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 colleagues[9] performed the first successful heart and lung transplant at Stanford University in 1981. Subsequently, in 1983, Cooper and the Toronto Lung Transplant Group[10] 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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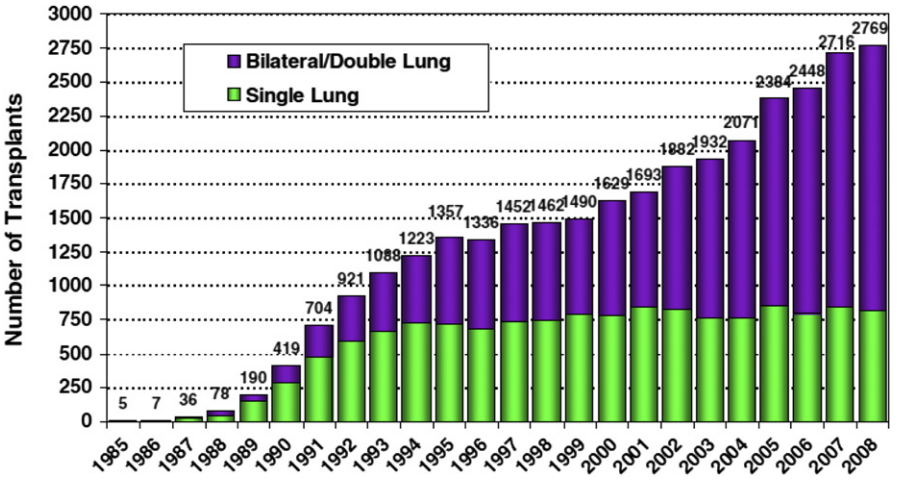

Fig. 1. Number of lung transplants and procedure type: 1985–2008. (*From* Christie JD, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: twenty-seventh official adult lung and heart-lung transplant report–2010. J Heart Lung Transplant 2010;29(10):1104–18;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

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 FEV_1 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 FEV_1 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.

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 colleagues[45] 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 colleagues[58] 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 allogragft 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 hyertension.[71–74] These series are limited by their small size and further data to define outcomes in this patient population are needed.

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (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 effusions[77]; 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 colleagues[83] 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 advance 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.

REFERENCES

1. Daniels CE, Lasky JA, Limper AH, et al. Imatinib treatment for idiopathic pulmonary fibrosis: randomized placebo-controlled trial results. Am J Respir Crit Care Med 2010;181(6):604–10.
2. Raghu G, Weycker D, Edelsberg J, et al. Incidence and prevalence of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2006;174(7):810–6.
3. Coultas DB, Zumwalt RE, Black WC, et al. The epidemiology of interstitial lung diseases. Am J Respir Crit Care Med 1994;150(4):967–72.
4. Araki T, Katsura H, Sawabe M, et al. A clinical study of idiopathic pulmonary fibrosis based on autopsy studies in elderly patients. Intern Med 2003;42(6):483–9.
5. Bjoraker JA, Ryu JH, Edwin MK, et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1998;157(1):199–203.
6. Collard HR, Ryu JH, Douglas WW, et al. Combined corticosteroid and cyclophosphamide therapy does not alter survival in idiopathic pulmonary fibrosis. Chest 2004;125(6):2169–74.
7. Daniil ZD, Gilchrist FC, Nicholson AG, et al. A histologic pattern of nonspecific interstitial pneumonia is associated with a better prognosis than usual interstitial pneumonia in patients with cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med 1999;160(3):899–905.
8. Nathan SD, Shlobin OA, Weir N, et al. Long-term course and prognosis of idiopathic pulmonary fibrosis in the new millennium. Chest 2011;140(1):221–9.
9. Reitz BA, Wallwork JL, Hunt SA, et al. Heart-lung transplantation: successful therapy for patients with pulmonary vascular disease. N Engl J Med 1982;306(10):557–64.
10. Unilateral lung transplantation for pulmonary fibrosis. Toronto Lung Transplant Group. N Engl J Med 1986;314(18):1140–5.
11. 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.
12. 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.
13. Christie JD, Edwards LB, Aurora P, et al. The registry of The International Society for Heart and Lung Transplantation: twenty-sixth official adult lung and heart-lung transplantation report—2009. J Heart Lung Transplant 2009;28(10):1031–49.
14. Conte JV, Borja MJ, Patel CB, et al. Lung transplantation for primary and secondary pulmonary hypertension. Ann Thorac Surg 2001;72(5):1673–9 [discussion: 1679–80].
15. Whelan TP, Dunitz JM, Kelly RF, et al. Effect of preoperative pulmonary artery pressure on early survival after lung transplantation for idiopathic pulmonary fibrosis. J Heart Lung Transplant 2005; 24(9):1269–74.
16. Huerd SS, Hodges TN, Grover FL, et al. Secondary pulmonary hypertension does not adversely affect outcome after single lung transplantation. J Thorac Cardiovasc Surg 2000;119(3):458–65.
17. Weiss ES, Allen JG, Merlo CA, et al. Survival after single versus bilateral lung transplantation for high-risk patients with pulmonary fibrosis. Ann Thorac Surg 2009;88(5):1616–25 [discussion: 1625–26].
18. Thabut G, Christie JD, Ravaud P, et al. Survival after bilateral versus single-lung transplantation for idiopathic pulmonary fibrosis. Ann Intern Med 2009; 151(11):767–74.
19. Neurohr C, Huppmann P, Thum D, et al. Potential functional and survival benefit of double over single lung transplantation for selected patients with idiopathic pulmonary fibrosis. Transpl Int 2010;23(9):887–96.
20. Algar FJ, Espinosa D, Moreno P, et al. Results of lung transplantation in idiopathic pulmonary fibrosis patients. Transplant Proc 2010;42(8):3211–3.
21. Force SD, Kilgo P, Neujahr DC, et al. Bilateral lung transplantation offers better long-term survival, compared with single-lung transplantation, for younger patients with idiopathic pulmonary fibrosis. Ann Thorac Surg 2011;91(1):244–9.
22. Nathan SD, Shlobin OA, Ahmad S, et al. Comparison of wait times and mortality for idiopathic pulmonary fibrosis patients listed for single or bilateral lung transplantation. J Heart Lung Transplant 2010; 29(10):1165–71.
23. 2009 Annual Report of the U.S. Organ procurement and transplantation network and the scientific registry of transplant recipients: transplant data 1999–2008. Rockville (MD): U.S. Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation.
24. de Perrot M, Liu M, Waddell TK, et al. Ischemia-reperfusion-induced lung injury. Am J Respir Crit Care Med 2003;167(4):490–511.
25. Fang A, Studer S, Kawut SM, et al. Elevated pulmonary artery pressure is a risk factor for primary graft dysfunction following lung transplantation for idiopathic pulmonary fibrosis. Chest 2011;139(4): 782–7.
26. Lee JC, Christie JD, Keshavjee S. Primary graft dysfunction: definition, risk factors, short- and long-term outcomes. Semin Respir Crit Care Med 2010;31(2):161–71.
27. Barr ML, Kawut SM, Whelan TP, et al. Report of the ISHLT working group on primary lung graft dysfunction part IV: recipient-related risk factors and markers. J Heart Lung Transplant 2005;24(10):1468–82.
28. Whitson BA, Prekker ME, Herrington CS, et al. Primary graft dysfunction and long-term pulmonary function after lung transplantation. J Heart Lung Transplant 2007;26(10):1004–11.
29. Cypel M, Yeung JC, Liu M, et al. Normothermic ex vivo lung perfusion in clinical lung transplantation. N Engl J Med 2011;364(15):1431–40.
30. 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):469–75.
31. Titman A, Rogers CA, Bonser RS, et al. Disease-specific survival benefit of lung transplantation in adults: a national cohort study. Am J Transplant 2009;9(7):1640–9.
32. Kotloff RM. Does lung transplantation confer a survival benefit? Curr Opin Organ Transplant 2009;14(5):499–503.
33. Kugler C, Fischer S, Gottlieb J, et al. Health-related quality of life in two hundred-eighty lung transplant recipients. J Heart Lung Transplant 2005;24(12): 2262–8.
34. Maurer JR, Ryu J, Beck G, et al. Lung transplantation in the management of patients with lymphangioleiomyomatosis: baseline data from the NHLBI LAM Registry. J Heart Lung Transplant 2007;26(12): 1293–9.
35. Santana MJ, Feeny D, Jackson K, et al. Improvement in health-related quality of life after lung transplantation. Can Respir J 2009;16(5):153–8.
36. Kugler C, Tegtbur U, Gottlieb J, et al. Health-related quality of life in long-term survivors after heart and lung transplantation: a prospective cohort study. Transplantation 2010;90(4):451–7.
37. Gerhardt SG, McDyer JF, Girgis RE, et al. Maintenance azithromycin therapy for bronchiolitis obliterans syndrome: results of a pilot study. Am J Respir Crit Care Med 2003;168(1):121–5.
38. Verleden GM, Dupont LJ. Azithromycin therapy for patients with bronchiolitis obliterans syndrome after lung transplantation. Transplantation 2004;77(9): 1465–7.
39. Yates B, Murphy DM, Forrest IA, et al. Azithromycin reverses airflow obstruction in established bronchiolitis obliterans syndrome. Am J Respir Crit Care Med 2005;172(6):772–5.

40. Vos R, Vanaudenaerde BM, Verleden SE, et al. A randomized placebo-controlled trial of azithromycin to prevent bronchiolitis obliterans syndrome after lung transplantation. Eur Respir J 2011; 37(1):164–72. [Epub 2010 Jun 18].
41. Lynch DA, Godwin JD, Safrin S, et al. High-resolution computed tomography in idiopathic pulmonary fibrosis: diagnosis and prognosis. Am J Respir Crit Care Med 2005;172(4):488–93.
42. Mogulkoc N, Brutsche MH, Bishop PW, et al. Pulmonary function in idiopathic pulmonary fibrosis and referral for lung transplantation. Am J Respir Crit Care Med 2001;164(1):103–8.
43. Gay SE, Kazerooni EA, Toews GB, et al. Idiopathic pulmonary fibrosis: predicting response to therapy and survival. Am J Respir Crit Care Med 1998; 157(4 Pt 1):1063–72.
44. 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(5):531–7.
45. Martinez FJ, Safrin S, Weycker D, et al. The clinical course of patients with idiopathic pulmonary fibrosis. Ann Intern Med 2005;142(12 Pt 1):963–7.
46. Collard HR, King TE Jr, Bartelson BB, et al. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2003;168(5):538–42.
47. Zappala CJ, Latsi PI, Nicholson AG, et al. Marginal decline in forced vital capacity is associated with a poor outcome in idiopathic pulmonary fibrosis. Eur Respir J 2010;35(4):830–6.
48. Hallstrand TS, Boitano LJ, Johnson WC, et al. The timed walk test as a measure of severity and survival in idiopathic pulmonary fibrosis. Eur Respir J 2005; 25(1):96–103.
49. Lama VN, Flaherty KR, Toews GB, et al. Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. Am J Respir Crit Care Med 2003;168(9):1084–90.
50. Lettieri CJ, Nathan SD, Browning RF, et al. The distance-saturation product predicts mortality in idiopathic pulmonary fibrosis. Respir Med 2006; 100(10):1734–41.
51. Lederer DJ, Arcasoy SM, Wilt JS, et al. Six-minute-walk distance predicts waiting list survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2006;174(6):659–64.
52. Caminati A, Bianchi A, Cassandro R, et al. Walking distance on 6-MWT is a prognostic factor in idiopathic pulmonary fibrosis. Respir Med 2009;103(1): 117–23.
53. Du Bois R, Albera C, Costabel U, et al. 6-Minute Walk Test Distance (6MWD) is a reliable, valid, and responsive outcome measure that predicts mortality in patients with IPF. Am J Respir Crit Care Med 2010; 181:A6026.
54. Collard HR, Moore BB, Flaherty KR, et al. Acute exacerbations of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2007;176(7):636–43.
55. Arcasoy SM, Christie JD, Pochettino A, et al. Characteristics and outcomes of patients with sarcoidosis listed for lung transplantation. Chest 2001; 120(3):873–80.
56. Shorr AF, Davies DB, Nathan SD. Outcomes for patients with sarcoidosis awaiting lung transplantation. Chest 2002;122(1):233–8.
57. Shorr AF, Davies DB, Nathan SD. Predicting mortality in patients with sarcoidosis awaiting lung transplantation. Chest 2003;124(3):922–8.
58. Shorr AF, Helman DL, Davies DB, et al. Sarcoidosis, race, and short-term outcomes following lung transplantation. Chest 2004;125(3):990–6.
59. Milman N, Burton C, Andersen CB, et al. Lung transplantation for end-stage pulmonary sarcoidosis: outcome in a series of seven consecutive patients. Sarcoidosis Vasc Diffuse Lung Dis 2005;22(3):222–8.
60. Hadjiliadis D, Sporn TA, Perfect JR, et al. Outcome of lung transplantation in patients with mycetomas. Chest 2002;121(1):128–34.
61. Milman N, Andersen CB, Burton CM, et al. Recurrent sarcoid granulomas in a transplanted lung derive from recipient immune cells. Eur Respir J 2005; 26(3):549–52.
62. Ionescu DN, Hunt JL, Lomago D, et al. Recurrent sarcoidosis in lung transplant allografts: granulomas are of recipient origin. Diagn Mol Pathol 2005;14(3): 140–5.
63. Yeatman M, McNeil K, Smith JA, et al. Lung Transplantation in patients with systemic diseases: an eleven-year experience at Papworth Hospital. J Heart Lung Transplant 1996;15(2):144–9.
64. Johnson BA, Duncan SR, Ohori NP, et al. Recurrence of sarcoidosis in pulmonary allograft recipients. Am Rev Respir Dis 1993;148(5):1373–7.
65. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. Ann Rheum Dis 2007;66(7):940–4.
66. D'Ovidio F, Mura M, Tsang M, et al. Bile acid aspiration and the development of bronchiolitis obliterans after lung transplantation. J Thorac Cardiovasc Surg 2005;129(5):1144–52.
67. Murthy SC, Nowicki ER, Mason DP, et al. Pretransplant gastroesophageal reflux compromises early outcomes after lung transplantation. J Thorac Cardiovasc Surg 2011;142(1):47–52.e3.
68. Palmer SM, Miralles AP, Howell DN, et al. Gastroesophageal reflux as a reversible cause of allograft dysfunction after lung transplantation. Chest 2000; 118(4):1214–7.
69. Hartwig MG, Anderson DJ, Onaitis MW, et al. Fundoplication after lung transplantation prevents the allograft dysfunction associated with reflux. Ann Thorac Surg 2011;92(2):462–8 [discussion: 468–9].

70. Berkowitz N, Schulman LL, McGregor C, et al. Gastroparesis after lung transplantation. Potential role in postoperative respiratory complications. Chest 1995;108(6):1602–7.
71. Rosas V, Conte JV, Yang SC, et al. Lung transplantation and systemic sclerosis. Ann Transplant 2000; 5(3):38–43.
72. Schachna L, Medsger TA Jr, Dauber JH, et al. Lung transplantation in scleroderma compared with idiopathic pulmonary fibrosis and idiopathic pulmonary arterial hypertension. Arthritis Rheum 2006;54(12): 3954–61.
73. Shitrit D, Amital A, Peled N, et al. Lung transplantation in patients with scleroderma: case series, review of the literature, and criteria for transplantation. Clin Transplant 2009;23(2):178–83.
74. Saggar R, Khanna D, Furst DE, et al. Systemic sclerosis and bilateral lung transplantation: a single centre experience. Eur Respir J 2010;36(4):893–900.
75. Taylor JR, Ryu J, Colby TV, et al. Lymphangioleiomyomatosis. Clinical course in 32 patients. N Engl J Med 1990;323(18):1254–60.
76. Kitaichi M, Nishimura K, Itoh H, et al. Pulmonary lymphangioleiomyomatosis: a report of 46 patients including a clinicopathologic study of prognostic factors. Am J Respir Crit Care Med 1995;151(2 Pt 1): 527–33.
77. Pechet TT, Meyers BF, Guthrie TJ, et al. Lung transplantation for lymphangioleiomyomatosis. J Heart Lung Transplant 2004;23(3):301–8.
78. Boehler A, Speich R, Russi EW, et al. Lung transplantation for lymphangioleiomyomatosis. N Engl J Med 1996;335(17):1275–80.
79. Kpodonu J, Massad MG, Chaer RA, et al. The US experience with lung transplantation for pulmonary lymphangioleiomyomatosis. J Heart Lung Transplant 2005;24(9):1247–53.
80. McCormack FX, Inoue Y, Moss J, et al. Efficacy and safety of sirolimus in lymphangioleiomyomatosis. N Engl J Med 2011;364(17):1595–606.
81. Groetzner J, Kur F, Spelsberg F, et al. Airway anastomosis complications in de novo lung transplantation with sirolimus-based immunosuppression. J Heart Lung Transplant 2004;23(5):632–8.
82. Dauriat G, Mal H, Thabut G, et al. Lung transplantation for pulmonary langerhans' cell histiocytosis: a multicenter analysis. Transplantation 2006;81(5): 746–50.
83. Vassallo R, Ryu JH, Schroeder DR, et al. Clinical outcomes of pulmonary Langerhans'-cell histiocytosis in adults. N Engl J Med 2002;346(7):484–90.
84. Sager JS, Kotloff RM, Ahya VN, et al. Association of clinical risk factors with functional status following lung transplantation. Am J Transplant 2006;6(9): 2191–201.
85. Kanasky WF, Anton SD, Rodrigue JR, et al. Impact of body weight on long-term survival after lung transplantation. Chest 2002;121(2):401–6.
86. Madill J, Gutierrez C, Grossman J, et al. Nutritional assessment of the lung transplant patient: body mass index as a predictor of 90-day mortality following transplantation. J Heart Lung Transplant 2001;20(3):288–96.
87. Gonzalez-Castro A, Llorca J, Suberviola B, et al. Influence of nutritional status in lung transplant recipients. Transplant Proc 2006;38(8):2539–40.
88. Lederer DJ, Wilt JS, D'Ovidio F, et al. Obesity and underweight are associated with an increased risk of death after lung transplantation. Am J Respir Crit Care Med 2009;180(9):887–95.
89. Allen JG, Arnaoutakis GJ, Weiss ES, et al. The impact of recipient body mass index on survival after lung transplantation. J Heart Lung Transplant 2010;29(9):1026–33.