Candidate Selection, Timing of Listing, and Choice of Procedure for Lung Transplantation

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KEYWORDS

• Lung transplantation • Selection criteria • Techniques

Lung transplant recipients face innumerable challenges posed by surgery, immunosuppression, drug toxicities, and rejection. To maximize the likelihood of a successful outcome, candidates selected to undergo this arduous procedure ideally must be free of significant medical comorbidities and sufficiently fit to handle these insults. Because of the inherent risks involved, it is also essential that patients are not listed prematurely, but only at a time when living with their underlying disease poses even greater risk. This strategy requires an appreciation of the natural history of lung disease to determine when the disease has entered an advanced and imminently life-threatening stage. Unique to lung transplantation, decisions must often be made about whether to replace 1 or both organs.

This review discusses the decision process leading up to the transplant surgery. These decisions (patient selection, timing of listing, and choice of procedure type) are critically important steps in optimizing the outcome of lung transplantation.

INDICATIONS FOR TRANSPLANTATION

The indications for lung transplantation include a diverse array of pulmonary diseases of the airways, parenchyma, and vasculature. Chronic obstructive pulmonary disease (COPD) represents the leading indication for lung transplantation worldwide, accounting for approximately one-third of all procedures performed to date.[1] The number of procedures performed for idiopathic pulmonary fibrosis (IPF) has been steadily increasing and although still second to COPD worldwide, IPF is now the leading indication in the United States.[2] Cystic fibrosis (CF) (16%), emphysema caused by α-$_1$-antitrypsin deficiency (7%), sarcoidosis (3%), non-CF bronchiectasis (3%), and lymphangioleiomyomatosis (1%) represent other less common indications.[1] Once a leading indication for transplantation, idiopathic pulmonary arterial hypertension (IPAH) now accounts for only 2% of procedures, reflecting major advances in the medical management of these patients. Transplantation of patients with lung involvement caused by scleroderma remains controversial because of concerns that esophageal dysmotility and reflux could increase the risk for aspiration and accelerated graft loss. Nonetheless, short-term functional outcomes and survival after transplantation of carefully selected patients with scleroderma are comparable with other patient populations.[3,4] Limited attempts to use lung transplantation for definitive cure of bronchoalveolar carcinoma,

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a subtype of lung cancer with a low metastatic potential, were met with an unacceptably high rate of cancer recurrence, leading most centers to view this as a contraindication.[5]

CANDIDATE SELECTION

There are few absolute contraindications to lung transplantation. There is general consensus that listing is contraindicated by: recent malignancy (other than nonmelanoma skin cancer); infection with the human immunodeficiency virus; hepatitis B or C virus with histologic evidence of significant liver damage; active or recent cigarette smoking, drug abuse, or alcohol abuse; severe psychiatric illness; documented and recurrent noncompliance with medical care; and absence of a consistent and reliable social support network.[6] The presence of significant extrapulmonary vital organ dysfunction precludes isolated lung transplantation, but multiorgan procedures such as heart-lung or lung-liver can be considered in highly select patients.[7,8] When extreme, obesity and malnutrition are commonly viewed as absolute contraindications but cutoffs vary among centers.[6] The risk posed by other medical comorbidities such as diabetes mellitus, osteoporosis, gastroesophageal reflux, and coronary artery disease must be assessed individually based on severity of disease, presence of end-organ damage, and ease of control with standard therapies.

Although the cutoff is admittedly arbitrary, most transplant centers define an upper age cutoff for transplant eligibility, commonly 65 years of age. However, there has been an increasing trend to expand the age range, based principally on the argument that suitability for transplant should be based on physiologic rather than chronologic age criteria. This trend has been most pronounced in the United States, where patients 65 years and older accounted for 19% of transplant recipients in 2008 compared with less than 5% before 2002.[2] A recent single-center study of 50 carefully selected patients 65 years or older found no difference in 1-year and 3-year posttransplant survival rates compared with a cohort less than the age of 65 years.[9] However, the Scientific Registry of Transplant Recipients (SRTR), a comprehensive database of US transplants, documents a 10-year survival rate among recipients 65 years and older of only 13% compared with 23% for those 50 to 64 years, and 38% for those younger than 50 years.[2]

Candidates for lung transplantation are functionally limited (New York Heart Association class III or IV) but, ideally, still ambulatory. Many programs screen for and exclude profoundly debilitated patients by requiring a minimum distance on a standard 6-minute walk test (6MWT).[10] An evolving area of controversy centers on the eligibility of ventilator-dependent patients in the intensive care unit (ICU), most of whom are nonambulatory. Ventilator dependence before transplantation has long been recognized as a risk factor for increased posttransplant mortality, and transplantation of these patients was typically discouraged in the past. The new lung allocation system in the United States, which prioritizes patients based on medical urgency and short-term net survival benefit, has forced transplant centers to reconsider this philosophy by assigning the highest allocation scores to ventilator-dependent patients. Many programs are now willing to maintain select ventilator-dependent patients on their active waiting list, anticipating that transplantation occurs in short order and reserving the option of delisting patients who develop intercurrent complications or progressive debility. A recent analysis of 586 ventilator-dependent patients documents inferior but not abysmal short-term outcomes; 1-year and 2-year survival rates were 62% and 57%, respectively, compared with 79% and 70% for unsupported patients.[11] Even more controversial is the transplantation of patients on extracorporeal membrane oxygenation support, for whom 1-year and 2-year posttransplant survival rates are only 50% and 45%, respectively.[11]

Previous pleurodesis is associated with an increased risk of intraoperative bleeding, particularly when cardiopulmonary bypass is used, but this is not a contraindication to transplantation in experienced surgical hands.[12,13] Previous lung volume reduction surgery (LVRS) in patients with COPD can similarly increase the risk of pleural bleeding but does not seem to adversely affect survival or functional outcomes.[14] In contrast, pleural thickening associated with mycetomas can render explantation of the native lung difficult and bloody, and there is the additional risk of soiling the pleural space with fungal organisms if the mycetoma cavity is violated. In 1 small series, the presence of a mycetoma in the native lung was associated with a perioperative mortality of 45%.[15] In light of this, it seems prudent to exclude those patients with mycetomas with either extensive pleural reaction or cavities abutting the pleural surface.

Chronic infection of the airways is a universal feature of CF and poses unique concerns in selecting patients with CF for transplantation. Most patients with CF are infected with *Pseudomonas aeruginosa* by the time they are considered for lung transplantation. Although these organisms are often highly resistant, the effect of the resistance

pattern on survival after transplantation seems to be small. Two single-center retrospective studies found that posttransplant survival of patients with CF with panresistant *Pseudomonas aeruginosa* was similar to that of patients harboring sensitive strains.[16,17] In contrast to these studies, Hadjiliadis and colleagues[18] found that patients harboring panresistant organisms had lower, albeit still highly favorable, survival rates compared with patients with sensitive strains: 87% versus 97% at 1 year and 58% versus 86% at 5 years. Taken in sum, these 3 studies suggest that patients with panresistant *Pseudomonas aeruginosa* should not be excluded from consideration for lung transplantation.

The situation is more complex in relation to pretransplant infection of patients with CF with *Burkholderia cepacia*. Published series document an adverse effect on outcomes, with 1-year survival rates in the range of 50% to 67% for patients with *B cepacia* compared with 83% to 92% for those without.[19,20] Using predictive models of pretransplant and posttransplant survival, Liou and colleagues[21] have suggested that patients with CF infected with *B cepacia* do not derive a survival benefit from transplantation. These and other negative reports have led most centers in the United States to exclude candidates with *B cepacia* from consideration for lung transplantation. However, it has become clear that *B cepacia* is not a single entity but a heterogeneous collection of species (previously referred to as genomovars) with varying pathogenicity and effect on posttransplant outcomes. Recent studies have attributed the observed excessive posttransplant mortality to *B cenocepacia* (genomovar III) and possibly to *B gladioli*.[22,23] In contrast, infection with other members of the *B cepacia complex* does not seem to adversely affect posttransplant survival. Should additional epidemiologic studies corroborate these observations, transplant eligibility in the future may be dictated by the particular species that the patient harbors.

Aspergillus species are isolated from pretransplant respiratory cultures in up to 50% of patients with CF. Although this finding may increase the risk of posttransplant *Aspergillus* infections of the bronchial anastomosis, it does not represent a contraindication to transplantation.[24,25] Nontuberculous mycobacteria are isolated in up to 20% of patients with CF referred for consideration of lung transplantation. The most common mycobacterium isolated is *Mycobacterium avium* complex; its presence does not adversely affect outcomes after lung transplantation. In contrast, pretransplant recovery of *Mycobacterium abscessus* has been associated with subsequent development of serious infections after transplantation, albeit not conclusively with reduced survival. Some centers view the presence of *Mycobacterium abscessus* as a relative contraindication[26]

DISEASE-SPECIFIC CONSIDERATIONS IN CANDIDATE LISTING

Familiarity with the natural history of the underlying disease and of disease-specific prognostic factors is essential in making decisions about the timing of listing of candidates for lung transplantation. Prognostic factors for the diseases constituting the most common indications for transplant are reviewed in the sections to follow. Many of these prognostic factors have been incorporated into guidelines published by the International Society of Heart and Lung Transplantation (ISHLT) (**Box 1**).[6] The prognostic indices that have been identified to predict the natural history of individual lung diseases are imprecise, identifying populations of patients at increased risk for death but of more limited usefulness in predicting the course of an individual patient. Thus, not every patient who fulfills the criteria set forth in the ISHLT guidelines necessarily warrants immediate listing, and such decisions should also take into account the patient's clinical trajectory, functional status, quality of life, and willingness to accept the attendant risks and uncertainties of transplantation.

COPD

COPD is associated with a highly variable and protracted natural history, typically evolving over many years in an insidious fashion. Even at an advanced stage, long-term survival is possible and as a result it is often difficult to determine the exact point at which lung transplantation should be offered. Historically, the postbronchodilator FEV_1 was touted as the best single predictor of prognosis in COPD.[27] Other risk factors that have been associated with an increased mortality risk include hypoxemia, hypercapnia, low body mass index, poor performance on a 6MWT, and magnitude of dyspnea.[28] More recently, Celli and colleagues[29] devised a multidimensional grading system referred to as the BODE index (body mass index [B], degree of airflow obstruction [O], dyspnea [D], and exercise capacity [E], measured by the 6MWT). The investigators prospectively validated the index and showed that it was a better predictor of risk of death than FEV_1 alone. The BODE index score ranges from 0 to 10, with the higher scores indicating higher risk of death. In the study, the highest quartile (BODE score of 7–10) was associated with a mortality of 80% at 4 years.

Box 1
Disease-specific guidelines for listing for lung transplantation

COPD

- BODE index of 7 to 10 or at least 1 of the following:
- History of hospitalization for exacerbation associated with acute hypercapnia (P_{CO_2} exceeding 50 mm Hg)
- Pulmonary hypertension or cor pulmonale, or both, despite oxygen therapy
- Forced expiratory volume after 1 second (FEV_1) of less than 20% and either carbon monoxide diffusion in the lung (D_{LCO}) of less than 20% or homogeneous distribution of emphysema.

IPF

- Histologic or radiographic evidence of usual interstitial pneumonia (UIP) and any of the following:
- A D_{LCO} of less than 39% predicted
- A 10% or greater decrement in forced vital capacity (FVC) during 6 months of follow-up
- A decrease in pulse oximetry less than 88% during a 6MWT
- Honeycombing on high-resolution computed tomography (HRCT) (fibrosis score of >2)

CF

- FEV_1 <30% of predicted, or rapidly declining lung function if FEV_1 >30% (females and patients <18 years of age have a poorer prognosis; consider earlier listing) and/or any of the following:
- Increasing oxygen requirements
- Hypercapnia
- Pulmonary hypertension

IPAH

- Persistent New York Heart Association (NYHA) class III or IV on maximal medical therapy
- Low (350 m) or declining 6MWT
- Failing therapy with intravenous epoprostenol, or equivalent
- Cardiac index of less than 2 L/min/m^2
- Right atrial pressure exceeding 15 mm Hg

Sarcoidosis

- NYHA functional class III or IV and any of the following:
- Hypoxemia at rest
- Pulmonary hypertension
- Increased right atrial pressure exceeding 15 mm Hg

Data 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;25:745–55.

A subsequent study by Martinez and colleagues[30] examined the predictive usefulness of serial measurements of the BODE index. The study examined patients who had participated in the National Emphysema Treatment Trial and who were therefore characterized by the presence of advanced airflow obstruction (mean FEV_1 predicted of 27%) and an average baseline BODE score of approximately 5. The investigators found that an increase in BODE score of greater than 1 point over a 6-month to 24-month period of observation was associated with a 2-fold increase in death among medically treated patients and a 3-fold increase among the group that had undergone LVRS.

The ISHLT guidelines have adopted the BODE score as the principle but not exclusive parameter to be used in determining the appropriate timing of listing patients with COPD.[6] Specifically, listing is recommended for patients with a BODE score of 7 to 10 or at least 1 of the following: (1) history of hospitalization for exacerbation associated with acute hypercapnia (P_{CO_2} >50 mmHg); (2) pulmonary hypertension and/or cor pulmonale, despite oxygen therapy; or (3) FEV_1 less than 20% and either D_{LCO} less than 20% or homogeneous distribution of emphysema.

Assuming that listing criteria for patients with COPD accurately identify candidates with a poor prognosis, lung transplantation would be expected

to confer a survival advantage but this has been difficult to show. Studies that have compared survival of patients with COPD on the waiting list with posttransplantation survival have yielded conflicting results, with 1 study from the United States[31] suggesting that transplantation does not confer a survival advantage whereas 2 European studies came to the opposite conclusion.[32,33] Recently, Thabut and colleagues[34] developed multivariate parametric models to simulate the survival of patients with COPD while on the waiting list and after transplantation to assess whether there were particular factors that portend a survival benefit from transplantation in this patient population. In building their models, the investigators used the SRTR database containing 8182 patients with COPD listed for lung transplantation between 1986 and 2004. A major determinant of survival benefit proved to be the type of transplant procedure used: approximately 45% of the patients with COPD in the United Network for Organ Sharing database were predicted to derive a survival benefit of at least 1 year by undergoing bilateral lung transplantation (BLT) compared with only 22% who would derive such a benefit if single lung transplantation (SLT) was used. In addition to the type of transplant procedure chosen, survival benefit was heavily influenced by FEV_1 and several other functional and physiologic parameters. As an example, nearly 80% of patients with an FEV_1 less than 16% but only 11% of those with an FEV_1 greater than 25% were predicted to gain at least a year of life with BLT. A calculator that generates an estimate of survival benefit for an individual patient with a particular set of parameters is available at http://www.copdtransplant.fr/ and, if validated in future studies, could serve an important role in patient selection.

A final issue specific to the COPD population is the potential effect of LVRS on listing for lung transplantation. For those patients with an FEV_1 less than 25% who meet criteria for both surgical procedures, there is the option of offering LVRS first, reserving transplantation for failure to respond to LVRS or to subsequent functional decline after a period of sustained improvement. Successful LVRS can postpone the need for transplantation for up to several years, and the associated improvement in functional and nutritional status can optimize the patient's suitability as a transplant candidate.[14,35–37]

IPF

IPF is a debilitating disorder with no proven treatment and a median survival from the time of diagnosis of 3 to 4 years. The decision to list a patient with advanced and progressive IPF for lung transplantation is usually straightforward but can be problematic for patients with early or more indolent disease. Many studies have attempted to define the factors that distinguish those who die quickly from those with a more chronic course; these factors are discussed in detail later.

Underlying pathology

The presence of UIP on pathology, the histologic sine qua non of IPF, generally portends a poor prognosis. In contrast, nonspecific interstitial pneumonitis (NSIP) is typically associated with slower progression and longer survival; within this histologic group, the cellular subset follows a more indolent course than the fibrotic subset.[38–40] Among patients with suspected IPF, surgical lung biopsies obtained from multiple sites show concurrent presence of UIP and NSIP in approximately 25% of cases.[41] In these cases of discordant UIP, the prognosis is identical to that of patients who exclusively show a pattern of UIP. The presence of a greater number of fibroblast foci within a pattern of UIP also has been associated with a poorer prognosis.[42,43]

Radiology

Several scoring systems have been developed to quantify the degree of fibrosis on HRCT scans in patients with IPF. Higher scores generally reflect a greater degree of reticulation and honeycombing, and a paucity of ground glass opacities. Although minor differences exist in the mechanics of the scoring systems, all have shown a direct correlation between higher fibrosis scores and mortality.[44–46] Among patients with biopsy-proven UIP, those who have the classic radiographic features of the disease may have a worse survival than those who have atypical features.[45–47] For example, Flaherty and colleagues[47] documented a median survival of 2.1 years for patients deemed to have definite or probable UIP by 2 expert radiologists compared with a median survival of 5.8 years for those with indeterminate features or features more suggestive of NSIP. Similarly, Sumikawa and colleagues[46] reported mean survival rates of 3.8 years, 4.8 years, and 6.4 years for patients with HRCT patterns interpreted as definite UIP, consistent with UIP, and suggestive of alternative diagnosis, respectively.

Pulmonary function testing

Mugolkuk and colleagues[48] found that baseline diffusing capacity measurement, in conjunction with HRCT fibrotic score, offered the best prediction of 2-year survival for patients with IPF. Using receiver operator character analysis, a 39% predicted diffusing capacity was the optimal cutoff

for distinguishing survivors from nonsurvivors. However, other studies have failed to consistently define which baseline parameters, if any, are best at predicting outcomes.[44,48–51] In contrast, multiple studies have reported that longitudinal changes in pulmonary function parameters over a 6-month to 12-month period from time of diagnosis are a more powerful predictor of outcome than are baseline values.[49,52,53] For example, in 1 study a decline in FVC of 10% or greater in the first 6 months was associated with a 2-fold increase in the risk of death compared with patients whose FVC was unchanged during this period.[52] A recent study found that even marginal declines in FVC (5%–10%) over 6 months were associated with an increased mortality compared with those with stable disease.[54]

6MWT

Both the lowest saturation achieved during a 6MWT and the absolute distance walked are independently associated with prognosis. In 1 study of patients with biopsy-proven UIP, those whose oxygen saturation decreased to 88% or less during a 6MWT performed on room air had a 4-year survival rate of only 35%, whereas those who maintained higher levels had a survival rate of 69%.[50] In another study, patients with IPF who were awaiting lung transplantation and who walked less than 207 m (679 feet) had a 4-fold increase in mortality compared with those who had a longer walk distance.[51] The persistence of significant tachycardia 1 minute after completion of the 6MWT (decrease in heart rate from last minute of test of less than 13 beats per minute) was recently documented to be a strong predictor of mortality, performing better than either distance walked or saturation.[55]

Pulmonary hypertension

Secondary pulmonary hypertension is encountered in 30% to 60% of patients with advanced IPF.[56,57] There is an emerging consensus in the literature that pulmonary hypertension is associated with significantly worse mortality.[57–59] For example, a study that relied on echocardiographic estimates of pulmonary artery pressures found median survival rates of 4.8 years, 4.1 years, and 0.7 years for patients with IPF with estimated pulmonary artery systolic pressures of less than 35 mm Hg, 35 to 50 mm Hg, and greater than 50 mm Hg, respectively.[59]

Acute exacerbations

Although IPF typically progresses in a stuttering fashion, seemingly stable patients may experience sudden and precipitous decline. These so-called acute exacerbations are characterized by unexplained worsening or development of dyspnea within 30 days, new bilateral ground glass opacities or consolidation superimposed on the background of UIP changes, and no evidence of infection, heart failure, pulmonary embolus, or other cause of acute lung injury.[60] In 1 study examining the natural history of patients with mild to moderate IPF, 21% of patients died during a 76-month period of observation, and half of these deaths were caused by acute exacerbations. Pulmonary function parameters before these acute events were generally stable and provided no signal of impending decompensation. Other studies have suggested rates of acute exacerbations in the range of 5% to 61%, with short-term mortality approaching 100% for those requiring admission to an ICU for respiratory failure.[60–62]

Combination of IPF and emphysema

There is increasing recognition of the unique features of a subgroup of patients with IPF who have concomitant emphysema.[63,64] Because of the counterbalancing effects of IPF and emphysema on elastic recoil, spirometric and lung volume parameters are typically well preserved in these patients and often belie the severity of the underlying condition. Characteristically, these patients are at greater risk of developing pulmonary hypertension than patients with IPF alone. When present, pulmonary hypertension portends an extremely poor prognosis in this group, with a 1-year survival of only 60% and 5-year survival of 25%.[63,64]

Guidelines for listing

In light of the generally poor prognosis and the possibility of rapid and unexpected decompensation, the ISHLT guidelines recommend that patients with histologic or radiographic evidence of UIP should be referred to a lung transplant center for evaluation at the time of diagnosis, independent of the degree of functional impairment. The intention is not to immediately list all patients, but to initiate the process of patient education and allow sufficient time to address potential barriers to transplantation (eg, obesity, deconditioning, high-dose corticosteroid use). In addition, the testing and consultations necessary for listing can be completed to facilitate expedited listing in the event of sudden decline in the future. The ISHLT guidelines for active listing incorporate many of the negative prognostic factors identified earlier: (1) diffusing capacity less than 39% predicted; (2) a 10% or greater decrease in FVC over a 6-month period; (3) desaturation less than 88% on a 6MWT; and/or (4) honeycombing on an HRCT. Although not stated in the ISHLT guidelines, patients with combined IPF and emphysema

are a special case; listing should be based on presence of pulmonary hypertension rather than standard pulmonary function parameters.

CF

Kerem and colleagues[65] published a landmark study in 1992 that identified FEV_1 as the single most significant predictor of mortality in patients with CF. These investigators found that an FEV_1 less than 30% predicted was associated with a 2-year mortality of 50%. For a given FEV_1, females and patients less than the age of 18 years had a higher 2-year mortality than their counterparts. Based on this study, the recommendation that patients with CF with an FEV_1 less than 30% be listed for transplantation became widespread, with consideration given to earlier referral of females and younger patients. Subsequent studies from several other CF centers documenting more favorable median survival rates of 3.9 to 4.6 years associated with an FEV_1 less than 30% challenged but did not alter this recommendation.[66,67]

More recent studies have attempted to assess the risk of death in patients with CF using models incorporating multiple patient characteristics. In 2001, Liou and colleagues[68] published a 5-year survivorship model that was derived from data on 5800 patients in the CF Foundation Patient Registry and validated using data from an additional 5800 Registry patients. In addition to FEV_1, age, gender, weight, presence of diabetes, pancreatic insufficiency, number of acute exacerbations per year, and infection with *Staphylococcus aureus* and *Burkholderia cepacia* were identified as independent predictors of prognosis by multivariate analysis and were incorporated into the model. When applied to the validation cohort, this complex model predicted survival in superior fashion to the simpler model proposed by Kerem and colleagues using FEV_1 alone.

Mayer-Hamblett and colleagues[69] developed and validated a 2-year mortality model using methods identical to those of Liou and a more current and larger cohort of patients (n = 14,572) from the CF Foundation Patient Registry. In contrast to the findings of Liou and colleagues, their multivariate model showed no greater ability to predict short-term mortality than the simpler FEV_1 criterion proposed by Kerem and colleagues. Both the multivariate model and the FEV_1 alone showed a positive predictive value for 2-year mortality in the range of only 50% (ie, half of the patients predicted to die within 2 years would actually survive). Because the Mayer-Hamblett model chose a different outcome than the Liou model (2-year vs 5-year mortality), it cannot be firmly concluded that the findings of the 2 studies are necessarily contradictory but these contrasting studies do serve to raise a degree of uncertainty about overreliance on predictive models to guide transplant decisions.

A potential limitation of both of these models is that they included all patients with CF, independent of disease severity and transplant eligibility. These models might not be applicable to the specific population of potential CF transplant candidates, a more homogenous population of patients with many shared clinical characteristics and a narrower spectrum of physiologic abnormalities. Addressing this concern, Vizza and colleagues[70] examined 146 patients with CF awaiting lung transplantation at Washington University. Shorter 6-minute walk distance, presence of diabetes mellitus, and higher pulmonary artery systolic pressure were predictive of mortality on the waiting list. However, the investigators noted that there was no threshold for any of these factors that reliably separated the patients who died from those still alive. In a larger analysis of 343 patients with CF listed at 4 transplant centers, Belkin and colleagues[71] identified FEV_1 less than 30%, hypercapnia, and need for nutritional intervention (appetite stimulant, placement of a gastrojejunostomy tube, or parenteral nutrition) as predictors of an increased risk of mortality.

Two studies have focused on the prognosis of patients with CF admitted to the ICU with severe pulmonary exacerbation. Sood and colleagues documented a 76% in-hospital mortality among 25 patients with CF with hypercapnic respiratory failure, most of whom required intubation and mechanical ventilatory support. Of the 6 patients successfully discharged, only 3 (12% of the original group) survived to 1 year after discharge. In contrast, 1-year survival was 82% for the subset of patients with respiratory failure who underwent lung transplantation while in the ICU. Ellaffi and colleagues[72] reported a 48% 1-year survival rate among 21 patients with CF admitted to the ICU with severe pulmonary exacerbations (excluding 2 patients who received lung transplants). This more favorable prognosis may relate to differences in the severity of exacerbations; most patients in the study by Ellaffi and colleagues were managed with noninvasive ventilation. All 4 of the patients reported by Ellaffi and colleagues who required intubation and conventional ventilation died.

Failure of these various studies to define a common set of reliable prognostic factors has limited the ability to make definitive recommendations on timing of listing for patients with CF. The

ISHLT guidelines state that an FEV_1 less than 30% predicted should prompt referral of the patient to a transplant center but not necessarily immediate listing. The decision to proceed with transplantation should be based on "a comprehensive evaluation that must take into account several indicators of disease severity such as FEV_1, increases in oxygen need, hypercapnia, need for noninvasive ventilation, functional status, and pulmonary hypertension".[6] Given the low expectation of survival for patients with CF who require intubation for CF exacerbations, these patients should be considered for emergent listing and transplantation.

IPAH

In 1991, the Patient Registry for Characterization of Primary Pulmonary Hypertension reported a median survival of 2.8 years for patients with IPAH.[73] Survival was shown to correlate with NYHA functional class and with hemodynamic indices of right ventricular function. Based on these data, an equation to predict mortality was developed, incorporating mean pulmonary arterial pressure, right atrial pressure, and cardiac index. This equation was used for many years in determining when to list patients with IPAH for lung transplantation.

The subsequent development of effective vasodilator therapy has markedly improved the prognosis of patients with IPAH and has undermined the usefulness of the previously described equation. Intravenous epoprostenol, the oldest and most extensively studied agent, is associated with a 5-year survival of 55%, compared with 28% for historical controls.[74] Long-term follow-up of patients taking the newer agents is more limited, but available data suggest a favorable effect on survival.[75] However, not all patients respond to vasodilator therapy and, for those who do show initial improvement, subsequent deterioration may ensue, often precipitously. Factors that portend a poor prognosis among patients receiving epoprostenol include pretreatment NYHA class IV functional status or history of right heart failure, persistence of class III to IV functional status after 3 months of treatment, and failure of pulmonary vascular resistance to decrease by 30% from pretreatment baseline.[74] For example, 3-year survival of those with persistent class III to IV functional status is only 33% compared with 88% for those who improve to class I to II.

Other factors associated with a poor prognosis in patients with IPAH include hyponatremia,[76] echocardiographic evidence of severe right ventricular dysfunction as assessed by the degree of tricuspid annular displacement,[77] and 6MWT distance of less than 332 m.[78]

Given the availability of potentially effective treatment, it is appropriate to delay evaluation for lung transplantation until response to maximum medical therapy can be assessed. Listing for transplantation is appropriate for those patients with persistent NYHA class III or IV despite a minimum of 3 months of maximum therapy. The ISHLT guidelines suggest several other parameters for listing, although not all of these are necessarily independent prognostic variables: (1) low (350 m) or declining 6MWT; (2) failing therapy with intravenous epoprostenol or equivalent; (3) cardiac index less than 2 L/min/m^2; or (4) right atrial pressure exceeding 15 mm Hg. Although patients with IPAH generally receive lower priority than patients with IPF and CF under the new allocation system in the United States., an exception is granted to increase the lung allocation score of a patient with IPAH to the 90th percentile of all scores nationally when (1) a patient is deteriorating on optimal therapy, (2) right atrial pressure is greater than 15 mm Hg, and (3) cardiac index is less than 1.8 L/min/m^2.[79]

Sarcoidosis

Sarcoidosis is associated with a highly variable but generally favorable natural history; only a few patients progress to a stage of advanced and irreversible pulmonary disease that prompts consideration of lung transplantation. Arcasoy and colleagues[80] studied a cohort of 43 patients with sarcoidosis listed for lung transplantation in an effort to identify factors predictive of a high risk of death. In univariate analysis, hypoxemia, increased pulmonary artery pressure, low cardiac output, and increased right atrial pressure all portended an increased short-term risk of death. Survivors and nonsurvivors did not differ with respect to standard pulmonary function parameters. In multivariate analysis, only a right atrial pressure exceeding 15 mm Hg proved to be independently predictive of death. In a subsequent study of 405 sarcoid patients entered into the SRTR database, increased pulmonary artery pressure and hypoxemia were again identified as strongly predictive of short-term mortality whereas pulmonary function parameters were not.[81] Right atrial pressure was not analyzed in this study. The ISHLT guidelines incorporate the findings of these 2 studies into their recommendation that sarcoid patients with the following characteristics be considered for listing for lung transplantation: NYHA functional class III to IV with hypoxemia, pulmonary

hypertension, and/or right atrial pressure exceeding 15 mm Hg.[6]

CHOICE OF PROCEDURE

At the time a patient is placed on the active waiting list, the transplant team must also identify the specific procedure for which the patient is listed. Three surgical options are available: heart-lung transplantation (HLT), SLT, and BLT. Indications for each are shown in **Box 2** and described in the sections to follow.

Historically, HLT was the first procedure to be successfully performed but it has been largely supplanted by lung transplantation alone. Fewer than 80 procedures are performed worldwide on an annual basis.[1] The principle indication is Eisenmenger syndrome with surgically irreparable cardiac lesions. HLT is still occasionally performed on patients with IPAH. However, experience with lung transplantation alone has shown that the right ventricle has a remarkable ability to recover once pulmonary artery pressures have normalized, obviating concurrent cardiac replacement in all but the most severely decompensated patients. HLT is also occasionally offered for patients with advanced lung disease and concurrent severe left ventricular dysfunction or extensive coronary artery disease. The small number of patients requiring HLT in the United States face potentially protracted waiting times because of the preferential allocation of hearts to status 1A cardiac transplant candidates.

Box 2
Major indications for lung transplant procedures

HLT

- Eisenmenger syndrome with unrepairable cardiac defects
- IPAH (with right ventricular decompensation)
- Advanced lung disease with concurrent severe left ventricular dysfunction or extensive coronary artery disease

BLT

- IPAH
- Eisenmenger syndrome with surgically correctable cardiac defects
- Advanced lung disease with significant secondary pulmonary hypertension
- CF
- Non-CF bronchiectasis
- COPD
- IPF

SLT

- COPD (particularly older patients)
- IPF

For most candidates, the choice is between SLT and BLT. This decision is dictated chiefly by the underlying disease but in cases in which both procedures are acceptable, additional factors such as the patient's age and functional status and center-specific preferences come into play. For patients with CF and other forms of suppurative lung disease, BLT is the exclusive procedure used, because leaving a chronically infected native lung behind runs the risk of infecting the allograft. BLT is also the procedure of choice for IPAH and for patients with severe, secondary pulmonary hypertension. This approach ensures that cardiac output is evenly distributed between 2 allografts as opposed to SLT, in which a single allograft must bear the burden of nearly the entire cardiac output (and the attendant risk of exaggerated pulmonary edema) because of exceedingly high vascular resistance in the native lung.

The situation with COPD and IPF, the 2 leading indications for transplantation, is more complex, because both SLT and BLT have been shown to be suitable. Historically, SLT was the predominant procedure for both diseases. However, over the past decade there has been a steady increase in the proportion of BLTs performed, and BLT now accounts for two-thirds of all procedures for COPD and just more than half of procedures performed for IPF.[1] Driving this preference in the population with COPD are studies that have suggested superior survival with BLT compared with SLT. In a cohort of 2260 adult lung transplant recipients with COPD entered into the ISHLT registry, a multivariate analysis performed by Meyer and colleagues[82] revealed that procedure type was an independent predictor of survival, with an overall risk ratio for mortality of 0.57 for BLT compared with SLT. Analysis of the interaction of age with procedure type showed that the survival benefit of BLT was apparent until approximately age 60 years, after which SLT was associated with a lower mortality, albeit not statistically significant. A subsequent analysis of more than 9000 COPD lung transplant recipients in the ISHLT registry by Thabut and associates[34] yielded similar findings. Median survival after BLT was superior to that after SLT (6.41 years vs 4.51 years) and the survival benefit of BLT was consistently shown for patients younger than 60 years across a variety of statistical methods to account for confounding factors. Again, a survival advantage to BLT could not be confirmed in recipients older than 60 years. In addition to a survival benefit, use of BLT for

patients with COPD avoids the serious, albeit uncommon, complications associated with leaving an emphysematous lung in place: lung cancer and native lung hyperinflation.

It is more difficult to identify a compelling rationale for the increased use of BLT in patients with IPF, in the absence of secondary pulmonary hypertension. Meyer and colleagues[83] assessed the effect of procedure type on outcomes in 821 patients with pulmonary fibrosis registered in the SRTR database. For patients younger than 60 years, survival was better after SLT compared with BLT. When posttransplant survival was reanalyzed contingent on survival beyond the first posttransplant month, there was no difference in outcomes between the 2 procedures. This finding suggests that the inferior survival associated with BLT was likely because of increased perioperative mortality. For patients older than 60 years, survival was similar after SLT and BLT but the analysis was limited by the small number of patients in the BLT group. Recently, Thabut and colleagues[84] published a larger multivariate analysis of the SRTR database, involving 3327 patients with IPF (2146 SLT and 1181 BLT recipients). After adjustment for baseline characteristics, survival associated with the 2 procedures was similar. Analysis of hazard ratio for death as a function of time after transplant showed an increased risk of death associated with BLT in the perioperative period that was offset by a lower mortality risk subsequently.

A recent analysis by Nathan and colleagues[85] of patients with IPF listed for transplantation exposes a hidden risk of BLT in this population. These investigators reported that listing for BLT was associated with longer waiting times and an increased risk of dying on the waiting list compared with listing for SLT. In the absence of an offsetting posttransplant survival advantage to BLT, the potential net effect is increased loss of life for the population with IPF.

SUMMARY

Decisions about patient selection, timing of listing, and choice of procedure are critically important steps in optimizing the outcome of lung transplantation. Selection of candidates for lung transplantation requires an appreciation of the effect of pretransplant patient characteristics on posttransplant outcomes. Familiarity with the natural history of the underlying disease and of disease-specific prognostic factors is essential in making decisions about when to list candidates. Decisions about transplanting 1 or 2 lungs are principally determined by the underlying disease, but in cases in which both procedures are acceptable, factors such as survival benefit, patient's age, and center-specific preferences come into play.

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