidance document published in January 2022.

Table 2. Variants and Their Impact on IC₅₀ of Monoclonal Antibody Preparations as of December 2021*

Lineage	Key Substitution ¹	WHO nomenclature	Bamlanivimab-Etesevimab Fold Change	Casirivimab-Imdevimab Fold Change	Sotrovimab
B.1.1.17 (UK)	N501Y	Alpha	No Change ²	No Change ⁵	No change ²
B.1.351 (South Africa)	K417N + E484K + N501Y	Beta	431 ³	No Change ⁵	No change ²
P.1 (Brazil)	K417N + E484K + N501Y	Gamma	252 ³	No Change ⁵	No change ²
B.1.617.2/AY.3	L452R+T478K	Delta	No change ²	No Change ⁵	No change ²
AY.1/AY.2 (B.1.617.2 sublineages)	L452R + T478K + K417N	Delta [+K417N]	1,235 ³	No Change ⁵	
B.1.427/429 (California)	L452R	Epsilon	9 ⁴	No Change ⁵	
B.1.156 (NY)	E484K	Iota	30	No Change ⁵	
B.1.617.1/B.1.617.3	L452R+E484Q	Kappa	6 ⁴	No Change ⁵	No change ²
C.37	L452Q+F490S	Lambda	No change ²	No Change ⁵	
B.1.621/B.1.621.1	R346K+E484K+N501Y	Mu	116 ³	No Change ⁵	
B.1.1.529	G339D + S371L + S373P + S375F + K417N + N440K + G446S + S477N + T478K + E484A + Q493R + G493S + Q498R + N501Y + Y505H	Omicron	>2,938 ³	>1013 ³	No change ²

*Package Insert Information

¹Key substitutions occurring in the receptor binding domain of spike protein are listed.

²No change: < 5-fold reduction in susceptibility

³ Unlikely to be active against variants from this lineage

⁴ Etesevimab retains activity against this variant.

⁵ No change: ≤2-fold reduction in susceptibility.

11. 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?

Data suggest that in patients with mild to moderate COVID-19 infection, infectivity decreases within 10 days of symptom onset (53, 54), whereas recovery of viable virus is rare in patients with severe COVID-19 infection who are more than 20 days from symptom onset (55). Importantly, there is no evidence that adults with symptom resolution who have persistence of viral RNA transmit SARS-CoV-2 to their close contacts (56). Because of this, CDC no longer recommends a test-based strategy to determine when an individual with SARS-CoV-2 infection is no longer infectious.

It is unknown how long virus detected by sensitive PCR assays remains infectious in transplant recipients and what risk remains of infection for social contacts, healthcare providers, and the community in general.

In one study, 25% of kidney transplant recipients displayed persistent viral shedding more than 30 days after symptom onset (57). Additionally, PCR positivity has been reported in a heart transplant recipient 35 days after symptom onset, and in a kidney transplant recipient 63 days after symptom onset (58, 59). Viable virus, using cell culture, was identified in four kidney transplant recipients more than 3 weeks from symptom onset (8). Rare cases of prolonged infective virus have also been reported in a patient after CAR-T cell therapy for multiple myeloma (up to 119 days from infection onset) (60), a patient with lymphoma on B-cell directed therapy (61), as well as a patient with anti-phospholipid syndrome on rituximab and eculizumab with relapsing and recurring COVID-19 (62).

Patients *with prior positive SARS-CoV-2 PCR assays* should have resolution of symptoms, including fever, before enhanced respiratory precautions are removed. 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. In patients with severe infection or severe immunocompromise, isolation should be extended up to 20 days for “normal” hosts (63).

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. The test-based strategy requires two negative PCR tests for SARS-CoV-2 from at least 2 consecutive respiratory samples collected more than 24 hours apart. It is unknown whether positive antibody testing (serology) is predictive of a protective immune response or of reduced infectivity, although this may be the case. 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.

12. 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 (64-66). A recent multicenter review reported a rate of reinfection of 0.2% (67). Whether reinfections result from deficient immune responses to the primary infection, are the result of waning immunity, or result from viral escape mutants remains to be determined. Hence, transplant recipients should continue to practice COVID-19 precautions (refer to #5) following natural infection with COVID-19 and after COVID-19 vaccination. It is especially important for close contacts (family, friends, co-workers) of transplant recipients to be vaccinated to avoid exposure to COVID-19.

13. 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](#)
- [AST Statement on Oral Antiviral Therapy for COVID-19 for Organ Transplant Recipients](#)
- [AST Statement on Use of Monoclonal Antibody for Pre-Exposure Prophylaxis](#)

Vaccines

- [American Society of Transplantation: COVID-19 Vaccine FAQ](#)

Drug-Drug interactions

- [COVID-19 Drug Interactions](#)

Donor Testing

- [AST Recommendations and Guidance for Organ Donor Testing](#)

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