Lung Transplantation*

Disease-Specific Considerations for Referral

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The timing of the referral and listing of patients for lung transplantation remains a difficult decision. Life expectancy and quality of life with and without transplantation are the pivotal issues that need to be considered by physicians and presented to prospective transplant candidates. The recognition of recent advances in the understanding of the various primary diseases, other potential therapies, and the latest posttransplant statistics are essential for a balanced discussion or decision about lung transplantation. This article provides a review of these and other pertinent issues for patients with various forms of advanced lung disease.

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Abbreviations: BODE = body mass, obstruction, dyspnea, exercise tolerance; CF = cystic fibrosis; DLCO = diffusing capacity of the lung for carbon monoxide; IPAH = idiopathic pulmonary arterial hypertension; IPF = idiopathic pulmonary fibrosis; LVRS = lung volume reduction surgery; NSIP = nonspecific interstitial pneumonia; NYHA = New York Heart Association; PAP = pulmonary artery pressure; PFT = pulmonary function test; UIP = usual interstitial pneumonia

The timing of referral for prospective transplantation in appropriate lung transplant candidates has always been and remains a moving target. The careful consideration of the natural history and prognosis of the underlying primary disease needs to be weighed against the projected survival time posttransplant. Quality of life with and without a transplant and the waiting time for the patient while on the transplant list also need to be factored into the timing of the listing. The ultimate goals remain obtaining "maximal mileage" from the patient's native lung, conferring a greater chance of survival with a new lung, and avoiding death while waiting on the transplant list. How does one then integrate these factors into the decision for referral and listing for lung transplantation?

Traditionally, transplant pulmonologists have looked at the median 2-year posttransplant survival rate and compared this to the projected survival of the patient's underlying primary condition. When the former is judged to be superior to the latter, patients have then been regarded as appropriate candidates based on the odds of survival. When making pretransplant and posttransplant comparisons, it is important to be aware that posttransplant survival is also dependent on the status of the patient's underlying primary disease. This distinguishes lung transplantation from other forms of solid-organ transplantation.

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The decision to look at the 2-year survival rate might appear somewhat arbitrary; however, there are two reasons that make this a reasonable time frame. First, the average waiting time for a lung allograft in the United States has been approximately 2 years, and therefore this appears to be the most appropriate posttransplant time interval for a pretransplant survival comparison.[1] Second, when making this comparison, one is also making the assumption of similar patterns and rates of attrition. However, this is not the case, especially early after the transplant when there is significant perioperative mortality. The perioperative mortality rate ranges from 7 to 24% during the first month, depending on the underlying primary lung disease (Table 1). Thereafter, mortality rates posttransplant appear to be relatively linear. Using a 2-year period compensates for this early exponential decrement, while longer periods of com-

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Table 1—*Post-Lung Transplant Kaplan-Meier Survival Rate by Disease

Time	α_1-Antitrypsin	CF	COPD	IPF	IPAH	Sarcoidosis
1 mo	91	91	93	86	76	85
1 yr	74	77	79	65	64	67
2 yr	65	69	69	57	58	61
3 yr	59	62	61	50	54	54
4 yr	54	56	53	42	50	51
5 yr	50	52	45	38	44	48

*Values given as %.

parison would further counteract the influence of this early precipitous mortality rate. The most recent data attest to a median wait time that has now increased to 46 months.[2] A case could therefore be made that patients should be listed when the 4-year mortality rate from their underlying primary disease exceeds the 4-year posttransplant mortality rate. This latter mortality rate varies from 42 to 56%, depending on the underlying primary disease (Table 1). If the pretransplant and posttransplant mortality rates are assumed to follow similar linear rates of attrition, then a comparison of 2-year or 4-year timeframes would likely yield similar results. Ideally, it is the area under the projected survival curves that should be compared, rather than one point in time. However, acceptable models of survival for most diseases do not yet exist to enable this.

The use of time-dependent, nonproportional hazard models, equity points, and crossover points have allowed comparisons of the length of survival while on the transplant list to posttransplant survival.[3–5] These types of analyses have demonstrated the survival benefit of transplantation for patients with cystic fibrosis (CF), idiopathic pulmonary fibrosis (IPF), and pulmonary hypertension. However, they have also raised questions about any survival benefit for patients with COPD and Eisenmenger syndrome. Even in the CF population, it appears that there may have been some patients who were disadvantaged from a survival standpoint by undergoing a transplant.[6] Studies such as this serve to underscore the need for a better understanding of the natural history of all advanced lung diseases to enable the appropriate selection of candidates who are most likely to benefit from transplantation.

In addition to survival, quality of life also needs to be taken into consideration in the decision about retransplant listing. There are a number of quality-of-life instruments available that have been validated in patients with various primary diseases as well as in lung transplant recipients.[7–11] When survival benefits appear to be marginal, for example, in COPD patients, changes in quality-adjusted life-years may be sufficient to justify transplantation.

The American Thoracic Society in conjunction with the European Respiratory Society and the International Society for Heart and Lung Transplantation published a consensus statement in 1998[12] that provided guidelines for the listing of patients for lung transplantation. Since then, there have been significant changes both on the pretransplant side of the equation as well as on the posttransplant side. On the posttransplant side, there is evidence of improving survival rates as well as an appreciation for disease-specific survival rates, which are now more readily available (Table 1).[5] On the pretransplant side, there have been a number of advances in our understanding of the natural history of various diseases, as well as changes in the availability and understanding of other therapeutic options. The goal of this review is to place newly available data in the context of these prior guidelines.

COPD

In the 1998 consensus statement,[12] the factors that were proposed as indicating the need for lung transplantation included the following:

- $FEV_1 < 25\%$ of predicted (without reversibility);
- And/or $PaCO_2 \geq 55$ mm Hg and/or elevated pulmonary artery pressure (PAP) levels with progressive deterioration (*eg*, cor pulmonale); and
- Preference to those patients with elevated $PaCO_2$ with progressive deterioration who require long-term oxygen therapy.

COPD is the one condition in which the survival benefit of transplantation has been challenged.[4] There are two possible explanations for this. First, the posttransplant survival time is not long enough to justify this group of patients undergoing transplantation, or, second, the candidate selection has been imprecise. The latter scenario appears to be more likely and, indeed, has been shown to be the case in the CF population when patient selection is based on FEV_1 alone.[6]

The FEV_1 has always been the parameter that has been most closely scrutinized in patients with COPD. However, there is a growing appreciation that the FEV_1 should not be viewed in isolation, but in the context of other pulmonary function test (PFT) results and other parameters. For example, dynamic hyperinflation correlates better with exercise limitation but remains unaccounted for by the FEV_1 alone.[13]

Other indexes also have been shown to correlate strongly with mortality, including subjective breathlessness, weight loss, exercise tolerance, hospitalizations, and lung morphology.[14–22] In one study,[15]

categorization of the level of dyspnea using a simple scale based on a series of questions has been shown to be a better predictor of mortality than the FEV_1. Patients were categorized as having grade IV dyspnea if they acknowledged having to stop for breath after walking about 100 yards on level ground. Patients with this level of dyspnea were shown to have a median survival time of about 3 years, which is comparable to the 3-year posttransplant survival rate (61%). In contrast, those patients with the most severe disease based on FEV_1 ($< 35\%$ predicted) had a median survival time in excess of 5 years.

There have been a number of studies that have shown weight loss to be a significant independent risk factor for mortality in COPD patients.[16–19] This is due to the elevated energy metabolism related to an increased work of breathing and a catabolic state related to inflammatory cytokines.[23,24] Patients with severe COPD are often only capable of small meals, and therefore this energy consumption is unmatched by an adequate dietary intake. Those patients with the lowest body mass indexes, especially $< 20\ kg/m^2$, are at the greatest risk of death.[16,19]

Similar to patients with CF, hospital admissions for acute exacerbations appear to have a significant impact on subsequent mortality. Interestingly, a small portion of this mortality occurs during the hospitalization itself, with rates of 8 to 11% having been reported in two large studies.[20,21] In one of these studies, the 1-year mortality rate post-ICU admission was 23%. However, if patients had been admitted to an ICU, the 1-year mortality rate then increased to 35%.[21] For those patients whose P_{CO_2} was > 50 mm Hg on ICU admission, the 1-year mortality rate was 43%. All of the above mortality rates exceed the current 1-year mortality rate for COPD lung transplant recipients (21%). Therefore, any patient with COPD requiring hospitalization for an exacerbation should be considered for transplantation if they are otherwise appropriate candidates.

With improving CT scanning techniques, lung morphology may ultimately provide the best index of outcomes. In patients with α_1-antitrypsin deficiency, it has recently been shown[22] that CT scan morphology, specifically in the upper lobes, correlates best with survival when compared to subjective symptoms, FEV_1, or diffusing capacity of the lung for carbon monoxide (DLCO). Although patients with emphysema due to α_1-antitrypsin deficiency may have a different course compared to patients with smoking-induced emphysema, these patients do represent a younger group of emphysema patients with less comorbidity. Therefore, any mortality is most likely related to their underlying lung disease. Thus, they represent a more desirable group to study prognostic factors directly attributable to COPD. It is also interesting that one of the two factors from the National Emphysema Treatment Trial[25] that determined the response to surgery was lung morphology, specifically upper-lobe-predominant disease vs non-upper-lobe-predominant disease.

Ultimately, a model incorporating a number of different parameters will likely be required to more accurately predict survival in patients with COPD. This is one of the lessons that can perhaps be learned from the CF population in which, through the comprehensive Cystic Fibrosis Registry Database, a model composed of nine parameters has been constructed and validated as a reliable indicator of 5-year survival.[26] An attempt to construct a model along these lines incorporating body weight, obstruction, level of dyspnea, and exercise tolerance (BODE) has been proposed and recently validated (*ie*, the BODE index).[27] This has been shown to be a better predictor of mortality than FEV_1 alone. Based on these four parameters, patients are scored on a 10-point scale. Those patients in the highest quartile (BODE score, 7 to 10) have an 80% mortality rate at 52 months, which is clearly worse than the expected mortality rate with transplantation. Patients with BODE scores of < 7 have 5-year survival rates of $> 50\%$, which is more than can be expected from transplantation. Therefore, these patients with less severe disease should not be considered for transplantation. The degree of obstruction in this study was based on the American Thoracic Society criteria of disease severity.[28] Therefore, patients with FEV_1 values of $< 35\%$ predicted were all given the same score for obstruction. The extension of this model to account for differing FEV_1 values within this severe category might further enable the appropriate selection of transplant candidates in the future.

Another issue that needs to be addressed when assessing patients with end-stage COPD, is whether the patient might be an appropriate candidate for lung volume reduction surgery (LVRS). Patients might be candidates for one or both of these surgical procedures. How does one then place these two procedures in context? It is important to be aware of the National Emphysema Treatment Trial[25,29] inclusion criteria before considering treatment with LVRS (Table 2). Based on these criteria, there were five groups of patients that were identified.[25,29] The first of these was identified in an earlier analysis and constituted those patients with an $FEV_1 < 20\%$ predicted accompanied by either homogeneous disease found on a chest CT scan and/or a DLCO of $< 20\%$ predicted.[29] These patients were shown to have a higher mortality rate with LVRS, and therefore their characteristics represent a contraindication to this form of surgery. Of the remaining patients,

Table 2—*Physiologic and Morphologic Inclusion/Exclusion Criteria for LVRS

Criteria	Description
Inclusion	CT scan evidence of bilateral emphysema
	$FEV_1 \leq 45\%$ predicted
	TLC ≥ 100% predicted
	RV ≥ 150% predicted
	$P_{CO_2} \leq 60$ mm Hg
	$P_{O_2} \geq 45$ mm Hg (at rest breathing room air)
Exclusion	FEV_1 15–20% predicted with homogeneous disease on CT chest or with DLCO ≤ 20% predicted
	Homogenous disease and exercise capacity > 40% predicted
	CT scan evidence of diffuse disease judged unsuitable for LVRS
	Significant pleural, interstitial disease or bronchiectasis
	Mean PAP ≥ 35 mm Hg or systolic PAP ≥ 45 mm Hg
	6-min walk test distance of ≤ 140 m postrehabilitation

*TLC = total lung capacity; RV = residual volume.

four groups were identified based on exercise capacity and CT scan appearance. Patients with homogeneous disease and a high exercise capacity constituted a second high-risk group of patients whose mortality rate was increased by LVRS. Two groups, one constituted of those patients with homogeneous disease and a low exercise capacity, and the second by those with a high exercise capacity and upper-lobe-predominant disease, did not have a survival advantage but enjoyed quality-of-life improvements after undergoing LVRS. The last group of patients was defined by having predominantly upper lobe disease and a low exercise capacity. This was the only group in which a survival advantage was demonstrated. Figure 1 shows a suggested algorithm for patients who are candidates for both LVRS as well as lung transplantation. For those patients who have a history of LVRS with an inadequate or unsustained response, it appears that lung transplantation remains a viable option without compromise of results, provided that they remain appropriate candidates.[30]

IPF

Prior to the description of nonspecific interstitial pneumonia (NSIP) as a separate disease entity, the median survival time of patients with IPF was touted as being in the range of approximately 5 years.[31] Patients with pathologic NSIP tend to have a more benign course and better prognosis.[31,32] Therefore, once extracted from the mix of cases of IPF/usual interstitial pneumonia (UIP), there is an appreciation that the prognosis for patients with the latter disease is worse, with median survival times of approximately 3 years from the time of diagnosis.[32,33] Two recent studies[34,35] reporting median survival

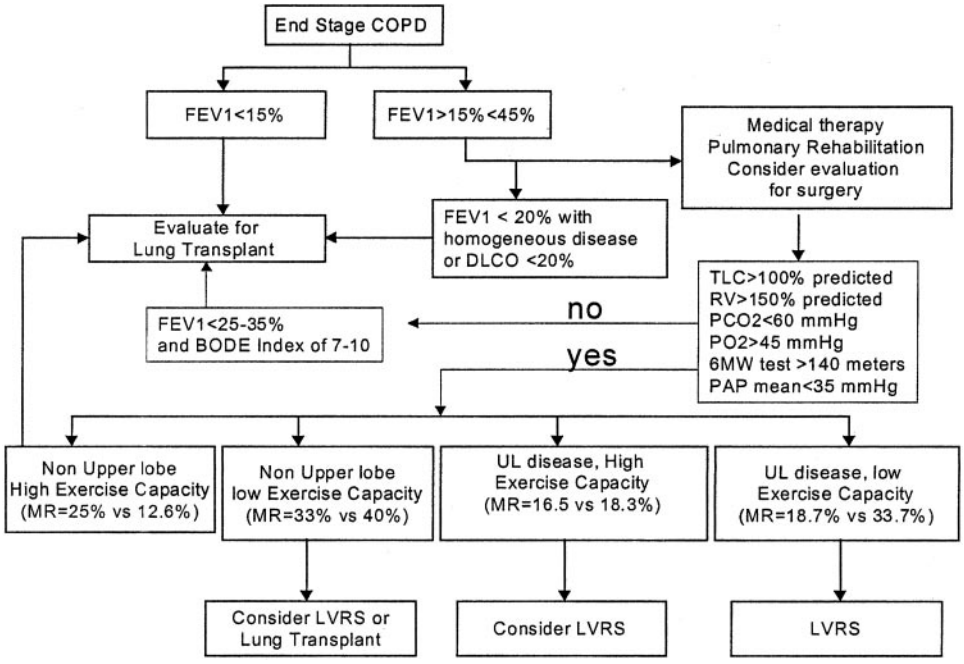

FIGURE 1. Suggested algorithm of surgical options for COPD patients. TLC = total lung capacity; RV = residual volume; 6MW test = 6-min walk test; UL disease = upper-lobe-predominant disease; Non Upper lobe = non-upper-lobe disease distribution; MR = mortality rates. Comparisons of LVRS vs medical therapy in each of the four groups were made with a median follow-up period of 29 months.

times of 4.3 and 5.8 years, respectively, were biased because patients had to survive 6 months to be included in the analyses.

In lieu of these survival statistics, it is not surprising that IPF patients have the highest attrition rate of those on the transplant waiting list with a mortality rate of > 30%.[36] In the 1998 consensus statement,[12] it was acknowledged that even patients with minimal symptoms should be referred for transplant evaluation. The poor prognosis of this condition and the high mortality rate of those on the transplant list were the impetus for this recommendation as well as for these patients being given 3 months credit on the transplant waiting list. The median waiting time for transplantation, which has now increased to 46 months in the United States, exceeds the median survival time from the time of diagnosis in IPF patients.[2,36,37] Survival appears to be age-dependent, and therefore the prognosis in the subgroup of patients who are transplant candidates is superior, with median survival times of 63 months in those 50 to 60 years of age and 116 months in those < 50 years of age being reported.[37]

Nonetheless, owing to the unpredictable nature of the disease, the prudent course of action in this group of patients appears to be transplant referral at the time of diagnosis. This approach is underscored by data showing that patients with IPF who die while on the list had received a diagnosis, on average, close to 2 years prior to their referral.[38]

If all patients with IPF are referred at the time of diagnosis, the issue then reverts to identifying the minority group of patients with a better prognosis who might live 5 to 10 years beyond their diagnosis without transplantation. Traditionally, the FVC and DLCO have been utilized as the parameters that indicated the need for transplant referral. Break points of 60 to 70% for FVC and 50 to 60% for DLCO have been regarded as indicative of a poor outcome.[38,39] The data attesting to the utility of FVC as an indicator, or any other lone pulmonary function parameter as a prognosticator for IPF, has been inconsistent and imperfect at best.[38]

There are many different factors that have been linked to prognosis including age, gender, smoking status, presence of clubbing, serial change in the FVC, DLCO, FEV_1/FVC ratio, biomarkers, presence of pulmonary hypertension, exercise desaturation, fibroblastic foci on surgical lung biopsy specimen, and CT scan characteristics.[37,40–43] Some of these factors, specifically clinical criteria, radiographic scores, pathologic features, and physiologic criteria have been incorporated into models of survival.[37,40,44,45] However, the utilization of features requiring input and expertise from various disciplines is difficult and impractical in most clinical settings.[46] The most recently described composite physiologic index is therefore attractive since it only includes physiologic criteria. It has been shown to be predictive of disease extent and correlates better with survival than any individual pulmonary function parameter.[45] Another of these models was specifically derived from a group of lung transplant candidates.[44] Of the data collected at the time of evaluation, it was found that a DLCO of < 39% predicted together with a high-resolution CT (HRCT) scan fibrosis score of 2.25 yielded a sensitivity and specificity for death within the next 2 years of 82% and 84%, respectively. The use of these or other models requires further prospective validation in other potential lung transplant candidates.[46]

Clinical and/or physiologic parameters aside, morphologic characteristics found on HRCT scans have been shown to be important in predicting outcomes.[41,47] In addition to the extent of fibrosis, it appears that the categorization of patients with histologic UIP into those with features found on HRCT scans that are typical for UIP and those with features that are atypical might have important prognostic implications. Patients with histologic UIP and HRCT scan findings that are consistent with definite or probable UIP have a median survival time of approximately 2 years, whereas those patients with histologic UIP and HRCT scan findings that are indeterminate for UIP or are suggestive of NSIP have a median survival time of 5.76 years[47]. The results of serial PFT, resting Pa_{O_2}, and desaturation on the 6-min walk test also might help to discern those patients with a better prognosis.[34,35,38,48] With regard to the latter test, it has recently been shown[48] that patients who desaturate to levels < 89% on a 6-min walk test had 4-year survival rates of 34.5% vs 69% for those who did not. This latter 4-year survival rate far surpasses the 42% survival rate for the same period in IPF transplant recipients. Therefore, it would appear that as long as patients maintain this level of saturation on serial 6-min walk studies, the need for transplantation might be deferred. However, when making the decisions to defer on listing, one always needs to be aware of the local waiting time, which can be as long as 4 years. Consideration should still be given to listing the "nondesaturators," since it is likely that they might progress and become "desaturators" during the ensuing follow-up period while waiting on the list. Patients should be listed before they have significant resting hypoxemia, since intuitively such patients would be at the highest risk of death. This has been underscored in a small series[38] of listed IPF patients with Pa_{O_2} levels of < 50 mm Hg measured while resting and breathing room air, none of whom survived beyond 15 months.

Two recent studies[34,35] described groups of pa-

tients whose FVC levels improved over the course of 6 months and of whom approximately two thirds survived beyond 5 years. These patients constituted only 11% and 19%, respectively, of the IPF patients in these respective studies. These low percentages underscore the folly of following up patients expectantly to assess for improvement before referring them for transplantation. Patients should rather be followed up simultaneously while undergoing an evaluation or while listed for transplantation. If they do show improvement, then they can be delisted or made inactive on the transplant list.

Approximately 30% of IPF patients will manifest serial deterioration in their spirometric indexes at 6 months after their initial presentation. This portends the worst prognosis, with median survival times of < 2 years.[35] What has previously been underappreciated is that even those patients who maintain their FVC levels within 10% of their baseline values are at risk of dying from their disease. While the prognosis for this latter group of patients is better than that of those who manifest serial deterioration, by virtue of the high proportion of patients falling into this group, it is likely that a significant number of the deaths will come from among these patients. Data from the recently completed study[49] of interferon γ-1b, in which spirometry was followed up every 3 months also attests to the fact that patients die prior to manifesting a significant reduction in their FVC levels. Therefore, the stability of spirometry indexes should not be regarded as stability of the disease, and these patients might still be best served with transplantation.

NSIP

There have been no prior transplant listing recommendations for patients with this relatively newly described condition. There is no separate designation for NSIP when patients are listed for transplantation, and such patients are listed as "IPF" with the United Network for Organ Sharing. In some of the series published to date,[32,33,50] the ratio of UIP to NSIP cases has varied from 1.5 to 4.5:1. Since NSIP carries a better prognosis, these numbers do not reflect the ratio of UIP to NSIP transplant patients. However, it is still likely that a sizable number of NSIP patients have undergone transplantation.

The pathologic pattern of NSIP was first described in 1994 as a separate entity with a more benign course than that of IPF.[51] That initial report described a mortality rate of only 11%, and subsequent reports[32,50] have attested to median survival times of anywhere from > 5 to > 10 years. Although this overall survival time is better than what can be expected with transplantation, there does appear to be a group of patients whose prognosis is worse and who might be served best by transplantation. The salient issue then becomes trying to identify these patients who are at the highest risk for progression and mortality.

Although pathologic temporal homogeneity is what binds these cases, it is apparent that NSIP can be seen in conjunction with a heterogeneous group of conditions. This pathologic injury pattern can be seen in association with collagen vascular diseases, various exposures, resolving diffuse alveolar damage, and UIP.[52] Thus, it is likely that there is a spectrum of outcomes among patients in such cases, including some whose prognosis warrants their consideration for transplantation. NSIP-like changes can be seen in conjunction with UIP in anywhere from 12.5 to 25% of cases.[52–54] If the two coexist, then UIP becomes the default diagnosis, since such cases have a prognosis that most closely approximates that of UIP.

The one group of NSIP patients whose prognosis is excellent are those with the cellular variant of the disease in whom 100% 5-year and 10-year survival rates have been reported.[50] Unfortunately, this variant is three times less common than the fibrotic form and likely represents a different disease with a course that more closely parallels that of desquamative interstitial pneumonia.[50] NSIP patients with DLCO values of $< 35\%$ predicted and/or a decrease in the DLCO of $> 15\%$ predicted have been shown to have an outcome that approximates that of UIP patients with a median survival of about 2 years. This appears to be the one PFT result characteristic that distinguishes those patients with NSIP who should be considered for transplant listing.[33] The result of the 6-min walk test may also pan out to be a useful parameter to follow. There are data attesting to its utility in prognosticating for this condition. However, in the only report thus far,[48] desaturation to $< 89\%$ portended a 4-year survival rate of 65.6%.This is still better than that expected from transplantation. Future studies will need to focus on lower levels of desaturation to try and distinguish those patients with a prognosis sufficiently poor to warrant transplant consideration.

CF

The 1998 consensus statement[12] proposed the following criteria for CF patients to be considered lung transplant candidates:

- $FEV_1 \leq 30\%$ predicted or rapid progressive respiratory deterioration with $FEV_1 > 30\%$ predicted. This rapid deterioration could be characterized by increasing hospitalizations, a rapid fall in FEV_1,

massive hemoptysis, and increasing cachexia despite optimal medical management;
- Resting arterial blood gas analysis while breathing room air showing a $Paco_2$ of > 50 mm Hg or a Pao_2 of < 55 mm Hg; and
- A woman whose conditions is deteriorating rapidly.

These recommendations were largely based on a single series[55] from one institution of 673 CF patients. Other factors have since been looked at in other individual series, including exercise tolerance, breathing reserve index, pulmonary hypertension, wasting, and perfusion abnormalities.[56–59]

The largest series reported were based on analyses from the Cystic Fibrosis Foundation National Patient Registry. The utility of the FEV_1 as a predictor of outcomes at 2 years has been examined with data derived from this registry. Based on this, an FEV_1 of $< 30\%$ predicted was shown to have a sensitivity for predicting death within the next 2 years of 42%, with a specificity of 95%. The associated negative predictive value was 97%, indicating that transplantation could be deferred if a patient's FEV_1 remained above this level. This FEV_1 cutoff performed as accurately as a multiple logistic regression model comprising six different factors.[60] These results pertain only to the 2-year survival rate and need to be viewed in the context of current wait times. A similar analysis from the same database was performed in which a predictive model of 5-year survival was developed and validated.[61] With wait times now close to 4 years, this model may currently have greater clinical utility. The nine criteria that constitute this model include the following: age; FEV_1; gender; weight for height z-score; pancreatic insufficiency; diabetes mellitus; *Staphylococcus aureus*; *Burkholderia cepacia*; and the number of acute exacerbations per year. The effect of each of these variables on the 5-year survival rate in FEV_1 equivalency is shown in Table 3.

In a follow-up article,[6] the same authors used this latter model to categorize all CF transplant recipients from 1992 to 1997 into one of five prognostic groups. Without undergoing transplantation, patients in group 1 had a projected 5-year survival rate of $< 30\%$, while patients in group 2 had projected survival rates of 30 to 50%. Considering that the 5-year survival rate of all CF transplant recipients is 52%, these two groups represent the only patients in whom transplantation conferred a potential survival advantage. These two groups represent 50% of all the CF patients who underwent transplantation during this time period. Based on this model, the other 50% of CF patients who underwent transplantation were disadvantaged from a survival standpoint by having a transplant. However, this type of analysis does not account for improvements in quality of life, including the need for hospitalization and therapy with IV antibiotics.

Table 3—*Covariate Influence on 5-Year Survival Expressed as FEV_1 Equivalent*

Covariate	FEV_1 Equivalence
Age (per year)	−0.7
Sex (male = 0, female = 1)	−6
FEV_1 (per %)	1
Weight-for-age z-score	10
Pancreatic sufficiency (0 or 1)	12
Diabetes mellitus (0 or 1)	−13
S aureus infection (0 or 1)	6
B cepacia infection (0 or 1)	−48
No. of acute exacerbations (0–5)	−12

The FEV_1 equivalence column shows the survival effect of each variable expressed as the effective equivalent change in FEV_1%. For example, a diagnosis of diabetes mellitus has the same survival effect as subtracting 13% from the actual measured FEV_1%. From Liou et al,[26] with permission of Oxford University Press.

As a corollary, in 1993 there were 882 patients in groups 1 or 2 who did not receive transplants, who could potentially have enjoyed a survival advantage with transplantation. It is likely that this number is an overestimation of patients who should have been referred, since the registry does not account for patients who were not transplant candidates for other reasons or who were listed for transplantation but did not survive while on the waiting list. However, 25% of these patients had FEV_1 levels of $> 30\%$ and perhaps were not considered for transplantation based on this parameter. Although follow-up times differ, this appears to be contrary to the inference of the model based on the 2-year survival rate, where it was shown that an FEV_1 of $> 30\%$ predicted had a high negative predictive value for death.

Idiopathic Pulmonary Arterial Hypertension (Primary Pulmonary Hypertension)

Of all the conditions for which lung transplantation is performed, idiopathic pulmonary arterial hypertension (IPAH) is the only one in which there have been significant strides made in medical management. An attestation to this is the ever-decreasing number of patients with IPAH who ultimately undergo transplantation. In 1990, approximately 10.5% of all lung transplants were for patients with primary pulmonary hypertension, whereas in 2001 only 3.6% of lung transplants were performed in patients with this condition.[5] There are now three medical thera-

pies (*ie*, epoprostenol, bosentan, and treprostinil) that have been approved by the Food and Drug Administration for the treatment of IPAH. Epoprostenol was the first of these agents to be made available, having received Food and Drug Administration approval in 1995. Initially touted as a bridge to transplantation, with experience it has been realized that the need for transplantation can be averted in some cases.[62–65] Prospective randomized studies with bosentan or treprostinil that are powered to test for a survival benefit are not ethical or feasible, but there is indirect evidence[66] that these agents also confer a survival advantage. There is also the promise of a number of new agents that are in various stages of development as well as studies[67–70] of combination therapy that may further diminish the need for lung transplantation.

Prior to the advent of these effective therapies, the decision to list patients with IPAH was relatively easy, since the median survival time was only approximately 2.8 years.[71] In the current era, patients who have New York Heart Association (NYHA) class III or IV symptoms and hemodynamics that are compromised to the point that they are considered to be transplant candidates should receive the "gold standard" of therapy, which remains continuous IV epoprostenol. Whether other agents should be added to therapy initially in combination is open to debate and requires further study. It is tempting to treat patients with multiple agents acting on different pathways upfront, especially when one considers that the alternative to lack of response to treatment is transplantation. Depending on the characteristics of the local median waiting time, consideration should be given to listing the patient at the same time that therapy is initiated. The response to therapy can be assessed as early as 3 months after its initiation.[63] Patients who remain at NYHA class III or IV after 3 months of therapy with IV epoprostenol have a 2-year survival rate of 46% and therefore warrant ongoing listing for transplantation. On the other hand, those patients who have been converted to NYHA class I or II have a 2-year survival rate of 93% and therefore can be made inactive or delisted.[63]

Eisenmenger Syndrome

Patients with Eisenmenger syndrome remain a very difficult group in whom to decide the appropriateness and timing of transplantation. These patients tend to have a better prognosis than patients with primary pulmonary hypertension despite similar PAP values.[72] They also constitute a group of patients in whom doubt has been cast as to the risk vs benefit of lung transplantation.[3] The conditions of these patients can also now be successfully managed with continuous IV epoprostenol therapy, and in some cases therapy may render previously inoperable patients operable.[73] It is hoped that this will further lessen the need for transplant consideration in this difficult group of patients. Historically, the procedure of choice for these patients has evolved from heart-lung transplantation to lung transplantation alone with repair of the cardiac defect. However, there are now data suggesting that heart-lung transplantation might be the procedure that confers the greatest survival advantage, especially in those patients with Eisenmenger syndrome due to ventricular septal defects.[74]

Sarcoidosis

After COPD, sarcoidosis is the second most common condition for which lung transplantation may be a treatment option. However, since most patients run a benign course and only about 10 to 20% sustain permanent sequelae, sarcoidosis patients constitute only 2.5% of all lung transplant recipients. Sarcoidosis is the fifth most common indication for lung transplantation but is likely to become the fourth leading indication as the need for transplantation in IPAH patients continues to decrease with the increase in effective medical therapies. In the guideline statement from 1998,[12] sarcoidosis was not among the diseases for which there were specific recommendations.

Since there is the chance in earlier stages of disease for spontaneous reversal, only those patients with stage IV sarcoidosis should be considered for transplantation. This stage is characterized by advanced fibrotic changes, honey-combing, hilar retraction, bullae, cysts, and emphysema.[75] Needless to say, there is little chance for spontaneous remission at this stage.

Sarcoidosis patients who are on the transplantation waiting list have a high risk of dying while awaiting transplantation, with 28% dying prior to undergoing transplantation.[36] This approximates the waiting list mortality rate of IPF patients who, because of their poor prognosis, are credited with 3 additional months of waiting at the time of listing. Sarcoidosis patients generally receive their diagnosis and are in the medical system long before IPF patients. Therefore, this high attrition rate while on the list likely reflects late consideration and referral for transplantation. The characteristics of listed sarcoidosis patients include a mean FVC of 42.6% predicted and a mean FEV_1 of 36% predicted.[36] With the growing wait time and attrition rate while on the list, consid-

eration for transplantation when the FVC is < 50% predicted and/or the FEV_1 is < 40% predicted seems reasonable. There is a paucity of data looking at PFT results as predictors of mortality in sarcoid patients. One such study[76] has shown that those patients with an FVC of < 1.5 L are at the greatest risk of death. For those patients whose highest FVC falls below this number, the positive predictive value for death is 46%, with a negative predictive value of 98%.[76] Predictors of mortality while on the transplant list include the presence of underlying pulmonary hypertension, the amount of supplemental oxygen needed, and African-American race.[77]

In summary, there are many different factors that need to be accounted for when deciding to evaluate and list patients for lung transplantation. These decisions are best made by transplant pulmonologists who have a more intimate knowledge of local waiting times. When there is doubt about the severity of a patient's disease, it is prudent to err on the side of early referral. Even when patients are reticent about transplantation, it is always best to encourage them to be seen at a local transplant center where the necessary education can be provided, thus enabling a fully informed decision on the part of the patient. Unfortunately, physicians often wait until the patient's symptoms are severe enough to significantly impair their activities of daily living. In many cases, this results in patients missing the window of opportunity for transplantation and contributes to unacceptable mortality rates of patients who are on the transplant list.[78]

A new allocation system for lungs has been accepted by the United Network for Organ Sharing/Organ Procurement and Transplantation Network Thoracic Organ Transplantation Committee and is due to be enacted in early 2005.[79] It is hoped that this will reduce the length of waiting times for the most appropriate candidates. The new system will assign a lung allocation score to each patient based on the difference between a patient's projected transplant benefit and the patient's waiting list urgency. A possible misconception with this system is that transplant referral can be deferred since sicker patients will always "jump ahead" on the list. However, the structure of the system is such that patients who are too sick may be disadvantaged if their posttransplant survival is deemed to be limited. Thus, early referral will remain prudent even when this new system is implemented.

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