Lung Transplantation for Coronavirus Disease-2019 Patients and Coronavirus Disease-2019 in Lung Transplant Recipients

Diego Avella, MD[a], Henry Neumann, MD[b], Ankit Bharat, MD[a,*]

KEYWORDS

• Lung • Transplant • COVID-19 • ARDS • ECMO

KEY POINTS

- Respiratory failure.
- Coronavirus disease-2019 infection.
- Acute respiratory distress syndrome.
- Extracorporeal membrane oxygenation.
- Lung transplantation.

BACKGROUND

Coronavirus disease-2019 (COVID-19) infection has affected millions of people, resulting in a wide spectrum of manifestations ranging from self-limited disease to severe acute respiratory distress syndrome (ARDS) requiring hospitalization and respiratory support, which, in some cases, can progress into lung fibrosis. For the most severe forms of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection resulting in ARDS, modalities of respiratory support include mechanical ventilation (MV) and extracorporeal membrane oxygenation (ECMO). After initiation of respiratory support, a certain percentage of patients will not recover sufficient lung function to remain free from mechanical respiratory support. In addition, certain patients infected with COVID-19 will develop long-lasting deterioration in their respiratory function, oxygen dependence, and overall deterioration in their performance due to the development of pulmonary fibrosis. Although these patients remain free from respiratory support, their quality of life is significantly affected, similar to patients with chronic respiratory diseases. In addition, they may be at risk for the development of secondary pulmonary hypertension and cardiac dysfunction.[1,2] Lung transplantation for respiratory complications secondary to COVID-19 infection has been performed in over 200 patients in the United States with outcomes comparable to transplants performed for the traditional indications of chronic lung diseases.[3] **Table 1** summarizes the relevant literature related to the lung transplantation in patients with respiratory failure secondary to COVID-19 infection.

Determination of the transplant candidacy for patients with respiratory failure secondary to COVID-19 requires careful consideration. Prior reports have used lung transplantation for COVID-19 in patients who are younger and with less

[a] Thoracic Surgery, Department of Surgery, Feinberg School of Medicine Northwestern University, 676 North St. Clair Street Suite 650, Chicago, IL 60611, USA; [b] Transplant Infectious Diseases, Division of Infectious Diseases, Department of Medicine, NYU School of Medicine, New York, NY, USA

* Corresponding author. Northwestern Medicine, 676 North Saint Clair Street, Suite 650, Chicago, IL 60611.
E-mail address: ankit.bharat@nm.org

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Table 1
Relevant published articles on lung transplantation for severe coronavirus disease-2019 infection

Demonstration of need and feasibility of lung transplantation for severe COVID-19 infection	Lung transplantation for patients with severe COVID-19. Bharat, A. et al. *Sci Transl Med*. 2020.[16]
Early recommendations of criteria for lung transplantation in patients with COVID-19 infection	When to consider lung transplantation for COVID-19. Cypel, M. *Lancet Respir Med*. 2020.[14]
Multi-institutional international early experience and outcomes of lung transplantation for severe COVID-19 infection	Early outcomes after lung transplantation for severe COVID19: a series of the first consecutive cases from four countries. Bharat, A. et al. *Lancet Respir Med*. 2021.[15]
Larger, single institutional experience with lung transplantation for COVID-19-associated ARDS	Clinical Characteristics and Outcomes of Patients With COVID-19–Associated Acute Respiratory Distress Syndrome Who Underwent Lung Transplant. Kurihara, C et al. *JAMA*. 2022.[17]
Experts' opinions on approaching lung transplantation for patients with COVID-19 infection	Lung transplantation for patients with COVID-19. King, C., et al. *Chest*, 2022.[29]
Reported national outcomes for patients that underwent lung transplantation for respiratory failure secondary to COVID-19; analysis of the UNOS data	Lung transplantation for COVID-19 related respiratory failure in the United States. Roach, A., et al. *NEJM*. 2022.[3]

comorbidities, and have had excellent performance status before the onset of COVID-19. However, prolonged hospitalizations, dependence on the ventilator, recurrent infections, malnutrition, physical deconditioning, and other respiratory complications, such as hemothorax and pneumothorax, make the transplant evaluation and the procedure quite challenging. It is imperative that the patients and their caregivers be provided with a clear understanding of the potential complications associated with changes in lifestyle and the need for lifelong immunosuppressive medications following transplantation.

SELECTION OF CANDIDATES FOR LUNG TRANSPLANTATION

Approximately 5% of patients infected with COVID-19 develop a severe form of the disease[4] although this is expected to reduce with the vaccination and is now less common with the most prevalent Omicron variants (BA.2, BA.4, and BA.5). The mortality of patients with severe disease is close to 30%[5,6] despite optimized medical care. The number of patients with severe disease or long-term sequelae after a COVID-19 infection is substantial when considering the number of patients infected with COVID-19. However, there is still a lack of strong data demonstrating the long-term course of the disease. The course of the disease differs significantly between patients that remain free of MV since the development of symptoms or after a period of mechanical respiratory support and the patients that cannot be weaned from ventilator support or ECMO.

In a Spanish study that investigated the incidence of COVID-19 infection in Catalonia, 1.83% of the patients had an outpatient COVID-19 diagnosis and mortality was 3.01%. In the same study, the patients that required hospitalization for COVID-19 represented 0.3% of the population but the mortality in this group was 19.16%.[7] Other studies have reported a decrease in the functional respiratory reserve shown by a reduction in the pulmonary function testing and exercise tolerance as well as radiographic evidence of lung fibrosis after 3 to 4 months of initial symptoms of COVID-19 infection.[8,9] However, there is a lack of understanding of the implications of these findings in the long term.

Radiographic findings after COVID-19 infection include ground glass opacities (GGO), frank lung consolidation, and atelectasis. These findings are considered early manifestations and do not necessarily represent signs of irreversible damage. However, the GGOs can represent fibrosis, particularly when they present late in the course of the disease and other signs of lung fibrosis are present simultaneously. Traction bronchiectasis, honey combing, and subpleural fibrosis are more definitive signs of lung fibrosis and irreversible changes[9,10]; however, anecdotally some patients have shown resolution of similar radiographic findings. The development of pleural effusions represents a

unique challenge, particularly in coagulopathic patients and patients receiving therapeutic anticoagulation and ECMO support due to spontaneous bleeding in the pleural cavity and bleeding associated with placement of chest tubes. Spontaneous pneumothorax is another frequent complication of COVID-19 infection more frequently seen in patients who are receiving MV likely related to the effects of positive pressure ventilation on a fibrotic, stiff lung parenchyma. Lung expansion after placement of thoracostomy tubes is frequently incomplete with persistent air in the pleural spaces and prolonged air leaks. However, the development of lung fibrosis after COVID-19 infection is not uniform in all hospitalized or ventilated patients and has been associated with advanced age, history of chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis, alcoholism, smoking, prolonged mechanic ventilation, and length of intensive care unit (ICU) stay.[11]

The COVID-19 findings closely resemble the course of the disease seen in patients with other coronavirus infections such as Middle East acute respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS). In patients with SARS and MERS, the majority recovered from their symptoms after two weeks, but about one-third of the patients developed severe respiratory complications, including pneumonia and ARDS, and a subgroup of patients developed chronic lung fibrosis.[12,13]

Waiting a reasonable period of time for the lungs to recover coupled with optimal respiratory care to maximize the chances of lung recovery is recommended before considering a patient for a lung transplant. Patients should be referred for a lung transplant evaluation after a multidisciplinary team with experience in the management of ARDS and lung transplant patients determines if there is: (i) no recovery after 4 to 6 weeks from the onset of symptoms of COVID-19, (ii) significant respiratory deterioration from base line and (iii) the need for oxygen supplementation, MV or extracorporeal life support. Contraindications for a lung transplant, such as an active or recent malignancy, severe chest wall deformities, irreversible bleeding disorders, compromise of other major organ systems, active substance abuse, inability to comply with a complex medical regimen, lack of adequate financial, or social support, should be ruled out first. Based on initial reports from our center and others, it is recommended that patients who undergo lung transplantation for COVID-19 include those younger than 70 years old, have been cleared of COVID-19 infection, single organ failure, no permanent neurologic damage, and a body mass index below 35.[14–17]

Once a patient has been deemed a suitable candidate for transplantation, any decision related to timing of the transplant should include several factors. The ideal time to perform a lung transplant in patients with lung disease after COVID-19 is determined by a combination of reasonable evidence indicating that the lung changes are irreversible, the physiologic reserve of the patient is adequate, and the physical deconditioning and complications associated with the disease have not placed the patient at too high a risk of death and complications–thus, reducing the benefit of a transplantation. For patients with significant functional limitations due to the COVID-19 infection or who require mechanical respiratory support, the risk of developing further complications affecting other organ systems, increasing physical deconditioning, and malnutrition should be considered. In such patients, there should be an emphasis on decreasing sedation, increasing the patients' involvement in their care, optimizing nutritional support, and minimizing threats to other systems. Judicious management of fluids is critical to improve the respiratory function without compromising other organ systems.

Approximately one-third of the patients admitted to the hospital for COVID-19 infection developed acute kidney injury and approximately 15% required renal replacement therapy.[18,19] Hospitalized patients requiring high ventilator support for a prolonged period have a low likelihood of recovery. In our series, without a lung transplant, there was a near 100% mortality rate for patients who required more than seven days of MV for COVID-19 ARDS.[20] Therefore, an early preliminary evaluation for lung transplantation candidacy of these patients before starting mechanical life support is recommended to help tailor individual therapy.

For patients who are not admitted to the hospital, a standard evaluation for lung transplantation should be performed. A sufficient time for recovery of 4 weeks, or ideally 8 weeks, from the beginning of COVID-19 symptoms is recommended before considering lung transplantation. Recently published high-quality studies support the use of ECMO for ARDS, and large multicenter studies have reported good outcomes with the use of ECMO for COVID-19-associated ARDS. Considering this evidence, prolonged ECMO support, extending past 28 days, may be necessary to bridge some patients with COVID-19-associated ARDS to recovery, instead of bridging to lung transplant.[21] A complete standard evaluation is recommended, including all the physiologic and socioeconomic factors used for the evaluation of all patients considered for lung transplantation.

To date, in the United States, patients who have received lung transplants for COVID-19 are younger than patients receiving lung transplants for other indications[3,17]

Demonstration of eradication of the COVID-19 infection is critical before performing a lung transplantation. Strong immunosuppression, needed immediately after the lung transplant, can be detrimental in patients with a persistent COVID-19 infection. We recommend that patients receive two negative polymerase chain reaction (PCR) tests 24 h apart performed using samples obtained from the distal airways with a bronchoalveolar lavage, as those areas have a higher viral load and have a lower false negative rate in comparison to the upper airway. When the patient is not intubated, we recommend two negative PCR tests from samples obtained from the upper airway at least 24 h apart.[15,17]

INTRAOPERATIVE CONSIDERATIONS DURING TRANSPLANT

To date, most transplanted patients for COVID-19 ARDS have received a double lung transplant as the most common procedure for any lung transplant recipient with acute respiratory failure requiring MV or ECMO support, and also in part due to the high prevalence of severe pulmonary hypertension.[3,17] However, a few single lung transplants in patients with respiratory disease secondary to COVID-19 infection have been performed successfully.[3] Many COVID-19 patients develop structural abnormalities such as cavitary lesions and recurrent pleural infections with recurrent bacterial infections. The presence of persistent infections or structural abnormalities, such as large cavities that could be potential sources of infection in the postoperative period, pose a high risk for patients' undergoing a single lung transplant for respiratory disease secondary to COVID-19 infection. As such, single lung transplantation should be considered on a case-by-case basis and mostly reserved for patients with long-term COVID-19 fibrosis rather than ARDS.

Owing to the high incidence of pulmonary hypertension and right ventricular dysfunction, in addition to the higher incidence of severe pleural adhesions, the use of intraoperative venoarterial (VA) ECMO support is highly recommended. As many of these patients are already on peripheral venous-venous (VV) ECMO support, it is important to consider conversion to VA ECMO for a better hemodynamic support. Pneumonectomies also pose significant challenges because of the presence of adhesions between the lungs and the pleura and mediastinum. In these patients, the dissection planes are frequently altered, and bleeding is often significant. Surgical teams, as well as perfusion and anesthesia teams, should be aware of this and prepare to transfuse and support the patient. The chest cavities are often small, requiring caudad retraction of the diaphragm to facilitate the operation. As expected, the operative time and organ cold ischemic time is longer in COVID-19 patients, as is the requirement for transfusion of blood products in comparison with other pathologies.[17]

A unique challenge in COVID-19 ARDS patients is the presence of diaphragmatic dysfunction. In a recent study, 76% of patients discharged to rehabilitation after severe COVID-19 ARDS had sonographic evidence of diaphragm dysfunction.[22] The mechanisms associated with the diaphragmatic dysfunction in these patients include critical illness myopathy, ventilator-induced diaphragmatic dysfunction, iatrogenic injury of the phrenic nerve during placement of central lines, post-infectious inflammatory neuropathy of the phrenic nerve, and direct neuromuscular involvement of the COVID-19 virus. Peripheral nerves and muscles express angiotensin-converting enzyme 2 (ACE2) receptor to which viral structural proteins bind. Autopsy studies have shown diaphragmatic fibrosis and a unique myopathic phenotype compared with other ICU patients.[23–25]

The prevalence and impact of these findings in transplanted patients is unknown, but they play a role in the increased number of complications, need for ventilator support, and ICU stay. A diaphragmatic and phrenic nerve evaluation with bedside ultrasound is a useful tool in ventilated patients to assess the function of the diaphragm longitudinally and detect improvement or deterioration of the diaphragmatic function. Although to date there are no studies evaluating the effect of any therapeutic intervention for diaphragmatic dysfunction after lung transplants for respiratory disease after COVID-19 infection, some transplant centers advocate for the early use of diaphragmatic pacing in a selected group of patients. However, the short and long-term results of this intervention are unknown. Nonetheless, these findings stress the importance of protecting the phrenic nerve during the conduction of the operation minimizing trauma or traction of the nerves.

POSTOPERATIVE CARE OF THE TRANSPLANTED PATIENTS

Postoperative care in the ICU involves respiratory support with MV and extracorporeal life support with VV and VA ECMO. The length of stay in the hospital and in the ICU after a lung transplant for

COVID-19 has been reported to be almost twice as long for patients receiving lung transplants for other reasons. In our series, the median length of stay for COVID-19 transplant patients versus other lung transplant patients was 28.5 versus 16 days in the hospital and 6.5 versus 2 days in the ICU. The need for care in the ICU was largely determined by the need for MV. Analysis of the United Network for Organ Sharing (UNOS) database for patients receiving transplants related to COVID-19, indicate that over 70% of such patients have needed MV for at least 48 h after the transplant.[3] In our series, the median time on a ventilator was 6.5 days.[17] In addition, according to the UNOS database, approximately 12.3% of patients needed postoperative ECMO,[3] and there was a 30-day mortality of 2.2% (4 of 183 patients analyzed) and a 6-month survival rate of 92%.

In our series, 1-year survival rate after transplantation of 30 patients for COVID-19 was 100% after a median follow-up of 351 days in comparison with 83.3% survival of patients that received transplants for a different pathology. Thirty percent of the patients needed ECMO support after transplant.[17] The difference in the need for ECMO support posttransplant is likely explained by institutional preferences in the postoperative management of these patients and the heterogeneity in patient complexity. The causes of early, postoperative deaths include respiratory failure, rejection after transplant, gastrointestinal infection, hyperammonemia, and COVID-19 infection. Other frequent postoperative complications after lung transplant for COVID-19 include primary graft dysfunction (PGD), stroke, acute renal failure, and transplant rejection, and pleural effusions.

Renal dysfunction occurs more frequently in patients with COVID-19. This is true also for patients after lung transplants due to COVID-19 in comparison with patients undergoing lung transplants for other reasons. Approximately 30% of patients hospitalized with COVID-19 develop kidney injury, and 50% of COVID-19 patients in the ICU with kidney injury require dialysis. Vascular endothelial injury associated with COVID-19 infection, hemodynamic instability, tissue inflammation, and immune infiltration may play a role in the origin of kidney injury.[26] Even though the long-term outcomes are unknown, patients with COVID-19 infection and renal failure have higher mortality and worse outcomes. Approximately 5% of COVID-19 patients who have received a lung transplant needed dialysis before transplantation.[3] In comparison with non-COVID-19 patients, the rate of permanent hemodialysis after lung transplant is significantly higher in COVID-19 patients (13.3% vs 5.5%). Of note, a similar percentage of COVID-19 patients that received a lung transplant (10%) required only temporary postoperative dialysis.[20] However, it is unclear what percentage of patients that had renal failure before transplant required permanent dialysis after lung transplant. Some centers have performed simultaneous lung and kidney transplants when the potential of recovery of kidney function was deemed low.

The degree of PGD after transplant is not clearly understood. In our series, 70% of the patients had some degree of PGD. However, their rate of acute rejection or development of donor specific antibodies was zero in comparison with a 12% in non-COVID-19 patients. A potential explanation for the low rate is the dilution of human leukocyte antigen titers due to a higher rate of bleeding and transfusions.[17] The impact of these findings in the development of chronic allograft dysfunction in these patients is unknown. Despite the higher frequency of PGD, the patients that received a lung transplant for respiratory diseases after COVID-19 infection had more significant improvement in their performance in comparison with the non-COVID-19 patients.[20] This is not surprising considering the more critical condition of the COVID-19 patients at the time of the transplant relative to the non-COVID-19 patients as well as the younger age and healthier base line of such patients before COVID-19 infection.

With the high prevalence of COVID-19 infection, a particular subject with impactful implications for the future is the selection of lungs from donors that could have had infection for COVID-19. The current recommendation from the UNOS is to obtain samples from the lower respiratory tract from donors and analyze those by PCR for COVID-19, due to the higher frequency of the viral receptor ACE2 in the lower respiratory tract and because the viral testing in samples obtained from bronchoalveolar lavage remains positive for a longer period in comparison to samples obtained from the upper respiratory tract.[27] However, to maximize the use of the organs and decrease the false positive rates of COVID-19 tests, if a positive test is found and the clinical probability of a positive infection is low, it is recommended to repeat the test in samples obtained from the distal airways. In donors with a history of infection of COVID-19 more than 21 days before the lung procurement, the likelihood of active COVID-19 infection and transmissibility is extremely low. The assessment of the organ at the time of procurement also provides valuable information about the condition of the organ. Evaluation of the donor lungs with a computed tomography scan looking for fibrotic changes, persistent hypoxia in central and selective arterial

gases sampling, thick and rigid lungs at in situ palpation of the organs, and reduced lung compliance in the ventilator are all indicators of fibrotic changes in the lung. **Fig. 1** shows an algorithm for evaluating the donor lungs in the setting of a potential history of COVID-19.[28]

In conclusion, lung transplant is a life-saving treatment for carefully selected patients with COVID-19-associated respiratory failure. Despite a complex pretransplant medical course, the post-transplant outcomes are excellent when performed by experienced centers.

PREVENTION AND SPECIFIC POST EXPOSURE PROPHYLAXIS

General measures that include avoiding close contact with sick individuals, frequent hand sanitation, social distancing, and mask wearing in public are important for the prevention of SARS-CoV-2 infection. There are multiple COVID-19 vaccines available worldwide; four are used in the United States. Pfizer/BioNTech® and Moderna® COVID-19 are FDA approved for two doses and two booster doses are approved including a bivalent booster. For up-to-date recommendations, please check www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html. Novavax® subunit vaccine and J&J/Janssen® adenovirus vaccine are only recommended as alternatives for patients who are hesitant about or have a contraindication for mRNA vaccines. Tixagevimab/cilgavimab (EVUSHELD®) has been administered as pre-exposure prophylaxis in lung transplant recipients beginning two weeks after completion of COVID-19 immunization or in cases where vaccination is contraindicated or deferred. It is important to note that Evusheld® lacks activity

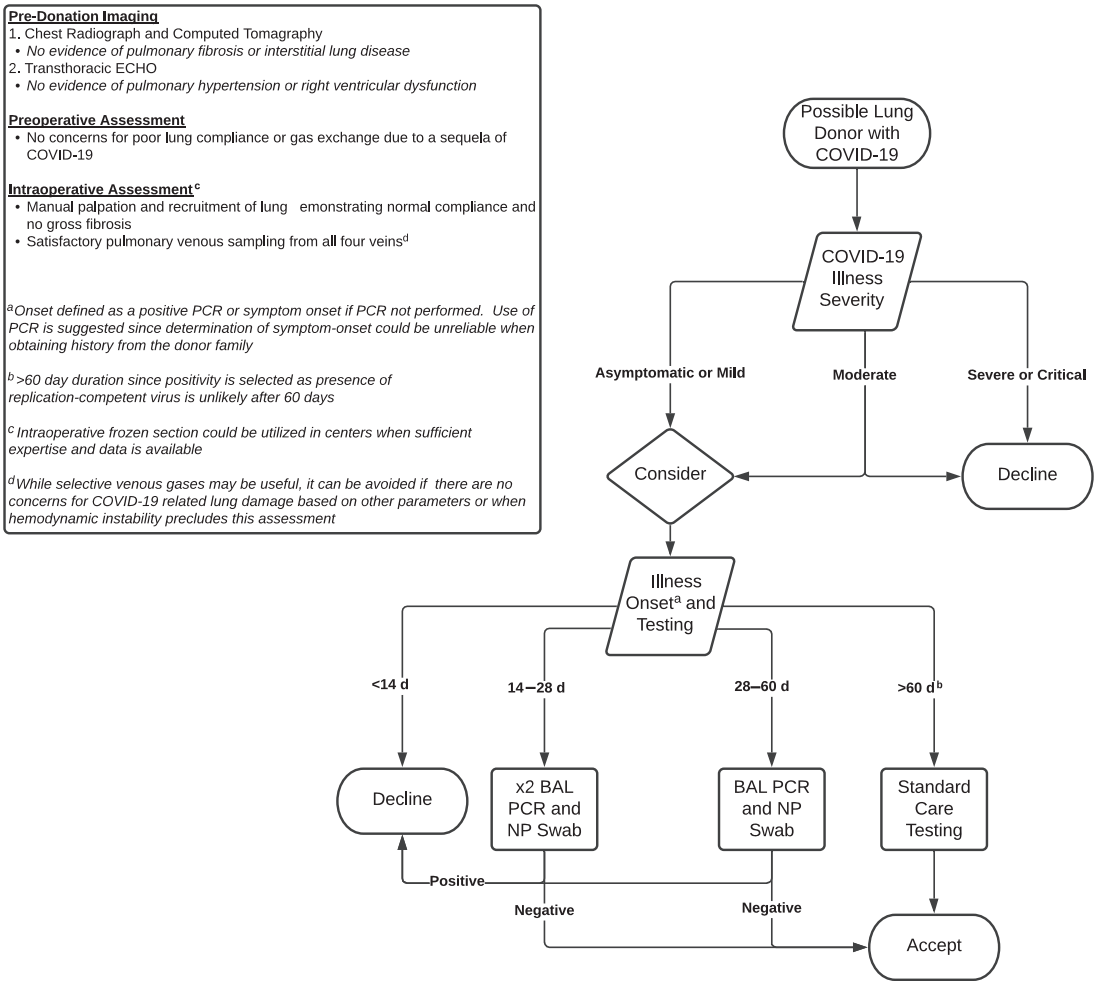

Fig. 1. Institutional practice for assessment of lungs from donor with historic COVID-19. (*From* Querrey M, Kurihara C, Manerikar A, et al. Lung donation following SARS-CoV-2 infection. Am J Transplant. 2021;21(12):4073-4078.[27])

against BA4.6 and other emerging variants such as BQ.1 and BQ.1.1. Post-exposure prophylaxis with monoclonal antibodies included Casirivimab/Imdevimab (REGEN-COV®) and Bamlanivimab/etesevimab, are no longer recommended as they lack sufficient activity against the omicron variants.

TREATMENT FOR POST LUNG TRANSPLANT PATIENTS WITH COVID 19 NOT REQUIRING HOSPITALIZATION

Monoclonal antibody therapy has been a mainstay for COVID-19 treatment for immunocompromised transplant recipients since late 2020. However, the most recently available monoclonal antibody treatment, Bebtelovimab, is no longer recommended due to lack of efficacy against omicron subvariants BQ.1 & BQ1.1, which are now the dominant subvariants circulating. Therefore, currently there are no monoclonal antibody options for treatment.

For patients with mild to moderate symptoms not requiring hospitalization, we recommend an antiviral within 5 days of symptom onset. The preferred antiviral treatment for outpatients at this time based on the available data of clinical efficacy is nirmatrelvir/ritonavir (Paxlovid®). However, its use is limited by renal function and drug-drug interactions, particularly with calcineurin inhibitors (CNIs). Molnupiravir is also an option for outpatient antiviral treatment, but data on the efficacy of molnupiravir in immunocompromised hosts is limited. Medications should be reviewed, if possible, with the help of a clinical ID and transplant pharmacist.

A 3-day course of Remdesivir to prevent progression of disease and hospitalization is recommended but is limited at this time logistically due to the need for daily infusion.

Molnupiravir (Lagevrio®) 800 mg PO twice daily for 5 days is the preferred antiviral therapy if the patient is on extended-release tacrolimus, or if Paxlovid® is contraindicated due to other drug-drug interactions, pregnancy or CrCl <30.

TREATMENT FOR POST LUNG TRANSPLANT PATIENTS WITH COVID 19 REQUIRING HOSPITALIZATION

Patients with no oxygen requirement have limited options. The most common antiviral used is Remdesivir for 3 days of therapy. It can be given to patients with severe renal failure/ESRD based on CATCO data [2]. Monitoring of AST/ALT is recommended, and remdesivir is not recommended if the ALT is 10 times the upper limit of normal. One should also monitor for bradycardia. Prophylactic anticoagulation (AC) is recommended while hospitalized. In patients requiring low flow supplemental oxygen: Remdesivir 5-10 days duration, plus dexamethasone 6 mg daily for 10 days (Oral or IV) is recommended. Therapeutic AC is recommended irrespective of D-dimer value, while hospitalized. If disease severity progresses to severe illness during the hospital admission and there is no evidence of thrombosis, the AC strategy should be modified to prophylactic doses of AC.

For patients requiring high flow oxygen, or non-invasive or invasive ventilation: Remdesivir for 5-10 days, and dexamethasone 6 mg daily for 10 days (Oral or IV) is recommended. Baricitinib, a JAK inhibitor, is the preferred agent if inflammatory markers are increased, for ARDS, and if there are no contraindications such as ESRD, severe neutropenia or leukopenia. The Baricitinib dose is 4 mg PO daily for 14 days, and the dose will need to be adjusted if the eGFR <60 mL/min/1.73m2.

When Baricitinib is contraindicated, tocilizumab, an IL-6 inhibitor, is recommended for patients with severe COVID-19, and if the patient has not already received more than 2 doses of baricitinib. The patient must have already received at least 1 dose of dexamethasone, have increased inflammatory markers (C-Reactive Protein > 75mg/L), and abnormal chest imaging with bilateral consolidation and ground glass opacities. Tocilizumab is given as a single dose that is weight based <40kg: 8mg/kg, 41-65kg: 400mg, 66kg-90kg: 600mg and > 90kg: 800mg.

Tocilizumab should be used with caution when the patient has elevated procalcitonin due to concern for secondary bacterial infection, and if there is a current uncontrolled serious bacterial, fungal, or non-COVID-19 viral infection, this agent should be avoided. Tocilizumab should also be avoided if alanine transaminase is >5 times the upper limit of normal, if there is a high risk for gastrointestinal perforation, neutropenia (Neutrophil count <500 cells/μL) or thrombocytopenia (Platelet count <50,000 cells/μL).[30–34]

CLINICS CARE POINTS

- Patients undergoing lung transplant for Coronavirus 2019 infection ARDS have a more complicated perioperative course than non-Coronavirus 2019 patients undergoing lung transplant.
- The long term results after lung transplantation for Coronavirus 2019 infection ARDS are comparable to outcomes in non-Coronavirus 2019 patients.

DISCLOSURE

D. Avella and A. Bharat have no commercial or financial conflicts.

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