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Pulmonary Fibrosis Identification:
Lessons for Optimizing Treatment

"IPF Updates" Monograph Series

LUNG TRANSPLANT

Steven D. Nathan, MD
Inova Fairfax Hospital
Falls Church, Virginia

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CME INFORMATION

Needs Statement/Intended Audience

This activity has been planned in accordance with the need to provide pulmonologists and other health care providers with a continuing medical education activity that addresses the best practices for management of patients with IPF.

Educational Activity Learning Objectives

Upon completion of this activity, the participants should be able to:

- Discuss recent evidence for treatments in the management of IPF

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FACULTY

Steven D. Nathan, MD

Medical Director, Lung Transplant Program
Medical Director, Advanced Lung Disease Program
Inova Fairfax Hospital
Falls Church, Virginia

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LUNG TRANSPLANT

Introduction

Lung transplantation (LTx) can be an attractive option for patients with severely impaired pulmonary function due to interstitial lung disease. The introduction of cyclosporine A (CsA) in the early 1980s extended the viability of the transplanted organ. The aim of transplantation is to improve longevity and the quality of life of the recipient. This requires an intimate knowledge of the prognosis and course of the primary disease as well as posttransplant outcomes. Despite this, a significant number of patients succumb to their disease while on the waiting list. In response to this, UNOS (United Network for Organ Sharing), the organization that oversees organ allocation in the United States has implemented a new lung allocation system (LAS) in the spring of 2005 based on need and outcomes to maximize the impact of this scarce resource. The new system sorts patients into one of four groups based on their underlying primary disease. Models incorporating numerous factors have been developed for each of these groups to determine the prognosis during the ensuing year with and without transplant. According to the new lung allocation system, transplant benefits for each patient are computed based on the difference between these projected outcomes. This then is balanced against wait list urgency based on the patient listing characteristics to determine organ allocation.[1]

This monograph will review LTx as a treatment option for patients with idiopathic pulmonary fibrosis (IPF), a chronic progressive restrictive disorder with no FDA-approved pharmacologic therapy. The first section will address candidate selection and preoperative considerations. After a brief section on perioperative matters, the last section will address postoperative management and the effects of the new lung allocation system.

IPF, a disease characterized pathologically by usual interstitial pneumonitis (UIP), is associated with a median survival time of approximately 3 years from the time of diagnosis.[2] It is therefore not surprising that IPF patients have previously had the highest attrition rate on the transplant wait list with mortality rates in excess of 30%. The 2005 ISHLT Consensus statement acknowledged that even patients with minimal symptoms should be referred for transplant evaluation.[3] The poor prognosis of this condition and the high mortality on the transplant list were the impetus for this recommendation as well as the reason these patients were given three months credit on the transplant list under the old allocation system.

Figure 1. Survival of Patients with IPF on Waiting List Compared with Survival of Those Who Underwent LTx.[4]

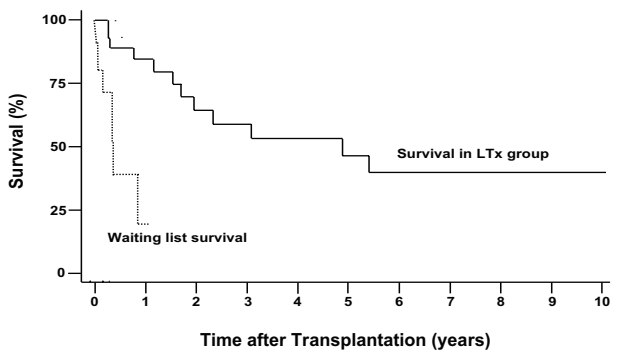
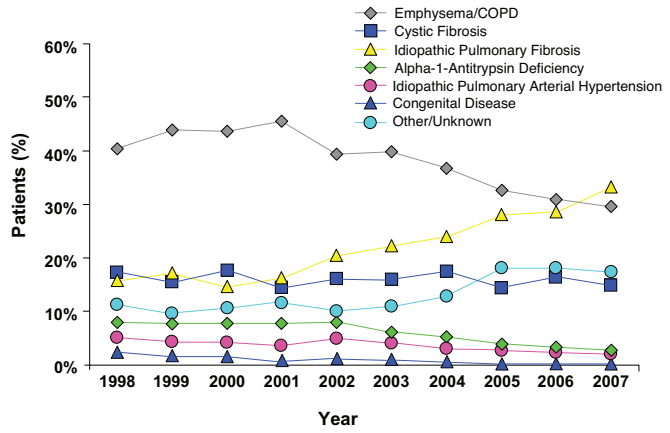


Figure 2. Proportion of LT Recipients by Indication.[5]



There is a dramatic difference in survival of IPF patients who receive or do not receive LTx.[4] The 50% survival time increases from approximately 0.5 years for patients awaiting transplantation to approximately 5 years for patients who received a lung transplant (Figure 1). Poor prognosis of IPF patients, lack of approved and effective pharmacotherapies, recent changes in the LAS scores described above, and improving survival rates post lung transplantation over the years have led to an increase in the number of LTx procedures performed for patients with IPF.

Approximately 1500 lung transplants are performed in the United States each year.[5] The proportion of recipients with IPF has increased in recent years, and the number of transplants in patients with IPF is now similar to COPD (Figure 2).[5]

Prior to Lung Transplantation

IPF is progressive and fatal; no medications have been proven to be effective. Though LTx is regarded as a therapy of last resort, patients should be referred for transplant evaluation at the time of diagnosis.[6] This permits a thorough evaluation and allows sufficient time to enable patients' physical and psychosocial preparation.

A set of inclusion and exclusion criteria has been developed that can help pulmonologists decide whether patients are suited for LTx.[3,7] Before initiating the involved LT listing process, a physician can evaluate a particular patient using these general criteria.

General inclusion criteria

- Age: < 65–70 for single lung transplants
  < 60 for bilateral lung transplants
  < 55 for heart-lung transplants
- Failed conventional treatment
- Limited life expectancy (less than 2-3 years)
- Ambulatory with oxygen
- Able to adhere to a disciplined medical regimen

Contraindications to lung transplantation

Absolute contraindications

- Smoking within 6 months (These patients might still be appropriate to refer for an assessment. Smoking cessation can then be monitored in conjunction with the transplant center)
- Unresolved psychiatric and psychosocial problems with negative impact on outcome
- Recent drug/alcohol abuse problems
- Noncompliance with medical care or treatment plans
- Active malignancy within the past 2 years (except basal cell and squamous cell cancer of the skin) with a 5-year disease free interval for extra-capsular renal cell tumors, breast cancer stage 2 or higher, colon cancer staged higher than Dukes A, and melanoma, level III or higher

- A history of primary or metastatic lung malignancy
- Morbid obesity
- Systemic disease
  - Renal (creatinine clearance < 50 mls/min)
  - Liver disease (cirrhosis, chronic active, chronic persistent hepatitis, Hepatitis B/Hepatitis C with evidence of liver disease)
  - Type 1 diabetes which is not well-controlled or with significant organ dysfunction
  - Chronic pancreatitis
  - Active connective tissue disorder
- HIV positive or other active chronic infection
- Disabling arthritis or other limitation to exercise
- Progressive neuromuscular disorders

Relative contraindications

- Coronary artery or other cardiac disease
- Systemic hypertension that requires more than 2 drugs for adequate control
- Severe right-sided heart failure
- Infection with multidrug resistant/pan-resistant organism(s)
- Colonization with fungi or atypical mycobacteria
- Type 1 diabetes
- Symptomatic osteoporosis
- Severe musculoskeletal disease affecting the thorax
- Poor nutritional status (BMI < 17 or > 32)
- Seizure disorder that is not well controlled
- Steroid dependency (> 20 mg/day)
- Significant pleural disease/prior chest surgery

After a full evaluation, patients can be expeditiously listed for transplant in the event of gradual disease progression or an acute decompensation. The evaluation

Table 1. Factors Used to Calculate LAS[8]

Factors used to predict waiting list survival	Factors used to predict posttransplant survival
FVC (% predicted)	FVC (% predicted)
PA systolic pressure	Mean PCWP
O_2 required at rest	Continuous mechanical ventilation
Age at offer	Age at transplant
Body mass index	$PaCO_2$
NYHA functional status	Serum creatinine
Diagnosis	NYHA functional status
6MWD	Diagnosis
Continuous mechanical ventilation	
Diabetes	

process undertaken at a transplant center includes:

- Patient Evaluation
  - Initial history and physical
  - Testing to establish the severity of disease and to rule out any potential contraindications to transplant
  - Psychosocial evaluation
  - Financial evaluation
- Patient/Caregiver Education
- Pulmonary Rehabilitation
- Calculation of an LAS
- Listing for transplantation and waiting period

Several steps can be taken to affect pulmonary and general functional status in the period prior to transplant and thereby increase the likelihood of LTx success, including physical conditioning. Pulmonary rehabilitation (PR) is a critical element of recovery from LTx, and should be undertaken prior to transplant for several reasons. It improves the physiologic function and performance status of the patient. In addition, patients who are active prior to surgery have a greater likelihood of earlier mobility, which is a key element to success. Pretransplant PR also establishes a behavioral pattern that can be resumed during and after recovery from surgery. Physical conditioning, nutritional counseling, and patient education help in the preparation for the surgery and ease the posttransplant transition and recovery. In addition, a structured program provides an opportunity to develop stress management methods and relaxation techniques.[7] It can also provide a forum for sharing social, financial, and logistic information with patients and act as an informal support group.

Prior to May 2005, priority for organ transplants was determined by length of time on the waiting list. UNOS revised this system to prioritize organ allocation based on the projected survival advantage of transplantation. This involves assessing the projected risk of death while waiting for an organ (urgency) and the projected life expectancy after transplant (benefit).[1] The elements of the LAS calculation are shown in Table 1. The details of the LAS and a sample calculation can be found at the UNOS Web site.[8]

Patients with IPF have a high mortality rate on the UNOS waiting list, but this has declined since the implementation of the LAS system in 2005 (Figure 3).[5] The 2006 ISHLT International Guidelines recommend possible transplantation for patients with IPF if any of the following conditions are met:

- A DLco of less than 39% predicted
- A 10% or greater decrement in FVC during 6 months of follow-up
- A decrease in oxygen saturation (pulse oximetry) below 88% during a 6MWT
- Honeycombing on HRCT (fibrosis score of > 2).

Figure 3. Annual Death Rate of Patients on UNOS Waiting List by Primary Diagnosis.[5]

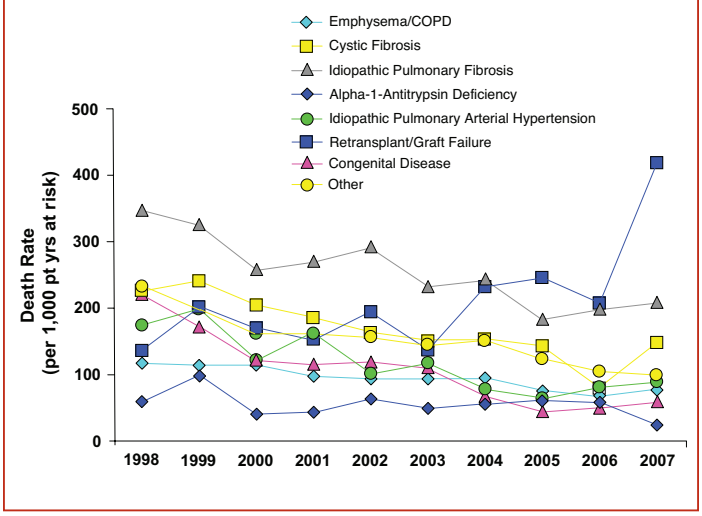
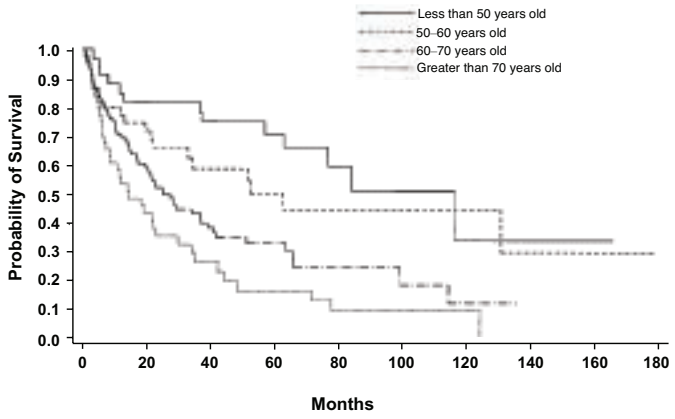


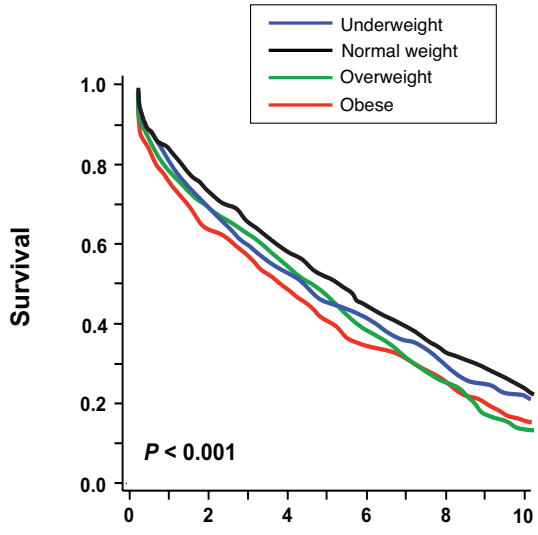
Figure 4. Kaplan-Meier Plot of Survival Probability from the Time of the Initial Visit Stratified by Age Group.[9]



One of the strong determinants of survival in patients with IPF is age. King et al[9] showed that the median survival from the time of the initial visit decreased from ~100 months in patients less than 50 years old to ~27 months in patients 60 to 70 years old (Figure 4). Age is also a relative contraindication for lung transplant. Many centers do not accept transplant recipients older than age 65. A recent ISHLT report showed that younger LTx recipients survive longer than older ones.[10] The risk of mortality at 1 year was 0.5 for 35-year-old recipients, while the relative risk (RR) increased to 1.3 for 65-year-old recipients ($P <$ 0.0001). However, there are data to suggest that select older patients without significant comorbidities can be successfully transplanted with acceptable outcomes.[11]

Lederer and colleagues[12] analyzed 5978 lung transplant recipients from the UNOS database and stratified patients by body mass index (BMI), using the WHO classification scheme: underweight, < 18.5 kg/m^2; normal weight, 18.5–24.9 kg/m^2; overweight, 25–29.9 kg/m^2; and obese, ≥ 30 kg/m^2.[13] This analysis included 1246 patients with IPF. The distribution of patients with IPF was 3% underweight, 30% normal weight, 43% overweight, and 24% obese. The median posttransplantation survival time was 4.8 years for the entire cohort, with the normal weight group having the best chance of survival over the 10-year observation period (Figure 5). The subgroup with IPF had a somewhat linear relationship between BMI in the range from 20 to 30 kg/m^2 and the 1-year risk of death. Compared to the normal weight group, overweight patients with IPF had a relative risk of death from primary graft failure of 2.58 ($P = 0.01$). The overweight and obese patients

Figure 5. Unadjusted Survival after Lung Transplantation by BMI.[12] *(Supplement)*



Underweight	862	583	445	272	136	49
Normal weight	2864	2056	1586	906	451	181
Overweight	1644	1117	840	412	173	50
Obese	608	393	280	151	66	23

had relative risks of death from respiratory failure of 1.78 ($P = 0.007$) and 1.54 ($P = 0.03$), respectively. The decision about LTx should depend on survival expectations but should account for quality of life (QoL) considerations as well.[14] As with the LAS survival calculation, current QoL and anticipated post-LT QoL must be weighed. There are multiple factors that contribute to patients' pre- and posttransplant QoL which depend on individual patient lifestyles and desires. Conceptually, it is desirable to get "maximum mileage" from the native lungs before subjecting patients to the inherent risks of transplantation.

The timing of LTx for a specific patient should be determined on an individual basis. Many factors, including the anticipated survival (as reflected in the LAS), QoL before and after LT, physical condition, costs, and patient willingness must be considered. It is important for patients to be aware of the survival statistics associated with transplantation, as this should weigh into their decision. The one- and five-year survival rates for all lung recipients are 78% and 50%. For IPF recipients, one- and five-year survival rates are 80.4% and 48.5%, respectively.[15,16] An integrated metric that accounts for both survival and QoL with and without transplantation would be useful in the decision-making process.[14,17] One conceptual approach is to combine quantity and quality of life in a single parameter, termed quality-adjusted life-years (QALY).

There are two types of transplant: single (SLTx) and bilateral (BLTx). The advantages of bilateral lung transplant versus single lung transplant in different patient groups are debatable. BLTx are generally reserved for younger patients (< 50 or 60 years), cases of simultaneously suppurative lung disease, and when the donor lungs are marginal.[18] Though historically there were almost twice as many SLTx as BLTx performed for IPF, BLTx has been increasing with 2006 rates for both procedures being almost the same.[10]

SLTx recipients who received their lungs in 2000–2006 had a median post-LT survival of 4.5 years (N = 1375), while BLTx recipients from the same period survived an average of 5.3 years (N = 966). However, the one-year mortality risk for IPF (relative to COPD) of SLTx performed between 1995 and 2006 was 1.4 ($P = 0.0002$) while BLTx was 1.64 ($P < 0.0001$).

Lung Transplant Surgery: A Collaborative Team Effort

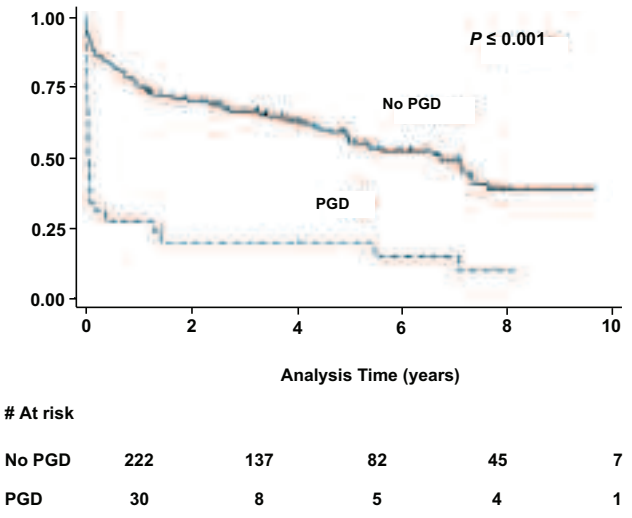
The period surrounding LTx surgery is critical and should be managed by an experienced multidisciplinary transplant team. This team should include[19]:

- Thoracic surgeons
- Pulmonologists
- Anesthesiologists
- LTx coordinators
- Physician assistants
- Physical therapists/Occupational therapists
- Pulmonary rehabilitation experts
- Pharmacists
- Nutritionists
- Social workers and psychologists or psychiatrists.
- Consultants (eg, infectious disease, nephrology, cardiology)

Postoperative Management

Immediate postoperative monitoring focuses mainly on hemodynamics, ventilatory strategies, and renal function. Patients should be treated as needed to

Figure 6. Kaplan-Meier Survival by PGD, with Analysis Time in Years. The P-value Was Derived from the Log-Rank Test between Subjects with PGD and Those without PGD.[22]



maintain cardiovascular homeostasis and glucose control. They should be given appropriate prophylaxis for peptic ulcer disease, infection, and deep vein thrombosis. Nutritional supplementation should be considered for patients who are likely to require protracted mechanical ventilation.[19,20]

Primary graft dysfunction (PGD) occurs in approximately 20% of LTx recipients.[19] PGD, also known as ischemia-reperfusion injury or primary graft failure (PGF), is characterized by diffuse infiltrates on chest X-ray and varying degrees of hypoxemia as assessed by the PaO_2/FiO_2 ratio. PGD is associated with significant mortality in the immediate postsurgical period (Figure 6). Management of PGD involves supportive care with mechanical ventilation and diuresis as tolerated and close monitoring of patients' hemodynamic status. Extracorporeal membrane oxygenation (ECMO) should be considered for persistent, refractory hypoxemia, especially in the first 24-36 hours.[21]

A key element of LT management is immunosuppression to prevent allograft rejection. There are no immunosuppressive agents specifically FDA-approved for lung transplantation. Most of the knowledge of the various agents has been gleaned from other solid organ transplant data. The best mode of immunosuppression for lung transplantation therefore remains open to debate. Induction cytolytic therapy is sometimes used to deplete the recipient's immune system immediately after transplant. The objective of this approach is to avoid early immunologic interaction between the donor and recipient and thereby decrease acute rejection as well as minimize inflammation.[23] Induction agents that have been used include OKT3, antithymocyte globulin, IL-2 receptor antagonists (daclizumab and basiliximab) and alemtuzumab. Although induction therapy appears to reduce the frequency and severity of episodes of acute rejection, this might come at the expense of a heightened risk of infections. Thus far, there is no conclusive evidence that induction therapy either prolongs survival or reduces the risk of chronic rejection.

There is also no consensus on the best combination of drugs for maintenance immunosuppression. Most protocols involve a combination of corticosteroids, a calcineurin inhibitor (CNI), and a purine synthesis inhibitor.[19,24] Table 2 lists the various agents along with their mechanism of action, toxicities, side effects, and drug interactions.

An active surveillance program is required after LTx. There needs to be an awareness of pulmonary complications including rejection and infection. Additionally, extrapulmonary systems may be affected by

Table 2. Immunosuppressive Agents Used in Lung Transplantation.[19]

Drug	Mechanism of Action/Target	Major Toxicities Nephrotoxicity	Common Side Effects	Drug-Drug Interactions
Tacrolimus	Inhibits T-lymphocyte activation (suppresses IL-2 production)	Diabetes mellitus Hypertension Hyperkalemia Hypomagnesemia	Dermal erythema Gastrointestinal motility disturbance Tremor Headache Insomnia	Levels increased by CYP3A4 inhibitors (eg macrolides, imipenem, azoles, calcium channel blocker, amiodarone, statins, HMG-CoA reductase inhibitors)
Cyclosporine	Inhibits T-lymphocyte Activation (suppresses IL-2 production)	Nephrotoxicity Hypertension Hyperkalemia Hypomagnesemia Pancreatitis Seizure	Tremor Headache Hirsutism Pruritis Gastrointestinal motility disturbance	Levels decreased by CYP3A4 inducers (eg phenytoin, rifampicin, sulfonamides)
Sirolimus (rapamycin)	Inhibits DNA and protein synthesis (IL-2 signaling and T-lymphocyte activation)	Hypertension Dyslipidemia Pulmonary toxicity Hepatotoxicity Pancytopenia	Arthralgia Headache Anemia Thrombocytopenia	Metabolized by CYP3A4 (similar to tacrolimus) Metabolized by CYP3A4 (similar to tacrolimus) CsA (increased level of sirolimus when administered at the same time)
Mycophenolic Acid	Inhibits purine biosynthesis (lymphocyte activation)	Myelosuppression Gastrointestinal hemorrhage	Insomnia Gastrointestinal motility disturbance	Altered absorption (↓by iron, cholestyramine, antacids) Oral contraceptives (↓efficacy) Sirolimus (↑MPA levels)
Azathioprine	Inhibits purine biosynthesis (lymphocyte activation)	Pancreatitis Bone marrow suppression	Gastritis	Allopurinol (↓azathioprine metabolism)
Corticosteroids	Inhibits cytokine gene transcription and secretion	Diabetes mellitus Osteoporosis Myopathy Obesity	Fluid retention Cataracts Weight gain	Warfarin (↓anticoagulant effect)

CsA: Cyclosporine A; CYP: Cytochrome P450; HMG-CoA: 3-hydroxy-3-methyl-glutaryl-CoA.

the immunosuppressive medications and other routine drugs. Complications that may be encountered include[19]:

- Allograft dysfunction
  - Rejection, acute and chronic
  - Airway complications
- Infections
  - Viral
    - Cytomegalovirus (CMV)
    - Epstein-Barr virus (associated with posttransplant lymphoproliferative disorder [PTLD])
  - Bacterial
    - Methicillin-resistant *Staph aureus*
    - Multidrug-resistant *Pseudomonas aeruginosa*
  - Fungal
    - *Aspergillus fumigatus*
    - *Candida albicans*
    - *Pneumocystis*
- Organ systems
  - Renal dysfunction (calcineurin inhibitor effect)
  - Cardiovascular
    - Hypertension
    - Atrial fibrillation
    - Hyperlipidemia
  - Gastrointestinal
    - GERD
    - Gastroparesis
    - Diarrhea
  - Drug toxicity: monitoring of drug levels
  - Other drug side effects
  - CNS
  - Osteoporosis
  - Hyperkalemia
  - Malignancy
    - Dermatologic
    - PTLD
  - Insulin resistance/diabetes
  - Weight

As with the pretransplant period, pulmonary rehabilitation is a well-accepted modality to help LTx recipients maximize pulmonary and daily function. Immediately after surgery the patient is restricted in movement both by surgical wounds and by supportive devices, but special adaptation of rehabilitation program for LTx recipients can aid mobility, strength, range of motion, and breathing pattern efficiency.[7]

Within 5 years of transplant, almost half of LT recipients develop chronic allograft dysfunction, the most common form of which is bronchiolitis obliterans syndrome (BOS).[15] BOS is characterized physiologically by a permanent > 20% reduction in the FEV_1 without other identifiable cause.[25] Progressive dyspnea with cough is a frequent feature. BOS is a significant cause

Figure 7. Cause of death for All LT recipients (left) and for Patients with ILD (right).[26] NSGF: non-specific graft failure.

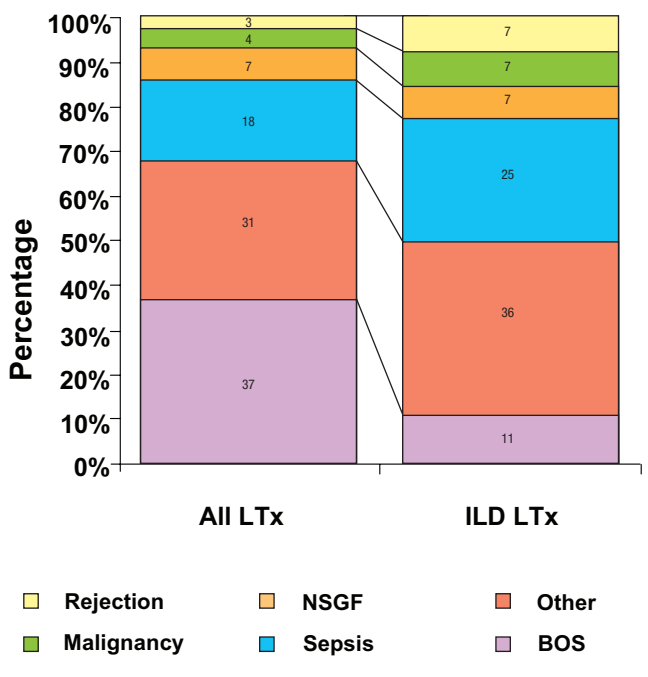
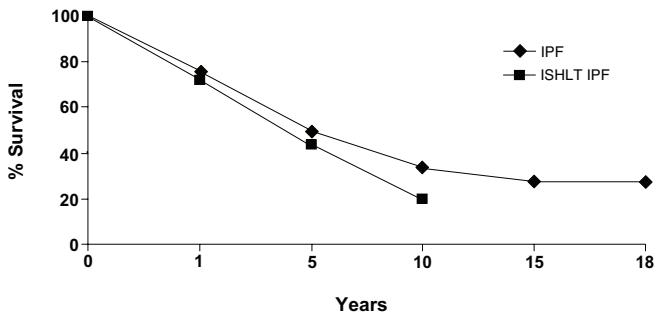


Figure 8. Survival of LT Patients with IPF. Long term data is from a single transplant center in Melbourne, Australia and from the ISHLT registry.[26]



of death among all LTx recipients, but may be somewhat less among those with interstitial lung diseases (Figure 7).[26] Though the clinical course of BOS is variable, the median survival after its onset is only 3 to 4 years. Multiple cellular and chemokine interactions have been implicated in the pathogenesis of BOS.[25] Predisposing risk factors for BOS include acute cellular rejection (ACR), CMV and other respiratory infections, injury to the allograft or airways, PGD, histocompatibility leukocyte antigen (HLA) mismatching, and organizing pneumonia.[25] Treatment of BOS frequently involves switching medications within the different classes and the institution of chronic macrolide therapy. However, no specific intervention has definitively been shown to modulate the course of BOS.

The major measurable outcome of LTx is survival, though QoL measures are also very important. Figure 8 shows the ISHLT survival statistics for patients with IPF after lung transplant.[26] The median survival is approximately 5 years, with 10-year survival rates of approximately 28%. In the ISHLT data set, there appears to be a survival benefit to the bilateral over single lung transplant procedure, however there is inherent bias in the data. For example, younger patients generally receive BLTx while older patients tend to receive single organs. For IPF, there is no definitive evidence that one procedure is better and either may therefore suffice.

Summary

Lung transplantation can be a life-saving procedure in the subset of IPF patients who are eligible for the procedure. Early referral of candidates to a transplant center is encouraged due to the unpredictable nature of the disease in most patients. The procedure may predispose to a myriad of complications and therefore has significant short- and long-term risks. The lung allocation system introduced in 2005 has reduced waiting time and mortality of listed patients with IPF. The overall change in survival after LTx for all patients is improving incrementally. However, since the inception of the LAS, survival has remained mostly unchanged, but this is likely due to the sickest patients now receiving high priority and being transplanted first.

Similar to IPF, there are no FDA-approved drugs for the management of lung transplant recipients. Immunosuppressive strategies are based on experience in other solid organ transplants. Therefore like IPF, where there is a dire need for effective medical therapies, the future of lung transplantation and the goal of reduced posttransplant mortality are to an extent dependent on new drug discoveries and improved immunosuppressive strategies.

REFERENCES

1. Nathan, SD. Lung transplant candidate selection and clinical outcomes: strategies for improvement in prioritization. *Curr Opin Organ Transplant*. 2005;10(3):216-220.

2. Latsi PI, du Bois RM, Nicholson AG, et al. Fibrotic idiopathic interstitial pneumonia: the prognostic value of longitudinal functional trends. *Am J Respir Crit Care Med*. 2003;168:531-537.

3. Orens JB, Estenne M, Arcasoy S, et al. International guidelines for the selection of lung transplant candidates: 2006 update – a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplant. *JHLT*. 2006; 25:745-755.

4. Thabut G, Mal H, Castier Y, et al. Survival benefit of lung transplantation for patients with idiopathic pulmonary fibrosis. *J Thorac Cardiovasc Surg*. 2003;126(2):469-475.

5. McCurry KR, Shearon TH, Edwards LB, et al. Lung transplantation in the United States, 1998-2007. *Am J Transplant*. 2009;9(4 Pt 2):942-958.

6. Nathan SD. Therapeutic intervention; assessing the role of the international consensus guidelines. *Chest*. 2005;128:533S-539S.

7. Nathan SD, Shlobin OA, Reese E, Ahmad S, Fregoso M, Athale C, Barnett SD. Prognostic value of the 6min walk test in bronchiolitis obliterans syndrome. *Respir Med*. 2009;103:1816-1821.

8. LAS calculator guide. http://www.unos.org/SharedContentDocuments/lung_allocation_score_updated_01072009.pdf. Accessed September 2009.

9. King TE Jr, Tooze JA, Schwarz MI, Brown KR, Cherniack RM. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. *Am J Respir Crit Care Med*. 2001;164(7):1171-1181.

10. Christie JD, Edwards LB, Aurora P, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-fifth official adult lung and heart/lung transplantation report—2008. *J Heart Lung Transplant*. 2008;27(9):957-969.

11. Mahidhara R, Bastani S, Ross DJ, et al. Lung transplantation in older patients? *J Thorac Cardiovasc Surg*. 2008;135(2):412-420.

12. Lederer DJ, Wilt JS, D'Ovidio F, Bacchetta MD, Shah L, Ravichandran S, Lenoir J, Klein B, Sonett JR, Arcasoy SM. Obesity and underweight are associated with an increased risk of death after lung transplantation. *Am J Respir Crit Care Med*. 2009;180(9):887-895.

13. World Health Organization Expert Committee on Physical Status. Physical status: the use and interpretation of anthropometry: report of a WHO expert committee. Geneva, Switzerland: World Health Organization; 1995.

14. Yusen RD. Technology and outcomes assessment in lung transplantation. *Proc Am Thorac Soc*. 2009;6(1):128-136.

15. Trulock EP, Christie JD, Edwards LB, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-fourth official adult lung and heart-lung transplantation report-2007. *J Heart Lung Transplant.* 2007;26(8):782-795.

16. Garrity ER, Moore J, Mulligan MS, Shearon TH, Zucker MJ, Murray S. Heart and lung transplantation in the United States, 1996–2005. *Am J Transplant.* 2007;7:1390-1403.

17. Yusen RD, Littenberg B. Integrating survival and quality of life data in clinical trials of lung disease. *Chest.* 2005;127:1094-1096.

18. Rinaldi M, Sansone F, Boffini M, et al. Single versus double lung transplantation in pulmonary fibrosis: a debated topic. *Transplant Proc*. 2008;40(6):2010-2012.

19. McCartney JG, Meyer KC. Optimizing post-transplant outcomes in lung transplantation. *Expert Rev Resp Med.* 2008;2(2):183-199.

20. Pierre AF, Keshavjee S. Lung transplantation: donor and recipient critical care aspects. *Curr Opin Crit Care*. 2005;11(4):339-344.

21. Fischer S, Bohn D, Rycus P, et al. Extracorporeal membrane oxygenation for primary graft dysfunction after lung transplantation: analysis of the Extracorporeal Life Support Organization (ELSO) registry. *J Heart Lung Transplant*. 2007;26(5):472-477.

22. Christie JD, Sager JS, Kimmel SE, Ahya VN, Gaughan C, Blumenthal NP, Kotloff RM. Impact of primary graft failure on outcomes following lung transplantation. *Chest*. 2005;127(1):161-165.

23. Bhorade SM, Stern E. Immunosuppression for lung transplantation. *Proc Am Thorac Soc*. 2009;6(1):47-53.

24. Lu BS, Garrity ER Jr, Bhorade SM. Immunosuppressive drugs: cyclosporine, tacrolimus, sirolimus, azathioprine, mycophenolate mofetil, and corticosteroids. Lung and heart-lung Transplantation. In: Lynch JP III, Ross DJ (eds). *Lung Biology in Health and Disease* (Volume 217). New York, NY: Taylor and Francis;2006:363-399.

25. Belperio JA, Weigt SS, Fishbein MC, Lynch JP 3rd. Chronic lung allograft rejection: mechanisms and therapy. *Proc Am Thorac Soc.* 2009;6(1):108-121.

26. Keating D, Levvey B, Kotsimbos T, et al. Lung transplantation in pulmonary fibrosis: challenging early outcomes counterbalanced by surprisingly good outcomes beyond 15 years. *Transplant Proc*. 2009;41(1):289-291.

ATTESTATION/EVALUATION

To obtain *AMA PRA Category 1 Credit™*, participants are required to:

1. Read the learning objectives, review the activity, and complete the posttest.
2. Complete this Attestation/Evaluation form.
3. Send, e-mail, or fax these forms to: The France Foundation
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Degree(s): ❑ MD/DO ❑ PharmD/RPh ❑ NP ❑ PA ❑ RN ❑ Other _____

Specialty: ❑ Pulmonology ❑ Pathology ❑ Radiology

❑ Other _____

Indicate the number of *AMA PRA Category 1 Credits*™ you are claiming _____ (Max 2 credits)

Signature: _____ Date: _____
I certify that I have completed this CME activity as designated.

BIAS, FAIR BALANCE

Was this activity fair, balanced, objective, and free from commercial bias? ❑ Yes ❑ No

If no, please state reason(s) _____

PRACTICAL APPLICATION

4 = strongly agree 3 = agree 2 = disagree 1 = strongly disagree

(a) _____ What I learned at this activity has increased my confidence in managing patients with IPF

(b) _____ What I learned at this activity will improve my patients with IPF

(c) _____ What I learned at this activity will result in an improvement in my patients' IPF management

(d) Do you intend to make changes or apply new information to your practice as a result of this activity?
_____ Yes, I plan to make changes*
_____ I'm not sure, but I'm considering changes*
_____ No, I already practice these recommendations

*If yes or considering changes, please check off what you intend to do differently or incorporate into your clinical management of patients with IPF as a result of this educational activity.
_____ Incorporate pulmonary rehabilitation into the management plan both prior to and after lung transplantation
_____ Use a quality of life instrument as a monitoring tool
_____ Refer patients for lung transplantation evaluation upon diagnosis
_____ Explain the lung allocation score (LAS) to patients who are candidates for transplantation
_____ Other, please specify

_____

BARRIERS

What are the top 3 barriers that might inhibit your ability to incorporate any of the above changes into your clinical practice?

1. _____ 2. _____ 3. _____

DEMOGRAPHIC QUESTIONS

How did you hear about this CME activity?

❑ Web Search ❑ Colleague ❑ Direct Mail

Number of years in practice: ❑ ≤ 5 ❑ 6–10 ❑ 11–15 ❑ 16–20 ❑ 21–25 ❑ > 25

How many of your patients are being managed for IPF?

❑ ≤ 5% ❑ 6-20% ❑ 21-40% ❑ 41-60% ❑ > 60%

May we contact you in the future with a brief survey to assess how you have used the information presented at this activity or to assess other educational needs? ❑ Yes ❑ No

ACTIVITY EVALUATION

4 = strongly agree *3 = agree* *2 = disagree* *1 = strongly disagree*

Upon completion of this activity, I will be able to:

_____ Discuss recent evidence for treatments in the management of IPF

Please rate the overall content presented in this activity: ❑ Too basic ❑ Appropriate ❑ Too complex

ONGOING UNMET EDUCATIONAL NEEDS

Recommendations for future CME topics in this disease area: _____

_____

_____

_____

POSTTEST ANSWERS

Record your Posttest answers by filling in the blank with the correct letter from the corresponding question:

1. ❑ a ❑ b

2. ❑ a ❑ b ❑ c ❑ d ❑ e ❑ f

3. ❑ a ❑ b ❑ c ❑ d ❑ e ❑ f

4. ❑ a ❑ b ❑ c

5. ❑ a ❑ b

6. ❑ a ❑ b ❑ c ❑ d

7. ❑ a ❑ b ❑ c ❑ d ❑ e

8. ❑ a ❑ b ❑ c ❑ d

POSTTEST

1. According to the 2005 ISHLT Consensus Statement, patients with IPF should be referred for lung transplant evaluation at the time of diagnosis, irrespective of their symptoms and functional status.

a. True
b. False

2. Which of these is not an absolute contraindication to lung transplant (LTx)?

a. History of smoking or drug/alcohol abuse problems within the previous 6 months
b. Malignancy in the previous 2 years
c. Morbid obesity
d. Age > 65 years
e. End-stage renal disease
f. Hepatitis B or Hepatitis C with evidence of liver disease

3. Which of the following is not an important component in determining the Lung Allocation Score (LAS)?

a. Time on waiting list
b. Diagnosis
c. Age
d. NYHA functional status
e. FVC (% predicted)
f. Body mass index (BMI)

4. Which statement is true concerning single lung transplantation (SLTx) and bilateral lung transplantation (BLTx) for IPF?

a. The numbers of SLTx and BLTx have been approximately constant for the last 15 years
b. BLTx is clearly preferable to SLTx for patients with IPF because of the lower mortality risk
c. In choosing a procedure for IPF patients, various factors should be considered, including age and the clinical status of the recipient and quality of the donor lung(s)

5. Primary Graft Dysfunction (PGD) occurs in approximately 5% of lung transplant patients and is characterized by hypoxemia and alveolar infiltrates.

a. True
b. False

6. Which of the following drugs has been shown to prolong survival in LTx population in phase III clinical trials?

a. Cyclosporine
b. Azathioprine
c. Rapamycin
d. None of the above

7. Which of the following are possible complications of lung transplantation?

a. Diarrhea
b. Hyperlipidemia
c. Hypertension
d. Osteoprosis
e. All of the above

8. Bronchiolitis obliterans syndrome (BOS) is always characterized by which of the following:

a. At least > 20% reduction in FEV_1
b. Dyspnea
c. Presence of infection
d. Median survival after onset of 10 years

NOTES

NOTES

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