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

REVISED: July 10, 2020

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 coronavirus disease 2019 (COVID-19). The group meets frequently 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.

NEW INFORMATION IN THIS REVISION:
- physical distancing and masking recommendation
- updated PCR and serological testing
- updated donor and recipient selection for cardiothoracic transplant
- updated recommendations for the safety of healthcare workers
- updated therapeutics
- updated section on research priorities

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1. Risk factors and severity of COVID-19

Published data thus far do not suggest that patients with transplant, ventricular assist device (VAD), or pulmonary vascular disease (PVD) have a higher risk of acquiring the virus. (1) Currently, risk factors are assumed to be similar to those for other individuals but risk may differ based upon location thus local general recommendations should be considered. An updated map regarding disease prevalence can be seen on the WHO website, Johns Hopkins website; or other local public health sources may be consulted to assess the level of community transmission.

In general, severe COVID-19 disease occurs more frequently with increasing age, in men, and in those with comorbidities, particularly cardiovascular disease including heart failure, hypertension, diabetes mellitus, cancer, renal disease, and chronic respiratory diseases. (2-4) Several recent studies indicate that transplant recipients are at increased risk of severe diseases and increased mortality. (5-8)

2. Reducing risk of infection with SARS-CoV-2

Measures to reduce the risk of infection need to be proportional to the prevalence of active SARS-CoV-2 infection in the population. While the following precautions are advisable during the active and overwhelmed pandemic phases, they may be cautiously re-modulated during the recovery or new normal phase. (9) Nevertheless, we advise that specific procedures and in-hospital pathways should be implemented and always active during all the pandemic phases, for patients with heart/lung transplant or end organ diseases.

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’ clinical stability 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, to rule out contacts, 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 recipients:
  - 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 to the patient and health care personnel. Local resources and capacity should also be considered.

• 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, 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. Lab PFTs, if available, may be preferable to validate home spirometry changes or establish a baseline in early post-transplant patients.

• Pulmonary vascular disease

• We recommend deferring routine right heart catheterizations and imaging if clinically feasible in patients with stable disease and a low risk of progression, until local resources and capacity allow.

• Clinically indicated testing should proceed considering factors such as time since diagnosis, risk score severity, clinical stability, and recent history of right heart failure hospitalization

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.

• Physical distancing of > 1m, routine face mask use, and eye protection independently reduce the risk of developing viral respiratory infections. (10) We recommend mask use when physical distancing is not feasible, such as attending indoor areas, public transportation, and crowded outdoor spaces for all patients to reduce the risk of developing COVID-19.
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, thus immunosuppression should be continued unless otherwise indicated to discontinue or reduce doses.
- **Angiotensin-converting enzyme inhibitors (ACEI)/Angiotensin receptor blockers (ARBs)**: Current data demonstrate lack of an association between use of ACE-I or ARB with severe disease or mortality in patients diagnosed with COVID-19. At this time, patients receiving these drugs as part of heart failure treatment/ hypertension should continue their therapy. (11)
- **Pulmonary Hypertension (PH) therapy**: There is some evidence that PH therapies, like endothelin antagonists, nitric oxide and prostacyclins may be beneficial in COVID-19 patients. However, in the absence of clinical evidence or progression in their primary disease, patients should not be advised to add or modify existing therapy.

3. SARS-CoV-2 testing

Pending further evidence, the same considerations apply to patients with 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 unless local or national public health guidelines recommend testing of asymptomatic individuals for contact tracing.
   - We recommend vigilant monitoring for the development of symptoms by using telehealth options and self-monitoring at home (such as daily temperature checks and/or symptom diary).

b. **Asymptomatic patients without known contact to a confirmed case of COVID-19**:
   - We recommend testing for SARS-CoV-2 via PCR-based tests in all patients undergoing invasive procedures and prior to proceeding with transplantation.

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, 12) The possibility of atypical presentations in transplant recipients, especially lack of fever, should be considered.(5, 6)
• 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. (13) Once positive, PCR-based testing can remain positive for several weeks after resolution of symptoms.
• In the case of negative swab but high clinical suspicion of COVID-19, computed tomography (CT) findings may assist in the diagnosis and repeat viral testing may be considered on an individual basis. (14, 15) 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. (16)

d. SARS-CoV-2 serology:
SARS-CoV-2 specific serology can detect patients with recent or previous infection and may be of special importance for epidemiological studies as seroconversion occurs in most patients 2-3 weeks after symptom onset, including in some transplant recipients. (17) Its use can be more challenging in the acute phase: preliminary data indicate IgM seroconversion can be seen as early as 4 days after symptom onset, thus repeat serological testing may be also informative in the acute setting, especially in patients who continue to follow a COVID-19-like disease course despite negative PCR results. (18, 19) Currently, serology is not suggested as the primary diagnostic test for acute SARS-CoV-2 infection. It is unclear currently if presence of SARs-CoV-2 specific antibodies are indicative of a protective or anamnestic immune response.

4. Management of a patient with chronic lung/heart disease and transplant, mechanical circulatory support or pulmonary vascular disease with confirmed COVID-19
Based on current literature, we recommend that patients 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 or degree of pulmonary hypertension and/or right heart failure will be affected by the viral infection.

General recommendations:
• 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.

• 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. However, early intubation is no long preferred due to high mortality and non-invasive ventilation is preferred as is feasible per 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.

• For transplant recipients, consider holding mycophenolate mofetil, mTOR inhibitors or azathioprine while admitted with moderate/severe illness though specific data are lacking at this time.

• 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 prostacyclins due to risk of virus aerosolization.

**COVID-19 directed therapies**

There are multiple ongoing clinical trials evaluating a variety of agents for treatment or prophylaxis of COVID-19. We strongly encourage investigators to facilitate inclusion of 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. Guidance regarding treatment and diagnostics in the general population overall is updated regularly by the Infectious Diseases Society of America; additional external resource by the American Society of Hospital Pharmacists listing drug dosage and summary of evidence is available at: ASHP COVID-19 drug resources.

At this time there is no evidence to guide decisions regarding the use of COVID-19 treatment strategies specifically in patients with thoracic transplant, VADs, or pulmonary vascular disease though careful extrapolation from published data may be done with caution. Treatment of this population requires careful consideration of the following: drug availability, disease severity, patient co-morbidities, pertinent drug-drug interactions, and expected toxicities of the agents particularly QTc prolongation or potential antibody stimulation.

Drug interactions with transplant, pulmonary hypertension and cardiac medications are likely to be the most important consideration prior to initiating COVID-19 directed therapies. An actively curated external resource addressing drug-drug interactions can be found at COVID-19 drug interactions. This website collaboration has comprehensive tables of drug interactions between experimental COVID-19 treatments and transplant immunosuppressants, pulmonary hypertension and other advanced lung disease medications, antimicrobials (including anti-fungals) and other groups of medications commonly used in patients with transplant and advanced lung and heart disease. QTc prolongation is another important consideration prior to initiating COVID-19 directed therapies in patients with end stage heart and lung disease, post-transplant, VAD and PH. An actively curated external resource addressing risks of QTc
prolongation with medications is available at [https://www.crediblemeds.org](https://www.crediblemeds.org). Table 1 lists common pertinent COVID-19 proven/ investigational therapies with a focus on safety issues.

Table 1. Common COVID-19 directed proven/ investigational therapies with focus on pharmacodynamic and drug interaction considerations for thoracic transplant/PH/VAD patients.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Considerations</th>
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<tbody>
<tr>
<td>Dexamethasone</td>
<td>Low potential for clinically significant interactions with immunosuppression, pulmonary vasodilators or anticoagulants;</td>
</tr>
<tr>
<td>Remdesivir</td>
<td>Low potential for clinically significant interactions with immunosuppression, pulmonary vasodilators or anticoagulants; however, potential risk of lower tacrolimus, cyclosporine and sirolimus levels.</td>
</tr>
<tr>
<td>IL-6 inhibitors</td>
<td>Low potential for clinically significant interactions with immunosuppression, pulmonary vasodilators or anticoagulants; however, potential risk of lower tacrolimus, cyclosporine and sirolimus levels.</td>
</tr>
<tr>
<td>*Combination HIV-related antivirals</td>
<td>Lopinavir/ritonavir, darunavir/ritonavir and darunavir/cobicistat should not be used in the thoracic transplant/PH patients due to significant drug-drug interactions with immunsuppressives and pulmonary vasodilators as well as their potential to act synergistically with other baseline medications to prolong the QTc interval. (8)</td>
</tr>
<tr>
<td>**Hydroxychloroquine, chloroquine</td>
<td>Demonstrated to carry a risk of QTc prolongation which is likely to add synergistically to baseline medications, such as macrolides. (20-22) If pursued, such therapy should be accompanied by daily ECG monitoring to follow the QTc interval. The risk of significant drug interactions with immunsuppressives, PH therapies, and anticoagulation is low, however there is a potential risk of elevated cyclosporine levels in conjunction with hydroxychloroquine. (23) One further potential risk that is not well described is that “loading doses” in patients with chronic kidney disease may carry the risk of accumulation and CNS excitation/seizures as well as suppression of bone marrow. (24)</td>
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*Randomized controlled trials do not show benefit in the treatment of COVID-19. (20, 21) We do not recommend these agents due to lack of benefit and known significant drug interactions. **Current data do not show clinical benefit in the setting of post-exposure prophylaxis and treatment, both in moderate disease in outpatients and severe disease in inpatients. (22-24) We do not recommend use of these agents due to lack of benefit and potential for adverse drug events especially related to QTc prolongation.

5. **Ongoing transplantation and VAD implantation during the COVID-19 pandemic**

Decisions regarding transplantation or mechanical support should be made on a local center level based on the 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. The center should consider the potential benefits and risks for the patient, including their capacity to provide the necessary post-operative and outpatient care to allow for a successful transplant outcome. 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. Weighing benefit and equity does not always require cessation of transplant/VAD in all programs, although temporary cessation in the setting of an overwhelmed local healthcare system may be unavoidable. (25-27)

- **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; prolonged shedding up to 5 weeks in a minority of patients has been described. (28, 29) 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 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.
  - 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. Deceased donor and recipient selection during the COVID-19 pandemic

Asymptomatic or pre-symptomatic viral shedding is well described with SARS-CoV-2 infection. (30, 31) Transmission of SARS-CoV-2 from donor to recipient has not yet been reported but is conceivable. (32) 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. Additionally, a waitlisted patient may be asymptotically infected at time of organ offer. (33, 34)

- If local testing strategy and rapid turn-around of PCR-based testing allow, we recommend testing for SARS-CoV-2 by nasopharyngeal/ oropharyngeal swab, sputum/ tracheal aspirate, or bronchoalveolar lavage less than 72 hours before organ donation; latter two are reported to have higher viral loads and thus higher sensitivity of test results. (16) BAL should only be performed if it is safe to do so within a closed ventilatory circuit with adequate personal protective equipment available. We also recommend PCR+ based tested in the asymptomatic waitlisted candidate prior to transplant surgery if there is high local SARS-CoV-2 transmission and a test with rapid turnaround is available. In the absence of evidence-based effective treatment, we recommend avoiding transplantation from PCR+ donors and deferring transplant on PCR+ waitlisted candidates. (32)

- Donor or candidate with a known exposure to a confirmed/ probable case of COVID-19 within past 14 days should be avoided as patients may be in an incubation phase even if asymptomatic.

- Donor or candidate currently suffering from a clinical syndrome compatible with COVID-19, regardless of known exposure within the past 14 days and negative PCR test results, should be avoided (unless alternative diagnosis is made).

- A thoracic CT scan may show signs of COVID-19 pneumonia even before development of symptoms or positive PCR and thus should be considered for donor and candidate assessment. This is based on availability of adequate personal protective equipment and other resources. If CT imaging is suggestive of a COVID-19 pneumonia, we recommend foregoing transplant.

- Donor with former COVID-19 following complete clinical recovery, at least 28 days from symptom onset, and two negative PCR tests 24-48 hours apart may carefully be assessed for donation and ultimately be considered eligible for donation if no permanent end-organ damage resulted from COVID-19 and appropriate donor organ function is confirmed.

- Regardless of donor screening, the center should have a discussion of risk-benefit with the recipient regarding transplantation during the ongoing pandemic.

The figure delineates screening pathway for donor and recipient screening at time of organ offer.
7. Protection of healthcare workers (HCW) during donor and recipient surgery and procedures

HCWs are at increased risk of infection with SARS-COV2 and thus specific precautions are recommended.(35-38) Transmission of SARS-COV2 to HCWs at the time of transplant can potentially occur from the donor and recipient, but also from hospital personnel with asymptomatic/mildly symptomatic infection. Thus, possible transmission of infection to the clinical transplant team is a distinct possibility, especially in the setting of lung transplantation, in which organ retrieval and transplant surgery are considered aerosol generating procedures. Data regarding infection risk during these specific procedures is lacking at this time.

Procurement travel:
- The minimum number of personnel should be involved in the procurement team and related travel to reduce the risk of exposure and infection.
- When possible, it is strongly recommended that organs should be procured by a local recovery team in order to reduce travel-related risk.
- Team members should use surgical mask during transportation.
- Screening questionnaire assessing COVID-19 symptoms should be administered to the procurement team prior to commencing travel in order to guarantee no symptomatic HCW are on duty.

Donor and recipient transplant surgery:
• Appropriate PPE should be available for the procurement team on site, either provided by the local organ procurement organization, the donor hospital, or carried by the procurement team according to their institutional guidelines. This should be negotiated in advance of commencing travel.

• N-95 masks (or equivalent) should be worn by all team members in the operating room during lung retrieval and lung transplantation; face shield is suggested as well. Negative SARS-CoV-2 testing of donors and candidates does not alter this recommendation. We recommend avoiding donor bronchoscopies in the operating room; if performed, only essential personnel with airborne precautions should be present.

• Standard surgical masks are considered sufficient for heart retrieval and transplantation, along with suggested face shield if no lung retrieval is being performed in the same donor.

• Where available, negative pressure operating room should be used for lung surgical procedures.

Protection of HCWs prior to invasive procedures:
PCR testing for SARS-CoV2 of patients prior to invasive procedures may identify patients with asymptomatic or pre-symptomatic SARS-CoV2 infection. A positive PCR will inform decisions regarding rescheduling of elective procedures or implementing additional precautions to prevent transmission to the HCW. Due to occurrence of negative PCR during the incubation period as well as false-negatives in general, infection prevention measures should not be relaxed in response to a negative test. The decision to implement pre-procedural testing in asymptomatic individuals should be according to local guidance, testing availability, and test turn-around time.

PPE recommendations for HCWs with positive SARS-CoV-2 serology
There are currently multiple serologic assays for SARS-CoV2. It is not yet known if the presence of antibodies is associated with protection from infection or progression to severe disease, how long antibodies persist, and if a minimum titer is needed. Until it is known if a correlation between antibody response and protection exists, those with a positive serology for SARS-CoV2 should follow the same precautions as those with negative serology.(39)

8. Recommendations for ECMO
Extracorporeal Membrane Oxygenation (ECMO) should be considered in patents with critical COVID-19 disease who fail conventional measures to improve hypoxemia and should not deviate from the usual indications per Extracorporeal Life Support Organization (ELSO).(40) Considerations during a pandemic are inherently different due to limited hospital capacity and several factors ought to be weighed in making a decision to judiciously offer this resource-intensive mode of support. These include availability of PPE, space, equipment and personnel to initiate, maintain and decannulate ECMO patients. More stringent inclusion/exclusion criteria, including age, frailty and single organ involvement, may be necessary as determined by hospital capacity and local guidelines.

Cannulation process should occur preferably at the bedside to avoid exposure of personnel and surfaces in the operating room or catheterization lab. Femoro-femoral or femoro-internal jugular
venovenous support using large (>23 Fr) multistage drainage cannula and single stage return cannula provide optimal flows.

Ongoing care on ECMO should follow existing guidelines and be based on optimal supportive care to maximize outcomes. (41-43) Centers should follow institutional anticoagulation ECMO protocols with a consideration to more intense therapy in light of the hypercoagulable state typical of these patients. Along these lines, low ECMO flows should be avoided. Weaning from ECMO ought to follow existing guidelines and decannulation should be performed with PPE precautions, as indicated. (40)

VA ECMO may be required in patients with COVID-19 who decompense hemodynamically as a result of cytokine storm and/or myocardial dysfunction. Similarly, patients with classical indications for VA ECMO including acute myocardial infarction, cardiogenic shock, regardless of COVID-19 status may require support.

9. Palliative care considerations in patients with cardiothoracic transplant, pulmonary vascular disease and VAD

While advance care planning is an essential element of care for patients with advanced heart and lung disease, the SARS-CoV2 pandemic has brought a greater urgency to this process. Patients with advanced heart/lung disease are likely at higher risk of death if they acquire severe COVID-19 disease, and may not have the option of ICU care in hospitals forced to ration these services during pandemic surges. (44) Higher transplant waiting list mortality may also be expected as transplant volumes are reduced during the pandemic, and the availability of bridging therapies such as mechanical ventilation or ECMO may be restricted. Moreover, due to pandemic visitor restrictions, patients may be unaccompanied by support persons during hospitalizations, even during critical illness when discussions of goals of care are required.

- We recommend engaging patients with advanced heart and lung disease (referred or listed for transplant, PAH, VADs, and post-transplant patients with severe chronic allograft dysfunction) and their support persons in advance care planning discussions prior to hospitalization. This can occur during virtual visits with the clinical team and/or through referral to Palliative Care.
- Palliative care discussions should include the usual general considerations as well as the specific pandemic considerations noted above. Patients ineligible for bridging to transplant should be made aware of this, to inform their advance care planning.
- During hospital admissions, we recommend attempting to involve support persons in discussions around goals of care through video or phone calls.

Additional resources to assist with advance care planning discussions can be found at the following links: https://respectingchoices.org/wp-content/uploads/2020/03/Proactive_Care_Planning_Conversation_COVID-19.pdf
https://www.vitaltalk.org/guides/covid-19-communication-skills/
10. Research areas pertinent to patients with cardiothoracic transplant, pulmonary hypertension and VADs

As the pandemic surpasses 10 million cases worldwide, there is much that remains unknown. We believe that it is imperative for all centers performing cardiothoracic transplantation and caring for patients with VADs and PH to collect key research data. Given relatively small numbers of such patients at individual sites, we support development of national and international collaborations, ideally with control arms where appropriate in order to make conclusions robust.

Susceptibility to infection, incubation period, disease manifestations including thromboembolic events, rate of asymptomatic infection, duration of illness and viral shedding, prognosis and risks for poor outcomes need to be described in patients with thoracic transplant, VAD or pulmonary vascular disease compared to appropriate controls. In particular, mortality on the waitlist compared to the early post-transplant period with COVID-19 needs to be examined to assess benefit of transplant prioritization.

A number of ongoing therapeutics trials exclude patients with immunosuppression and we strongly recommend that such patients be included, especially where risk of harm from a potential therapeutic agent related to drug interactions or known adverse events is outweighed by potential benefit. Risk of infectious complications related to immunomodulatory agents being investigated for COVID-19 may be balanced with appropriate antimicrobial prophylaxis. Effect of such agents on survival and risk of acute rejection/ graft dysfunction is unclear; survival in patients with PH and VADs is also not known at present.

Management of immunosuppression and risk of rejection remains unclear when a cardiothoracic transplant recipient develops COVID-19 as is duration of illness and immune response to the virus. As vaccine trials start to enroll patients, inclusion of immunosuppressed patients will be important to gauge the presence or absence of an effective vaccine response; this will have implications for patients regarding ongoing need for physical distancing etc. Acquisition and persistence of humoral and cellular immunity in patients with cardiothoracic transplant, VADs or PH will need to be studies with appropriate controls. Trials of differential approaches to immunosuppression, especially alterations in CNI or withholding of adjunctive therapy must be undertaken. The appropriate use of higher than baseline administration of corticosteroids needs to be investigated. The development of multisystem inflammatory syndromes in immunosuppressed individuals remains an area for discovery. Furthermore, once the episode of a first COVID-19 infection has resolved, it is unclear if second infections may occur and under what conditions.

Optimal donor and recipient selection criteria where previous or recent COVID-19 is known to have occurred remains to be elucidated. In particular as there is increasing need for lung transplant for COVID-19 related ARDS, it is important to collect pertinent data in a systematic manner to develop an international set of criteria.
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5. Farhana Latif MD; Maryjane A. Farr M MKJC, MD, MSc; Marlena V. Habal, MD; Koji Takeda, MD, PhD; Yoshifumi Naka, MD, PhD; Susan Restaino MGS, MD; Nir Uriel, MD, MSc: : Characteristics and Outcomes of Recipients of Heart Transplant With Coronavirus Disease 2019. . JAMA Cardiology 2020.
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