REVIEW ARTICLE

Lung Transplant in Idiopathic Pulmonary Fibrosis

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Objective: To review the present status of lung transplant (LTx) in patients with idiopathic pulmonary fibrosis (IPF).

Data Sources: Current English-language literature review using MEDLINE.

Study Selection: Prospective and retrospective trials, series, reviews, databases, and editorials regarding the clinical and basic science aspects of LTx in patients with IPF.

Data Extraction: We analyzed results from trials and series.

Data Synthesis: Idiopathic pulmonary fibrosis is an incurable disease with a dismal prognosis. The only treatment of proven benefit is LTx. Since the introduction of the Lung Allocation Score, IPF has become the most common indication for LTx in the United States. These patients have a limited life expectancy and benefit from early referral for transplant. Although controversial, the most recent data suggest that bilateral LTx is superior to single LTx in the population of patients with IPF. For this population, LTx increases the length and quality of their lives.

Conclusion: Although patients with IPF have a dismal prognosis, LTx is a safe and effective treatment to improve their survival and functional status.

Arch Surg. 2011;146(10):1204-1209

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DESPITE MUCH RESEARCH, idiopathic pulmonary fibrosis (IPF) remains an incurable disease, with only 30% to 50% 5-year survival.[1-4] Potential medical therapies for IPF are limited to corticosteroids and cytotoxic agents,[5] and approximately 70% to 90% of patients experience failure of medical management.[3,6] Because medical therapies are rarely effective and disease progression is inevitable, lung transplant (LTx) remains the only viable treatment option.[1]

See Invited Critique at end of article

Idiopathic pulmonary fibrosis was the indication for the first successful LTx with long-term survivors,[7,8] performed at the University of Toronto in 1983. Since then, IPF has risen as a prominent indication for LTx in patients with end-stage lung disease (ESLD). In May 2005, the United Network for Organ Sharing (UNOS) implemented the Lung Allocation Score (LAS).[9] In 2000, IPF was the indication for LTx in 15% of patients, rising to 37% of LTx in 2009, replacing chronic obstructive pulmonary disease as the most common indication (**Figure 1**).[10-12] Because IPF is now the most common indication for LTx and because LTx has the poorest 1- and 5-year survival rates of any solid organ transplant (**Table**), it is incumbent on health care professionals to maintain a working knowledge of the disease, its natural history, LTx recipient selection, waiting list outcomes, operations performed, and outcomes after LTx to fully optimize the use of this scarce resource.

To evaluate the state of LTx in patients with IPF, we undertook a MEDLINE search of published, English-language articles dealing with LTx and IPF. After evaluating the references cited in these articles, we also cross-referenced citations in existing literature reviews of LTx for completeness.

PATIENT SELECTION CRITERIA

Patients with IPF should undergo LTx when their posttransplant life expectancy exceeds their current life expectancy without the transplant. Transplant in patients with IPF includes the following contraindications[13]:

- Malignant neoplasm in the past 2 years (excluding cutaneous squamous cell and basal cell cancers).
- Active extrapulmonary infection (eg, human immunodeficiency virus or hepatitis B or C virus).
- Major organ system failure in another organ (eg, heart, liver, or kidney). For patients with coronary artery disease not amenable to revascularization or se-

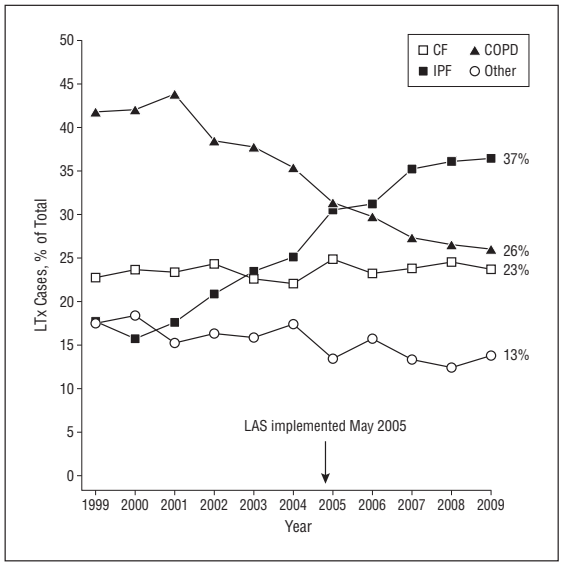

Figure 1. Distribution of lung transplant (LTx) by etiology of end-stage lung disease from 1999 to 2009. Data are presented as a percentage of the total yearly adult LTx cases. The Lung Allocation Score (LAS) was implemented in May 2005. CF indicates cystic fibrosis; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis. Data were obtained from the Organ Procurement and Transplantation Network, August 2010.

vere ventricular dysfunction, combined heart-lung transplantation may be an option.

- Anatomically prohibitive chest or spinal deformity.
- Untreatable psychiatric conditions.
- Absence of a social support network.
- Documented problems with adherence to a medication regimen or inability to take medications or attend follow-up appointments.
- Active substance abuse in the past 6 months.

Relative contraindications include the following:

- Recipient older than 65 years.
- Unstable clinical condition (eg, shock or ventilator dependence).
- Limited functional status with poor rehabilitation potential.
- Body mass index (calculated as weight in kilograms divided by height in meters squared) of greater than 30.

Each relative contraindication has been violated in some cohorts of patients with success. As a result, careful patient selection in this group is paramount.

Different clinical tests have been used to appropriately prioritize listing for transplant. Because IPF is a subtype of idiopathic interstitial pneumonia, a broader class of pulmonary disease with variable and better survival rates, biopsy results are helpful in determining the exact diagnosis.[13,14] Patients whose histologic findings show usual interstitial pneumonia–like changes have poorer survival than those with fibrotic nonspecific interstitial pneumonia changes.[14]

Traditionally, many physicians have used pulmonary function testing to determine the timing of listing for LTx. A large retrospective study[15] has found a diffusion lung capacity for carbon monoxide of less than 39% to have optimal sensitivity and specificity for early mortality. Patients with a predicted forced vital capacity of less than 60% also have been presumed to a have higher mortality rate, but more recent data[13] suggest that patients with preserved lung volumes have similar outcomes and thus should not be precluded from early referral for transplant. Although others have shown that a decline in forced vital capacity of more than 10% in 6 months is predictive of increased mortality, the time delay in such a test can have fatal consequences for those whose pulmonary function declines. Similarly, although failure of a 6-month course of corticosteroids is another traditional indicator for referral for LTx, limited data support a benefit to this strategy; thus, waiting for a response causes inappropriate delays in referral.[13] Finally, desaturation on pulse oximetry to 88% or less on the 6-minute walk test (6MWT) predicts early mortality.[16]

Radiologic studies also can be helpful in stratifying patients according to risk. High-resolution computed tomography has demonstrated that a higher degree of fibrosis predicts higher mortality.[15,17,18]

Therefore, given the difficulty in predicting which patients with IPF have the highest mortality, current guidelines recommend early referral of all patients with histologic or radiographic evidence of the disease. Consensus guidelines[13] suggest that these patients should be listed as follows:

- Histologic or radiographic evidence of usual interstitial pneumonia and 1 or more of the following: diffusion lung capacity for carbon monoxide of less than 39% predicted; decrease in forced vital capacity by 10% during a 6-month period; decrease in pulse oximetry to less than 88% during a 6MWT; and pulmonary fibrosis score of greater than 2 on computed tomography.
- Histologic evidence of nonspecific interstitial pneumonia and 1 or more of the following: diffusion lung capacity for carbon monoxide of less than 35% predicted; decrease in forced vital capacity by 10% during a 6-month period; and decrease in diffusion lung capacity for carbon monoxide of 15% during a 6-month period.

No randomized trials exist to validate thse recommendations. Therefore, careful clinical judgment by experienced health care professionals is important in caring for this complex patient population.

Table. Unadjusted Patient Survival by Transplant Type[a]

Organ	% of Patients	
	1-y Survival	5-y Survival
Lung	83.3	54.4
Heart	88.3	74.9
Kidney (deceased donor)	95.6	81.9
Kidney (living donor)	98.5	91.0
Liver (deceased donor)	88.4	73.8
Liver (living donor)	91.0	79.0
Intestine	89.3	57.9

[a] Data represent unadjusted survival from 2007. Based on Organ Procurement and Transplantation Network data, December 2010.

THE WAITING LIST

Unfortunately, even if a patient with IPF is placed on the waiting list for LTx, he or she remains at significant risk. Historically, patients with IPF have the highest waiting list mortality rates among patients with the common indications for LTx.[19,20] Before the LAS, patients with IPF had waiting list mortality of 28% to 47%[4,6] compared with approximately 15% for patients with other diagnoses.[5] Moreover, another 10% of patients with IPF were removed from the waiting list because they were no longer deemed suitable candidates for LTx.[6] Fortunately, with adoption of the LAS, IPF mortality on the waiting list declined significantly to as low as 11%.[2] Although this change represents significant improvement, this mortality is still higher than for other diseases. Moreover, preoperative quality of life has been shown to be much lower than that for patients with other causes of ESLD, and their lung function also deteriorates faster.[21,22]

Given the significant morbidity and mortality associated with the waiting list, physicians have investigated various measures to further optimize the LTx process. The amount of oxygen a patient requires at rest and his or her outcomes on the 15-step oximetry test and the 6MWT are predictive of mortality.[5,23] The LAS incorporates some of these factors by including results from the 6MWT, although a much higher distance cutoff may be optimal.[24] Although the LAS has helped improve waiting list outcomes for patients with IPF, further refinement likely is possible.

PREOPERATIVE CONSIDERATIONS

Although LTx outcomes have improved, patients with IPF tend to be sicker than patients with other causes of ESLD undergoing LTx. Although not designed specifically to predict mortality, the LAS is strongly correlated with 90-day and 1-year survival in patients with IPF. Specifically, an increase in the LAS by 1 point correlates to a 2% increase in mortality at 1 year.[25]

Other factors predictive of posttransplant mortality include pulmonary hypertension,[25] body mass index,[25] mechanical ventilation,[9,25] history of coronary artery disease at the time of listing,[9] and P_{CO_2} at the time of transplant.[9] Patients with IPF have a higher percentage of pulmonary hypertension than patients with other causes of ESLD,[4] and elevated pulmonary arterial pressure is an independent risk factor for death.[26,27] Patients with IPF also tend to be overweight. Extremely high or low body mass index in LTx is also an independent risk factor for mortality.[28] Patients requiring preoperative ventilation are at higher risk of death at 1 and 5 years after transplant; however, careful patient selection results in satisfactory outcomes, especially because patients with IPF who are receiving mechanical ventilation have an intensive care unit mortality of almost 100%.[4,29] Prior thoracic surgery does not increase short- or long-term mortality; however, it does predict increased intraoperative blood loss and longer intensive care unit stays.[4]

TYPE OF PROCEDURE

An ongoing controversy in LTx for patients with IPF is the choice between single LTx (SLTx) or bilateral LTx (BLTx).[30] This controversy is complicated because, in evaluating the best decision, one must consider not only the outcomes for individual patients but the impact of that decision on the availability of an already scarce resource.

Historically, SLTx was performed almost exclusively for all indications. Surgeons assumed that the more limited operation with less cardiac manipulation and shorter ischemic times would result in better outcomes in these already frail patients.[11] Theoretically, however, BLTx could provide the recipient with better compliance (eg, better change in lung volume per unit of pressure), greater improvement in lung volumes, and complete avoidance of native lung pathologic manifestations after the procedure. In any case, the number of BLTxs performed has steadily increased since the inception of LTx; now, almost 50% of LTx for IPF are bilateral, as are 69% of LTxs performed for all indications.[10] Further complicating this debate is the lack of randomized controlled trials. Such data do not currently exist and likely never will because such a study would require a prohibitively large sample.[31]

However, several groups have retrospectively examined their own institutional and UNOS data to determine which procedure would be preferable. Meyers et al[6] reported their institutional experience from 1988 through 1998 with 45 patients with IPF. There was no difference in 1- or 5-year survival or in the length of hospital or intensive care unit stay. Subsequently, Charman et al[32] also reviewed their own institutional experience with 60 patients with IPF. Again, they found no statistically significant difference in overall survival, although there was a trend toward increased early mortality in the BLTx group.

Meyer et al[8] reviewed the UNOS database from 1994 through 2000 for 821 patients who underwent LTx for IPF, with 636 receiving SLTx and 185 BLTx. Although univariate analysis demonstrated improved short- and long-term survival benefits for patients younger than 60 years undergoing SLTx, this finding did not persist after risk adjustment in multivariable analysis. Nwakanma et al[33] also reviewed the UNOS database, this time looking at patients older than 60 years from 1998 through 2004. In that series of 429 patients with IPF, 349 underwent SLTx and 80 underwent BLTx. Although there was a trend toward better long-term (5-year) survival in patients undergoing BLTx, no statistically significant difference was found. Thabut et al[31] also reviewed the UNOS database, analyzing all 3327 patients with IPF who had undergone LTx from 1987 through 2009. Although they also did not find statistically significant differences in mortality, they observed a trend toward an early survival benefit of SLTx but a long-term survival benefit of BLTx. They also observed that patients who underwent BLTx had higher rates of primary graft dysfunction than those who underwent SLTx. The idea that BLTx may have better long-term outcomes but worse short-term outcomes has been observed in several other studies. These studies found that SLTx was associated with a slightly higher late risk of death,[27] whereas BLTx was an independent predictor of 90-day mortality.[26] Registry review also confirms this trend.[10]

Weiss et al[11] analyzed UNOS data from 2005 through 2007, evaluating the results of transplant after implementation of the LAS in patients with IPF. Of 1256 patients with

IPF, 655 underwent SLTx and 601 underwent BLTx. When patients were stratified into quartiles according to the LAS, BLTx was associated with a 14.4% decrease in mortality at 1 year in the highest LAS quartile. Although these data suggest that certain high-risk patients benefit from BLTx, aside from the LAS, the exact definition of high risk remains elusive. Although there is a tendency to perform more BLTx in patients with pulmonary hypertension, no definitive benefit has been shown.[8]

Finally, Neurohr et al[34] analyzed their single-institution experience and found that 1- and 5-year survival rates were better in patients who underwent BLTx rather than SLTx. Moreover, these patients had a lower rate of bronchiolitis obliterans syndrome (BOS) and better 6MWT and forced expiratory volume in the first second of expiration. Other data[35] suggest that the course of BOS in patients who underwent BLTx is milder and less progressive than in SLTx patients.

Although the question of optimal procedure remains unanswered, there is an increasing tendency in the transplant community to perform BLTx rather than SLTx for IPF. The data, while inconclusive and conflicting, seem to suggest that, although BLTx may increase early mortality, it promotes long-term survival. It is possible that the early mortality caused by BLTx has been ameliorated by improvements in surgical technique and critical care, which may explain why more recent data demonstrate benefits of BLTx. A recent study[36] suggests that patients put on the waiting list for only BLTx have longer waits and higher waiting list mortality, possibly offsetting any improved long-term benefits.

CARDIOPULMONARY BYPASS

Cardiopulmonary bypass (CPB) is not always necessary for LTx; however, during pulmonary artery clamping, some patients experience hemodynamic compromise or refractory hypoxemia necessitating CPB. In addition, pulmonary hypertension is thought to be a risk factor for requiring CPB.[37] Because IPF is associated with secondary pulmonary hypertension, one would expect many patients with IPF undergoing LTx to require CPB. However, CPB is associated with an increased risk of bleeding and a potentially increased rate of early graft dysfunction.

Multiple studies have demonstrated that an accurate preoperative assessment of need for CPB is difficult.[38-40] Hirt et al[38] demonstrated that preoperative hemodynamics, including pulmonary hypertension, did not predict the need for CPB; rather, intraoperative changes, particularly a decrease in the cardiac index by 1.5 L/min/m^2 in the face of rising pulmonary vascular resistance predicted the need for CPB. Another study[39] has shown that, although preoperative hemodynamic measures may predict the need for CPB in SLTx, they are not helpful in predicting the need for CPB in BLTx. Overall, as with other causes of ESLD, the decision to use CPB for LTx should be made intraoperatively.

IMMUNOSUPPRESSION

Although the pathogenesis of IPF remains unknown, it is thought to have an immunologic component. Because much of the existing medical therapy consists of corticosteroids and cytotoxic agents, it was hoped that patients who underwent SLTx would demonstrate slowing of the disease progression in the native lung, thus affecting the selection of the maintenance immunosuppressive regimen. Early studies[3,41] with older immunosuppressive regimens and a more recent study[10] with contemporary regimens have shown no benefit in treating the native lung.

One area of controversy remains the use of induction therapy. Approximately 62% of patients receive induction therapy, and there appears to be a long-term benefit in survival, although there are no conclusive data.[10]

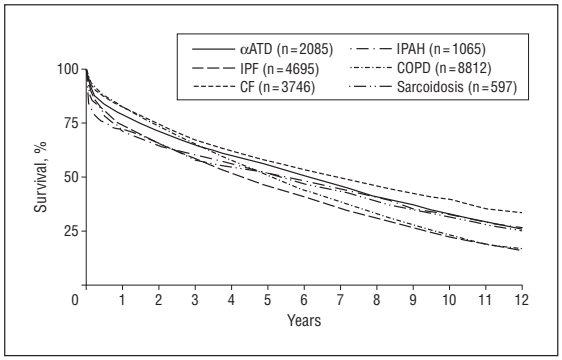

Figure 2. Kaplan-Meier survival analysis for lung transplants by etiology of end-stage lung disease from 1990 to 2008. αATD indicates α_1-antitripsin deficiency; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; IPAH, idiopathic pulmonary arterial hypertension; and IPF, idiopathic pulmonary fibrosis. For survival comparisons, $P<.001$ for αATD vs CF, COPD, and IPF; for CF vs COPD, IPF, IPAH, and sarcoidosis; and for COPD vs IPF; $P=.04$ for αATD vs sarcoidosis; and $P=.005$ for IPAH vs IPF. Survival of 50% for αATD is 6.1 years; for CF, 7.0 years; for COPD, 5.1 years; for IPAH, 5.6 years; for IPF, 4.3 years; and for sacoidosis, 5.3 years. Reprinted with permission from Elsevier Inc.[10]

OUTCOMES

Current outcomes in LTx for IPF show significant survival benefit. Current 1-, 5-, and 10-year survival rates are 74%, 45%, and 22%, respectively.[10] These survival rates are significantly poorer than those for other causes of ESLD (**Figure 2**), including α_1-antitrypsin deficiency, pulmonary hypertension, cystic fibrosis, and chronic obstructive pulmonary disease.[10,32,42] Survival also can be predicted by LAS because patients with IPF in the highest quartile of LAS have a 7.1% lower 1-year survival than those in quartiles 1 through 3.[25] Notably, survival has improved over time.[8,27] Although outcomes for patients with IPF tend to be poorer than those for other transplant recipients, they are improving and still exceed the outcomes of optimal medical management.

COMPLICATIONS

Although overall outcomes continue to improve, LTx for IPF remains a difficult operation, with many potential complications. Infection remains the most common complication of LTx in general and of IPF recipients in particular, occurring in 56.5% of patients.[43] Moreover, overt sepsis occurs in 15.2% of patients with IPF and is the most common cause of death in the first 6 months, account-

ing for 60% of 6-month mortality.[42] Another common complication is acute rejection, with approximately 36% of all patients with LTx experiencing at least 1 episode of acute rejection.[10]

Some of the other more common complications and their frequencies include hemodynamic instability (39.2%), renal failure (19.6%), myopathy (13.2%), hemorrhage (13.3%), and the need for reoperation (6.6%).[43] Approximately 9% of LTx recipients have some form of airway complication; 5.4% experience stenosis, excessive granulation tissue, bronchomalacia, or dehiscence.[42] Malignant neoplasm is also a long-term problem, with an incidence of 13% at 5 years and 28% at 10 years.[10] Pulmonary embolism is more common in LTx recipients with IPF, occurring in as many as 27% of patients.[44]

Primary graft dysfunction (PGD) continues to plague all LTx recipients, including patients with IPF. Although the cause is likely multifactorial, ischemia-reperfusion injury is thought to be the major mechanism of pathogenesis.[45] The incidence of PGD ranges from 10% to 25%.[45,46] Patients who experience PGD have significantly worse short-term mortality. In the long term, PGD is associated with an increased risk of BOS, thereby also increasing long-term mortality.[47] Although patients with pulmonary hypertension have the highest incidence of ischemia-reperfusion injury, patients with fibrotic lung disease are more likely to experience it than those with obstructive lung disease, placing them at higher risk of PGD.[48]

Bronchiolitis obliterans syndrome is the major factor limiting long-term survival. Unfortunately, it is also a common complication of LTx, with an incidence of 28% by 2.5 years and 74% by 10.0 years.[10] Patients with IPF are at higher risk of PGD and thus at higher risk of BOS, as suggested herein, but they have a more severe decline in pulmonary function and higher mortality than patients without IPF who have BOS.[35,49]

COST OF LTx

The implementation of the LAS has decreased waiting list time and mortality by giving transplant priority to more critically ill patients. In analyzing post-LAS charges at a single institution, Arnaoutakis et al[50] demonstrated that recipients in the highest LAS quartile (range, 44.9-94.3) had an almost 2-fold increase in index charges and 50% higher charges in the first year after LTx compared with patients in the 3 lower quartiles. Performing LTx in patients with a higher LAS results in greater resource use, necessitating careful stewardship of this scarce and expensive resource.

In summary, IPF remains an incurable disease with a dismal prognosis. The only currently available treatment of proven benefit remains LTx. With adoption of the LAS, IPF eclipsed chronic obstructive pulmonary disease as the most common indication for LTx. Although outcomes are not quite as impressive as for other LTx indications, they are improving and will likely continue to do so as patient selection criteria, surgical techniques, and the science of critical care continue to evolve.

Accepted for Publication: December 16, 2010.
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Author Contributions: *Study concept and design:* George, Arnaoutakis, and Shah. *Acquisition of data:* George. *Analysis and interpretation of data:* George. *Drafting of the manuscript:* George, Arnaoutakis, and Shah. *Critical revision of the manuscript for important intellectual content:* George, Arnaoutakis, and Shah. *Statistical analysis:* George, Arnaoutakis, and Shah. *Obtained funding:* George, Arnaoutakis, and Shah. *Administrative, technical, and material support:* George, Arnaoutakis, and Shah.
Financial Disclosure: None reported.
Funding/Support: This study was supported by a Ruth L. Kirschstein National Research Service Award from the National Institutes of Health; T32 training grant 2T32DK007713-12 from the US Department of Health and Human Services; a Hugh R. Sharp Cardiac Surgery research fellowship (Dr George); and an Irene Piccinini Investigator in Cardiac Surgery award (Dr Arnaoutakis).

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INVITED CRITIQUE

Donor Lung Allocation

Who Shall Live; Who Shall Die?

The introduction of the LAS significantly changed the face of LTx,[1] but the question remains, has the change been for the better or for the worse? Instead of accruing time on the waiting list, the LAS seeks to identify those most likely to benefit by taking the difference between factors associated with 1-year posttransplant survival and the likelihood of dying while on the waiting list. The fact remains that fewer than 50% of all LTx recipients are alive at 5 years, which begs the question as to whether posttransplant survival should be given increased weight in the LAS calculation.

Under the current allocation system, patients with IPF, the group with the poorest 1-year survival, have the highest likelihood of undergoing a transplant. A higher LAS,