Selection of Candidates for Lung Transplantation

Maryl Kreider1 and Robert M. Kotloff1

1Pulmonary, Allergy, and Critical Care Division, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania

The selection of candidates for lung transplantation requires an appreciation of the natural history of lung disease to determine when the disease has entered an advanced and imminently life-threatening stage. It also requires an understanding of the impact of preexisting medical comorbidities on transplant outcomes. Finally, selection is influenced by the particular metric by which outcomes are judged to be successful (e.g., maximizing short-term net survival benefit versus maximizing post-transplant longevity). This article will discuss general and disease-specific criteria used to select patients for lung transplantation and determine the appropriate timing of listing. It will highlight current guidelines put forth by the International Society of Heart and Lung Transplantation and will explore the published data upon which these guidelines are based.

Keywords: lung transplantation; lung diseases; contraindications; patient selection; prognosis

Despite a collective experience that now spans over 40 years, lung transplantation remains a risky endeavor with a median survival among recipients of only 5 years. Because of the inherent risks involved, it is essential that this option not be used prematurely, but reserved for a time in the course of disease when life expectancy is limited and quality of life is unacceptably poor. Given the rigorous nature of the surgery, the potential toxicities of the post-transplant immunosuppressive agents, and the frequent nature of post-transplant complications, it is also essential that candidates are selected who are deemed to be sufficiently fit to handle these insults. Indeed, stringent candidate selection is paramount in maximizing the chances for a successful outcome.

Selection of candidates requires an appreciation of the natural history of lung disease to determine when the disease has entered an advanced and imminently life-threatening stage. It also requires an understanding of the impact of preexisting medical comorbidities on transplant outcomes. Finally, selection is influenced by the particular metric by which outcomes are judged to be successful. For example, there is likely to be a greater willingness to transplant older patients or patients who have developed ventilator-dependent respiratory failure if the goal is to maximize short-term net survival benefit rather than post-transplant longevity.

This article discusses general and disease-specific criteria used to select adult patients for lung transplantation and determine the appropriate timing of listing. It highlights current guidelines put forth by the International Society of Heart and Lung Transplantation (ISHLT) and explores the published data upon which these guidelines are based.

GENERAL INDICATIONS AND CONTRAINDICATIONS

Lung transplantation is a therapeutic option for a broad spectrum of chronic debilitating pulmonary disorders of the airways, parenchyma, and vasculature. Chronic obstructive pulmonary disease (COPD) represents the leading indication for lung transplantation and, together with α1-antitrypsin deficiency, accounts for nearly half of all procedures performed worldwide (1). Other leading indications include idiopathic pulmonary fibrosis (IPF) (19% of cases) and cystic fibrosis (CF) (17% of cases). Once a common indication for transplantation, idiopathic pulmonary arterial hypertension, now accounts for less than 5% of procedures, reflecting major advances in the medical management of these patients. Transplantation of patients with lung involvement due to collagen vascular disease (e.g., scleroderma) remains controversial due to concerns that extrapulmonary manifestations of the systemic disease could compromise the post-transplant course. Nonetheless, short-term functional outcomes and survival following transplantation are comparable to other patient populations and many centers are willing to offer transplantation to carefully selected patients without significant extrapulmonary organ dysfunction (2). In contrast, lung transplantation for bronchoalveolar carcinoma, a subtype of lung cancer that tends to remain localized to the lung parenchyma, has largely been abandoned due to an unacceptably high rate of cancer recurrence (3).

The scarcity of organs and the somewhat inferior outcomes achieved with recipients of advanced age have prompted many lung transplant programs to establish an upper age limit of 65 years. Nonetheless, there has been a modest increase in the percentage of patients exceeding this traditional age cutoff who have undergone transplantation in recent years; patients 65 years and older accounted for 5.3% of transplant recipients between 2000 and 2005 compared with 2.8% in the preceding 5-year epoch (1). Candidates should be functionally disabled (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, commonly set at 600 feet (4). The presence of significant extrapulmonary vital organ dysfunction precludes isolated lung transplantation, but multi-organ procedures such as heart-lung or lung-liver can be considered in highly select patients (5, 6).

Other absolute contraindications include recent malignancy (other than non-melanoma skin cancer); active 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 (7). When extreme, obesity, malnutrition, and progressive, unintentional weight loss are commonly viewed as absolute contraindications. The risk posed by other chronic medical conditions 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. Prior thoracic surgery and pleurodesis render the native lung more difficult to explant and increase the risk of intraoperative

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Correspondence and request for reprints should be addressed to Robert M. Kotloff, M.D., 838 West Gates, University of Pennsylvania Medical Center, 3400 Spruce Street, Philadelphia, PA 19104. E-mail: kotloff@uphs.upenn.edu


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bleeding, particularly when cardiopulmonary bypass is required, but do not contraindicate transplantation in most instances. Pleural thickening associated with mycetomas similarly complicates anatomic dissection and explantation of the native lung and carries the additional risk of soiling the pleural space with fungal organisms. In one small series, the presence of a mycetoma in the native lung was associated with a perioperative mortality rate of 45% (8). A cautious approach to selecting these patients appears justified, and those patients with extensive pleural reaction and cavities abutting the pleural surface should generally be excluded.

Finally, it can be difficult to find compatible donors for candidates with a high level of preformed antibodies against human leukocyte antigens (HLA). At best, this can result in prolonged waiting times and, in cases where the incompatible antigens are common in the donor pool, it can render transplantation highly unlikely. In such cases, maneuvers to reduce the level of these antibodies in the potential candidate can be attempted, such as administration of rituximab or intravenous immunoglobulin (9, 10). Even if a compatible donor is ultimately found, there is preliminary evidence that high levels of anti-HLA antibodies pretransplant are associated with lower post-transplant survival rates (11).

DISEASE-SPECIFIC GUIDELINES FOR CANDIDATE SELECTION AND LISTING

Disease-specific guidelines for selection and listing of patients have recently been updated and published by the International Society for Heart and Lung Transplantation (ISHLT) and are summarized in Table 1 (7). The specific guidelines and the evidence behind the recommendations will be reviewed for the major diagnostic indications in the sections below. It must be acknowledged that the prognostic indices that have been identified to predict the natural history of lung disease are imprecise, identifying a population of patients at increased risk for death but of more limited use in predicting the course of an individual patient. Thus, not every patient who fulfills the criteria set forth in these 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

Long-term survival is possible for many patients with advanced COPD, and as a result it is often difficult to determine the exact point at which lung transplantation should be offered. Historically, the best single predictor of prognosis in COPD was the post-bronchodilator forced expiratory volume in one second (FEV1) (12). Other risk factors such as hypoxemia, hypercapnia, a low body mass index, poor performance on a 6-minute walk test, and magnitude of dyspnea have also been associated with increased risk of death (13). More recently, Celli and colleagues incorporated a number of these factors into the multidimensional BODE index (body mass index [B], degree of airflow obstruction [O], dyspnea [D] and exercise capacity [E], measured by the 6-minute walk test) (14). 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 rate of 80% at 4 years. The investigators prospectively validated the index and demonstrated that it was a better predictor of risk of death than FEV1 alone.

A subsequent study by Martinez and colleagues examined the predictive utility of serial measurements of the BODE index (15). The study used the database of patients who had participated in the National Emphysema Treatment Trial and who therefore were characterized by advanced airflow obstruction (mean FEV1 predicted of 27%) and a mean baseline BODE score of approximately five. The investigators found that an increase in BODE score of greater than one point over a 6- to 24-month period of observation was associated with a twofold increase in death among medically treated patients and a three-fold increase among the group that had undergone lung volume reduction surgery.

The current ISHLT guidelines embrace the BODE score as the principle but not exclusive parameter to be used in the listing of patients with COPD. Specifically, listing is recommended for patients with a BODE score of 7 to 10 or with at least one of the following: (1) history of hospitalization for exacerbation associated with acute hypercapnia (PCO2 > 50 mm Hg); (2) pulmonary hypertension and/or cor pulmonale, despite oxygen therapy; or (3) FEV1 <20% and either DLCO <20% or homogenous distribution of emphysema.

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<tr>
<th>TABLE 1. DISEASE-SPECIFIC GUIDELINES FOR LISTING FOR LUNG TRANSPLANTATION*</th>
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<td>Chronic Obstructive Pulmonary Disease</td>
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<td>• BODE index of 7 to 10 or at least one of the following:</td>
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<tr>
<td>• History of hospitalization for exacerbation associated with acute hypercapnia (PCO2 exceeding 50 mm Hg)</td>
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<tr>
<td>• Pulmonary hypertension or cor pulmonale, both, despite oxygen therapy</td>
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<tr>
<td>• FEV1 &lt;20% and either DLCO &lt;20% or homogenous distribution of emphysema</td>
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<th>Histologic or radiographic evidence of UIP and any of the following:</th>
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<tr>
<td>• A 10% or greater decrement in FVC during 6 mo of follow-up</td>
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<tr>
<td>• A decrease in pulse oximetry &lt;88% during a 6-minute walk test</td>
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<td>• Honeycombing on HRCT (fibrosis score &gt;2)</td>
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<th>Cystic Fibrosis</th>
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<tr>
<td>• FEV1 &lt;30% of predicted, or rapidly declining lung function if</td>
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<td>• FEV1 &gt;30% (females and patients &lt;18 years of age have a poorer prognosis; consider earlier listing) and/or any of the following:</td>
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<tr>
<td>• Increasing oxygen requirements</td>
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<td>• Hypercapnia</td>
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<td>• Pulmonary hypertension</td>
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<th>Idiopathic Pulmonary Arterial Hypertension</th>
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<tr>
<td>• Persistent NYHA Class III or IV on maximal medical therapy</td>
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<td>• Low (350 m) or declining 6-minute walk test</td>
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<tr>
<td>• Failing therapy with intravenous epoprostenol, or equivalent.</td>
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<tr>
<td>• Cardiac index of &lt;2 L/min/m²</td>
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<td>• Right atrial pressure &gt;15 mm Hg</td>
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<th>Sarcoidosis</th>
<th>NYHA functional Class III or IV and any of the following:</th>
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<tr>
<td>• Hypoxemia at rest</td>
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<tr>
<td>• Pulmonary hypertension</td>
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<tr>
<td>• Elevated right atrial pressure &gt;15 mm Hg</td>
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* Modified from (7).

**Definition of abbreviations:** BODE = Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity; HRCT = high-resolution computed tomography; NYHA = New York Heart Association; UIP = usual interstitial pneumonitis.
Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a debilitating disorder with no proven treatment and a median survival from the time of diagnosis in the range of 3 to 4 years. Although the overall prognosis is poor, the pace of decline is variable, with periods of stability often interrupting the stepwise deterioration in lung function. 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 will discriminate those who will die quickly from those with a more chronic course. Risk factors that have been studied include (1) underlying pathology features, (2) radiographic features, (3) pulmonary function testing results, (4) 6-minute walk testing, (5) pulmonary hypertension, and (6) acute exacerbations and/or acute respiratory failure. Underlying pathology. The presence of usual interstitial pneumonitis (UIP) on pathology, the histological sine qua non of IPF, generally portends a poor prognosis. In contrast, non-specific interstitial pneumonitis (NSIP) is typically associated with slower progression and longer survival; within this histological group, the cellular subset follows a more indolent course than the fibrotic subset (23–25). Among patients with suspected IPF, surgical lung biopsies obtained from multiple sites demonstrate the concurrent presence of UIP and NSIP in approximately 25% of cases (26). In these cases of “discordant UIP,” the prognosis is identical to that of patients who exclusively demonstrate 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 (27, 28).

Radiology. Several groups have developed scoring systems to quantify the degree of fibrosis on high resolution CT (HRCT) scan in patients with IPF. Higher scores generally reflect a greater degree of reticulation and honeycombing, and a paucity of ground glass opacities. Although differences exist with respect to the specifics of the scoring systems used, there is consistency in the demonstration of a direct correlation between higher fibrosis scores and mortality (29–31). Additionally, studies have suggested that patients with biopsy-proven UIP who have the classic radiographic features of the disease have a worse survival than those who have atypical features (30–32). For example, Flaherty and colleagues documented a median survival of 2.1 years for patients deemed to have “definite” or “probable” UIP by two expert radiologists compared with a median survival of 5.8 years for those with indeterminate features or features more suggestive of NSIP (32). Similarly, Sumikawa and colleagues demonstrated 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 (31).

Pulmonary function testing. Mugolkuk and colleagues found that baseline diffusing capacity measurement, in conjunction with HRCT fibrotic score, offered the best prediction of 2-year survival for patients with IPF (33). Using receiver operator characteristic analysis, a 39% predicted diffusing capacity was the optimal cutoff for distinguishing survivors from nonsurvivors. Other studies, however, have failed to consistently define which baseline parameters, if any, are best at predicting outcomes (29, 33–36). In contrast, multiple studies have demonstrated that longitudinal changes in pulmonary function parameters over a 6- to 12-month period from the time of diagnosis are a more powerful predictor of outcome than are baseline values (34, 37, 38). In one study, for example, a decline in forced vital capacity of 10% or greater in the first 6 months was associated with a twofold increase in the risk of death compared with patients whose forced vital capacity was unchanged during this period (37).

Six-minute walk test. Both the lowest saturation achieved during a 6-minute walk test and the absolute distance walked are independently associated with prognosis. In one study of patients with biopsy-proven UIP, those who desaturated to 88% or below during a 6-minute walk test performed on room air had a 4-year survival rate of only 35%, whereas those who did not desaturate had a survival rate of 69% (35). In another study, patients with IPF who were awaiting lung transplantation and who walked less than 207 meters (679 ft) had a fourfold increase in mortality compared with those who had a longer walk distance (36).

Pulmonary hypertension. The development of secondary pulmonary hypertension is relatively common in fibrotic lung disorders, occurring in up to 60% of patients presenting for lung transplant evaluation (39). Despite its high prevalence, there is only limited information on its impact on prognosis. One recent retrospective 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 IPF patients with estimated pulmonary artery systolic pressures of less than 35, 35 and 50, and greater than 50 mm Hg, respectively (40).

Acute exacerbations/respiratory failure. Occasionally, seemingly stable patients may experience a precipitous decline leading rapidly to profound hypoxemic respiratory failure. These “acute exacerbations” have recently been defined as an...
unexplained worsening or development of dyspnea within 30 days, with new bilateral ground glass opacities or consolidation superimposed on the background of UIP changes, and with no evidence of infection, heart failure, pulmonary embolus, or another cause of acute lung injury (41). Analysis of the placebo arm of the IFN-γ trial provided insight into the natural history of patients with mild to moderate IPF and the risk of sudden deterioration (35). Twenty-one percent of patients died during a 76-month period of follow-up, and half of these deaths were due to acute decompensation. For many patients, physiologic variables such as FVC and DLCO changed only minimally, providing little warning of impending decompensation. Other studies have suggested rates of acute exacerbations in the range of 5 to 61%, with short-term mortality rates approaching 100% for those requiring ICU admission for respiratory failure (41–43).

**Guidelines for transplantation.** 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 intent 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 (e.g., obesity, deconditioning, high-dose corticosteroid use). Additionally, the testing and consultations necessary for listing can be completed to facilitate expedited listing in the event of sudden decline in the future. The guidelines for proceeding with transplantation incorporate the negative prognostic factors identified above: (1) diffusing capacity less than 39% predicted, (2) a 10% or greater decrease in FVC over a 6-month period, (3) desaturation below 88% on a 6-minute walk test, and/or (4) honeycombing on an HRCT. The guidelines also recommend consideration of a listing for patients with fibrotic NSIP and a DLCO of less than 35%.

Cystic Fibrosis

Analyzing a cohort of 673 patients with cystic fibrosis (CF) from the Hospital for Sick Children in Toronto, Kerem and colleagues published a landmark study in 1992 that identified FEV1 as the single most significant predictor of mortality (44). They found that an FEV1 less than 30% predicted was associated with a 2-year mortality rate of 50%; for a given FEV1, females and patients under the age of 18 years had a higher 2-year mortality rate than their counterparts. Based on this study, the original version of the ISHLT candidate selection guidelines published in 1998 recommended that patients with CF with an FEV1 less than 30% be listed for transplantation, with consideration given to earlier referral of females and younger patients. However, subsequent studies from several other CF centers documenting more favorable median survival rates of 3.9 to 4.6 years associated with an FEV1 less than 30% challenged this recommendation (45, 46).

In 2001, Liou and colleagues published a 5-year survivorship model that was derived from data on 5,800 patients in the CF Foundation Patient Registry and was validated using data from an additional 5,800 Registry patients (47). Nine parameters, including FEV1, were identified as independent predictors of mortality 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 using FEV1 alone. In subsequent studies, Liou and colleagues used this model to compare predicted natural history survival with post-transplant outcomes to identify subgroups of patients likely to derive a survival benefit from transplantation. They found that only those patients with a predicted 5-year survival without transplantation of less than 50% and without *Burkholderia cepacia* and CF-arthropathy are likely to demonstrate enhanced survival with transplantation (48). An extremely controversial and unsettling prediction of this model is that lung transplantation rarely improves survival in patients with CF under the age of 18 years (48, 49).

Mayer-Hamblett and colleagues 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 (50). In contrast to the findings of Liou and colleagues, their multidimensional model demonstrated no greater ability to predict short-term mortality than the simpler FEV1 less-than-30% criterion. Both the multivariate model and the FEV1 alone demonstrated a positive predictive value for 2-year mortality in the range of only 50% (i.e., 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 versus 5-year mortality), it cannot be firmly concluded that the findings of the two studies are necessarily contradictory, but these contrasting studies do raise a degree of uncertainty about over-reliance on predictive models to guide transplant decisions.

The ongoing uncertainties in predicting the natural history of CF have resulted in a rather vague set of recommendations on candidate selection for transplantation, as contained in the updated ISHLT guidelines. These guidelines state that an FEV1 less than 30% predicted should prompt referral of the patient to a transplant center but not necessarily to 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 FEV1, increases in oxygen need, hypercapnia, need for noninvasive ventilation, functional status, and pulmonary hypertension” (7).

Chronic infection of the airways is a universal feature of cystic fibrosis and poses additional concerns in selecting patients for transplantation. *Pseudomonas aeruginosa* is by far the most common pathogen encountered, but other gram-negative organisms and *Staphylococcus aureus* may also be present. Due to the selective pressures of repeated antibiotic administration, patients with CF presenting for consideration of lung transplantation are often infected with highly resistant bacterial pathogens, prompting reservations about the suitability of candidates who harbor these organisms.

Aris and colleagues from the University of North Carolina compared the outcomes of 21 CF transplant recipients with pan-resistant *P. aeruginosa* to 39 CF recipients with sensitive strains (51). The two groups had a similar incidence of lower respiratory tract infections and demonstrated similar 1- and 2-year post-transplant survival rates. Hadjiliadis and colleagues from Duke University and the University of Toronto performed a similar analysis comparing 45 patients with CF who had pan-resistant pathogens (96% with *P. aeruginosa*) to 58 recipients with CF who had sensitive strains (52). In contrast to the University of North Carolina group, these authors found that patients harboring pan-resistant organisms had lower survival rates than those with sensitive strains: 87 versus 97% at 1 year and 58 versus 86% at 5 years. Nonetheless, the survival rates in the pan-resistant group were virtually identical to cumulative outcomes achieved for all transplant recipients with CF in the United States, as recorded in the UNOS database. Taken together, these two studies suggest that patients with pan-resistant bacterial pathogens (excluding *Burkholderia cepacia* –
post-transplant mortality to \textit{B. cenocepacia} comes. Recent studies have attributed the observed excessive collection of species (previously referred to as "genomovars") dictated by the particular species that the patient harbors. In contrast, infection with other members of the United States to exclude candidates with \textit{B. cepacia} from consideration for lung transplantation. However, it has become clear that \textit{B. cepacia} is not a single entity but a heterogeneous collection of species (previously referred to as "genomovars") with varying pathogenicity and impact on post-transplant outcomes. Recent studies have attributed the observed excessive post-transplant mortality to \textit{B. cenocepacia} (also known as "genomovar III") and possibly to \textit{Burkholderia gladioli} (55, 56). In contrast, infection with other members of the \textit{B. cepacia} complex does not appear to adversely impact post-transplant survival. Should additional epidemiological studies corroborate these observations, transplant eligibility in the future may be dictated by the particular species that the patient harbors.

\textbf{Idiopathic Pulmonary Arterial Hypertension}

In 1991, the Patient Registry for Characterization of Primary Pulmonary Hypertension reported a median survival of 2.8 years for patients with primary pulmonary hypertension (57). Survival was shown to correlate with functional status and indices of right ventricular hemodynamic function. Patients categorized as New York Heart Association (NYHA) Class I or II had a median survival of 59 months, whereas patients who were NYHA Class III or IV had median survival of 32 and 6 months, respectively. A regression equation was developed to describe the relationship between pulmonary arterial pressure, right atrial pressure, cardiac index, and mortality. This equation was used for many years to determine when to list patients for lung transplantation.

The subsequent development of effective vasodilator therapy has favorably impacted the natural history of idiopathic pulmonary arterial hypertension and has undermined the utility of the previously described equation. The most extensively studied agent is intravenous epoprostenol, whose administration has been demonstrated to result in sustained improvement in hemodynamic and functional parameters as well as in improved survival. Five-year survival for epoprostenol patients is on the order of 53\% compared with 28\% for historical controls (58). However, it is clear that not all patients respond to vasodilator therapy and that, for those who do, 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–IV functional status after 3 months of treatment, and failure of pulmonary vascular resistance to fall by 30\% from pretreatment baseline (58). For example, 3-year survival of those with persistent Class III–IV functional status is only 33\% compared with 88\% for those who improve to Class I–II. The impact of other currently available vasodilator agents on survival and the degree to which the prognostic indices defined in association with epoprostenol can be extrapolated to these other agents is not yet clear.

Other factors associated with a poor prognosis include hypoxemia (59), echocardiographic evidence of severe right ventricular dysfunction as assessed by the degree of tricuspid annular displacement (60), and a 6-minute walk test distance of less than 332 meters (61).

With 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 most appropriate for those patients with persistent NYHA Class III or IV despite a minimum of 3 months of maximum therapy. In addition to this recommendation, the ISHLT guidelines suggest several other parameters for listing, though not all of these are necessarily independent prognostic variables: (1) low (350 m) or declining 6-minute walk test, (2) failing therapy with intravenous epoprostenol or equivalent, (3) cardiac index less than 2 liters/min/m², or (4) right atrial pressure exceeding 15 mm Hg.

\textbf{Sarcoidosis}

Sarcoidosis is associated with a highly variable and protracted natural history, often spanning several decades and marked by spontaneous remissions. Only a minority of patients progress to a stage of advanced and irreversible pulmonary disease that prompts consideration of lung transplantation. Predictors of short-term mortality that can be used in making decisions about transplantation have only recently been identified. Arcasoy and colleagues analyzed a cohort of 43 patients with sarcoidosis listed for lung transplantation at the University of Pennsylvania (62). In univariate analysis, hypoxemia, elevated pulmonary artery pressure, low cardiac output, and elevated right atrial pressure, all portended an increased risk of death on the transplant waiting list. Notably, 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 patients with sarcoid who were entered into the national UNOS database, elevated pulmonary artery pressure and hypoxemia were again identified as strongly predictive of short-term mortality, whereas pulmonary function parameters were not (63). Echoing these observations, the ISHLT guidelines recommend that patients with sarcoid who had the following characteristics be considered for listing for lung transplantation: NYHA functional Class III-IV with hypoxemia, pulmonary hypertension, and/or right atrial pressure exceeding 15 mm Hg.

\textbf{IMPACT OF THE LUNG ALLOCATION SYSTEM ON CANDIDATE SELECTION AND LISTING}

Decisions about listing of candidates for transplantation in the United States have been impacted by changes in the lung allocation policy. The previous policy prioritized patients based on time accrued on the waiting list. With waiting times approximating 2 years or more at many of the larger centers, early referral and immediate listing of patients was advocated so that they could begin to accrue time. Those patients who remained “too healthy” at the time they rose to the top of the list could be removed from the active waiting list rather than undergo transplantation. The new lung allocation policy, introduced in May of 2005, allocates lungs on the basis of medical urgency and “net transplant benefit,” the difference between predicted 1-year survival with and without transplantation (64). Because time accrued is no longer a factor, there is no rationale for listing patients until they are in imminent need of transplantation, although early referral is still encouraged to facilitate
patient education and address issues that could compromise suitability for future listing. By prioritizing patients with more rapidly progressive diseases, the new system has resulted in preferential and expeditious transplantation for patients with IPF at the expense of the COPD population. Finally, the underlying philosophy of the new system, which focuses on short-term survival benefit rather than post-transplant longevity, provided implicit justification for listing sicker patients and relaxing the traditional selection standards.

SPECIAL CONSIDERATIONS

The High-Risk Patient

There is no single way to define the “high-risk” lung transplant candidate and use of such a designation is likely to vary depending upon the experience of a particular transplant center. Analysis of the ISHLT database has identified a number of factors associated with increased probability of 1- and 5-year mortality that can assist in assessing risk (Table 2) (1). It is possible that stringent selection of patients who possess one or several of these factors may to some extent mitigate the adverse impact on outcomes. For example, a study of 50 patients 65 years of age or older who received transplants at the University of California Los Angeles found no difference in 1-year and 3-year post-transplant survival rates compared with a cohort under the age of 65 (65). To be selected, however, older patients had to be nutritionally sound, lack significant medical comorbidities, and have a reasonable functional status. Additionally, a more conservative strategy of single lung transplantation was preferentially used in this group. Similarly, although pretransplant mechanical ventilation has been identified as a risk factor for early mortality, a study of 9 patients on mechanical ventilation for 13 to 2160 days prior to transplantation, but who were ambulatory and able to participate in physical therapy, demonstrated a 1-year survival rate similar to that of patients who were not on mechanical ventilation (66).

The new U.S. allocation system that prioritizes patients based on medical urgency and short-term net survival benefit, has made it increasingly difficult to define when high risk becomes prohibitive risk, particularly when patients otherwise face certain death without transplantation. Indeed, this system assigns the highest scores to a population of patients previously deemed by many programs to be potentially too sick for transplantation (i.e., those who have succumbed to respiratory failure requiring intensive care, high concentrations of supplemental oxygen, and mechanical ventilatory support). Data from UNOS reveals that patients who received transplants between May 2005 and May 2007 with lung allocation scores greater than 80% for those with lower scores (67). In the May 2005 and May 2007 with lung allocation scores greater than 80% for those with lower scores (67). In the

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<th>TABLE 2. RECIPIENT FACTORS ASSOCIATED WITH INCREASED MORTALITY AT 1 AND 5 YEARS*</th>
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<td>Use of IV inotropes prior to transplantation</td>
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<td>Pretransplant mechanical ventilation</td>
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<td>Hospitalized at time of transplantation</td>
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<td>Prior sternotomy</td>
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<td>Older age (&gt;55 y)</td>
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* Derived from multivariate analysis of the International Society of Heart and Lung Transplantation lung-transplant database (1)

Retransplantation

Retransplantation has been used as a salvage technique for refractory graft failure, but results vary widely depending on the underlying cause. Outcomes following early emergent retransplantation for primary graft dysfunction are poor, and consequently, its use in this setting is discouraged (68–70). Experience with retransplantation for refractory airway complications (dehiscence, strictures) is more limited, and published results have been conflicting (68, 70). In contrast, retransplantation of carefully selected patients with chronic graft failure due to bronchiolitis obliterans syndrome results in survival rates that approach that of initial transplantation (68–70). Such patients should ideally be ventilator-independent and ambulatory at the time of retransplantation and should otherwise meet all standard criteria for suitability, including absence of significant medical comorbidities. The new allocation system assigns high priority to candidates with bronchiolitis obliterans syndrome, on par with that afforded to patients with IPF. This has shortened waiting times and has made the option of retransplantation more accessible to this population, as indicated by a recent doubling in the number of retransplant procedures performed annually (69).

SUMMARY

The selection of candidates for lung transplantation requires an appreciation of the natural history of advanced lung disease as well as the impact of pretransplant patient characteristics on post-transplant outcomes. Ultimately, the selection also involves a decision on the part of the transplant team as to how much risk is acceptable and how success following transplantation is to be defined. The selection guidelines discussed in this article, although inexact, are intended to assist the clinician in making these difficult and weighty decisions.

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References


