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 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 care providers of patients with chronic lung/ heart disease and transplant, mechanical circulatory support, and pulmonary vascular disease.

NEW INFORMATION IN THIS REVISION:
-COVID-19 vaccination recommendations
-updated donor and recipient selection for cardiothoracic transplant
-updated COVID-19 specific therapeutics

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1. Risk factors and severity of COVID-19

Several recent studies indicate that transplant recipients are at increased risk of severe COVID-19 and increased mortality.(1-5) Additionally, severe COVID-19 disease occurs more frequently with increasing age, in men, and in those with comorbidities, particularly heart failure, hypertension, diabetes mellitus, cancer, renal disease, and chronic respiratory diseases.(6-8) Risk factors for infection acquisition are similar to those for other individuals. 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.

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)

a. Minimize medical facility visits:

During the active/ overwhelmed phases of the COVID-19 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, video 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:
    - Based on local transmission of SARS-CoV-2 and individual risk: benefit ratio for each patient, consider 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, are on stable immunosuppression, have no recent history of rejection, and those that are not sensitized or with a positive cross match.
    - 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 necessary for airway issues in lung transplant recipients, these should be done with appropriate protection for the bronchoscopist and support team 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 and mask use 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.
- 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, 12)

- 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.(13)

3. SARS-CoV-2 testing

Recommendations regarding testing for SARS-CoV-2, quarantine/isolation, and proactive monitoring for asymptomatic patients may vary based on local policies and healthcare resources, and the phase and severity of the pandemic. We recommend testing for SARS-CoV-2 via PCR-based tests in all patients undergoing invasive procedures when a positive result will cancel or postpone the procedure and prior to proceeding with transplantation.

Samples for testing should be taken as per local guidelines, usually nasopharyngeal, nasal, or oropharyngeal swabs for PCR-based testing. Of note, tests may be negative even in individuals who later prove to be infected or later in the disease course when lower respiratory samples are more sensitive.(14, 15) 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. (16, 17)

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.(18) 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.(19, 20) 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. In general, management of COVID-19 for patients with chronic heart/lung disease, cardiothoracic transplant, MCS or PVD is the same as for the general population with some specific considerations, detailed below.

- 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 PVD 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. 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.

Dexamethasone, other steroids	Low potential for clinically significant interactions with immunosuppression, pulmonary vasodilators or anticoagulants.
Remdesivir	Low potential for clinically significant interactions with immunosuppression, pulmonary vasodilators or anticoagulants;

	however, potential risk of lower tacrolimus, cyclosporine and sirolimus levels.
IL-6 inhibitors	Low potential for clinically significant interactions with immunosuppression, pulmonary vasodilators or anticoagulants; however, potential risk of lower tacrolimus, cyclosporine and sirolimus levels.
Baracitinib	Low potential for clinically significant interactions with immunosuppression, pulmonary vasodilators or anticoagulants; however, potential risk of lower tacrolimus, cyclosporine and sirolimus levels. Potential for herpes simplex virus reactivation in the setting of pre-existing immunosuppression.
Convalescent plasma	Potential for volume overload and transfusion-related acute lung injury (TRALI), especially in patients with limited heart/ lung function.
SARS-CoV-2 specific monoclonal antibodies	Low potential for clinically significant interactions with immunosuppression, pulmonary vasodilators or anticoagulants; however, potential risk of lower tacrolimus, cyclosporine and sirolimus levels.

*Randomized controlled trials do NOT show benefit of combination antiretrovirals (eg lopinavir-ritonovir) and hydroxychloroquine in the management of COVID-19.(21-25) We do not recommend these agents due to lack of benefit, known significant drug interactions with immunosuppressive agents, and potential for adverse drug events especially related to QTc prolongation from hydroxychloroquine.

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 (USA); https://www.clinicaltrialsregister.eu/ctr-search/search?query=covid-19 (European Union) and https://www.nihr.ac.uk/covid-studies (United Kingdom).

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 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.(26-28)

· 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 14-21days after initial diagnosis AND a negative PCR-based test 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.(29, 30) 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 at least two negative PCR based tests 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

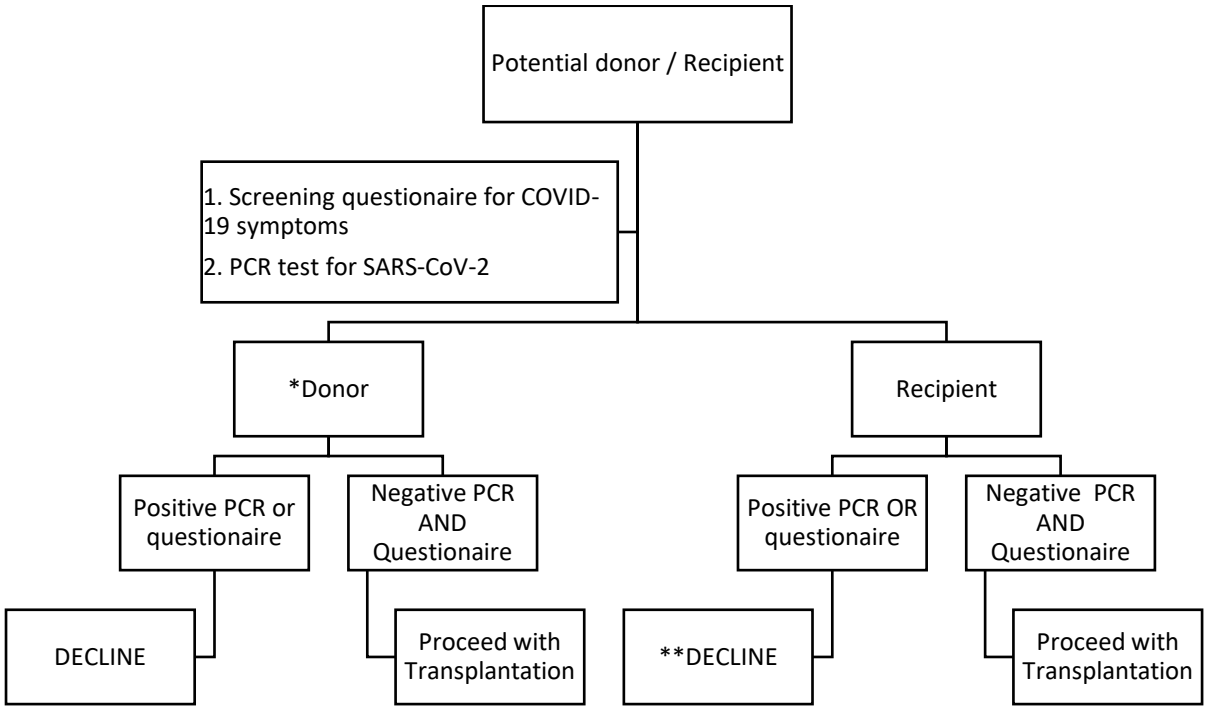
Asymptomatic and/or pre-symptomatic viral shedding is well described with SARS-CoV-2 infection and thus we recommend testing of both donor and recipient prior to proceeding with transplantation.(31, 32) Confirmed transmission of SARS-CoV-2 from donor to recipient has not yet been reported but is conceivable.(33) 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.

Figure 1 delineates the screening pathway for donor and recipient screening at time of organ offer.

- *Pre-transplant testing in donor:* We recommend testing for SARS-CoV-2 by nasopharyngeal/ oropharyngeal swab, sputum/ tracheal aspirate, or bronchoalveolar lavage (BAL) less than 72 hours before organ donation; latter two are reported to have higher viral loads and thus higher sensitivity of test results.(15) We recommend a deep respiratory specimen, BAL, mini-BAL, or tracheal aspirate, for a lung donor if it is safe to do so within a closed ventilatory circuit with adequate personal protective equipment available. In the absence of evidence, we recommend avoiding transplantation from PCR+ donors

- *Pre-transplant testing in candidate:* We also recommend PCR based test in the asymptomatic waitlisted candidate prior to transplant surgery and recommend deferring transplant on PCR+ waitlisted candidates except in specific circumstances as noted in Table 2.(33)
- *Pre-transplant symptom assessment:* 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). Figure 1 summarizes these considerations for cardiothoracic transplant.
- *Known exposure:* Donor or candidate with a known exposure to a confirmed/ probable case of COVID-19 within past 14 days without a clinical syndrome consistent with COVID-19 may be considered for transplantation if certain conditions are met as noted in Table 2.
- *Donor imaging:* 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 assessment. If donor CT imaging within 72 hours prior to organ donation is suggestive of a COVID-19 pneumonia, we recommend foregoing transplant.
- *Previous COVID-19 in donor:* Donor with former COVID-19 following complete clinical recovery, at least 21 days from symptom onset, and a negative PCR test may carefully be assessed and ultimately be considered eligible for donation based on criteria noted in Table 2.
- *Previous COVID-19 in candidate:* For patients with end-stage heart or lung disease waitlisted for transplant who contract COVID-19, we recommend waiting until clinical resolution of symptoms related to COVID-19, at least one negative PCR-based test and at least 21 days from symptom onset have elapsed prior to reactivation and transplantation if possible. For candidates who are found to have asymptomatic COVID-19 infection, we recommend a negative PCR-based test and >14 days since diagnosis unless the candidate is at high risk for mortality without organ transplantation as noted in Table 2.
- Prolonged viral shedding up to 5 weeks in a minority of immunocompetent patients has been described.(29, 30) For patients with end-stage heart or lung disease waitlisted for transplant who contract COVID-19 and show prolonged viral shedding beyond 21 days, we recommend a case-by-case approach to reactivation and transplantation. Considerations include complete resolution of symptoms related to COVID-19 and the acute need for organ transplantation, as noted in Table 2.
- Regardless of donor screening, the center should have a discussion of risk-benefit with the recipient regarding transplantation during the ongoing pandemic.

Figure 1. Screening pathway for donor and recipient screening at time of organ offer.



*consider CT chest for donor and decline if concerning for COVID-19
** Exceptions can be made on a case-by-case basis as noted in Table 2

- Recommend deep respiratory sample in lung donor for SARS-CoV-2 testing
- N-95 mask or equivalent plus face shield in operating room for lung transplant
- Current data does not suggest a change in induction or maintenance immunosuppression

Table 2. Criteria for proceeding with cardiothoracic transplantation based on COVID-19 related clinical scenarios.

WAITLISTED CANDIDATE	
Exposure to confirmed or suspected case of COVID-19 within past 14 days	May be considered for transplant if: Asymptomatic AND >7 days since exposure AND One negative SARS-CoV-2 PCR test AND High risk of mortality without organ transplantation If above criteria not met, recommend avoiding transplant within the 14-day incubation period.

Previous symptomatic COVID-19	Clinical resolution AND >21 days from onset of symptoms* AND one negative SARS-CoV-2 PCR test AND lack of COVID-19 related end-organ damage *time period may be shortened to at least 14 days in candidate with high risk of mortality without transplant if other criteria are met If PCR remains positive after resolution of illness > 28 days from initial diagnosis may be considered for transplant if high risk of waitlist mortality
Candidate with asymptomatic positive SARS-CoV-2 PCR	May be considered for transplant if: >14 days since diagnosis unless high risk of mortality without organ transplantation AND one negative SARS-CoV-2 PCR test within 72 hours of transplant If PCR remains positive in an asymptomatic patient > 28 days from initial diagnosis may be considered for transplant if high risk of waitlist mortality
DONOR	
Exposure to confirmed or suspected case of COVID-19 within past 14 days	Organ may be considered for transplant if: Donor has been asymptomatic AND >7 days since exposure AND at least one negative *SARS-CoV-2 PCR test AND CT chest negative for pulmonary infection AND potential candidate with high risk of mortality without organ transplantation *Deep respiratory specimen recommended for lung donors
Donor with prior confirmed COVID-19	May be considered for transplant if: Clinical resolution of symptoms due to COVID-19 AND >21 days from onset of symptoms AND no significant pulmonary disease due to COVID-19 (for e.g. required intubation) AND at least one negative *SARS-CoV-2 PCR AND CT scan of the chest negative for evidence of pulmonary infection/chronic lung injury AND lack of other COVID-19 related end-organ damage *Deep respiratory specimen recommended for lung donors

LUNG TRANSPLANT LISTING FOR COVID-19 RELATED RESPIRATORY FAILURE	
	May consider lung transplant in carefully selected patients based on the following criteria: Severe lung injury has been present for > 28 days AND markers of irreversibility noted on imaging and ventilatory studies AND Single organ disease from SAR-CoV-2 AND Two negative SARS-CoV-2 PCR tests 24-48 hours apart (including deep respiratory specimen), AND otherwise considered to be a candidate based on the transplant center's local policies

7. Lung transplant listing criteria for a candidate with COVID-19 related acute respiratory distress syndrome

A few cases of lung transplantation for COVID-19 related acute respiratory distress syndrome have been described in China, Europe and the US. We believe that lung transplantation will be appropriate for a small minority of patients with COVID-19. We recommend proceeding with listing for an otherwise healthy patient with COVID-19 related respiratory failure in carefully selected cases based on the severity and irreversibility of respiratory failure, at least 28 days since onset of severe lung injury, negative SARS-CoV-2 PCR test separated at least 24-48 hours (at least one PCR is of a deep respiratory specimen), presence of single organ failure related to COVID-19, nutritional status and rehabilitation potential of the patient, assuming other listing criteria based on local center policies are met (Table 2).

8. 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.(34-37) 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.

<u>Procurement travel:</u>

- 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 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.(38)

9. 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).(39) 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.(40-42) Centers should follow institutional anticoagulation ECMO protocols and while some have recommended consideration to more intense therapy in light of the hypercoagulable state typical of these patients, there is considerable uncertainty in this regard. 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.(39) Recent data suggests that prolonged VV ECMO support may be necessary. An early extubation strategy shortly after institution of ECMO has been associated with superior survival outcomes.(43)

VA ECMO may be required in patients with COVID-19 who decompensate 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.

10. 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/

11. COVID-19 vaccination

Several COVID-19 vaccines have either achieved or are close to achieving regulatory approval and will be available for selected patients in the upcoming weeks-months. These include mRNA based vaccines (Moderna, Pfizer/BioNTech) and those utilizing replication deficient viral vectors (Oxford/AstraZeneca, Johnson and Johnson) among many others undergoing investigation.(45, 46) Current efficacy data are impressive and range from 70% for the Oxford/AstraZeneca vaccine to >90% for the mRNA vaccines. Additionally, vaccination appears to protect against severe COVID-19. Serious adverse events have not been noted in vaccine recipients, other than local injection site reactions. Currently > 60,000 people have participated in clinical trials and longest follow-up has been for ~6 months. In general, heart and lung transplant recipients and other immunocompromised patients were excluded from recent vaccine trials and thus efficacy in these populations is unknown. Based on previous experience with other vaccinations, immunogenicity could potentially be reduced compared to immunocompetent patients. Similarly, specific data on safety in immunocompromised transplant recipients is also unavailable but it is not expected to differ from the studied population. Concerns for increased rates of rejection have not been substantiated in previous vaccine studies in transplant recipients but is currently unknown for mRNA vaccines. Considering the targeted action of mRNA to create spike proteins it appears less likely that they would elicit widespread immune response.

Given widespread use of other vaccinations in heart and lung transplant recipients, we do not expect safety to be different in this instance. We believe that the potential advantage of vaccination in transplant recipients outweighs concerns for reduced vaccine efficacy and/ or perceived lack of safety. We encourage immunization in patients with advanced heart or lung disease, MCS and PVD or in those awaiting or after cardiothoracic transplantation, when a vaccine is locally available (regardless of prior infection with SARS-CoV-2).

As an initial immune response to the COVID-19 vaccination is seen within 2-3 weeks of immunization with a single dose for some vaccines,(45, 46) we recommend initiating vaccinations in patients on the transplant waitlist who are unlikely to receive an organ donor within that time-frame. In the post transplantation setting, the ideal timing of vaccination is uncertain. We recommend delaying vaccination at least a 1 month from transplant surgery and 3-6 months from use of T-cell depleting agents such as anti-thymocyte globulin or specific B-cell depletion agents such as rituximab; in the latter case assessment for recovery of B-cells prior to vaccine initiation may be considered. We also strongly recommend the enrollment of cardiothoracic transplant recipients in vaccine trials or registries where available.

Up to date vaccine recommendations are available at the CDC COVID-19 vaccine and NHS COVID-19 vaccine websites.

12. Research areas pertinent to patients with cardiothoracic transplant, pulmonary hypertension and VADs

As the pandemic surpasses 66 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 *vaccination trials* 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.

Conflict of Interest Statements:

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