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#### Chapter

# Lung Transplant for Interstitial Lung Diseases

Brandon Nokes, Eugene Golts and Kamyar Afshar

# Abstract

Lung transplant is an important treatment modality for select cases of advanced interstitial lung disease. However, the pre- and postoperative management requires several unique considerations. The decision to transplant is based largely on clinical severity of illness and the lung allocation score. Transplant improves overall mortality across the interstitial lung diseases, though not all ILD subtypes experience equal benefit from lung transplant. Broadly speaking, there is no difference in benefit between single- and bilateral-lung transplants, though we will discuss some important clinical nuances to this decision as well. Lastly, there are a number of immunosuppression, coagulation, and malignancy risk considerations that must be carefully understood in caring for the lung transplant patient. This chapter will provide a general overview of the indications for lung transplant, risk stratification for lung transplant across the interstitial lung diseases, as well as general postoperative management details.

**Keywords:** interstitial lung diseases, usual interstitial pneumonia, lung transplant, lung allocation score, immunosuppression

#### 1. Introduction

Lung transplantation is a therapeutic surgical option for selected patients with severe pulmonary disease who are refractory to medical therapy and continue to have progressive clinical deterioration [1]. As is discussed elsewhere in this book, the idiopathic interstitial pneumonias (IIPs) that require lung transplantation include idiopathic pulmonary fibrosis (IPF)/usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), and acute interstitial pneumonia (AIP). The non-IIP ILD groups that are routinely evaluated for lung transplant include sarcoidosis, hypersensitivity pneumonitis (HP), rheumatologically associated UIP and NSIP, as well as lymphangioleiomyomatosis (LAM).

The general guidelines for lung transplantation consideration include (1) high (>50%) risk of death from lung disease within 2 years without transplant, (2) high (>80%) likelihood of surviving at least 90 days after lung transplantation, and (3) high (>80%) likelihood of 5-year posttransplant survival from a general medical perspective provided that there is adequate graft function [1]. Within the United States, between 1995 and 2015, ILDs accounted for 29.7% (n = 14,828) of lung transplants [1]. Collectively, the ILDs were the second most common indication for transplant behind chronic obstructive pulmonary disease without alpha-1-antitrypsin deficiency [1]. Of those patients, 6956 received single-lung transplant, and 7872 received bilateral-lung transplants [1]. Importantly, the ILD diagnostic subclasses were subdivided into idiopathic interstitial pneumonias (IIP) (n = 12,243) as well



Table 1.

Common drug-drug interactions with immunosuppressants—adapted from [37].

as ILD, not-IIP (n = 2585) (**Table 1**). Sarcoidosis, obliterative bronchiolitis (OB), and connective tissue disorder (CTD) were also listed diagnostic indications, and so there exists the potential for overlapping and misclassification of the underlying disease leading to lung transplant in a small proportion of cases. Irrespective of the subtype, ILDs present a unique challenge from pretransplant selection to postoperative care. The pre- and posttransplant clinical courses for each of these pathologies will be detailed within this chapter.

# 2. The lung allocation score (LAS) and the decision to transplant

An important part of the preoperative evaluation is individual assessment of patient risk with and without transplant. Some European countries, like France and Switzerland, have a national urgency list. Others, including the United Kingdom, allocate donor lungs according to individual transplant center decisions. More than 60% of the worldwide lung transplant activity, however, is allocated by the lung allocation score (LAS) [2]. The LAS has been adopted in many countries as a means of minimizing waitlist mortality [2]. The LAS is a calculated score (from 0 to 100) used to predict waitlist survival probability with and without a lung transplant for patients over the age of 12. Higher LAS scores impart a higher likelihood of waitlist mortality and allow for a prognostic stratification within regional transplant waitlists and associated organ allocation preference [2]. This multifactorial system combines pulmonary function data with clinical comorbidity data. The implementation of this system has resulted in a substantial reduction in waitlist mortality and for the more expeditious mobilization of organs on a needs-based assessment [3]. Moreover, the median waitlist time in the United States has dropped from 4.1 to 2.1 months since the adoption of the LAS [2]. As such, the LAS has since been adopted in a number of other countries' transplant programs [4, 5]. Similar OLT outcomes research has been conducted on healthcare-related quality of life (HRQL) after transplant, and in general, higher LAS imparts a greater improvement in HRQL after OLT [6]. This benefit appears to diminish with greater age, especially after age 65 [6].

Despite the shorter waitlist time with higher LAS score, some patients may remain on the waitlist for longer periods of time. This is a reflection of a number of logistic limitations underpinning the lung transplant process. Notably, the number of available lung allografts does not meet the current US or global need. Up to

20% of lung transplant candidates are inactivated or die before an adequate donor becomes available [7]. Moreover, explanted lungs are inherently fragile, which further complicates the transplant process. Recipient underlying lung disease greatly matters in the type of transplant procedure required, e.g., unilateral vs. bilateral OLT. Donor and recipient lung size match is essential for adequate function of the allograft as well as survival [8]. Shorter patients may require lung donors from pediatric patients. However, pediatric lungs are first offered to pediatric candidates (age < 18 years) before they become available to other potential recipients.

Donors and recipient ABO blood type and human leukocyte antigen (HLA) compatibility must also be considered. Ideally, patients will have absent panel-reactive antibodies (PRA). Notably, only 69.8% of lung transplant candidates had 0% PRA since 2009. Patients with a higher PRA, particularly PRA greater than 25%, have a higher 30-day and overall mortality [9]. This makes the waitlist time for an appropriate crossmatch significantly longer and can potentially exclude the candidate from transplantation due to elevated risk of rejection.

The underlying diagnosis necessitating transplant also impacts the LAS. With respect to ILD, individuals with IPF and sarcoidosis are more likely to have a higher LAS than more common diagnoses such as COPD [3]. With LAS scores greater than 60, individuals with IPF have a greater risk of posttransplant mortality. Although no strict stratification exists to say at which LAS transplant should be avoided, this decision is left to local transplant centers when the risk is exceedingly high [3].

#### 3. Idiopathic pulmonary fibrosis (IPF) lung transplant overview

Given the relative preponderance of IPF as a pretransplant diagnosis in comparison to the other ILDs, a brief overview of IPF outcomes following transplant is included here. The most common of the ILDs to necessitate transplant is IPF, which accounts for roughly 46% of patients on the lung transplant waiting list according to 2011 data from the Organ Procurement and Transplantation Network (OPTN) [10]. Importantly, IPF has no definitive treatment and an average survival of 2–3 years after diagnosis. It is associated with older age, male sex, and smoking history. It has also been associated with shortened telomere length, both in familial and sporadic forms [11]. This finding has been demonstrated in both peripheral blood leukocytes and postmortem lung tissue samples [11]. There are no targeted therapies readily available to curtail this epigenetic proclivity, but as IPF progresses, OLT remains a life-saving measure, with a median survival of 4.5 years after transplant for both bilateral- (BLT) and single-lung transplant (SLT) [12]. A recent meta-analysis suggested that those with BLT may have improved survival when compared to SLT, but this may be a result of selection bias [12]. Importantly, only those with end-stage bronchiectasis and idiopathic pulmonary arterial hypertension (IPAH) require BLT, and essentially all other diagnoses are suitable for SLT [12].

The clinical time course for IPF is heterogeneous, but there is invariably a clinical and functional decline, and many of these patients will have to go for transplant (**Figure 1**) [13]. The survival after transplant is the poorest for IPF relative to other indications for OLT, with the exception of re-transplant (**Figure 2**) [1]. As noted, the implementation of the LAS has allowed more rapid allocation of allografts for IPF and has improved prognosis tremendously. Further, although the median FVC for IPF at time of transplant is ~40–45%, this improves to 65% after transplant, contingent on selecting appropriate donor size [14]. Predicted total lung capacity (pTLC) can be used to approximate appropriate donor lung size for SLT or BLT [14]. In the absence of postoperative graft dysfunction, improvements can also be expected in HRQL, 6-minute walk test (6MWT), PaO2, and dyspnea severity [15, 16].



Figure 1.

Clinical course of patients with idiopathic pulmonary fibrosis. Many follow the course of the slow progressive decline. A minority will have a rapidly progressive course. An acute exacerbation can occur at any point in the course of functional decline. Rapidly progressive; acute exacerbations; and slowly progressive. Adapted from [51].



Kaplan-Meier survival by diagnosis for adult lung transplants performed between January 1990 and June 2010. Alpha-1, α1-antitrypsin deficiency emphysema; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; PAH, pulmonary arterial hypertension—adapted from [38].

# 4. Issues addressed while awaiting lung transplantation

#### 4.1 Short telomere length

Rare mutations in the telomere pathways (NAD1, PARN, RTELI, TERC, TERT) are found in familial pulmonary fibrosis [11, 17]. Having short telomere length is characterized by earlier onset of IPF, associated liver disease, impaired CMV immunity, and bone marrow suppression [11, 17, 18]. Newton et al. conducted an observation cohort study of IPF patients who underwent lung transplantation [19]. Patients were stratified into two groups based on the telomere length; 32 patients were in Group 1 (telomere length < 10th percentile). They were compared to the 56 patients in Group 2 (telomere length  $\geq$  10th percentile). There were no difference between the two groups with regard to baseline demographics and severity of lung disease.

Group 1 lung transplant recipients had higher incidence of primary graft dysfunction grade 3 and earlier time to chronic allograft dysfunction. There was no difference in the incidence of acute allograft rejection, cytopenias, or infections. Popescu et al. reported the increased risk of *Cytomegalovirus* (CMV) infections in the short telomere IPF lung transplant recipients [18]. Given this knowledge, some lung transplant centers will only accept CMV-negative donor lungs in order to reduce risk of transmission and CMV-related complications. In the case series of eight patients by Silhan et al., these lung transplant recipients with short telomere tolerated a dual drug immunosuppression [20]. The antimetabolites could be easily withdrawn. Hematological complications occurred in four lung transplant recipients, with two cases of known bone marrow failure prior to lung transplantation. There was a 12% platelet transfusion rate. Several patients had infectious complications with gram-negative pneumonia/sepsis, fungal infections, and CMV disease (pneumonitis). These patients developed acute kidney injury, with half of them requiring renal replacement therapy.

# 5. Studies on OFEV/Esbriet prior to lung transplantation

Many centers were initially reluctant to the use of nintedanib in IPF patient listed for lung transplant due to its potential to increase perioperative bleeding risk and impaired wound healing, thereby causing bronchial anastomotic complications. These concerns have been alleviated with recent publications that indicate no worsening of airway complications or bleeding risks [21, 22]. Four of the nine patients in Balestro et al.'s study required intraoperative venoarterial or veno-veno extracorporeal membrane oxygenation (ECMO) [21]. No patient experienced major bleeding, despite being on nintedanib as well as aspirin + clopidogrel. There were also no reports of airway anastomotic dehiscence.

The exact mechanism of action of pirfenidone may be from the inhibition of transforming growth factor beta (TGF-b) [23]. A few case reports describe the safety of pirfenidone use as a bridge to lung transplantation [24, 25].

Mortensen et al. reported the largest retrospective analysis of 18 IPF patients who took pirfenidone prior to lung transplantation [25]. Only one patient developed sternal dehiscence that was more related to a surgical issue. There was no airway dehiscence in any of the 18 patients.

# 6. Other preoperative immunosuppressive considerations

Many patients with sarcoidosis, hypersensitivity pneumonitis, and rheumatologically induced ILD require corticosteroids to help control respiratory symptoms and further lung parenchymal inflammation. Chronic steroid use can lead to thinning of the skin, myopathy, and delayed wound healing [26]. McAnally et al. reported the deleterious effects of pretransplant corticosteroids [27]. Sixty six percent of their patients awaiting lung transplantation were on corticosteroids. The 132 patients in the low-dose steroid group ( $<0.42 \text{ mg/kg/m}^2$ ) were compared to the 69 high-dose steroid group ( $\ge0.42 \text{ mg/kg/m}^2$ ). Patients were clinically similar based on underlying lung disease, severity of lung function, transplant type, and donor lung ischemic time. The high-dose steroid group had higher rates of serious infections and delayed wound healing as well as higher risk of early posttransplant death. The general recommendations are not only to minimize the steroid dose to allow for continued stabilization of underlying ILD but also to minimize complications with bridge to lung transplantation.

#### Interstitial Lung Diseases

Lymphangioleiomyomatosis is characterized by proliferation of LAM cells, the abnormal smooth muscle-like cells that metastasize to lead cystic changes seen on chest radiograph. The cysts are present throughout both lung fields, although they predominate in the lower lung region. Their size can vary from 3 mm up to 3 cm. Larger cysts (>0.5 cm) are more likely to cause pneumothoraces [28]. Pneumothoraces occur in up to 60–70% of women with LAM. A majority of first-time pneumothoraces occur in the third and fourth decade of life [29]. Unfortunately, they are not a one-time event for most LAM patients. Four percent of these individuals can have simultaneous bilateral pneumothoraces. Recurrence rates for pneumothoraces are upward of 70%. Sirolimus, an mTOR inhibitor, is currently recommended as therapy for LAM. It blocks the signaling pathway for the growth and proliferation of the LAM cells that cause all the clinical manifestations described. Common adverse events when taking sirolimus include mucositis, diarrhea, nausea, hypercholesterolemia, and lower extremity edema. The most relevant adverse events of sirolimus in the context of this chapter are poor wound healing and anastomotic dehiscence in perioperative periods [30–32]. Dilling et al. reported their experience of continued use of sirolimus in patients with LAM while awaiting lung transplantation [33]. All patients were continued on their maintenance sirolimus dose up to the day of lung transplantation. None of the patients developed increased bleeding or wound dehiscence. In select patients, the use of sirolimus may be required. Lymphangioleiomyomatosis can recur following lung transplantation. It may present itself primarily as a chylous effusion. If a single-lung transplant is performed, the cystic lung disease can continue to progress. Sirolimus can be added to the maintenance immunosuppression to help the underlying process. There is varying reports on the safety of sirolimus use in early post-lung transplantation [31, 34].

#### 7. Medical care of the lung transplant patient

The medical care after OLT requires close coordination between a multidisciplinary transplant team, including but not limited to transplant pulmonologists, cardiothoracic surgeons, pharmacists, physical/occupational/respiratory therapists, social workers, transplant nurses, and patient advocates. The transplant committee decision-making process for transplant eligibility is complex and beyond the scope of this text. However, important consideration elements of note are functional status, including physical ability to tolerate and recover from OLT [1]. To this end, physical therapy and nutritional optimization are paramount in the pretransplant process in order to ensure posttransplant success. Many inpatients that are listed for transplant have achieved benefit from early veno-venous extracorporeal membranous oxygenation (VV-ECMO) in order to facilitate mobilization and engagement with physical therapy [35, 36].

Transplant infectious disease specialists can be helpful in directing regionally appropriate infectious disease screening/treatment prior to transplant. *Cytomegalovirus* (CMV) and Epstein-Barr virus (EBV) status assessments between donor and recipient are paramount in guiding postoperative antiviral therapy, with CMV +/- and CMV -/+ being prophylaxed with valganciclovir and CMV -/- receiving acyclovir. EBV status is helpful in determining immunosuppressive needs. Over-immunosuppression can increase the risk of posttransplant lymphoproliferative disorder (PTLD), a lymphoma-like condition that responds to reduction in immunosuppression. All lung transplant recipients receive high-dose glucocorticoid treatment and require pneumocystis prophylaxis, typically with trimethoprim-sulfamethoxazole.

#### 7.1 Complications following lung transplant

Acute rejection rates are extremely common in the first year after lung transplantation with approximately 30–40% of recipients having at least one episode in the first year after transplant. Triple-drug immunosuppressive agents have become the standard of care and are prescribed to minimize this risk [37]. Immunosuppressive dosing must be carefully considered so as to minimize acute rejection risk without leading way to infections. The regimen typically prescribed in lung and most solid organ transplants typically includes prednisone, a calcineurin inhibitor (tacrolimus or cyclosporine), and an antimetabolite (azathioprine or mycophenolate mofetil). Despite the unique side effects of each of these drug classes, the cumulative effect of immunosuppression may predispose individuals to opportunistic infections, renal failure, malignancies, posttransplant hypertension, diabetes, and dyslipidemia. **Table 1** reviews common drug interactions that can alter immunosuppressant clearance or therapeutic drug levels.

The lung allograft is subject to a variety of insults resulting in various parenchymal abnormalities. These complications are broadly classified as infectious and noninfectious. The development of infections is the leading cause of morbidity and mortality in the first 3 years following lung transplantation [38]. Bacterial pathogens are the most common, but fungal and viral infections are also particularly important (especially *Aspergillus* and *Cytomegalovirus*).

Despite their ubiquitous and potentially ominous nature, radiographic pulmonary parenchymal abnormalities predicting posttransplant complication can be nonspecific (**Figures 3–5**). Bacterial and fungal radiographic features are highly varied and include consolidation, ill-defined nodules, cavitation, and ground-glass opacifications, making them difficult to identify. Viral infections (especially CMV) may have normal radiographs. They can also show ground-glass, micronodules, consolidation, and/or reticulonodular opacities.

Moreover, acute cellular rejection (ACR) can present similar to any of the previously mentioned complications. ACR radiographic features can appear as normal radiograph, ground-glass opacities, alveolar opacities, consolidation, nodules, as well as a new or evolving pleural effusion (seen in 43% of patients) [39, 40].

Due to the radiographic overlap in postoperative lung pathologies, broadspectrum antimicrobial therapy is often instituted in the acutely ill lung transplant



**Figure 3.** Chest X-ray of a single-lung transplant recipient for IPF.



**Figure 4.** *Chest X-ray of a bilateral-lung transplant recipient for IPF.* 

recipient. A broad infectious differential must be maintained given the triple-drug immunosuppression when considering treatment options. Similarly, acute rejection is on the differential, and differentiating between the two is imperative. Clinical correlation and transbronchial biopsy are often indicated for discerning the diagnosis. The number of acute cellular rejections and infections contribute to a higher risk of developing chronic rejection.

Primary graft dysfunction (PGD) accounts for the main cause of death within the first 30 days following lung transplantation [38]. The underlying diagnosis leading to transplant is not predictive of developing PGD (restrictive disease with PGD 22.1% vs. without PGD 20.3%) [37]. More recently, patients with IPF and associated pulmonary hypertension have been shown to have a higher incidence of developing PGD [41]. Moreover, higher pulmonary artery pressures impart a greater risk of developing severe PGD (grade 3).

Early diagnosis and management may impart a lower incidence of chronic allograft rejection. Chronic allograft rejection manifests as bronchiolitis



**Figure 5.** Chest X-ray of a single right-lung transplant recipient for LAM.

obliterans syndrome (BOS) or restrictive allograft syndrome (RAS). BOS is typically a progressive airflow limitation demonstrated on pulmonary function testing (PFT). Grading of BOS depends on the severity of airflow limitation relative to the patient's best posttransplant FEV<sub>1</sub>. The radiographic presentations of BOS include a mixture of hypo- and hyperattenuation (mosaic attenuation) regions produced by air trapping and decreased peripheral vascularity, bronchiectasis, and subsegmental atelectasis. RAS is hallmarked by upper lobe fibrosis. Radiographic RAS may have reticulonodular opacities, honeycombing, traction bronchiectasis, loss of lung volume, and interlobular septal thickening (**Figure 6**). In comparison to BOS however, these patients have restrictive physiology on PFTs [40, 42].

By bronchoscopy, the presence of eosinophilia and neutrophilia, airway infection and/or colonization, and acute cellular/lymphocytic bronchiolitis all impart increased risk of developing both BOS and RAS [37]. The underlying pathology necessitating transplant does not seem to influence the development of one form of chronic allograft rejection (24% BOS and 20.8% RAS).

Altering medications within therapeutic classes or augmenting existing therapy has been advocated when patients develop chronic rejection. There is clearly a small subset of patients who derive benefit from this therapy. However, alteration of immunosuppression may also increase the risk of opportunistic infections and development malignancy.

One alternative therapy for BOS is chronic azithromycin. Several small case series as well as one prospective, randomized, double-blind, placebo-controlled trial have suggested a benefit with azithromycin in lung transplant recipients [43–45]. Azithromycin may prevent the development of BOS, as well as treat a subset of patients with BOS. The mechanism for the positive effect of azithromycin in BOS prevention and treatment is believed to be related to its anti-inflammatory properties. Chronic azithromycin therapy is well tolerated. Gastrointestinal side effects, QTc prolongation, and auditory disturbances are common side effects. Clinicians should be aware that this medication is often taken chronically in lung transplant patients when considering antibiotic choices for acute respiratory infections in this population.



**Figure 6.** *CT chest for a bilateral-lung transplant recipient for sarcoidosis in chronic allograft rejection.* 

#### 7.2 Airway complications

Currently, the bronchial anastomosis is created in an "end-to-end" fashion, and bronchial artery circulation is lost. Thus, the donor bronchus and anastomosis depend solely on the poorly oxygenated pulmonary artery, portending to the development of local ischemia. Early complications (<3 months) from airway/anastomotic ischemia include necrosis and wound dehiscence. During the healing and remodeling phase (>3 months), typical complications are airway stenosis, granulation tissue accumulation, and malacia (typically a later occurrence). Graft rejection, immunosuppression, and bronchopulmonary infections have also been associated with airway complications. Lung transplantassociated airway complications manifest in up to 30% of patients [46, 47]. Management strategies include airway dilation with silicone or self-expandable metallic stents, cryoablation, and laser photoresection. Airway stents are generally placed when respiratory symptoms are refractory to the abovementioned modalities (Figure 7). Most patients experience improvement in symptoms and lung function. However, complications from the above interventions include mucus plugging, obstructive granuloma, stent migration, fracture, or infectious colonization.

#### 7.3 Complications of native lung in single-lung transplantation

It bears mention that patients' native lung disease progression is not halted with the contralateral lung transplantation despite robust immunosuppression. The amount of native lung ground-glass opacification or fibrosis does not change or increases for the majority of single-lung transplant recipients with IPF [48]. Patients with IPF lose 10.8% of native lung volume and have an 11% increase in fibrosis in the first 4 years following SLT [49]. Up to 52% of the native lungs had evidence of fibrosis at the time of transplant, and this number grows to 92% at 4 years posttransplant.

Common complications reported in IPF patients following SLT include bacterial or fungal infections, retention of secretions with associated airway obstruction and atelectasis, as well as pneumothoraces [50]. Moreover, posttransplant acute exacerbation of IPF is increasingly recognized [51]. Bronchogenic carcinomas have been reported at higher rates in single-lung transplant recipients. Significant





contributing risk factors include advanced recipient or donor age, smoking history (>60 pack years), and COPD or IPF as the underlying lung disease [52].

#### 7.4 Thromboembolic events following lung transplantation

Deep vein thrombus (DVT) and pulmonary emboli (PE) occur in up to 29% of lung transplant recipients. Two-thirds of these events occur in the first year of transplantation, and 20% of these events develop within the first month. Reduced mobility and recent surgery are risk factors. Inflammation also inhibits anticoagulant factors [53]. Other risk factors include, most notably, an underlying diagnosis of IPF. Male gender, advanced age, pneumonia, diabetes mellitus, and utilization of cardiopulmonary bypass are other well-defined risk factors [41, 54]. Most of the pulmonary emboli occur within the allograft (86%) [54, 55].

The intrinsically thrombogenic surface of the allograft vasculature anastomosis and increased allograft perfusion with concurrent drop in pulmonary vascular resistance in single-lung transplant recipients are postulated predilections for allograft predominant clot formation. Notably, clots can still occur in the native lung. Most posttransplant PEs are 5.8 months following lung transplantation. Many centers advocate prophylactic anticoagulation for 6–9 months following transplant for this reason. Luckily, most patients tolerate an embolic event, even in the presence of large clot burden, without a loss of lung allograft function [56].

#### 8. Conclusion

Lung transplantation is an important treatment option for patients with interstitial lung disease after medical therapy has failed. However, pulmonary fibrosis patients have the worst survival following lung transplantation. Nonetheless, there is a survival advantage for those with pulmonary fibrosis who proceed with lung transplant [57, 58]. Moreover, lung transplantation improves quality of life. ISHLT registry data denotes that lung transplant recipients have better quality of life, general health, and many are even able return to work. Up to 30% of patients are working at 1 year, and 50% are working at 5 years [59–62].

Lung transplantation, however, is not without its risks, and patient awareness of these risks is important before lung transplantation is entertained or pursued. All appropriate measures should be taken to mitigate risk factors surrounding lung transplantation. So doing can potentially improve long-term outcomes. Lastly, as a growing number of lung transplant recipients make their way into the community, the onus for and access to working lung transplant knowledge now extend far beyond the transplant center, into our communities at large.

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# **Conflict of interest**

The authors have no conflicts of interest to disclose.

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