

## Lung transplantation for interstitial lung disease

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Interstitial lung disease (ILD) comprises a heterogeneous group of disorders that leads to significant morbidity and mortality. Patients often suffer from significant dyspnea and ultimately die from respiratory failure. The exact prevalence of ILD is unknown because of the large number of diseases and changes in disease definitions and classifications [1]. In the only published epidemiologic study of ILD in the United States, Coutas et al [2] cited a prevalence of 80.9 per 100,000 in men from Bernalillo County, New Mexico. Whereas some diseases can be treated, others progress to end-stage lung disease despite therapy. Lung transplantation is often the last therapeutic option for patients who have exhausted all medical therapies. Between 1995 and 2002, approximately 20% of adult lung transplants were performed on patients with ILD, with idiopathic pulmonary fibrosis (IPF) being the most common (Table 1) [3]. In this article, we discuss different lung transplant procedures, indications for lung transplantation, outcomes following transplant, and the role of transplantation for specific ILDs. We also describe medical issues encountered by patients with ILD who undergo lung transplantation.

### Recipient selection

The number of patients with end-stage lung disease far exceeds the number of donor organs available, which results in waiting times of more than 2 years for 42% of persons on the waiting list [4]. To ensure proper allocation of limited organs and optimal outcomes, an international committee has formulated guidelines for selection of appropriate candidates for lung transplantation [5]. In general, candidates should have end-stage lung disease that is progressing on therapy with no other medical or surgical options. Patients should not be acutely critically ill and should be free from any comorbid medical conditions with the potential for end-organ damage. Current contraindications to lung transplant include renal dysfunction (creatinine clearance <50 mg/mL/minute), HIV infection, active malignancy within the past 2 years, hepatitis B antigen positivity, and biopsy-proven hepatitis C. Relative contraindications are symptomatic osteoporosis, severe musculoskeletal disease that affects the thorax, and requirement for invasive ventilation.

For patients with ILD, special considerations must be taken into account. Box 1 lists the guideline for transplant referral for patients with ILD. Patients with pulmonary fibrosis from a systemic disease (eg, systemic sclerosis, sarcoidosis) should produce evidence that the systemic disease is quiescent before being considered for transplant. Many patients with ILD have pulmonary hypertension as a result of their primary lung disease, and vasodilator therapy with prostacyclin or calcium channel blockers should be considered before transplantation. The following hemodynamic parameters are guidelines for referral for transplantation in ILD patients with secondary

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Table 1  
Indications for adult lung transplants performed between January 1995 and June 2002

| Diagnosis                         | Single-lung transplants<br><i>n</i> = 5000 (%) | Bilateral/double-lung transplants<br><i>n</i> = 4488 (%) | Total <i>n</i> = 9488 (%) |
|-----------------------------------|--|--|---------------------------|
| COPD/emphysema                    | 2698 (54)                                      | 1000 (22)  | 3698 (39)                 |
| <b>IPF</b>                        | 1186 (24)                                      | 403 (9)  | 1589 (17)                 |
| CF                                | 49 (1)   | 1447 (32)  | 1496 (16)                 |
| Antitrypsin deficiency            | 429 (8.6)                                      | 434 (9.7)  | 863 (9.1)                 |
| PPH                               | 66 (1.3)                                       | 367 (8)  | 427 (4.5)                 |
| <b>Sarcoidosis</b>                | 127 (2.5)                                      | 113 (2.5)  | 240 (2.5)                 |
| Bronchiectasis                    | 11 (0.2)                                       | 192 (4.3)  | 203 (2.1)                 |
| Congenital heart disease          | 10 (0.2)                                       | 99 (2.2)   | 109 (1.1)                 |
| <b>LAM</b>                        | 45 (0.9)                                       | 58 (1.3)   | 103 (1.1)                 |
| Re-Tx: OB                         | 47 (0.9)                                       | 47 (1)   | 94 (1)                    |
| OB (Non-reTX)                     | 30 (0.6)                                       | 52 (1.2)   | 82 (0.9)                  |
| Re-Tx: Non-OB                     | 35 (0.7)                                       | 37 (0.8)   | 72 (0.8)                  |
| <b>Connective tissue disorder</b> | 21 (0.4)                                       | 22 (0.5)   | 43 (0.5)                  |
| Cancer                            | 3 (0.1)  | 25 (0.6)   | 28 (0.3)                  |
| <b>Histiocytosis X</b>            | 11 (0.2)                                       | 8 (0.2)  | 19 (0.2)                  |
| Other <sup>a</sup>                | 232 (4.6)                                      | 190 (4.2)  | 422 (4.4)                 |

*Abbreviations:* CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; LAM, lymphangioliomyomatosis; PPH, primary pulmonary hypertension; Tx, transplant.

<sup>a</sup> Bronchiectasis, congenital heart disease, re-Tx, cancer, and miscellaneous.

*Adapted from* Trulock E, Edwards LB, Taylor DO, Boucek MM, Mohacsai PJ, Keck BM, et al. The Registry of the International Society of Heart and Lung Transplantation: twentieth official adult lung and heart-lung transplant report — 2003. *J Heart Lung Transplant* 2003;22:625–35.

pulmonary hypertension: a cardiac index of less than 2 L/minute/m<sup>2</sup>, a right atrial pressure of more than 15 mm Hg, and a mean pulmonary artery pressure of more than 55 mm Hg [5,6].

### Surgical options

Surgical options for lung transplantation have increased since the first unilateral lung transplant performed in 1963 [7], but patients with ILD most often receive single-lung transplants (SLTs) [3]. There are currently four ways to perform a lung transplant:

1. SLT is the most commonly performed procedure and can be offered to patients with either obstructive or restrictive lung diseases. More than half of all SLTs are performed on patients with chronic obstructive pulmonary disease (COPD)/emphysema, and since the initial success reported by the Toronto Lung Transplant Group on SLT for pulmonary fibrosis [8], approximately 25% of SLTs are performed on patients with IPF [3]. SLT is a simpler and shorter operation, with aortic cross-clamp time of 4:30, compared with an ischemic time of 7:15 for the second graft in a bilateral lung transplant (BLT) [9].
2. BLT is almost always offered to patients with septic lung disease (eg, cystic fibrosis and bronchiectasis) to prevent soiling of the allograft lung with bacteria from the native lung [9]. Bilateral sequential lung transplant (BSLT) involves implantation of two lungs, one at a time. It has supplanted the original en bloc double-lung operation by avoiding the complications of cardiopulmonary bypass and tracheal anastomosis [10,11]. Patients with ILD who receive a BSLT tend to be younger, more physically fit, and larger in physical stature. Although it is a longer procedure, the perioperative mortality of BSLT is similar to that of SLT, and survival after the first year favors BSLT [3].
3. Heart-lung transplantation is reserved for patients who have end-stage combined cardiopulmonary diseases, with congenital heart disease, primary pulmonary hypertension, and cystic fibrosis accounting for more than 70% of all cases. Although mortality rate is high in the first 3 months, the conditional half-life of heart-lung transplantation is higher at 8.1 years, compared with 6.5 years for lung transplantation [3]. Only a few heart-lung transplants are performed on patients with ILD—almost exclusively on patients with severe secondary pulmonary hypertension.

4. Living lobar lung transplantation was introduced in 1990 as a procedure for patients considered too ill to await cadaveric transplantation [12,13]. Although initially conceived for pediatric lung and cystic fibrosis patients, the technique has been applied to adults with other end-stage lung diseases, including IPF, pulmonary hypertension, and obliterative bronchiolitis [14–16]. The right lower lobe and the left lower lobe are taken from two donors and implanted into the right and left chest cavities of the recipient, respectively [17].

### Lung transplantation in specific interstitial lung diseases

#### *Idiopathic pulmonary fibrosis*

IPF is a rapidly progressive disease with a predilection for middle-aged men and a mean age at diagnosis of 66 years [18–20]. The histopathologic pattern of usual interstitial pneumonia on lung biopsy

distinguishes IPF from other forms of idiopathic interstitial pneumonias. The median survival of biopsy-proven IPF is less than 3 years [21], and currently no therapy has been shown clearly to improve morbidity or mortality [22–25]. Lung transplantation has emerged as a viable option for some patients with IPF, but with almost 40% mortality rate after 1 year on the waiting list [26], it seems that many patients may have missed the window of referral for transplantation. A recent study provided a prediction model for survival of 2 years based on the diffusion capacity for carbon monoxide (DL<sub>CO</sub>) percent predicted and high-resolution CT fibrosis score to assist in optimizing the timing of referral [27]. To reduce the high mortality rate on the waiting list, the United Network for Organ Sharing has mandated that patients with IPF be given a bonus 90 days of waiting time upon registration on the waiting list [4,28].

The survival benefit of lung transplantation for patients with IPF has been examined by several groups [26,29,30]. Under the United Network for Organ Sharing organ allocation system in the United States, Hosenpud et al [26] found that the survival benefit of transplantation over continued waiting was apparent within 6 months after transplant. Similarly, in parts of Europe governed by the Eurotransplant system, De Meester et al [30] showed the benefit of transplantation for patients with IPF within 3 months. While the United Network for Organ Sharing and Eurotransplant are waiting time–based allocation systems, France uses a system that allows the attending physician to prioritize patients with the poorest life expectancy. Lung transplantation also was found to improve survival in patients with IPF under that system [29]. The decision to perform SLT or BSLT for IPF is often dictated by organ availability. A recent study by Meyers et al [31] showed that BSLT did not confer a survival advantage when compared with SLT for patients with IPF. This finding was confirmed by data from the registry of the International Society for Heart and Lung Transplantation [3].

#### *Sarcoidosis*

Sarcoidosis is a multisystemic disease of unknown origin characterized by noncaseating granulomas. Although the lungs are the most commonly affected organ, more than 80% of pulmonary sarcoidosis resolves spontaneously. For patients who are symptomatic from their disease, corticosteroid therapy is usually effective. Despite treatment, however, some individuals progress to end-stage lung disease [32].

#### **Box 1. Guidelines for transplant referral for idiopathic pulmonary fibrosis**

- Symptomatic, progressive disease persists despite steroids or other immunosuppressive drug therapy
- Withdraw steroids or other cytotoxic agents if no meaningful benefit has been achieved
- Vital capacity <60%–70% predicted and/or the diffusing capacity (corrected for alveolar volume) <50%–60% predicted
- Evaluate for bronchogenic carcinoma, pulmonary tuberculosis, bronchiectatic areas, and mycetomas
- Assess and treat steroid-related morbidities and symptoms of coronary artery disease
- Consider referral to transplant center, although patient may be minimally symptomatic

*Data from Maurer JR, Frost AE, Glanville AR, Estenne M, Higenbottam T. International guidelines for the selection of lung transplant candidates. Am J Respir Crit Care Med 1998;158:335–9.*

Although patients with systemic disease such as sarcoidosis initially were excluded from lung transplantation, good medium-term results [33] have made sarcoidosis the second leading cause of lung transplantation for ILD [3]. Guidelines for referring patients with sarcoidosis for transplantation are presented in Box 1. Compared with patients with IPF who are on the waiting list, patients with sarcoidosis have significantly worse pulmonary function and higher pulmonary artery pressure, yet they are less likely to receive a transplant [34]. Arcasoy et al [35] observed that almost half of 43 patients with sarcoidosis listed for transplant died before transplantation over a 9-year period.

The question of SLT or BLT for sarcoidosis remains unclear. It is accepted that patients with fibrocystic sarcoidosis with associated bronchiectasis should receive BLT [9,36], but no literature supports either SLT or BLT as the procedure of choice for sarcoidosis without suppurative infection.

Recurrence of sarcoid granulomas in the allograft lung is frequently reported, and it occurs in more than 50% of transplants [33,37–40]. Diagnosis is usually made incidentally on surveillance transbronchial biopsies without clinical symptoms. In rare cases, recurrence can lead to pulmonary symptoms that resolve with medical therapy [39]. Johnson et al [38] noticed more severe early acute rejection episodes in patients with sarcoidosis who underwent transplantation. Recurrent sarcoidosis may develop within weeks to more than 2 years after transplantation [38,40].

Mycetomas are commonly found in patients with end-stage sarcoidosis and portend a poor prognosis in lung transplantation [32]. In a retrospective pathologic review of more than 300 lung transplants, Hadjiliadis et al [41] found nine cases of mycetoma in the explanted lungs, six of which were from patients with sarcoidosis. The median survival after transplantation for the mycetoma group was 16 months, significantly shorter than 56.7 months for the group without mycetomas. The authors concluded that mycetomas should be sought aggressively and treated with antifungal therapy before transplantation, especially in patients with sarcoidosis, and patients with extensive disease should not undergo lung transplantation.

#### *Lymphangioleiomyomatosis*

Lymphangioleiomyomatosis (LAM) is a rare disease that primarily affects women in their reproductive years. It is characterized by dyspnea, pneumothoraces, hemoptysis, cough, and chylous pleural effusion and ascites. LAM has a variable rate of progression and eventually leads to respiratory failure

and death. Hormonal manipulation, including progesterone, antiestrogen agents, and oophorectomy, have been inconsistent in slowing progression [42,43]. Lung transplantation is currently indicated for patients with end-stage LAM; 1.1% of lung transplantation is performed for patients with LAM [3].

The unpredictable rate of disease progression has led investigators in search of markers to grade the severity and progression of disease. The most common abnormalities of pulmonary function in LAM are airflow obstruction, indicated by decreased forced expiratory volume in one second (FEV<sub>1</sub>) and decreased DL<sub>CO</sub>. Reversible airflow obstruction was found to be associated with accelerated loss of lung function, whereas DL<sub>CO</sub> correlated best with the LAM histologic score, a predictor of survival or time to lung transplantation [44,45]. Cardiopulmonary exercise testing was able to detect hypoxemia in patients with near normal FEV<sub>1</sub> and DL<sub>CO</sub> while determining maximum oxygen uptake, which also correlated with LAM histologic score [46].

The actuarial survival rates after lung transplantation for LAM are similar to those achieved by lung transplant for other indications, although the operation is fraught with disease-related complications, especially intraoperative hemorrhage caused by extensive pleural adhesions and postoperative chylous fistulae [47,48]. There have been at least five reported cases of recurrent LAM in the allograft lung of SLT [37,49–52]. Genetic analyses of these cases have revealed that histologically benign LAM cells migrate to the transplanted lung by a metastatic mechanism [51,52]. No adverse outcome from recurrence has been reported to date, however.

#### *Interstitial lung disease associated with collagen vascular disease*

End-stage lung disease can occur in most collagen vascular diseases and accounts for less than 1% of all lung transplantations [3]. ILD has become the leading cause of mortality in systemic sclerosis since the introduction of angiotensin-converting enzyme inhibitors for the treatment of renal crisis [53]. The prevalence of pulmonary fibrosis in systemic sclerosis varies from 25% to 90%, but only a subset of these patients develops severe restrictive lung disease that requires transplantation [54]. A histopathologic study of 80 patients with ILD from systemic sclerosis revealed a nonspecific interstitial pneumonia pattern in 77.5% of lung biopsies, far greater than the prevalence of usual interstitial pneumonia (7.5%). Surprisingly, no survival difference existed between the two groups despite the better prognosis usually

associated with nonspecific interstitial pneumonia. The authors found that predictors for poorer survival in patients with systemic sclerosis and nonspecific interstitial pneumonia were lower baseline DL<sub>CO</sub>, higher eosinophil levels on bronchoalveolar lavage, and deterioration in DL<sub>CO</sub> during the following 3 years [55].

Because ongoing systemic disease can affect transplant outcome adversely, caution must be exercised when performing transplantation in patients with collagen vascular diseases. Two series have documented similar 4- to 5-year survival rates for selected systemic sclerosis patients compared with patients with COPD or IPF who undergo lung transplantation [56,57]. Although sample sizes were small—9 and 12, respectively—the studies demonstrated that lung transplantation is a viable option for carefully selected patients with systemic sclerosis lung disease. Concerns specific to systemic sclerosis include renal dysfunction, aspiration pneumonitis from esophageal dysfunction, skin lesions, and secondary pulmonary hypertension [56].

Eighty percent of patients with rheumatoid arthritis have radiographic evidence of ILD, although nearly half are asymptomatic, and the disease tends to follow a more benign course than IPF [58]. Lung transplantation is an option for end-stage disease, but no studies have reported the outcome. Systemic lupus erythematosus infrequently manifests as ILD, only accounting for 5 of 120 patients in one series [59]. Published experiences with transplantation for SLE are few, but one report noted two deaths from underlying vasculitis after transplantation [60].

#### *Pulmonary Langerhans' cell histiocytosis*

Pulmonary Langerhans' cell histiocytosis is a rare disease that almost exclusively affects smokers. The course is one of spontaneous resolution in 25%, stabilization with mild lung function defect in 50%, and progressive disease in 25%. Approximately 5% of affected persons die from respiratory failure or cor pulmonale. Lung transplantation became an indication for treatment of end-stage pulmonary Langerhans' cell histiocytosis in the early 1990s, and SLT, BLT, and heart-lung transplant have been performed. Case reports suggest that medical therapy is effective in stabilizing lung function for disease recurrence after transplantation [61–63]. A prominent feature of patients with pulmonary Langerhans' cell histiocytosis who present for lung transplant evaluation is severe pulmonary hypertension (mean pulmonary artery pressure 55.9 mm Hg). Despite having higher degree of pulmonary hypertension, patients with

pulmonary Langerhans' cell histiocytosis have significantly better survival rates compared with patients with IPF on the transplant waiting list [64].

#### *Desquamative interstitial pneumonia*

Desquamative interstitial pneumonia is a distinct form of idiopathic interstitial pneumonia that affects cigarette smokers. It often responds well to corticosteroid therapy and carries a more favorable prognosis than IPF, with overall survival of 70% after 10 years. Patients can progress to end-stage disease and require lung transplantation, however. There are two case reports of recurrent desquamative interstitial pneumonia in the allograft lung after SLT in the literature. The recurrence of a disease that is believed to be confined to the lungs argues for a systemic involvement of desquamative interstitial pneumonia. In the first case, the patient experienced a slow decline in lung function that responded to repeated steroid bursts [65]. The second recurrent case was confirmed by autopsy after the patient experienced rapidly progressive respiratory failure, despite augmented therapy, that led to her eventual death [66].

#### **Outcome after transplantation**

Lung transplantation has improved drastically since its inception in 1963, which has led to significantly higher survival rates over the last decade. The current benchmark survival rates are 83% at 3 months, 73% at 1 year, 57% at 3 years, 45% at 5 years, and 23% at 10 years [3]. Although perioperative mortality is similar between SLT and BLT, the conditional half-life of 8.2 years for BLT is significantly longer than 5.9 years for SLT. Caution must be exercised in interpreting these data because survival has not been adjusted for confounding variables (eg, age and indication for transplant).

Underlying lung disease serves as a predictor of early survival after transplantation. During the first 3 to 6 postoperative months, IPF and sarcoidosis carry higher mortality rates than all other diagnoses, except for primary pulmonary hypertension. The actuarial survival rate conditional on survival to 1 year also shows that patients with IPF have the lowest survival rates. Patients with sarcoidosis have the highest survival rates, however. Whether the poor outcome of patients with IPF after transplantation is related to older age or other factors remains to be seen.

The major causes of death during the first 30 days after lung transplantation are graft failure and non-cytomegalovirus infections, both of which contribute



to mortality during subsequent days. Ceriana et al [67] reported that for patients who underwent SLT, individuals with restrictive disease had less adverse postoperative outcome (eg, in-hospital death, mechanical ventilation longer than 7 days) than patients with obstructive or vascular diseases. In their study, graft failure was the main cause of early death, whereas sepsis and multiple organ failure represented late causes of in-hospital mortality. Of the different variables analyzed, intraoperative use of cardiopulmonary bypass was the only factor that predicted an adverse outcome. This finding was corroborated by Chatila et al [68], who found cardiopulmonary bypass to have a strong association with prolonged ventilatory support.

After the first posttransplantation year, approximately 30% of deaths are attributed to bronchiolitis obliterans, which is the most important contributor to late mortality [3]. Bronchiolitis obliterans is the histopathologic diagnosis of chronic rejection characterized by dense eosinophilic hyaline fibrous plaques in the submucosa of the small airways, which result in partial or complete luminal compromise [69]. Bronchiolitis obliterans syndrome is the clinical diagnosis of bronchiolitis obliterans, made in the presence of graft deterioration without tissue diagnosis. Bronchiolitis obliterans syndrome contributes to significant morbidity among survivors. By 5 years

Table 2

Risk factors for mortality within 1 year after adult lung transplantation

| Risk factor                     | Odds of 1-year mortality >1 |
|---------------------------------|-----------------------------|
| Donor age                       | >45 y                       |
| Recipient age                   | >50 y                       |
| Donor/recipient body mass index | <1                          |
| Center volume                   | <20 cases/y                 |
| Ischemia time                   | >2 h                        |
| Serum creatinine                | >1 mg/dL                    |
| Serum bilirubin                 | >1 mg/dL                    |
| Oxygen requirement at rest      | Any <sup>a</sup>            |
| Predicted FEV <sub>1</sub>      | <80% <sup>b</sup>           |

<sup>a</sup> Hazard ratio increased from 1.0 to 1.8 as pretransplantation oxygen requirement rose from 0 to 4 L/min then decreased to 1.5 at an oxygen flow rate of 8 L/min.

<sup>b</sup> Only for patients with IPF; hazard ratio is >1 at FEV<sub>1</sub> of 80% predicted and increased as FEV<sub>1</sub> declined, especially below 50% of predicted.

Data from Trulock E, Edwards LB, Taylor DO, Boucek MM, Mohacs PJ, Keck BM, et al. The Registry of the International Society of Heart and Lung Transplantation: twentieth official adult lung and heart-lung transplant report — 2003. *J Heart Lung Transplant* 2003;22:625–35.

Table 3

Risk factors for mortality within 5 years after adult lung transplantation

| Risk factor                   | Odds of 5 year mortality >1 |
|-------------------------------|-----------------------------|
| Recipient age                 | <30 or >50 y                |
| Donor age                     | <20 or >30 y                |
| PA systolic <sup>a</sup>      | >40 mm Hg                   |
| Bilirubin <sup>a</sup>        | >1 mg/dL                    |
| pCO <sub>2</sub> <sup>a</sup> | <35 mm Hg                   |

Abbreviation: PA, pulmonary arterial.

<sup>a</sup> Denotes pretransplantation value.

Data from Trulock E, Edwards LB, Taylor DO, Boucek MM, Mohacs PJ, Keck BM, et al. The Registry of the International Society of Heart and Lung Transplantation: twentieth official adult lung and heart-lung transplant report — 2003. *J Heart Lung Transplant*. 2003;22:625–35.

after transplantation, 50% of recipients develop bronchiolitis obliterans syndrome.

Pretransplant diagnosis of IPF or sarcoidosis increases the risk of death within 1 year after transplantation (odds ratio 1.91 and 2.15, respectively). Other categoric risk factors for 1-year mortality include ventilator and intravenous inotrope use, repeat transplant, humoral sensitization (panel reactive antibody [PRA]>10%), cytomegalovirus mismatch, and all pretransplant diagnoses other than COPD. Risk factors for 5-year mortality include diagnosis of cystic fibrosis, cytomegalovirus mismatch, and infection that requires intravenous drug therapy within 2 weeks of transplant. Continuous variables for 1- and 5-year mortality are presented in Tables 2 and 3, respectively.

Quality of life after lung transplantation has been examined by several investigators. Although the studies used different designs, a few conclusions could be made: (1) Lung transplant recipients reported a significantly better quality of life than transplant candidates; (2) recipients were satisfied with their decision for transplant; and (3) few recipients returned to work despite improvement in quality of life and function [70].

### Special considerations for lung transplantation in interstitial lung disease

#### Coronary artery disease

IPF accounts for most lung transplantations for ILD. Because the median age of diagnosis for IPF is 66 years and there is a male predominance, coronary artery disease is a potential comorbid condition. Current guidelines advise against lung transplantation in cases with significant coronary artery disease [5],

but evidence exists for successful outcome of transplantation after coronary revascularization [71–73]. Snell et al [71] retrospectively reviewed the use of coronary angiography in assessing coronary artery disease and found that patients who required surgical or percutaneous cardiac revascularization can undergo lung transplantation safely. Patel et al [73] noticed similar results with combined coronary artery bypass grafting and lung transplantation. Survival at 1 year was similar in the revascularized group compared with all other transplant recipients. Although larger trials are needed, it seems that careful selection of patients with coronary artery disease can lead to successful lung transplantation.

#### *Steroid-induced osteoporosis*

Corticosteroids often are used to treat patients with ILD, which predisposes these patients to the known risk of osteoporosis. Eighty-five percent of lung transplant candidates have abnormal bone mass density before transplant. Although patients with COPD and cystic fibrosis are most commonly affected, 75% of patients with IPF also have abnormal bone mass density [74,75]. When treated with only vitamin D and calcium supplementation after transplantation, the mean bone mass density for the lumbar and femoral spine decreased significantly by 4.76% and 5.3%, respectively, and 18% of patients suffered osteoporotic fractures within 12 months [74]. Pamidronate has been shown not only to decrease the rate of lumbar spine bone loss during the first 6 months but also to increase the bone mass density significantly at 1 year [76]. Recently, progressive lumbar spine resistance training also was shown to improve lumbar bone mass density after lung transplantation [77]. Because most immunosuppressive medications, including glucocorticoids, increase the rate of osteoporosis, transplant recipients who receive life-long immunosuppression require close monitoring and treatment of osteoporosis.

#### *Secondary pulmonary hypertension*

End-stage ILD is often accompanied by pulmonary hypertension, sometimes to a severe degree. The mechanism seems to involve obliteration of the pulmonary vasculature in pulmonary Langerhans' cell histiocytosis [78], sarcoidosis, and ILD associated with collagen vascular diseases [79]. Although some transplant centers routinely perform BSLT with cardiopulmonary bypass in patients with pulmonary hypertension, Huerd et al [80] demonstrated that patients with secondary pulmonary hypertension had

successful outcomes after SLT without cardiopulmonary bypass. Heart-lung transplant is usually not performed even when severe right heart dysfunction exists because remodeling of the right heart is often reversible after isolated lung transplant.

#### *Venous thromboembolism*

Patients with IPF seem to be at increased risk of thromboembolic disease after lung transplantation. In a group of 72 lung transplant patients, Nathan et al [81] reported six patients who developed pulmonary embolism after lung transplantation, all of whom had a diagnosis of IPF. Magro et al [82] discovered evidence of microvascular injury with corresponding immunologic evidence of antiphospholipid antibodies in open-lung biopsies from 19 patients with IPF. Eighteen of the 19 patients tested positive for antiphospholipid antibodies, 4 had a positive lupus anticoagulant, and 4 had at least one episode of venous thrombosis. Definitive studies are needed to confirm a hypercoagulable state in IPF, but taken together with the increased risk of thrombosis in patients with lupus and collagen vascular diseases, venous thromboembolism should be considered in any lung transplant recipient with ILD who presents with dyspnea.

### **Summary**

Lung transplantation has evolved as a definitive therapy for patients with end-stage ILD that is refractory to medical therapy. Early referral of patients with ILD is important to ensure appropriate timing for transplantation. Currently, lung transplantation has been associated with improved lung function, exercise capacity, quality of life, and survival in this group of patients. Donor availability and the long-term complications of infection and rejection after transplantation limit lung transplantation, however. With continued investigation into increasing the donor pool, improving immunosuppressive strategies, determining immune tolerance, and improving surgical techniques, outcomes after lung transplantation will continue to improve.

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