



# ISHLT

A Society that Includes Basic Science, the Failing Heart, & Advanced Lung Disease

## **Guidance from the International Society of Heart and Lung Transplantation regarding the SARS CoV-2 pandemic**

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An international group of ISHLT members representing Infectious Diseases, Pulmonology, Cardiology, Cardiothoracic Surgery and Pharmacy was appointed by the Executive Board of the ISHLT to discuss frequently asked questions related to the current pandemic caused by SARS-CoV-2 (virus) causing the disease COVID-19. The group meets on a weekly basis to update this document as more data and experience become available. This guidance is pertinent to patients with chronic lung/ heart disease and transplant, mechanical circulatory support, and pulmonary vascular disease.

### **1. Are patients with chronic lung/heart disease and transplant, mechanical circulatory support, and pulmonary vascular disease at increased risk of acquiring SARS-CoV-2 infection?**

At this time, it is unknown if specific patient populations are at higher risk of SARS-CoV-2 infection. Published case series and personal reports thus far do not suggest that transplant recipients in particular have a higher risk of acquiring the virus.(1) Currently, risk factors are assumed to be similar to those for any individual but risk may differ based upon location; local general recommendations apply. Updated map on the [WHO website](#), [Johns Hopkins website](#), or other public health sources may be consulted to assess level of community transmission.

### **2. Are patients with chronic lung/ heart disease and transplant, mechanical circulatory support, and pulmonary vascular disease at greater risk of developing severe disease if infected by SARS-CoV-2?**

In general, severe COVID-19 disease occurs more frequently with increasing age, in men, and in those with comorbidities, particularly cardiovascular disease including hypertension, diabetes mellitus, cancer, renal disease, and chronic respiratory diseases.(2, 3) Severe disease manifestations include bilateral pneumonitis and acute respiratory distress syndrome (ARDS) in the majority of cases and a new onset cardiomyopathy in up to a third of cases.(4) Currently, no evidence has been published to suggest that cardiothoracic transplant recipients (or recipients of any solid organ) are at greater risk of developing severe COVID-19 disease once infected with respect to the general population.

### **3. How can I reduce the risk of infection with SARS-CoV-2 in my patients?**

#### *a. Minimize medical facility visits:*

During this pandemic we recommend that centers minimize medical facility visits by:

- All patients:

- Seeing only essential patients in clinic and reducing clinic volume by deferring outpatient visits for patients that are clinically well.
  - Implementation of telemedicine approaches based on telephone or web contact, as locally available, to assess patients and to screen for symptoms consistent with COVID-19. The remote contact should be noted formally and be part of the patient's medical record.
  - For patients who will be attending appointments in the clinic or hospital, consider pre-visit phone calls or screening questionnaires to ensure patients do not have current symptoms of COVID-19 and to remind them to alert the program before presenting to the medical facility with active symptoms so they may be appropriately triaged.
- Heart and lung transplant patients:
    - We recommend deferring routine surveillance biopsies if clinically feasible in patients with stable allograft function and a low risk of rejection, until local resources and capacity allow. Such patients may include those that are > 3 months from transplant, have no recent history of rejection and those that are not sensitized or with a positive cross match.
    - For patients < 3 months post-transplant or with a history of recent rejection or at high risk for rejection, performing surveillance biopsies should be weighed against the risk of exposure of the patient and health care providers.
    - Surveillance biopsies and bronchoscopies may need to be further curtailed when local supply constraints limit availability of personal protective equipment.
    - Clinically indicated testing should proceed considering factors such as time since transplant, clinical stability, and prior rejection history. Bronchoscopy should not be performed solely as a diagnostic test for COVID-19 due to virus aerosolization and risk of infection transmission to the medical team. If bronchoscopy is absolutely necessary for airway issues in lung transplant recipients, these should be done with appropriate protection for the bronchoscopist as directed by local recommendations and guidance.
    - For lung transplant patients, in order to minimize exposure to the Pulmonary Function Test (PFT) laboratory personnel we recommend using home spirometry for routine monitoring of lung function rather than performing spirometry in the PFT lab. We recommend incorporation of home spirometry data into virtual outpatient visits, reinforcing expected home spirometry schedules, and establishing criteria for patients to notify the transplant team if there is a decline in the forced expiratory volume in 1 second (FEV1) of 10% over several readings.

*b. Minimizing social interactions in the community:*

- For patients with work or other activities that necessitate interactions with many people, we recommend working from home, if possible. For some patients, medical leave or temporary reassignment to non-public facing work in order to minimize possible exposure may be necessary

- Basic precautions for patients and their caregivers include staying at home and reducing contact with other people as much as possible.
- Stringent hand hygiene with soap and water or hand sanitizer should be reinforced.
- Avoid non-essential travel.

*c. Ongoing medical therapies*

- All prior disease-specific therapy or immunosuppression should be continued unless otherwise instructed.
- Immunosuppression: there is currently no evidence to suggest transplant patients are at greater risk of acquiring infection or severe disease thus immunosuppression should be continued unless otherwise indicated to discontinue or reduce doses.
- Angiotensin-converting enzyme inhibitors (ACEI)/Angiotensin receptor blockers (ARBs): There is ongoing controversy regarding a potential role of ACEI/ARB in the rate of SARS-CoV-2 infection as well as potential role in influencing disease severity. In the absence of clinical evidence, patients receiving these drugs as part of heart failure treatment should not be advised to discontinue or modify therapy.

**4. When and how should patients with chronic lung/heart disease and transplant, mechanical circulatory support, or pulmonary vascular disease be tested and monitored for SARS-CoV-2?**

Pending further evidence, the same rules apply to chronic lung/heart disease and transplant, mechanical circulatory support, or pulmonary vascular disease as to other individuals. Of note, recommendations regarding testing for SARS-CoV-2, quarantine, and proactive monitoring for asymptomatic patients may vary based on local policies, healthcare resources, and the phase and severity of the pandemic.

*a. Asymptomatic patient who has been in contact with a confirmed case of COVID-19:*

- For asymptomatic patients we recommend home quarantine for 2 weeks and testing for SARS-CoV-2 by PCR-based test only if symptoms occur (or as per local public health guidelines).
- We recommend vigilance for development of symptoms by using telehealth options and self-monitoring at home (such as daily temperature checks, symptom diary etc).

*b. Asymptomatic patients during this pandemic:*

- We do not recommend routine testing for SARS-CoV-2 via PCR- based tests in asymptomatic patients, including when bronchoscopies are performed.
- For transplant centers continuing to perform surveillance biopsies, we recommend deferring routine viral testing in asymptomatic patients so that the resources in the viral laboratory are not strained unnecessarily.

*c. Testing in Symptomatic Patients:*

- Patients with symptoms of COVID-19 (fever, cough, headaches, myalgia, fatigue, nasal congestion, sudden loss of smell/ taste, diarrhea etc.) should be treated like any other patient considered at increased risk of developing severe disease as per

local guidelines.(1, 3, 5) The possibility of atypical presentations in transplant recipients, especially lack of fever, should be considered.

- Samples for testing should be taken as per local guidelines, usually nasopharyngeal and/or oropharyngeal swabs for PCR-based testing. Of note, tests may be negative even in individuals who later prove to be infected.(6) In this situation, computed tomography (CT) findings may assist in diagnosis, and repeat viral testing may be considered on an individual basis.(7, 8) Additionally, although the sensitivity of lower respiratory tract samples is higher than other sources, bronchoscopies carry a greater risk of aerosol spread of the virus, and thus diagnostic bronchoscopies are discouraged.(9)

d. *Testing on Waitlisted Patient at Time of Organ Offer:*

- In addition to routine pre-transplant checks, the patient should report no new onset clinical syndrome compatible with COVID-19, no close contact with a confirmed case of COVID-19 within 14 days, and no previous travel to risk areas within 14 days in order to proceed with transplantation. Additionally, if local testing strategy and rapid turn-around of PCR-based testing allow, we recommend testing for SARS-CoV-2 by nasopharyngeal/ oropharyngeal swab or sputum/ tracheal aspirate prior to transplant.(9) In the absence of evidence-based effective treatment, patients with positive tests for SARS-CoV-2 should not undergo transplantation.

**4. How do I approach management of a patient with chronic lung/heart disease and transplant, mechanical circulatory support or pulmonary vascular disease with confirmed COVID-19?**

Although formal definitions have been proposed for stratification, no consensus exists to date.(5) For the purpose of this document, patients with COVID-19 will be stratified into mild, moderate, and severe disease based on clinical triage as follows:

Mild	Mild symptoms, no shortness of breath or hypoxia
Moderate	Shortness of breath or hypoxia requiring supplemental oxygen via nasal cannula
Severe	Respiratory failure requiring intensive care unit admission. Need for ventilatory support, acute respiratory distress syndrome, circulatory collapse, acute kidney failure, cardiomyopathy, and/ or clinical syndrome compatible with cytokine storm

- Based on current literature, we recommend that patients should be assessed for treatment based on disease severity. Vigilance is important in all patients, especially if concern for increasing disease severity, usually noted 7-10 days into symptom onset. It is unclear if rejection rates will be affected by the viral infection.
- General recommendations based on disease severity:

- For mild disease, we recommend quarantine at home for 2 weeks with frequent follow-up via telehealth modalities to assess for worsening symptoms. There is currently no data to suggest a change in immunosuppression and we recommend continuing baseline maintenance immunosuppression.
- For moderate and severe disease, we recommend admission for supportive care. For COVID-specific therapies, see recommendations below.
- As with all patients, we recommend caution when using non-invasive positive pressure ventilation and high-flow nasal cannulae because of the risk of viral spread via aerosolization, and early intubation should be considered depending upon local practices. Lung protective ventilation strategies are considered advantageous. Additionally, prone positioning during both mechanical ventilation and otherwise has been described to improve oxygenation.
- Centers may develop local guidelines on criteria for proceeding with extracorporeal membrane oxygenation (ECMO) use in carefully selected patients based on availability of ECMO and availability of critical care resources.
- Concomitant antibacterial or antifungal treatment can be considered for transplant recipients as per local center policy though rates of bacterial/fungal co- or superinfection are not well defined at this time.
- For transplant recipients, consider holding mycophenolate mofetil or azathioprine while admitted with moderate/ severe illness (with close monitoring for rejection).
- Ventricular assist device (VAD) recipients may safely be placed in a prone position if needed with special attention paid to the driveline to avoid tugging and skin trauma. Driveline exit site dressings may be changed when not prone.
- Specific pulmonary hypertension vasodilators should not be changed/stopped or titrated without prior consultation with a specialist. During active SARS-CoV-2 infection, consider avoiding inhaled epoprostenol due to risk of virus aerosolization.

• COVID-19 directed therapies

We strongly encourage investigators to include patients with chronic lung/heart disease and transplant, mechanical circulatory support and pulmonary vascular disease in clinical trials directed at COVID-19 so that data are available to guide future treatment recommendations. A variety of agents are under investigation; a curated and up to date external resource by the American Society of Hospital Pharmacists listing drug dosage and summary of evidence is available at the following website: [ASHP COVID-19 drug resources](#).

At this time there is no evidence to guide decisions regarding the use of COVID-19 treatment strategies in patients with thoracic transplant, VADs, or pulmonary vascular

disease. Extrapolation of the limited published data to these populations should be done with caution, ideally in a clinical trial setting, based on drug availability, disease severity, pertinent drug-drug interactions, and toxicity. An actively curated external resource addressing drug-drug interactions with emphasis on immunosuppressive medications can be found at [COVID-19 drug interactions](#). Current COVID-19 directed therapies under investigation include:

- **Remdesivir** – antiviral agent with *in vitro* activity against SARS-CoV-2 and currently in multiple clinical trials. Of note, compassionate single use is no longer available in most countries (except for pregnant women and infants), although limited expanded access availability through the manufacturer available. The risk of significant drug interactions with immunosuppressives from the data available is low.
- **Interleukin-6 (IL-6) inhibitors** – IL-6, secreted by monocytes and macrophages, is considered to be a driver of the immunologic response to SARS-COV-2 in patients with severe disease and cytokine-release syndrome. There are two main agents in clinical trials currently assessing efficacy in COVID-19 - tocilizumab and sarilumab. Non-comparative data suggest efficacy and the drugs may be used off-label where available; however, we recommend treatment under the auspices of a clinical trial. (7) There are limited data regarding drug interactions at this time.
- **Combination antivirals** with activity against human immunodeficiency virus (HIV) are under investigation as potential therapeutic option for COVID-19. However, in thoracic transplant recipients, we DO NOT recommend lopinavir/ritonavir, darunavir/ritonavir and darunavir/cobicistat due to lack of evidence of efficacy in a recent randomized clinical trial and significant drug-drug interactions with immunosuppressive medications.(8)
- **Antimalarials** – Chloroquine and hydroxychloroquine are under investigation for COVID-19 based on *in vitro* antiviral activity as well as anecdotal clinical data. Given lack of evidence demonstrating efficacy and known toxicity potential (including prolonging the QTc interval and attendant risk of arrhythmias) we recommend against empiric therapy in a non-clinical trial setting, especially in combination with other drugs that may increase the QTc interval such as macrolides (azithromycin, clarithromycin). If pursued, such therapy should be accompanied by daily ECG monitoring to follow the QTc interval. The risk of significant drug interactions with immunosuppressives from the data available is low.
- **Prophylaxis**: Due to lack of evidence in addition to potential toxicity and drug interactions, we do not recommend prophylactic therapies (chloroquine, hydroxychloroquine) outside of a clinical trial setting at this time.

Information on COVID-19 related clinical trials can be found at the World Health Organization International Clinical Trials Registry Platform at <http://apps.who.int/trialsearch/default.aspx> and at <http://clinicaltrials.gov>.

## 5. Can my patient with chronic lung/heart disease be transplanted or undergo VAD placement during the current pandemic?

Decisions regarding transplantation or mechanical support should be made on a local center level based on rate of SARS-CoV-2 infection in the community and availability of health care resources, unless otherwise directed by regional or national authorities. This decision should be continually reassessed as conditions evolve and the center should consider the potential benefits and risks for the patient. The risk of receiving a transplant during the pandemic with ongoing community exposure, the risk of mortality if not transplanted, and the adequate and fair allocation of resources (particularly related to intensive care) should be considered. We do not recommend a general cessation of all transplant or VAD activity due to the COVID-19 pandemic solely to liberate resources for treating COVID-19 patients, as it is not certain that weighing of benefit and equity merits cessation of transplant/VAD in all programs though temporary cessation in the setting of an overwhelmed local healthcare system may be unavoidable.(10, 11)

- Heart/ Lung Transplant
  - While actively infected with SARS-CoV-2, we recommend foregoing transplantation and making the patient inactive on the waitlist.
  - For patients with end stage heart or lung disease who contract COVID-19 while waitlisted and recover from illness, we recommend waiting at least 14 days after initial diagnosis AND two successive negative PCR-based tests at least 48 hours apart PRIOR to transplantation if possible as viral shedding has been demonstrated to occur following resolution of clinical symptoms.(12) This timeframe is based on the higher acuity of heart and lung waitlisted patients and lesser opportunities for organ availability.
  - Lung transplant specifically for COVID-19 related lung disease should be considered with grave caution in carefully selected cases following two negative PCR based tests as noted above, and after a sufficient observation period for natural recovery of lung function as is often seen after other viral causes of ARDS. Recent data indicate that myocarditis may occur at this stage, and thorough cardiac evaluation is warranted.(4)
  - Induction therapy: current experience does not suggest a change in induction protocols with ongoing use of lymphocyte depleting agents if indicated, but it should be noted that COVID-19 is frequently associated with lymphopenia.
  - When considering appropriate resource allocation in such settings, the expected need for prolonged postoperative care after a transplant in such patients should be weighed against the opportunity of liberating ICU capacity by performing the transplant.
- Mechanical circulatory support:
  - Based on COVID-19 disease prevalence and resource availability at the local center, consider limiting VAD implantation to INTERMACS status 1-3 patients. For VAD patients who are otherwise stable and using their 30 days of prioritization (as allowed in the US), centers should consider deprioritizing until the pandemic abates.

## **6. How does the COVID-19 pandemic affect deceased donor selection?**

Asymptomatic or pre-symptomatic viral shedding is well described with SARS-CoV-2 infection.(13, 14) Transmission of SARS-CoV-2 from donor to recipient has not yet been reported but is conceivable. The risk of viral transmission must be balanced against the risk to the recipient associated with not using the organ and losing an opportunity for transplant.

- Donors with a history suggestive of increased probability of SARS-CoV-2 infection without any availability of SARS-Cov-2 testing should be avoided.
  - This includes travel to or residing in an area in the preceding 14 days where local SARS-CoV-2 transmission is occurring.
  - Exposure to a confirmed or probable case of COVID-19 within past 14 days as patients may be in an incubation phase.
  - Compatible clinical syndrome regardless of known exposure within the past 14 days
- Keeping in mind the unknown false negative rate, we recommend that all donors should be tested for SARS-CoV-2 infection where testing is available. If available, we recommend PCR-based donor testing for SARS-CoV-2. Sampling may be done via nasopharyngeal swabs, deep tracheal aspiration (as a substitute for sputum), or bronchoalveolar lavage; latter two are reported to have higher viral loads and thus higher sensitivity of test results, however should only be performed if it is safe to do so within a closed ventilatory circuit with adequate personal protective equipment available.(9) We recommend avoiding transplantation from PCR+ donors.
- A thoracic CT scan may show signs of SARS-CoV-2 infection even before development of symptoms or positive PCR and hence may be useful in donor assessment, again this is based on availability of adequate personal protective equipment and other resources. If CT imaging is suggestive of a viral pneumonitis, we recommend declining the donor offer.
- Regardless of donor screening, the center should have a discussion of risk-benefit with the recipient regarding transplantation during the ongoing pandemic.

## **7. How do we get more knowledge regarding SARS-CoV-2 infection in patients with cardiothoracic transplant, pulmonary hypertension and VAD?**

We request that all centers performing cardiothoracic transplantation and VADs collect key data of the course of disease in recipients who develop COVID-19, as per local regulatory guidelines.

These data should at a minimum include:

- gender and age
- transplant date
- date of proven COVID-19 infection
- date of hospital admission
- date of organ replacement therapy or ventilatory support
- specific treatment (if any)
- change to immunosuppression (if any)
- occurrence, treatment and outcome of acute and chronic rejections
- outcome.

Clinical, laboratory and radiological findings would also be helpful.



The collaborative effect of collecting such data could at a later time allow our community to compile evidence beyond the anecdotal, to the benefit of future patients.

Specifically, the group identifies the following research questions that should be prioritized:

1. Presentation and symptoms in thoracic transplant and VAD recipients infected with SARS-CoV-2 compared to appropriate controls.
2. Disease progression and prognosis in thoracic transplant and VAD recipients infected with SARS-CoV-2 compared to compared to appropriate controls.
3. Effects of adjustment of immunosuppressive medication and risk of acute rejection and graft dysfunction in SARS-Cov-2 infected thoracic transplant recipients.
4. Effects of experimental antiviral and anti-inflammatory medication on survival and risk of acute rejection and graft dysfunction in SARS-Cov-2 infected thoracic transplant and VAD recipients.
5. Risk of severe or lethal COVID-19 in patients with VAD or pulmonary vascular disease compared to recently transplanted patients to determine whether this particular group of patients should have higher priority for transplant in the current situation.
6. Assessment of acquisition of specific protective immunity by thoracic transplant and VAD recipients.

Additional guidance is also available from the following resources:

- WHO SARS-CoV-2 dashboard  
<https://experience.arcgis.com/experience/685d0ace521648f8a5beeeee1b9125cd>
- CDC:<https://www.cdc.gov/coronavirus/2019-ncov/index.html>
- ECDC <https://www.ecdc.europa.eu/en/covid-19/all-reports-covid-19>

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### **References:**

1. Ren Z-L HR, Weng Z-W, et al. : Epidemiological and Clinical Characteristics of Heart Transplant Recipients During the 2019 Coronavirus Outbreak In Wuhan, China: A Descriptive Survey Report. doi:10.1016/j.healun.2020.03.008 Journal of Heart and Lung Transplantation 2020.
2. Liang W, Guan W, Chen R, et al.: Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020;21:335-7.
3. Guan WJ, Ni ZY, Hu Y, et al.: Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020.
4. Arentz M, Yim E, Klaff L, et al.: Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. *JAMA* 2020.
5. Giacomelli A, Pezzati L, Conti F, et al.: Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. *Clin Infect Dis* 2020.
6. Wang W, Xu Y, Gao R, et al.: Detection of SARS-CoV-2 in Different Types of Clinical Specimens. *JAMA* 2020.
7. Zhou Z, Guo D, Li C, et al.: Coronavirus disease 2019: initial chest CT findings. *Eur Radiol* 2020.
8. Ai T, Yang Z, Hou H, et al.: Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. *Radiology* 2020:200642.
9. Yu F, Yan L, Wang N, et al.: Quantitative Detection and Viral Load Analysis of SARS-CoV-2 in Infected Patients. *Clin Infect Dis* 2020.
10. Emanuel EJ, Persad G, Upshur R, et al.: Fair Allocation of Scarce Medical Resources in the Time of Covid-19. *N Engl J Med* 2020.
11. Kumar D, Manuel O, Natori Y, et al.: COVID-19: A Global Transplant Perspective on Successfully Navigating a Pandemic. *Am J Transplant* 2020.
12. Wolfel R, Corman VM, Guggemos W, et al.: Virological assessment of hospitalized patients with COVID-2019. *Nature* 2020.
13. Kimball A, Hatfield KM, Arons M, et al.: Asymptomatic and Presymptomatic SARS-CoV-2 Infections in Residents of a Long-Term Care Skilled Nursing Facility - King County, Washington, March 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:377-81.
14. Qian G, Yang N, Ma AHY, et al.: A COVID-19 Transmission within a family cluster by presymptomatic infectors in China. *Clin Infect Dis* 2020.