

Lung Transplantation for Interstitial Lung Disease

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KEYWORDS

- Lung transplantation • Lung disease
- Parenchymal lung disease • Interstitial lung disease

There are more than 100 distinct interstitial or diffuse parenchymal lung diseases (DPLDs). These diseases are associated with underlying autoimmune disease, environmental/occupational exposures, and drug exposures. In addition, a large percentage of these disorders (approximately 30%–40%) are idiopathic. It is believed that previous prevalence estimates in the population have been grossly underestimated. Although DPLDs remain extremely rare in children, in adults the prevalence for parenchymal lung diseases is approximately 70 per 100,000 population.^{1–3} Newer information indicates that the prevalence of the most common form of idiopathic interstitial pneumonia, idiopathic pulmonary fibrosis (IPF), is likely greater than previously expected. Clinical courses and prognoses across all types of DPLD are variable and dependent on the underlying subtype of lung disease. For IPF, there are no current medical therapies that clearly alter the progression of disease. In addition, the current literature consistently estimates the median survival for patients with newly diagnosed IPF is 3 to 5 years.^{1,4–8} For IPF and the other DPLDs that progress despite best medical therapy, lung transplantation remains an appropriate treatment option for a select group of patients. Reitz and colleagues⁹ performed the first successful heart and lung transplant at Stanford University in 1981. Subsequently, in 1983, Cooper and the Toronto Lung Transplant Group¹⁰ successfully performed the first single lung transplant on a patient with IPF. During the past 25 years, the number of transplants performed worldwide has increased from the single digits per year to

approximately 3000 per year (**Fig. 1**). The major indications for lung transplantation include chronic obstructive pulmonary disease, cystic fibrosis, and IPF. The proportion of transplants for IPF has consistently increased and this has been particularly true during the past decade. Worldwide, transplantation for IPF now approaches the proportion for non- α_1 -antitrypsin deficiency chronic obstructive pulmonary disease transplants performed in 2008 (approximately 30% of all transplants).¹¹ In the United States, IPF and other DPLDs account for more than half of the lung transplants performed since 2008. This increase in the number of transplants contrasts with trends for idiopathic pulmonary arterial hypertension. With the advance of successful therapies for the treatment of pulmonary arterial hypertension, the number of transplants for this condition has significantly declined, accounting for approximately 2% of all transplants in 2008 compared with approximately 13% of transplants performed in 1990. This underscores the challenge that patients with IPF face: there is a lack of beneficial therapy for this devastating disease.

WHO SHOULD BE REFERRED AND LISTED FOR TRANSPLANT?

In 2006 the International Society for Heart and Lung Transplantation published a consensus report outlining appropriate guidelines for referral for transplantation.¹² The document also includes guidelines for actively placing an individual on a waiting list for transplant. The balance between

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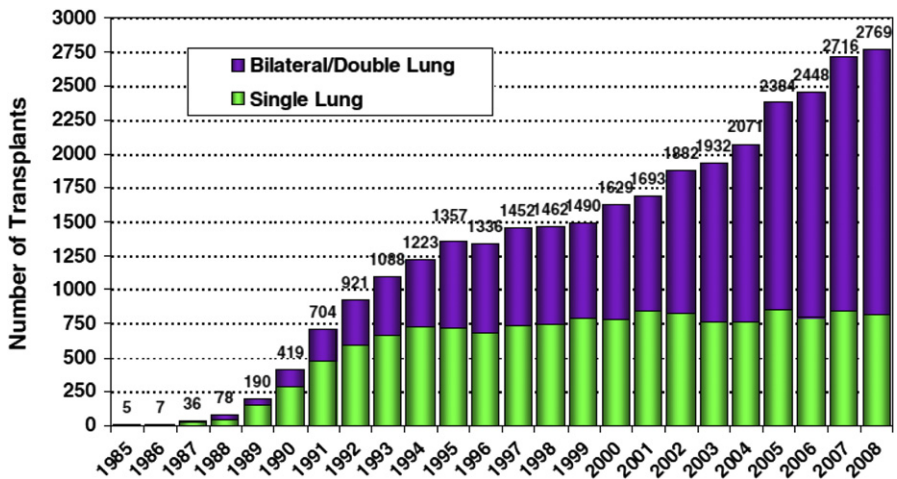


Fig. 1. Number of lung transplants and procedure type: 1985–2008. (From Christie JD, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: twenty-seventh official adult lung and heart-lung transplant report–2010. *J Heart Lung Transplant* 2010;29(10):1104–18; with permission.)

providing a short-term survival benefit must be weighed against the reality that donor lungs are a limited resource. Therefore, it is paramount that the appropriate transplant candidate be expected to have a reasonable opportunity to attain long-term survival. Assessment for potential long-term survival must include an appraisal of potential recipients' comorbidities. The 2006 guideline statement outlines several absolute and relative contraindications to performing lung transplantation (**Table 1**). In addition to medical considerations, lung transplant recipients must actively participate in the management of a complex medical regimen. Adherence to this treatment is central to good outcomes. As a result, a social support system that enhances adherence is beneficial, if not vital.

Transplantation centers agree that the moment of referral should allow the potential recipient adequate time to consider this treatment option. The initial transplantation discussion should not occur as a last-ditch effort at improving a patient's outcome. In this, or any, document, there are limitations in defining the appropriate time for referral and transplantation. Consideration of referral to a transplant center should include the referring physician's assessment of the individual's quality of life as well as overall life expectancy without a transplant. In addition, the potential recipient's desire to learn more about this treatment option is a factor in considering referral. The decision to actively list for transplant, alternatively, is based on organ allocation for a particular region, estimated risks and benefits based on the expertise of the individual

transplant center, and the personal assessments of the transplant recipient.

Choice of Procedure

There are 3 potential procedures for the interstitial lung disease recipient. These include heart and lung, single lung, and bilateral lung transplantation. Heart and lung transplantation was initially the procedure of choice during the 1980s and many centers continued this practice into the 1990s. After successful lung transplantation and the realization that the dilated right ventricle can remodel with good outcomes, heart and lung transplantation numbers have significantly declined. In 2008, there were 73 heart and lung transplants worldwide.¹³ Currently, heart and lung transplant is only performed on those patients with significant left ventricular dysfunction or nonoperable congenital abnormalities.

The decision to perform single lung versus bilateral lung transplant remains controversial today. The only absolute criterion for the performance of bilateral lung transplant is suppurative lung disease. This is due to concerns that the native lung will soil the transplanted allograft in a chronically immunosuppressed host and lead to poor outcomes. In addition to this absolute indication, it is now common practice to perform bilateral lung transplant for patients with idiopathic pulmonary hypertension. This population is at high risk of developing primary graft dysfunction or early acute lung injury after transplantation. This risk is lower in patients who undergo bilateral lung transplantation.¹⁴ For patients with very high pulmonary

Table 1
Absolute and relative contraindications to lung transplantation

Absolute Contraindications	Comment
Malignancy within past 2 years (excluding basal and squamous cell skin cancers)	Given effects of chronic immunosuppression on malignancy, a 5-year disease-free interval is prudent. Lung transplantation for bronchoalveolar cell carcinoma remains controversial
Untreatable advanced dysfunction of another major organ system	Coronary artery disease not amenable to intervention or associated with significant left ventricular dysfunction is an absolute contraindication but heart-lung transplant could be considered for select patients
Noncurable chronic extrapulmonary infection	Chronic active hepatitis B, hepatitis C, and HIV
Significant chest wall/spinal deformity	Abnormalities that preclude either safe removal of the native lung(s) or implantation of the donor lungs
Documented nonadherence or inability to follow through with medical therapy	Includes the need for a consistent and reliable social support system. In addition, untreatable psychiatric conditions that would impair the ability of the recipient to remain adherent are included here
Substance addiction within the last 6 months	Alcohol, tobacco, illicit drug use
Relative Contraindications	Comment
Age >65 years old	There is an increased risk of worse long-term survival with higher age likely related to increased comorbidities at transplant ¹¹
Severely limited functional status	Decreased exercise tolerance has been associated with worse outcomes ⁸⁴
Colonization with highly resistant or virulent bacteria, fungi, or mycobacteria	Increased risk of perioperative sepsis as well as potential empyema and/or wound infections
Obesity with a body mass index >30 kg/m ²	Obesity has been cited in several studies to increase the risk of both long-term and short-term poor outcomes ^{85–89}
Mechanical ventilation	Increased perioperative mortality is associated with mechanical ventilation ¹¹
Other chronic comorbidities that have not resulted in end-stage organ damage	All medical conditions should be optimized before consideration for listing for transplant, including chronic management of diabetes, hypertension, gastroesophageal reflux, and coronary artery disease

Absolute contraindications are determined by individual transplant programs and the balance of the risks and benefits is determined by the individual transplant center. Similarly, the presence of several relative contraindications may significantly increase the risk of poor transplant outcome and preclude listing for transplant.

Adapted from 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 Transplantation. J Heart Lung Transplant 2006;25(7):745–55; with permission.

vascular resistance before transplant, the right ventricle becomes acutely unloaded with the reanastomosis of the normal allograft pulmonary vasculature. High cardiac output ensues with high flow rates that may increase the risk of endothelial injury and subsequent pulmonary edema. This impact is likely attenuated by double the vascular volume of a bilateral transplant. For

patients with DPLD, it is less clear that individuals with secondary pulmonary hypertension receive an absolute benefit from bilateral lung transplantation. Several investigators have come to differing conclusions regarding the benefits of a particular procedure type in this population.^{14–16} Because there are no randomized controlled trials evaluating single lung versus bilateral lung

transplantation for pulmonary fibrosis, there are inherent selection biases that confound any retrospective cohort. With this limitation, several recent analyses suggest that there may be a benefit to bilateral lung transplant in selected patients with IPF. It seems there is an increased risk of complications early with bilateral lung transplant but a longer-term potential survival benefit may ultimately prevail.^{17–21}

Regardless of the rationale for the choice of procedure, recent data indicate that bilateral lung transplantation is increasing in frequency. In 2008, 71% of transplant procedures were bilateral lung transplants. During the same period, cystic fibrosis accounted for approximately 15% of transplants and idiopathic pulmonary hypertension less than 5%, and the frequency with which patients with an underlying diagnosis of IPF are transplanted is increasing. This suggests a trend toward increased bilateral transplantation in DPLD. One report evaluating waiting list mortality demonstrated a higher risk for those IPF patients listed for bilateral lung transplant as their only option.²² The impact on the donor pool and, subsequently, the waiting list mortality from an increased number of bilateral lung transplant procedures remains unknown at this time.

Outcomes After Transplantation

The majority of information about outcomes after lung transplantation in DPLD comes from what is known about IPF recipients. Because the majority of DPLDs result in similar physiologic changes with restrictive lung disease and high risk for the development of secondary pulmonary hypertension, some generalizations across the disease type are accurate. More specific disease considerations are discussed later.

Survival after lung transplantation has consistently improved by era from 1988 through June of 2008.²³ The most striking improvements in outcome are during the perioperative period. These improvements are likely due to improved donor preservation, operative technique, and critical care management early after transplant. Currently, the median survival estimate for all recipients from 1994 through 2008 was 5.3 years. The 90-day survival rate was 88%. Although the impact has not been as great for long-term survival, this too is slowly improving. In the same era, unadjusted 10-year survival rates were 29%. Survival for patients with an underlying diagnosis of DPLD is generally consistent with these reported outcomes. The largest cohort of interstitial lung disease transplanted remains IPF and the median survival for this group is 4.3 years. For those patients with sarcoidosis, median survival was

5.1 years. These unadjusted survival rates need to be evaluated cautiously because additional recipient factors have an impact on survival after lung transplantation.

Early survival after transplantation is hampered by the development of primary graft dysfunction (PGD). PGD is the consequence of ischemia-reperfusion injury with resultant development of reactive oxygen species. Ultimately, this leads to acute lung injury and capillary leak.²⁴ PGD is based on clinical findings early after transplantation (**Table 2**). Several studies have identified pulmonary fibrosis and pulmonary hypertension as having strong associations with the development of this complication.^{25–27}

PGD is the primary cause of death early after lung transplantation.¹¹ The severest form of PGD (grade 3 at 72 hours after transplant) affects long-term survival and pulmonary function and increases the risk for development of bronchiolitis obliterans syndrome (BOS).²⁸ In addition to the recipient risk factors, there are donor factors that increase the risk of development of this complication. Currently there are no recipient interventions to prevent its development. Further work into defining the best match for donor and recipient as well as the potential for conditioning of donor lungs may lead to improvements in the future.²⁹

Patients are on lifelong immunosuppression and are typically treated with corticosteroids, a calcineurin inhibitor (tacrolimus or cyclosporine), and an antimetabolite (mycophenolate mofetil or azathioprine). Chronic immunosuppression places patients at risk for the development of comorbidities, including hypertension, diabetes, chronic kidney disease, and malignancy (**Table 3**). Notwithstanding

Table 2
Grading of primary graft dysfunction severity

Grade	Pao ₂ /Fio ₂	Radiographic Infiltrates Consistent with Pulmonary Edema
0	>300	Absent
1	>300	Present
2	200–300	Present
3	<200	Present

Assessments are measured within 6 hours of reperfusion of the graft and out to 72 hours.

Values obtained at 72 hours seem to be the most predictive of subsequent outcome after transplant.

Adapted from Christie JD, Carby M, Bag R, et al. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction part II: definition. A consensus statement of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2005;24(10):1454–9; with permission.

Table 3
Morbidity after lung transplant

Outcome	≤1 Year	≤5 Years
Hypertension	53%	84%
Renal dysfunction		
Creatinine <2.5 mg/dL	17%	23%
Creatinine >2.5 mg/dL	6%	8%
Chronic dialysis	1.6%	3%
Renal transplant	0.1%	0.5%
Hyperlipidemia	24%	57%
Diabetes	26%	38%
Bronchiolitis obliterans	9.6%	37%

Adapted from Christie JD, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: twenty-seventh official adult lung and heart-lung transplant report—2010. *J Heart Lung Transplant* 2010;29(10):1104–18; with permission.

the medical complexity, patients with DPLD who undergo lung transplantation garner a survival advantage from the procedure.^{30–32} In addition, quality of life is significantly improved after transplantation in several studies.^{33–36}

The main limitation to long-term survival after lung transplantation remains the development of BOS, or chronic rejection. BOS is defined by persistent airflow obstruction in comparison to a recipient's peak baseline values (Table 4). Complications that affect the allograft (acute rejection, anastomosis issues, disease recurrence, and

Table 4
Criteria for grading of bronchiolitis obliterans syndrome

BOS 0	FEV ₁ >90% of Baseline and FEF _{25%–75%} >75% of Baseline
BOS 0p	FEV ₁ 81%–90% of baseline and/or FEF _{25%–75%} <75% of baseline
BOS 1	FEV ₁ 66%–80% of baseline
BOS 2	FEV ₁ 51%–65% of baseline
BOS 3	FEV ₁ 50% or less of baseline

FEF_{25%–75%}, midexpiratory flow rate.

Baseline FEV₁ is based on the average of the 2 highest values obtained after transplant that are at least 3 weeks apart.

BOS grade is based on the subsequent average of 2 FEV₁ values that are obtained at least 3 weeks apart and compared with the baseline value.

Adapted from Estenne M, Maurer JR, Boehler A, et al. Bronchiolitis obliterans syndrome 2001: an update of the diagnostic criteria. *J Heart Lung Transplant* 2002; 21(3):297–310; with permission.

so forth) must be ruled out in addition to documenting a decline in pulmonary function. There are several probable and possible risk factors that set up the lung transplant recipient for the development of chronic small airways disease, including recurrent acute rejection, lymphocytic bronchiolitis, donor antigen-specific reactivity, and aspiration of gastroesophageal refluxate. Ultimately, chronic obstruction increases the risk of infection and sets the stage for respiratory failure. The rate of BOS varies in different series but has an estimated prevalence of approximately 45% at 5 years. Treatment interventions for this syndrome are limited but recent data suggest a role for the use of chronic azithromycin in these patients.^{37–40}

DISEASE-SPECIFIC CONSIDERATIONS

Idiopathic Pulmonary Fibrosis

IPF remains a DPLD without a medical therapy of proved benefit and a consistently demonstrated median survival of 3 to 5 years. The increase in number of transplants for patients with IPF may be reflective of increasing incidence of IPF, increase in the awareness of this disease and subsequent increased diagnosis, and increased awareness of the severely poor prognosis associated with IPF or consistent with increasing trends to transplant older patients whom this disease most often afflicts. Regardless, this and other forms of pulmonary fibrosis are now the number one indication for lung transplantation in the United States, accounting for 52% of procedures performed in 2010 (United Network for Organ Sharing, personal communication, 2011). Worldwide, 29% of all procedures performed in 2008 were for an indication of IPF compared with 16% in 2000.¹¹

The appropriate time for listing for transplantation must consider the potential survival benefit of the procedure. In the past decade there has been much work to define risk factors associated with worse outcomes in those with IPF before transplantation. Although the overall prognosis is grim, disease course remains variable for individual patients. As a result, identifying patients who are at particularly high risk is most appropriate when considering listing for lung transplantation.

Studies have focused on baseline characteristics as well as the change in study values over time to identify the group of patients at high risk for short-term mortality and, therefore, who are appropriate candidates for lung transplantation. Most of these publications are based on small series of retrospective data that have not been prospectively validated. Nonetheless, several clinical indicators (Box 1) are worth discussion

Box 1**Factors associated with increased risk of death in idiopathic pulmonary fibrosis**

High-resolution CT scan imaging

Extensive reticulation or honeycomb change on CT scan imaging

Pulmonary function testing

Decline in FVC of 10% from baseline

6-Minute walk testing

Oxygen desaturation to <89% during testing

Overall walk distance of <212 m

Decline of ≥ 50 m distance from baseline walk distance

Development of an acute exacerbation

Abbreviation: FVC, forced vital capacity.

because they likely portend a worse outcome and herald the need for lung transplantation.

CT scan fibrosis scoring has consistently correlated with risk for death. In several studies, the extent of the fibrosis is an independent predictor of outcome.^{41–43} The extent of honeycomb change and reticulation is scored based on the percentage involvement of the lung parenchyma. Although these findings are consistent in the literature when interpreted by a thoracic radiologist, the lack of consistently trained radiologists limits its use in routine clinical practice. Nonetheless, extensive reticulation and/or honeycombing should raise the suspicion for future poor outcome.

Unlike the CT scan fibrosis score, baseline pulmonary function tests seem less helpful than serial measurements. This is borne out in both retrospective and prospective cohorts.^{44,45} Martinez and colleagues⁴⁵ demonstrated that IPF patients enrolled in a clinical trial seemed at equal risk for subsequent decline regardless of their baseline pulmonary function. Despite the lack of risk assessment from a single measurement, there are consistent data that indicate repeated measures of pulmonary function that demonstrate decline in the FVC are predictive of worse outcomes.^{44,46} Several studies have used 10% declines in FVC as a definition of significant decline to identify high-risk patients; however, a recent report suggests that smaller declines in FVC can also be clinically significant.⁴⁷ At this time, the absolute threshold for the decline in FVC to identify the highest-risk patient population remains unclear; however, any decline in FVC should warrant careful re-evaluation for a change in a patient's clinical status.

Assessment of a patient's exercise tolerance is also of independent value. Evidence of oxygen desaturation on 6-minute walk testing has demonstrated an increased risk for poor outcome in several studies.^{48–50} These studies consistently demonstrate an increased risk for those who desaturate below 89% during a 6-minute walk test on room air. In addition, overall walk distance seems independently associated with future outcome.^{51,52} In 2 separate cohorts of IPF patients, one awaiting lung transplantation and another evaluated at a referral center, similar poor 6-minute walk performance was associated with worse outcomes. One found a walk distance of less than 207 m associated with a 4-fold increased risk of death over the subsequent 6 months. The other found a walk distance of less than 212 m placed those individuals at high risk for mortality over the next 18 months. Consistent with the findings of pulmonary function testing, changes in exercise tolerance over time also seem predictive of outcome. Using data from a large randomized controlled trial, declines in 6-minute walk distance of greater than 50 m over 24 weeks were associated with a 4-fold increased risk of death during the next year.⁵³ These data indicate that poor exercise tolerance or falling exercise tolerance over time is indicative of a high-risk patient for mortality without transplantation.

Unfortunately, there remains a subset of patients who develop acute respiratory deterioration that suggests a less predictable course for patients with IPF. When the cause for the acute decline is unknown, this is termed, *acute exacerbation of IPF*.⁵⁴ Outcomes from different series seem variable but an exacerbation can be the defining event leading to frank respiratory failure. As a result, when there are no identifiable absolute contraindications to transplant, it is reasonable to refer all patients diagnosed with IPF to a transplant center.

The average IPF patient is diagnosed in the seventh decade. At this time, there is no absolute upper age limit for lung transplantation. Worldwide data demonstrate an increase in the number of lung transplants for those over age 65, accounting for 5% of all lung transplants performed in 2008. The International Society for Heart and Lung Transplantation Registry data indicate that those who are over age 65 suffer from worse long-term outcomes (median survival 3.3 years) compared with those who are under age 50 (median survival 6.3 years).¹¹ Although these survival outcomes are also affected by confounders because they are not adjusted, IPF patients are on average older and, therefore, may have worse outcomes than average. This fact does not preclude a potential survival benefit or quality-of-life improvement but

is assessed by the transplant center for each individual patient with IPF.

Sarcoidosis

Sarcoidosis has a highly variable clinical course that is often extended over decades with the possibility of spontaneous remissions. Determining the right time for transplantation is challenging and characteristics associated with high risk for mortality come from limited data sources.^{55–57} Patients who are African American, have higher mean pulmonary artery pressure, or require supplemental oxygen were found at increased risk of death while on the United Network for Organ Sharing (United States) waiting list. In addition, patients from a single-center cohort with right atrial pressure greater than 15 mm Hg had significantly increased risk of death while on the waiting list. Sarcoidosis accounted for approximately 3% of all transplants between 1995 and 2009.¹¹ Outcomes after transplantation are consistent with those for other indications although there is an increased risk of early mortality.^{58,59} This may be reflective of the increased rates of pulmonary hypertension. Shorr and colleagues⁵⁸ also identified that African American patients are at higher risk of perioperative death. Despite this, the most recent data indicate a 5-year median survival after transplant. For those patients who fail to respond to conventional therapy and develop advanced lung disease, lung transplantation remains a viable therapeutic option.

Special considerations for those with sarcoidosis include its systemic nature. A thorough evaluation of sarcoidosis patients to ensure there is no clinically significant end organ damage is relevant to the preoperative evaluation of these patients. In addition, mycetomas are a common complication of cavitary lung disease and these can have an impact on transplant candidacy as well as management.⁶⁰ One unique feature of sarcoidosis after transplant is its common recurrence in the transplanted lung.^{59,61–64} The reported prevalence of recurrent disease ranges from 20% to 80%. The granulomas are of recipient origin and disease recurrence typically is of little clinical significance after transplantation. Because patients are living longer after transplant, it remains to be seen if there are any longer-term complications from recurrence of disease.

Scleroderma Lung Disease and Connective Tissue Disease–Associated DPLD

The number of lung transplants performed for underlying connective tissue disease remains low, accounting for less than 1% of all lung

transplants in 2008.¹¹ Systemic sclerosis, rheumatoid arthritis, and undifferentiated connective tissue disease are associated with DPLD. The majority of data outlining outcomes after lung transplantation are from patients with systemic sclerosis. With the advent of angiotensin-converting enzyme inhibitors, renal crisis is no longer the main cause of death and this has been replaced with respiratory failure due to fibrosis and/or pulmonary hypertension.⁶⁵ As with sarcoidosis, connective tissue diseases are systemic, and careful consideration of comorbidities that hamper transplant outcome is imperative. One salient feature of systemic sclerosis is esophageal dysmotility. Several reports have associated chronic allograft dysfunction or BOS with gastroesophageal reflux.^{66,67} Esophageal dysmotility may not only increase reflux episodes but also preclude fundoplication that has been associated with improvements in lung function in selected patients.^{68,69} Gastroparesis is a common complication after lung transplantation as well.⁷⁰ Combining esophageal dysmotility and gastroparesis can lead to significant aspiration events that lead to graft dysfunction and loss. Guidelines that specifically outline criteria for acceptable esophageal function in systemic sclerosis remain elusive. Individual transplant programs assess this feature of disease on a case-by-case basis. Although the data are limited on outcomes for patients with systemic sclerosis, selected patients seem to have similar outcomes as patients with IPF and idiopathic pulmonary hypertension.^{71–74} These series are limited by their small size and further data to define outcomes in this patient population are needed.

Lymphangiomyomatosis

Lymphangiomyomatosis (LAM) remains a rare indication for lung transplantation accounting for 1% of all transplants performed between 1995 and 2009. Initial reports suggested a far worse natural history for LAM than is currently known.⁷⁵ Despite this, there is a subset of patients who decline over time and develop significant morbidity associated with the disease.⁷⁶ For this group, transplant is a reasonable therapeutic option. From a single-center cohort, perioperative complications included significant blood loss with the removal of the explanted lungs and chylous effusions⁷⁷; however, these findings did not preclude good long-term outcomes.⁷⁸ An additional evaluation of the US transplant registry demonstrated outcomes with statistically significantly better 5-year survival (65%) compared with other indications for lung transplant.⁷⁹ In addition to mortality data, there is

now information that demonstrates an improved quality of life for those who have undergone lung transplantation compared with those who have severe advanced disease due to LAM.³⁴

A novel intervention for patients with LAM deserves special mention. Sirolimus has been studied in a cohort of patients with moderate obstructive lung disease and found to reduce the decline in forced expiratory volume in 1 second (FEV1) over time.⁸⁰ This medication may be used more frequently in the future in patients with LAM; however, once the decision to list for transplant has been made, this medication should be avoided. Sirolimus has a prolonged half-life in those who are on a stable dose. It has been associated with the development of bronchial wound dehiscence in a previous randomized trial evaluating its safety and efficacy after lung transplantation.⁸¹ This potentially fatal complication precludes the use of sirolimus in the perioperative period of lung transplantation.

Pulmonary Langerhans Cell Histiocytosis

Pulmonary Langerhans cell histiocytosis (PLCH) accounts for less than 0.5% of all lung transplants. Patients with this disorder typically have significant pulmonary hypertension. Lung transplant outcomes seem compatible with those for other patients with idiopathic pulmonary hypertension although recurrence of disease does occur in the allograft at a high rate (20% in one series).⁸² The greatest risk factor for disease recurrence was a past history of systemic disease. The recurrence of disease was not reported to have an impact on survival; however, conclusions regarding the impact of disease recurrence are limited due to the small numbers and short follow-up. PLCH has also been associated with malignancy in several reports. Vassallo and colleagues⁸³ attempted to determine the risk for development of malignancy in their cohort, and a relationship could not be ruled in or ruled out. These past reports suggest it is prudent to carefully prescreen potential lung transplant recipients for malignancy. Given the small numbers of transplants and the reported outcomes to date, lung transplantation remains an appropriate therapeutic option for patients with advanced disease due to PLCH.

SUMMARY

For selected DPLD patients who fail to respond to medical therapy and demonstrate declines in function that place them at increased risk for mortality, lung transplantation should be considered. Lung transplantation remains a complex medical intervention that requires a dedicated

recipient and medical team. Despite the challenges, lung transplantation affords appropriate patients a reasonable chance at increased survival and improved quality of life. Lung transplantation remains an appropriate therapeutic option for selected patients with DPLD.

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