Navigating the Road to Transplantation for Pulmonary Arterial Hypertension

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Transplantation is an important component of treatment for pulmonary arterial hypertension (PAH) patients with severe limitations despite optimal medical therapy. Although the risks of transplantation remain significant, appropriate candidates may achieve excellent functional outcomes and long-term survival. As PAH therapy and transplantation have advanced, the approaches to transplant referral and listing have changed. This article will review criteria and thresholds for transplant referral and listing, novel approaches to expanding the pool of donor organs, options for bridging to transplantation, and the ways in which the current system for organ allocation have evolved. Knowledge of these concepts will help to ensure timely referral and navigation of the course to successful transplantation for PAH patients.

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Transplantation has been used to treat advanced lung disease successfully for more than 30 years. During this time, therapy for patients with pulmonary arterial hypertension (PAH) has evolved substantially. Along with changes in organ allocation, this has prompted alterations in the approach to referral and timing for transplantation for these patients. Functional and prognostic improvements attributable to PAH treatment have led to deferral or reduction in the need for transplantation for PAH. Nonetheless, for patients with conditions not responsive to treatment or those who experience disease progression despite maximization of medical PAH therapy, transplantation remains an important component of the therapeutic arsenal. In order to avail patients of transplant as an option for escalation in therapy, practitioners require familiarity with indications for timely transplantation referral, general criteria for listing or exclusion, as well as the US Lung Allocation Score (LAS) and other factors that affect waiting times and organ allocation for PAH patients.

This article will address the pathway to referral, waiting list placement, and transplantation for PAH patients. Double-lung transplantation (as opposed to heart-lung transplantation or single-lung transplantation) is currently the primary transplant procedure for PAH patients, and the majority who ultimately undergo this procedure are adults. There is international variability in the approach to organ allocation. This article will focus primarily on lung transplantation for PAH patients in the United States.

HISTORY

Successful heart-lung transplantation was first accomplished in 1981. The first 3 reported patients were transplanted due to PAH that was termed "primary pulmonary hypertension" (PPH) in 1 patient and complex congenital heart disease in the remaining 2.[1] Single and bilateral lung transplantations were accomplished in 1983 and 1986.[2,3] While all 3 procedures have been utilized in the treatment of patients with advanced PAH, the current approach is to consider bilateral lung transplantation for most patients, with the utilization of heart-lung transplantation for patients with PAH in the setting of complex congenital heart disease or significant left ventricular dysfunction. Single-lung transplantation has been performed for PAH, but its current role in this setting is minimal due to risks and complications arising from the resulting profound mismatch of ventilation and perfusion.

Prior to May 2005, lung transplant waiting list priority was determined by "time accrued" on the list, so patients who were referred and listed at an earlier juncture in their disease course or who had less rapid disease progression had greater opportunity to receive organs. The Department of Health and Human Services' Final Rule establishing requirements for broader sharing of organs and allocation based on medical urgency instead of waiting time went into effect in 2000. In response, the LAS was instituted in the United States in 2005. The multivariable model used to develop the LAS evaluated waiting list and post-transplant mortality. The mortality cohorts were composed of patients added to the lung transplant waiting list before 1999. The "PPH" cohort included 636 patients added to the waiting list from 1995 through 1998. Broad variation in waiting list mortality according to diagnosis was observed (chronic obstructive pulmonary disease [COPD] 13.8%, idiopathic pulmonary fibrosis [IPF] 33%, cystic fibrosis [CF] 28%, and PPH 30%), and diagnosis-specific risk factors for mortality were identified and incorporated into the model. The post-transplant mortality cohort of lung transplants performed from 1996 to 1999 included a total of 146 "PPH" patients.[4] The LAS has made it feasible to transplant patients with more advanced and/or rapidly progressive disease and has had significant impacts on waiting list composition, wait times, mortality, and transplant numbers. Up

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Table 1. Number of Transplants Overall and for PAH From 1995 to June 2014

	Overall	PAH
Single-Lung Transplants (1995 to June 2014)	16,226	184
Bilateral Lung Transplants (1995 to June 2014)	29,457	1583
Heart-Lung Transplants (1982 to June 2014)	3356	2115

until a recent extensive revision, the LAS model had not undergone substantial alteration.

CURRENT TRANSPLANT VOLUMES AND OUTCOMES

The Organ Procurement and Transplant Network (OPTN) reports US national lung transplant volumes and outcomes. In 2014, 1925 lung transplants (45 for recipients ≤17 years of age) and 24 heart-lung transplants (6 for recipients ≤17 years of age) were performed. In the past 3 years, a total of 3 living donor lobar transplants have been reported in the United States. Approximately 3% of adult lung transplants, 40% of pediatric lung transplants, and 40% of heart-lung transplants were for PAH. Lung transplant procedure volumes for PAH as reported by the International Society for Heart and Lung Transplantation (ISHLT) are shown in Table 1.[5]

Six percent of approximately 1500 US patients listed for lung transplantation have PAH diagnoses. Current 1-, 3-, and 5-year survival rates after lung transplantation for PAH are 75%, 60%, and 48%.[6] Recent median waiting times for all lung transplant patients have been in the range of 3.9 to 4.8 months, while those for PAH patients have ranged from 8 to 9.7 months. Wait-list mortality rates are 15 deaths per 100 wait-list years overall and 18 deaths per 100 wait-list years for PAH patients.[7]

Transplant volumes and waiting times reflect a scarcity of suitable donor organs. Before the implementation of the LAS in 2005, the annual volume of adult lung transplants was approximately 1000. This number increased after LAS implementation, with most recent volumes of 1898 in 2013, and 1880 in 2014.[6] In recent years, efforts to expand the use and availability of donor lungs have included the use of donation after circulatory determination of death (DCDD) and use of expanded-criteria lung donors with and without ex-vivo lung perfusion (EVLP). The ISHLT Registry recently reported outcomes of 306 DCDD lung transplants with no difference in 1- and 5-year survival between DCDD (88% and 61%) and donation after brain death (DBD) (89% and 61%) recipients.[8] In a single-center study, survival of 50 recipients receiving donor lungs from extended criteria or DCDD donors treated with EVLP showed no difference in 1-year survival compared with DBD recipients (87% vs 86%), and the authors estimated that use of EVLP led to a 10% to 15% increase in transplant volume.[9] A follow-up study of 63 patients showed no difference in 1-, 3-, and 5-year survival, lung function, 6-minute walk distance (6MWD), or incidence of chronic lung allograft dysfunction compared with non-extracorporeal life support (ECLS) recipients.[10]

TRANSPLANT INDICATIONS AND CONTRAINDICATIONS

The ISHLT guidelines suggest considering lung transplantation for adults with advanced lung disease portending a >50% 2-year mortality risk, but with an expected likelihood of post-transplant survival of >80% at 90 days and >80% at 5 years assuming adequate graft function. To minimize potential for delay in referral and in recognition of potential for prolonged or uncertain waiting times, these guidelines suggest transplant referral for patients with pulmonary vascular disease with any of the following: New York Heart Association (NYHA) Class III or IV symptoms during escalating therapy; rapidly progressive disease; use of parenteral PAH therapy; or known or suspected pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis (Table 2). Listing for transplantation is suggested for patients who meet any of the following criteria: NYHA Class III or IV despite combination therapy including prostanoids; cardiac index of 2 L/min/m^2; mean right atrial pressure >15 mm Hg; 6MWD of <350 m; development of significant hemoptysis, pericardial effusion, or signs of worsening right heart failure including renal insufficiency, rising bilirubin, rising brain natriuretic peptide, or recurrent ascites (Table 3).[11] Referral in the setting of severely advanced disease or acute decompensation limits the likelihood of evaluation and listing for transplantation and increases the risk for adverse outcomes.[12,13]

Table 2. ISHLT Criteria for PAH Patient Referral

NYHA Class III or IV during escalating therapy
Rapidly progressive disease
Use of parenteral PAH therapy
Known/suspected pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis

Absolute contraindications to lung transplantation include: recent history of malignancy (disease-free interval of 2 to 5 years depending on type and recurrence risk); untreatable extrapulmonary organ dysfunction; uncorrected atherosclerotic disease with end-organ ischemia or dysfunction; acute medical instability; uncorrectable bleeding diathesis; chronic uncontrolled infection; significant chest wall or spinal deformity; body mass index >35 kg/m^2; nonadherence to therapy; psychiatric or psychological barriers to care and adherence; lack of adequate social support; and severe functional limitations with poor rehabilitation potential.[11] Additional relative contraindications cited are considered in the context of center-specific criteria as well as overall combined morbidities of individual patients.

The decision for referral and listing is multifaceted. Thresholds for timing of referral may vary according to treating practitioners' experience and knowledge of transplantation and relationship with transplant centers to which they refer. Direct, frequent, and timely dialogue between referring and transplant programs is essential to make the overall process less daunting and confusing for patients, families, and providers. Transplant centers need to be informed of changes in the patient's therapy and condition that might affect waiting list status.

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Table 3. ISHLT Criteria for PAH Patient Listing

Transplant Listing
NYHA Class III or IV despite combination therapy including prostanoids
Cardiac index of <2 L/min/m^2
Mean right atrial pressure >15 mm Hg
6MWD <350 m
Development of significant hemoptysis, pericardial effusion, or signs of worsening right heart failure including renal insufficiency, rising bilirubin, rising brain natriuretic peptide, or recurrent ascites

NONPHARMACOLOGIC BRIDGES TO TRANSPLANTATION

Some patients with advanced and progressive disease despite medical therapy or with acute decompensation may be candidates for nonpharmacologic interventions that may serve as bridges to transplantation. Treatments including atrial septostomy (discussed in another article in this issue) and ECLS have been utilized to bridge PAH patients to transplantation. A recent series reported 46 balloon atrial septostomy procedures performed in 32 patients with significant functional limitations, right heart failure, or presyncopal or syncopal symptoms. The majority of patients were on multiple pharmacologic agents, and 54% were receiving infused prostanoids. Overall 1- and 5-year lung transplant-free survival rates were 66% and 44%. While the number of patients listed for lung transplantation was not reported, a total of 7 patients underwent lung transplantation at a mean of 760 days after septostomy.[14] As with all patients where anatomic right-to-left shunting is present, perioperative management typically includes careful attention and monitoring, including intraoperative transesophageal echocardiograpy to minimize the risk of complications due to paradoxical embolism of air or thrombus. The anatomic shunt may be repaired at the time of transplantation.

Prioritization based on transplant urgency embodied in the LAS as well as advances in ECLS have increased the potential to obtain organs for critically ill patients requiring life support for circulatory and/or respiratory failure. In 2013, the OPTN reported that 14.1% of lung recipients aged 12 or over were in an intensive care unit (ICU) at the time of transplant, with 5.2%, 1.7%, and 3.1% supported by mechanical ventilation alone, ECLS alone, or the combination of mechanical ventilation and ECLS.[7] As reported by the ISHLT Registry, hospitalization (including ICU hospitalization) at the time of lung transplantation is associated with a greater risk for 1-year mortality (hazard ratio [HR] 1.63), as is mechanical ventilation (HR 1.47).[5] Similar registry data do not exist for patients supported with ECLS. Early experience with ECLS as a bridge to lung transplantation suggested a high 1-year mortality but good long-term outcomes in surviving patients. Patients being bridged to lung transplant with ECLS may have significant risks for critical illness myoneuropathy and prolonged mechanical ventilation including: systemic inflammation, corticosteroid use, neuromuscular blocking agents, diabetes, and immobility.[15] A recent review of reported case series from 16 centers noted 1-year post-transplant survival for patients receiving ECLS as a bridge to transplant ranging from 33% to 100%.[16] The largest reported single-center experience (26 patients) noted 1- and 2-year post-transplant survival of 68% and 53% for patients requiring ECLS as a bridge to transplant, compared with 85% and 79% for nonbridged patients. This series included 6 patients treated with awake ECLS who had a 100% survival at median follow-up of 10.8 months.[16] Newer ECLS techniques do not require mechanical ventilation, permit patients to remain awake and ambulatory, and thus may reduce risks for prolonged ventilation and ICU stay after lung transplantation. Patients with pulmonary hypertension (PH) and right heart failure have been successfully bridged using venoarterial extracorporeal membrane oxygenation (ECMO) or through the use of a pumpless oxygenator interposed between the pulmonary artery and left atrium and driven by pulsatile flow.[17,18]

Table 4. LAS Groups

A	Obstructive Disorders
B	Pulmonary Vascular Disorders
C	Bronchiectasis
D	Restrictive Disorders

ORGAN ALLOCATION

Allocation of lungs for candidates aged 12 and older is based on the LAS. This model categorizes patients into one of 4 lung-disease groups (Table 4): A – obstructive, B – pulmonary vascular, C – bronchiectasis, and D – restrictive. The LAS incorporates predictive models of 1-year waiting list mortality and 1-year post-transplant survival. Variables used in calculating the LAS are shown in Tables 5 and 6.[19]

If a program believes the LAS does not reflect a patient's urgency for trans-

Table 5. Pretransplant Covariates Used in LAS Determination

Age
Bilirubin value
Bilirubin increase of at least 50%
Body mass index
Cardiac index
Central venous pressure
Continuous mechanical ventilation
Creatinine
Diagnosis group (A, B, C, or D)*
Specific within-group conditions Bronchiectasis (in Group A) Eisenmenger's syndrome (in Group B) Lymphangioleiomyomatosis (in Group A) Obliterative bronchiolitis not re-transplant (in Group D) Pulmonary fibrosis, not idiopathic (in Group D) Sarcoidosis with mean pulmonary artery pressure >30 mm Hg (in Group D) Sarcoidosis with mean pulmonary artery pressure ≤30 mm Hg (in Group A)
Forced vital capacity
Functional status
Resting oxygen requirement
pCO_2
pCO_2 increase of at least 15%
Resting pulmonary artery systolic pressure
6-minute walk distance

*A – obstructive, B – pulmonary vascular, C – bronchiectasis, D – restrictive.

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Table 6. Post-Transplant Covariates Used in LAS Determination

Age
Cardiac index
Continuous mechanical ventilation
Creatinine
Creatinine increase >150%
Diagnosis group (A, B, C, or D)*
Specific within-group conditions Bronchiectasis (in Group A) Eisenmenger's syndrome (in Group B) Lymphangioleiomyomatosis (in Group A) Obliterative bronchiolitis not re-transplant (in Group D) Pulmonary fibrosis, not idiopathic (in Group D) Sarcoidosis with mean pulmonary artery pressure >30 mm Hg (in Group D) Sarcoidosis with mean pulmonary artery pressure ≤30 mm Hg (in Group A)
Functional status
Resting oxygen requirement
6-minute walk distance

*A – obstructive, B – pulmonary vascular, C – bronchiectasis, D – restrictive.

plantation, a request for approval of a specific priority or LAS may be submitted to the United Network for Organ Sharing (UNOS) Thoracic Organ Committee Lung Review Board (LRB). To compensate for the limited number of organ donors under the age of 12, programs may request that candidates less than 12 years of age be classified as adolescents to be eligible for allocation of adult lungs according to the LAS. Pulmonary hypertension patients deteriorating despite optimal therapy who have right atrial pressure >15 mm Hg or cardiac index <1.8 L/min/m^2 may qualify for LAS adjustment to the 90th percentile value if a request for this exception is submitted to the LRB. Referring and transplant centers should inform each other of patient deterioration and consider repeat right heart catheterization in anticipation of possible LAS exception. Exceptions to the LAS may also be considered in the setting of other factors that affect prognosis or waiting time, such as: significant hemoptysis, suspected diagnosis of pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis, or a high degree of allosensitization.

Lungs from donors aged 18 and over are allocated first to ABO-identical candidates aged 12 and over based on LAS, then to candidates under 12 years of age. Lungs from donors aged 12 to 17 are allocated first to recipients aged 12 to 17 based on LAS, then recipients under age 12, and then to recipients over the age of 17. Lungs from donors under 12 years of age are allocated first to recipients under age 12, then 12 to 17, then 18 and above. Candidates under the age of 12 receive a priority score of 1 or 2 based on medical urgency. Priority 1 criteria include: respiratory failure (continuous mechanical ventilation, supplemental oxygen requirement >50%, arterial pCO_2 >50 mm Hg, or venous pCO_2 >56 mm Hg) or PH (pulmonary vein stenosis involving 3 or more vessels, cardiac index <2 L/min/m^2, syncope, hemoptysis, or suprasystemic pulmonary artery pressure as assessed by catheterization or echocardiogram). As stated previously, recipients under age 12 can be granted an exception through the LRB to be classified as adolescents and be eligible for lung allocation based on LAS.[19]

Allocation of heart-lung blocks is driven by the highest-priority organ. When a heart-lung candidate is allocated a heart, the lung from the same deceased donor is allocated to the candidate. When a heart-lung candidate is allocated a lung, the heart from the same deceased donor is allocated to the candidate if no suitable Status 1A isolated heart candidates are eligible to receive the heart.[19]

Several notable trends have been evident since LAS implementation in 2005. There has been considerable regional variation in lung transplant rates and waiting times. There have been increases in: the total number of lung transplants; recipient age; and severity of illness as reflected by the LAS. The volume of transplants performed for patients with restrictive disorders (Group D) has increased, while volumes for groups A, B, and C have remained relatively unchanged. Group B waiting times increased dramatically in the first few years after the LAS was initiated. Although these times have subsequently declined, they have remained highest for all diagnosis groups at just under 10 months.[7] After LAS implementation, Group B patients were shown to have the highest cumulative risk of death on the waiting list with the lowest likelihood of transplantation.[20] While a small percentage of the overall waiting list, Group B patients have accounted for a disproportionate percentage of LAS exception requests (91 of 143 in 2013).[21]

The initial wait-list mortality data used in the development of the LAS was for "PPH" patients added from 1995 to 1998. This was an era during which new and effective therapies for PAH became available. During this period, the lung transplant waiting list was prioritized based on time accrued. Patients were listed in anticipation of potential for ongoing decline, often at the time that treatment was initiated. Many improved with treatment, leading to deferral of transplantation.[22] Physiologic measurements at the time of listing used in the LAS model would have subsequently improved with treatment. Therefore, it is not surprising that these variables for PPH patients starting treatment did not accurately reflect the prognosis of subsequent PAH patients who were listed in the setting of deterioration despite medical therapy. Indeed, evidence from the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) demonstrated that the LAS underestimated mortality for PAH patients with advanced disease as reflected by right heart failure (mean right atrial pressure 14 mm Hg) or exercise capacity (6MWD 300 m).[23] These observations, combined with the high waiting list times and mortality rates for Group B patients, engendered concern as to whether the LAS appropriately prioritized these patients.

In February 2015, the LAS model was revised with the goal of more accurately reflecting current disease severity and post-transplant survival for candidates aged 12 and over. The waiting list model incorporated data for patients added from September 2006 through September 2008, while the post-transplant survival model used data for patients transplanted between May 2005 and September 2008. Validation analysis

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for these models included patients listed or transplanted in the subsequent 14 months. Changes included addition of new covariates as well as modification of previous covariates and their coefficients in the LAS equation. The addition of central venous pressure, cardiac index <2 L/min/m^2, creatinine, and bilirubin to the LAS model, as well as the treatment of 6MWD as a continuous variable and modification of other coefficients has the greatest effect on the LAS for Group B patients.[19] The impact of this recent change on transplant waiting times, wait-list mortality, transplant volumes, and post-transplant survival will be need to be assessed in the future.

CONCLUSION

Pulmonary arterial hypertension remains an indication for a small number of lung and heart-lung transplants annually. Areas for growth and improvement in transplantation include: identification of patients who are likely to benefit from transplantation; appropriate support of patients failing medical therapy; increasing donor organ availability; and prioritization of organ allocation to minimize wait-list mortality and maximize post-transplant survival. Recent PAH registry studies such as REVEAL have enhanced our ability to assess prognosis. Knowledge of transplant referral and listing criteria as well as communication between PAH and transplant programs is necessary to determine when transplantation is appropriate and feasible. Techniques including ECLS to bridge patients to transplantation and DCDD and EVLP to improve donor organ availability continue to evolve. The 2005 LAS did not achieve its goals for PAH patients as evidenced by the persistent high wait-list mortality, low rate of transplantation, and frequent need for LAS exceptions. Recent LAS revisions should more accurately reflect wait-list mortality and transplant benefits for current PAH patients. The changes in PAH therapy and transplantation will need to be evaluated on an ongoing basis to determine their impact and identify areas for future refinement.

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