

## COVID-19: FAQs for Organ Transplantation

**Updated: February 1, 2023**

*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.

Since the start of the pandemic, multiple [SARS-CoV-2 variants](#) have evolved and circulated in the United States and globally because of viral mutations. SARS-CoV-2 Omicron is the current predominant variant worldwide. While initial lineages of Omicron have waned ( B.1.1.529, BA.1, BA.1.1, BA.3, BA.4) and others are waning (BA.2, BA.4.6, BA.5, BF.7), new Omicron subvariants are on the rise, including XBB.1.5, BQ.1 and BQ.1.1 (1). Some of the newer variants appear to be more transmissible and able to evade natural and vaccine-induced immunity.

### 2. How is SARS-CoV-2 transmitted?

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

Healthcare transmissions of COVID-19 have occurred. Strict isolation precautions should be followed for anyone with suspected SARS-CoV-2 infection in healthcare setting. 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 (PPE) 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 PPE.

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

Data on transplant recipients with COVID-19 suggest that although mild infections are common in transplant recipients, infection 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 initial surge of infection that hit the city (3, 4). Data from other centers suggested similar outcomes in transplant recipients compared to other higher risk populations when outcome analysis is corrected for comorbidities such as diabetes and hypertension, although this may vary based on organ transplant type and virus variant (5-9).

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 certain conditions are at [increased risk of severe COVID-19](#) (10). Risk factors for severe disease in transplant recipients include advanced age and the presence of other comorbidities (4, 11).

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

The CDC recommends that travel be delayed unless fully vaccinated. However, SOT recipients often do not mount as robust an immune response to vaccine when compared to the general population (12, 13). Accordingly, we continue to recommend that transplant patients delay travel to areas of high COVID-19 incidence 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. As a result of court order, effective April 18, 2022, mask requirement on public transportation and at transportation hubs is no longer in effect. CDC continues to recommend mask use in indoor public transportation settings, so a high-quality mask or respirator should be utilized as much as possible (14, 15).

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 (16, 17)

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](#)

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

The CDC has recently updated the guidance on masks for fully vaccinated individuals (18). 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 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 have re-emerged 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 (19). 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 (20).

Specific testing for SARS-CoV-2 must be requested. Testing is done via a nucleic acid test or antigen detection assay on nasopharyngeal, anterior nasal, mid-turbinate, or oropharyngeal swab, or on saliva 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 results 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 and the hospital environment. 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. 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). 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 COVID Surg Collaborative Group did attempt to answer ideal timing of surgery in general, following SARS-CoV-2 infection (21). 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  $\geq 7$  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  $\geq 7$  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 ideally, 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?**

Several therapeutic options are available for the management of COVID-19. Antiviral drugs are most effective when it is given early in the course of the disease. Patients should therefore be tested as soon as possible after symptom onset.

For hospitalized patients with severe symptoms, there are several therapeutic approaches that appear to provide benefit.

Stable transplant patients with COVID-19 may be managed with supportive care at home if they have social support and have access to medical care should the infection progress. In late 2022, two oral antiviral agents received emergency use authorization for treatment of COVID-19 in the outpatient setting for individuals with mild to moderate infection who are at high risk of disease progression and are discussed below. Unfortunately, SARS-CoV-2 variants with reduced to no susceptibility to anti-spike monoclonal antibody therapies have emerged in 2022 resulting in the withdrawal of their authorization for use and limiting options for treatment and prevention of COVID-19.

### **A. Anti-spike Monoclonal Antibodies**

Although anti-spike monoclonal therapy has been available since 2020, were widely used and shown to be successful in treating solid organ transplant recipients with COVID-19, newer variants (in particular BQ.1 and BQ.1.1) were not susceptible to available monoclonals, prompting the US FDA to remove Emergency Use Authorization for bebtelovimab on 11/30/2022. As of 1/2023, there are no anti-spike monoclonal antibody authorized for treatment of COVID-19 in the United States.

Similarly, many of these Omicron subvariants, beginning with BA.4.6, BA.5, BQ.1 and BQ.1.1, were found to be significantly less susceptible to tixagevimab/cilgavimab (Evusheld). Based on this, the US FDA also removed authorization of Evusheld for pre-exposure prophylaxis on 1/26/2023.

## **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%) (22). 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 (23, 24). 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 the experience with antiviral therapy for influenza, starting 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 (25). The FDA issued an Emergency Use Authorization (EUA) for remdesivir on May 1, 2020 and later formally approved on October 22, 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 (SpO<sub>2</sub>)  $\leq$  94% on room air or requiring supplemental oxygen or mechanical ventilation or extracorporeal membrane oxygenation (26). The SOLIDARITY multicenter trial of repurposed antiviral agents also failed to

demonstrate an impact on mortality in patients receiving remdesivir (27). 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. The dosing is 200 mg IV on day one followed by 100 mg IV daily for 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 (28). 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 (28). Use of longer courses of remdesivir in combination with convalescent plasma in immunocompromised patients with prolonged COVID-19 disease have been reported, especially in patients receiving B-cell depleting therapies (29).

Remdesivir was studied in outpatients with mild to moderate COVID-19 at high risk of progressing to severe disease. The PINETREE trial (30) 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  $\geq 12$  years who weight at least 40 kg (31).

### ***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™)*

Nirmatrelvir is a protease inhibitor with activity against the SARS-CoV-2 viral protease. It is co-formulated with ritonavir as Paxlovid™. Ritonavir is used to increase drug levels of nirmatrelvir. Because ritonavir is a strong inhibitor of CYP3A4, it has significant drug-drug interactions and clinicians should review the patient's medications to evaluate for drug interactions. Recently, the NIH COVID-19 Treatment Guidelines were updated to include a section on drug-drug interactions with nirmatrelvir/ritonavir and provide strategies for managing these drug interactions (32). If drug interactions can be safely managed, nirmatrelvir/ritonavir should be considered for treatment of COVID-19 as it remains the only highly effective oral treatment option for individuals with mild to moderate COVID-19.

For solid organ transplant recipients taking calcineurin inhibitors or mTOR inhibitors, doses of these immunosuppressants should be either held or reduced during treatment with nirmatrelvir/ritonavir. Two studies recently evaluated the impact of nirmatrelvir/ritonavir on CNI levels in solid organ transplant recipients. In the first study, tacrolimus drug levels declined very slowly during the 5-day course of nirmatrelvir/ritonavir, despite tacrolimus being held, and became sub-therapeutic several days after completing treatment (33). In the second study, solid organ transplant recipients prescribed nirmatrelvir/ritonavir were instructed to hold tacrolimus while taking nirmatrelvir/ritonavir and resume it within 2-5 days of completing treatment. Four of 21 patients taking tacrolimus experienced a supratherapeutic tacrolimus concentration after resuming tacrolimus following completion of nirmatrelvir/ritonavir (34). Thankfully, only one out of the four individuals experienced an increase in creatinine. These data demonstrate the inherent difficulty in predicting the optimal timing and dose of tacrolimus re-introduction following completion of nirmatrelvir/ritonavir and suggest that resumption of tacrolimus should ideally be guided by drug levels, when feasible.

Nirmatrelvir/ritonavir received emergency use authorization from the U.S. FDA in December 2021 based on data from the EPIC-HR trial which demonstrated that in non-vaccinated, non-hospitalized adults with mild to moderate COVID-19 who were at high risk of progression to severe disease, nirmatrelvir/ritonavir reduced the risk of hospitalization or death through day 28 by almost 90% when compared to placebo, if the medication was started within 5 days of symptom onset (35). Although this trial was conducted prior to the current surge of the Omicron variant, data from animal models suggest that nirmatrelvir/ritonavir should maintain anti-viral activity against Omicron and its subvariants (36). Whether nirmatrelvir/ritonavir maintains the same efficacy in adults with mild to moderate COVID-19 who are at lower risk of disease progression or have received COVID-19 vaccination is not yet known. The EPIC-SR trial enrolled approximately 1150 participants with mild to moderate COVID-19 who are either at standard risk of disease progression or high risk for disease progression but vaccinated against COVID-19, and randomized them to either 5 days of nirmatrelvir/ritonavir or placebo. When an interim analysis failed to find a significant difference in the primary and secondary endpoints, Pfizer ceased to enroll further patients in the study (37). Finally, nirmatrelvir/ritonavir is being evaluated for post-exposure prophylaxis in a phase 2/3 study, EPIC-PEP. Interim data from this study found that nirmatrelvir/ritonavir reduced the risk of confirmed and symptomatic COVID-19 infection by 32% and 37% in adults receiving nirmatrelvir/ritonavir for five and ten days, respectively, but the results did not achieve statistical significance (38).

In patients treated with nirmatrelvir/ritonavir, clinicians should be aware of the potential for symptom relapse and viral rebound following completion of the five-day treatment course (39, 40). The reasons for this viral rebound and symptom relapse are not clear and the clinical implications of this are not known. There are no data demonstrating efficacy of longer courses nirmatrelvir/ritonavir.

### *Molnupiravir*

The mechanism of action of molnupiravir is to induce mutations in the virus. Molnupiravir was studied in a randomized, placebo-controlled trial of more than 1400 non-vaccinated outpatients diagnosed with COVID-19 who were symptomatic for 5 days or less and had at least one risk



factor for severe COVID-19. Patients receiving molnupiravir had a lower risk of hospitalization or death through day 29 than those in the placebo group (6.8% vs. 9.7%; 95% CI, -5.9 to -0.1). The risk of COVID-19 related hospitalization or death was similarly lower in the molnupiravir group (6.3% vs 9.2%: 95% CI -5.7 to 0.0) (41) . A recent retrospective study (42) evaluating outpatient COVID-19 therapies in solid organ transplant recipients found that while rates of overall hospitalization in those receiving molnupiravir were lower compared to those receiving no therapy (16%, 8/49 vs. 27%, 13/48), there was no difference in rates of hospitalization attributable to COVID-19 (14.3%, 7/49 vs. 14.6%, 7/48). It is possible that the outcomes observed in the retrospective study could have been influenced by differences in vaccination coverage between study groups. In the PANORAMIC study, compared to placebo, molnupiravir was not efficacious in preventing COVID-related hospitalizations or death in high-risk vaccinated patients (43). Therefore, the relatively low efficacy of molnupiravir and lack of efficacy in a vaccinated population makes this oral anti-viral a less desirable option for outpatient treatment of COVID-19. In addition, based on the mechanism of action of molnupiravir, there is a theoretical risk for viral evolution in immunocompromised patients. However, due to fewer drug-drug interactions, some transplant centers have used molnupiravir only if remdesivir or nirmatrelvir-ritonavir are not available. Further data are needed to understand the efficacy and role of molnupiravir in the transplant population.

#### **D. Convalescent plasma:**

A 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 (44). The current IDSA recommendation (45) is that this therapy be limited to patients participating in a clinical trial.

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 (46). In addition, a placebo-controlled study of early outpatient use of high-titer convalescent plasma therapy demonstrated a reduced risk of hospitalization (47). 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 (48, 49), 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 (50). 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 (51-53). 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 (54, 55). The NIH and IDSA guidelines recommend that tocilizumab should be used in patients with severe COVID-19 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 (56).”

## **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 (57). 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 (58). 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* (59) may occur in patients receiving steroids or immunomodulation.

Several agents including interferon-1 $\beta$ , 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 (60).

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 (61). Prophylactic-dose heparin for hospitalized ICU patients (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 (44, 56). 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 fluvoxamine (44, 67), colchicine (68) and ivermectin (69), HIV protease inhibitors, 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 (44, 56).

#### **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	+	+	+	+
Nirmatrelvir/ritonavir (Paxlovid™)	+/- <sup>a</sup>	-	-	-
Molnupiravir (Lagevrio™)	+/-	-	-	-

<sup>a</sup> Given concern for drug-drug interactions, nirmatrelvir/ritonavir (Paxlovid™) should not be used together with calcineurin or mTOR inhibitors. **See full discussion in the AST guidance document published in January 2022** on strategies to mitigate this drug-drug interaction, including the temporary discontinuation of calcineurin or mTOR inhibitors during Paxlovid use.

## 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 (70, 71), whereas recovery of viable virus is rare in patients with severe COVID-19 infection who are more than 20 days from symptom onset (72). Importantly, there is no evidence that adults with symptom resolution who have persistence of viral RNA transmit SARS-CoV-2 to their close contacts (73). 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 (74). 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 (75, 76). 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) (77), a patient with lymphoma on B-cell directed therapy (78), as well as a patient with anti-phospholipid syndrome on rituximab and eculizumab with relapsing and recurring COVID-19 (79).

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 (80).

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?**

Reinfection is being increasingly reported with emerging variants (81). 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.

### **1. 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](#)

## **REFERENCES**

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