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Guidance for Cardiothoracic Transplant and Ventricular Assist Device Centers 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 a disease termed COVID-19. The group meets on a weekly basis to update this document as more data and experience become available.

1. **Are patients with chronic lung/ heart disease, cardiothoracic transplant, and VAD recipients at increased risk of acquiring SARS-CoV-2 infection?**

   At this time, it is unknown if cardiothoracic transplant recipients are at higher risk of SARS-CoV-2 infection.

   Chinese investigators surveyed 87 heart transplant recipients from a transplant center in Wuhan during the period December 2019-February 2020 and noted that only four developed mild respiratory complaints, of which three were tested for SARS-CoV-2 and were negative (one was not tested). Most patients and families practiced self-isolation, hand hygiene and wearing a mask while taking public transport. Maintenance immunosuppression was continued during this time. (1)

   Currently, risk factors are assumed to be similar to those for any individual who has not had a transplant, but risk may differ based upon your location; local general recommendations apply. Updated map on the WHO website or other public health sources may be consulted to assess level of community transmission.
   https://experience.arcgis.com/experience/685d0ace521648f8a5beeeee1b9125cd

2. **Are patients with chronic lung/ heart disease, cardiothoracic transplant, pulmonary hypertension, and VAD 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 and possibly chronic respiratory diseases.(2, 3) Severe disease manifestations include 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 upon infection acquisition.

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

a. Minimize medical facility visits:

If SARS-CoV-2 transmission is occurring within a community, and/or patients with COVID-19 are known to be in the facility, we recommend that transplant/VAD centers minimize medical facility visits by:

· 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 also to screen for symptoms consistent with COVID-19. The remote contact should be noted formally and be part of the patient's clinical chart. Checklists may be helpful.

· Postponing routine surveillance heart and lung biopsies in patients that are more than 3-6 months from transplantation, have not had a prior episode of rejection, and are clinically stable.

· For patients who will be attending appointments in the clinic or hospital, consider pre-visit phone calls or other contact to ensure patients do not have current symptoms of COVID-19 and to remind them to alert the transplant program before presenting to the medical facility with active symptoms so they may be appropriately triaged.

· Screening patients prior to physically arriving in the clinic should be done as per local guidelines.

b. Minimizing social interactions in the community:

· For patients with work or other activities that necessitate interactions with many people, we recommend medical leave or temporary reassignment to non-public facing work in order to minimize possible exposure. Work from home is strongly preferred.

· Basic precautions for transplant recipients and caregivers include staying at home and reducing contact with other people as much as possible.

· Stringent hand hygiene should be reinforced.

· Avoid non-essential travel.

c. Continue optimal medication

· Transplanted patients should continue immunosuppressive medication as before, since there is currently no evidence to suggest that they are at greater risk of acquiring infection or severe disease, and it is important to maintain optimal medical management to prevent rejection.

· Patients on the heart/ lung waitlist should continue current medical regimen if not otherwise instructed.

4. When and how should patients with cardiothoracic transplant, pulmonary hypertension or VAD be tested for SARS-CoV-2?

Until further evidence suggests otherwise, the same rules apply to cardiothoracic transplant or VAD recipients as to other individuals.

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

· For asymptomatic patients we recommend home quarantine for two weeks and testing for SARS-CoV-2 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 in asymptomatic patients, including when surveillance bronchoscopies are performed in lung transplant recipients.

· We recommend transplant centers performing surveillance biopsies to consider deferring other 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, nasal congestion, diarrhea etc.) should be treated like any other patient who may be considered to be at increased risk of developing severe disease as per local guidelines. The possibility of atypical presentations in these patients should be kept in mind.

· 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, and computed tomography (CT) imaging may show signs of disease even in absence of symptoms and negative testing.(6) Additionally, although the sensitivity of bronchial samples is higher than other sources, bronchoscopies may carry a great risk of aerosol spread of the virus.

5. **How do I approach management of a patient with cardiothoracic transplant, pulmonary hypertension or VAD with confirmed COVID-19?**

· As it is yet unclear if patients with transplant, pulmonary hypertension or VAD have greater risk for progression to severe disease, consider performing computed tomography (CT) scan of the chest when respiratory symptoms are present and imaging is available.

· 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 as follows:

Mild	Mild symptoms, no shortness of breath
Moderate	Hypoxia requiring supplemental oxygen via nasal cannula
Severe	Severe respiratory failure requiring ICU admission. Need for ventilatory support, ARDS, circulatory collapse (shock), acute kidney failure and cardiomyopathy may complicate this stage, and may be related to a strong systemic inflammatory response (cytokine storm).

· Based on current literature, we recommend that patients with a cardiothoracic transplant, pulmonary hypertension or VAD should be assessed for treatment based on disease severity, as any other patient. In those patients that transition to a higher severity level, vigilance is important. It is unclear if rejection rates will be affected by the viral infection.

- 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 no data at this time to suggest a change in immunosuppression and we recommend continuing on maintenance immunosuppression.
- For moderate and severe disease, we recommend admission and assessment for treatment though evidence for treatment recommendations is sparse.
- 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.
- As for non-transplanted patients, we recommend caution when using non-invasive ventilation and high-flow nasal cannulae because of the high risk of viral spread via aerosolization and early intubation should be considered.
- Concomitant antibacterial or antifungal treatment should be considered as per local center policy though rates of bacterial/fungal co- or superinfection are unknown at this time.

· Immunosuppression:

- Consider holding mycophenolate mofetil or azathioprine while admitted with severe/critical illness (with close monitoring for rejection).

· Experimental/compassionate off label drug use

- Consider therapy based on drug availability and disease severity. Several drugs have been used with some success in non-transplant patients with COVID-19 and there are ongoing trials investigating a variety of agents. Some of these drugs may be available on a compassionate use basis from the manufacturer as well. At this time, evidence for and against such agents remains weak and mostly anecdotal. Drugs that can be considered for

treatment of COVID-19 in transplant recipients include chloroquine, hydroxychloroquine, intravenous immune globulin, convalescent serum from persons recovered from COVID-19, remdesivir, high dose steroids, and IL-6 inhibitors, such as tocilizumab and sarilumab.

- Uncontrolled observations suggest that steroids and IL-6 inhibitors may be useful in ARDS.
- We do not recommend lopinavir/ritonavir, darunavir/ritonavir and darunavir/cobicistat due to lack of evidence showing efficacy as well as significant drug-drug interactions with immunosuppressive medications.(7)
- Additionally, chloroquine and hydroxychloroquine may increase the QTc interval and we recommend caution with use, especially in combination with other drugs that may increase the QTc interval, such as macrolides (azithromycin).
- We encourage investigators to include patients with cardiothoracic transplant, pulmonary hypertension and VAD in clinical trials so that evidence for and against treatment of such vulnerable patients is available to guide future treatment recommendations.

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

6. Can my patient with end stage heart/lung 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. Both the higher risk of receiving a transplant, the higher risk of not being transplanted and the adequate and fair allocation of resources (particularly related to ICU beds) should be considered.

- We do not recommend a general cessation of all transplant activity due to the COVID-19 pandemic merely to liberate resources for treating COVID-19 patients, as it is not certain that weighing of benefit and equity merits such a general shut down in all programs.
- In selected patients, we suggest proceeding with transplantation in the absence of recent exposure as well as absence of symptoms compatible with COVID-19 in the previous 2 weeks, although the risk of an undetected infection remains. If timing and testing availability allows, we suggest PCR-based testing for SARS-CoV-2 be performed prior to transplant on patients for whom an organ is accepted.
- We recommend foregoing transplantation and making the patient inactive on the waitlist while actively infected with SARS-CoV-2.

· For waitlisted patients who have recovered from COVID-19, 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. This timeframe is based on the higher acuity of heart and lung waitlisted patients and lesser opportunities for organ availability.

· If proceeding with transplantation, 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.

· For (non-transplanted) patients with COVID-19 who are treated with ECMO, lung transplant should be considered with grave caution and if done at all, only in carefully selected cases in the setting of two negative PCR based tests a week apart. Anecdotal reports indicate that myocarditis may occur at this stage, and thorough cardiac evaluation seems warranted. When considering the appropriate resource allocation in such settings, the expected need for prolonged postoperative after a transplant care in such patients should be weighed against the opportunity of liberating ICU capacity by performing the transplant.

· Based on COVID-19 disease prevalence and ICU bed availability at the local center, consider limiting VAD implantation to INTERMACS status 1-3 patients.

. VAD patients who are otherwise stable and using their 30 days of prioritization (as allowed in the US), centers may consider deprioritizing until the pandemic abates.

7. How does the COVID-19 pandemic affect deceased donor selection?

Transmission of SARS-CoV-2 from donor to recipient has not yet been reported but is conceivable. The risk of virus 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 COVID-19 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
  - 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 if testing is available. If available, we recommend PCR-based donor testing for SARS-CoV-2 by nasopharyngeal/ oropharyngeal swabs or bronchoalveolar lavage fluid and 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.

· Regardless of donor screening, the center should have a discussion of risk-benefit with the recipient.

8. **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.
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)
- 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.

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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