New ISHLT COVID-19 Therapeutics Guidance
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Introduction
Patients with advanced heart and lung disease, particularly those who are immunocompromised due to a heart or lung transplant, are at higher risk of hospitalizations, complications and death when infected with SARS-CoV-2. (1, 2) Outcomes have improved over time with the availability of vaccines and a range of therapies for COVID-19, including monoclonal antibodies, antivirals and immune modulators (See Table 1). (3) This document will review the available literature and make current recommendations on the use of these therapies in this at-risk population. Early therapy has been consistently demonstrated to be associated with the best outcome in all populations, including those with underlying heart and lung disease, including those on the transplant wait list. Therapy should be initiated as soon as a diagnosis of COVID-19 is made; waiting to see if the patient worsens and then starting therapy may deprive the patient of the benefit of the specific therapies.

COVID-19 therapies available or under review:


Outpatient Management of COVID-19

Key Recommendations

- Transplant teams should have ongoing educational efforts, including with each patient contact, about the need to call the team as soon as they develop symptoms to facilitate early initiation of therapy and to check with the transplant team if other providers wish to start therapy to avoid drug-drug interaction issues.
- Vaccination in line with local schedules should continue to be encouraged.
- Outpatient therapies are most effective when started as quickly as possible after onset of symptoms.
Three daily doses of IV remdesivir is the preferred treatment option for where there is suspicion that circulating viral variants are less susceptible to available monoclonal antibodies.

Monoclonal antibodies active against circulating variants would be preferred therapy due to lack of significant drug interactions in transplant recipients and one time infusion. Thus, there is a strong need for the development of new monoclonals which are effective against new SARS-CoV-2 variants.

Nirmatrelvir-ritonavir has significant drug-drug interactions that limit its routine use in transplant recipients, advanced heart failure patients and patients on targeted treatments for pulmonary hypertension. Drug interactions should be assessed prior to initiation of therapy in the context of a well-developed protocol for drug level monitoring if indicated.

We do not recommend molnupravir use as data regarding efficacy is not robust and the drug increases the risk of viral mutations.

Alterations to baseline immunosuppressive therapy should only be undertaken in conjunction with the patient’s transplant center though potentially only needed in the inpatient setting with severe/critical illness.

In general, management of cardiothoracic patients requiring inpatient admission to the hospital should be consistent with local guidelines such as the NIH Treatment Guideline https://www.covid19treatmentguidelines.nih.gov/tables/management-of-hospitalized-adults-summary/.

In patients admitted to the hospital for reasons other than COVID-19 (i.e. admission with COVID-19), consider use of 3 days of remdesivir to prevent progression of disease.

Adjustment of immunosuppression has not been well studied in heart and lung transplantation, but outcomes are similar with and without adjustment in studies in abdominal transplant.

Risk of bacterial and fungal superinfection should be suspected with clinical worsening or new signs or symptoms of infection during the course of COVID-19, particularly if steroids, IL-6 or JAK inhibitors are utilized.

The available agents have been studied in populations without many immunocompromised patients and generally in patients without prior immunity, infected with variants prior to Omicron; advice for their use in transplant patients is extrapolated from these more general populations. In this context the risk of adverse effects and interactions becomes more important. A publically available interaction checker is available from the University of Liverpool https://www.covid19-druginteractions.org/checker

### Considerations for use of COVID-19 therapies in transplant / VAD / PH patients

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Likely interactions</th>
<th>Considerations in thoracic transplant / VAD / Pulmonary Hypertension</th>
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<tr>
<td>Drug</td>
<td>Interactions</td>
<td>Notes</td>
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<tr>
<td>Monoclonal antibodies</td>
<td>No clinically significant interactions with calcineurin inhibitors (CNIs), mTOR inhibitors, PH targeted therapy or advanced heart failure medications identified.</td>
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<tr>
<td>Remdesivir</td>
<td>No clinically significant interactions with CNIs, mTOR inhibitors PH targeted therapy or advanced heart failure medications identified.</td>
<td>Not licensed for patients with eGFR below 30 mLs / min though data in the setting of renal failure is emerging.</td>
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<tr>
<td>Nirmatrelvir / ritonavir</td>
<td>Significant interactions with immunosuppressants, anticoagulants, antiplatelet agents and PH medications limit use in transplant / PH/ advanced heart failure patients.</td>
<td>In patients with moderate renal impairment (eGFR ≥ 30 to &lt; 60 mL/min), the dose should be reduced to Nirmatrelvir/ ritonavir 150 mg / 100 mg every 12 hours for 5 days to avoid over-exposure (this dose adjustment has not been clinically tested). Nirmatrelvir / ritonavir should not be used in patients with severe renal impairment [eGFR &lt; 30 mL/min, including patients with End Stage Renal Disease (ESRD) on haemodialysis].</td>
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<td>Tocilizumab and other interleukin-6 blockers:</td>
<td>No clinically significant pharmacokinetic interactions with immunosuppressants / PH medications identified. Higher rates of toxicity from IL-6 blockers demonstrated in transplant recipients when IL-6 agents used for other indications.</td>
<td>Potential for increased risk of infections and adverse effects in transplant recipients due to immunosuppressant activity.</td>
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<tr>
<td>Molnuprivir</td>
<td>No pharmacokinetic interactions identified.</td>
<td>Limited data available for evaluation. Trial conducted in</td>
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<tr>
<td>Disease stage</td>
<td>Supportive management</td>
<td>COVID-19 Specific Management</td>
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<td>Mild or moderate COVID-19 in a patient at high risk of progression to severe disease (use appropriate local guidelines to stratify patient)</td>
<td>Symptomatic treatment (avoid non-steroidal anti-inflammatory medications in patients on calcineurin inhibitors due to nephrotoxicity). Consider alteration in immunosuppressant doses including augmentation of corticosteroid dose in conjunction with transplant center. Active surveillance for secondary bacterial and opportunistic fungal and viral infections such as aspergillus and CMV.</td>
<td><strong>1&lt;sup&gt;st&lt;/sup&gt; line Remdesivir for 3 days</strong> Remdesivir 200 mg IV on day 1 and 100 mg IV on days 2 and 3 (PINETREE regimen). <strong>2&lt;sup&gt;nd&lt;/sup&gt; line nirmatrelv / ritonavir</strong> Only after careful check of interacting agents – most transplant / PH / VAD patients will have interactions which are unmanageable with ritonavir. Calcineurin inhibitor / mTOR inhibitor levels should be frequently checked while on therapy and dosing adjusted following both initiation and completion of therapy. This drug should be used in the...</td>
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setting of a well-developed protocol at the transplant center to manage drug interactions and closely monitor immunosuppressive drug levels.

Of note, monoclonal antibodies were initially the drug of choice given one time dose and no major drug interactions. If new monoclonal antibodies active against circulating viral variants are available, we suggest first-line use at that time.

| COVID-19 severe disease | Optimal supportive care in hospital ward or or ICU. Provide supplemental oxygen. Administer LMWH according to local guidelines, if not contraindicated. Antibiotics or antifungals according to local epidemiology for active secondary infections. Consider alteration in immunosuppressant dose in conjunction with transplant center. Active surveillance for secondary bacterial and opportunistic fungal and viral infections such as aspergillus and cytomegalovirus. | Dexamethasone 6 mg once a day for up to 10 days (or until hospital discharge, if sooner), IV or PO. Equivalent doses of corticosteroids can be used (hydrocortisone 150 mg/ day or methylprednisolone 32 mg/ day or prednisone 40 mg/ day). Consideration of tocilizumab and other interleukin-6 blockers. If patient has ongoing viral shedding, consider using antiviral as well (remdesivir). |
| COVID-19 critically ill disease | Optimal supportive care in ICU. Administer LMWH according to local guidelines, if not contra-indicated. Specific prevention & treatment of ARDS and subsequent lung fibrosis. Active surveillance for secondary bacterial fungal and viral opportunistic infections. Antibiotics or antifungals according to local epidemiology for treatment of active infections. | Dexamethasone 6 mg IV once daily (or equivalent doses of corticosteroids, as above). Consideration of tocilizumab, or baricitinib or other interleukin-6 blockers. If patient has ongoing viral shedding, consider using antiviral as well (remdesivir). |

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.

**References**


