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

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In 1998, the first edition of the International Guidelines for the Selection of Lung Transplant Candidates was developed with the support of the International Society for Heart and Lung Transplantation (ISHLT), the American Society of Transplant Physicians, the American Thoracic Society, the European Respiratory Society, and the Thoracic Society of Australia & New Zealand. These guidelines were published in several formats, including in the *Journal of Heart and Lung Transplantation*.[1] Evolving technology and advances in medical knowledge mandate a need to update these guidelines.

The aim of this report is to assist physicians throughout the world in referring potential candidates for lung transplantation. It is important to recognize that few data exist from randomized controlled trials upon which to support the recommendations outlined in this report. Therefore, these guidelines are based primarily on a consensus of opinion rendered by experts in the field and on analysis of retrospective single-center, multicenter, and multinational registries. These guidelines must remain a general statement of suitability, as further advances in knowledge and different societal values, specific local expertise, and donor allocation systems demand some flexibility.

Lung transplantation is now a generally accepted therapy for the management of a wide range of severe lung disorders, with evidence supporting quality of life and survival benefit for lung transplant recipients.[2] However, the number of donor organs available remains far fewer than the number of patients with end-stage lung disease who might potentially benefit from the procedure. It is of primary importance, therefore, to optimize the use of this resource, such that the selection of patients who receive a transplant represents those with realistic prospects of favorable long-term outcomes. There is a clear ethical responsibility to respect these altruistic gifts from all donor families and to balance the medical resource requirements of one potential recipient against those of others in their society. These concepts apply equally to listing a candidate with the intention to transplant and potentially de-listing (perhaps only temporarily) a candidate whose health condition changes such that a successful outcome is no longer predicted.

In addition to considering absolute and relative contraindications to lung transplantation, this document discusses factors that may be used in deciding when a patient should be referred to a transplant center and when transplantation should be considered. It is important to underscore that the criteria used to recommend referral may differ from those used to recommend transplantation. The timing of referral depends on the individual patient and referring physician's impression of survival prospects and quality of life, and the patient's desire for information.

Ideally, listing for transplantation should occur when life expectancy is greatly reduced but nonetheless greater than the expected waiting time for a suitable organ, and transplantation should be performed when life expectancy after transplantation exceeds life expectancy without the procedure. In addition to prognostic factors, appropriate timing for listing depends on the criteria used in different parts of the world to

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allocate the organs (e.g., time waited vs disease severity) and therefore cannot be based on broad guidelines. In general, this decision resides with the expertise and practice of individual transplant centers and will vary from country to country.

This document does not address specific selection criteria for recipients of living-donor lung transplants, for pediatric recipients (younger than 18 years), and for recipients of a second transplant. There are no data to support changes in the guidelines for pediatric transplantation (about 60 procedures per year)[3] from the guidelines that were proposed in 1998. Similarly, few new data have been published regarding the selection of appropriate candidates for retransplantation. In light of the severely limited pool of donor organs, efforts should be made to limit retransplantation to those individuals with the highest likelihood of successful outcome. In this regard, retransplantation should be considered largely for patients with advanced and progressive bronchiolitis obliterans syndrome (chronic rejection) who are ambulatory, ventilator-independent, and free of significant comorbidities that might compromise their general suitability as a transplant candidate.

PATIENT SELECTION

1. Indications

Lung transplantation is indicated for patients with chronic, end-stage lung disease who are failing maximal medical therapy, or for whom no effective medical therapy exists. Potential candidates should be well informed and demonstrate adequate health behavior and a willingness to adhere to guidelines from health care professionals.

The primary goal of lung transplantation is to provide a survival benefit. Several studies have demonstrated that lung transplantation confers such benefit, particularly in patients with advanced cystic fibrosis, idiopathic pulmonary fibrosis, and primary pulmonary hypertension.[4-7] Reports for emphysema patients are conflicted,[8] and 2 studies including patients with Eisenmenger's syndrome did not find a survival benefit.[4,5] Uncertainties regarding the methodology and the validity of several assumptions used in the analysis together with improved post-transplant survival rates over time affect conclusions drawn from these studies.

How to weigh expected survival benefit with gains in quality of life is a topic of considerable discussion in the transplant community. Lung transplantation for most patients is a palliative rather than curative treatment, and improvements in quality of life in addition to survival should be used to assess the effectiveness of the procedure,[9,10] a view shared by patients themselves.[11] Thus, the patient's quality of life should be taken into account when the need for a lung transplant is assessed, but owing to the shortage of donor organs, it is not currently possible to support transplantation solely for quality of life purposes.

2. General Contraindications

Lung transplantation remains a complex therapy with a significant risk of perioperative morbidity and mortality; therefore, it is important to consider the overall sum of contraindications and comorbidities. The following lists are not intended to include all possible clinical scenarios, but rather to highlight common areas of concern.

Absolute contraindications.

- Malignancy in the last 2 years, with the exception of cutaneous squamous and basal cell tumors. In general, a 5-year disease-free interval is prudent. The role of lung transplantation for localized bronchioalveolar cell carcinoma remains controversial.
- Untreatable advanced dysfunction of another major organ system (e.g., heart, liver, or kidney). Coronary artery disease not amenable to percutaneous intervention or bypass grafting, or associated with significant impairment of left ventricular function, is an absolute contraindication to lung transplantation, but heart-lung transplantation could be considered in highly selected cases.
- Non-curable chronic extrapulmonary infection including chronic active viral hepatitis B, hepatitis C, and human immunodeficiency virus.
- Significant chest wall/spinal deformity.
- Documented nonadherence or inability to follow through with medical therapy or office follow-up, or both.
- Untreatable psychiatric or psychologic condition associated with the inability to cooperate or comply with medical therapy.
- Absence of a consistent or reliable social support system.
- Substance addiction (e.g., alcohol, tobacco, or narcotics) that is either active or within the last 6 months.

Relative contraindications.

- Age older than 65 years. Older patients have less optimal survival,[2] likely due to comorbidities, and therefore, recipient age should be a factor in candidate selection. Although there cannot be endorsement of an upper age limit as an absolute contraindication (recognizing that advancing age alone in an otherwise acceptable candidate with few comorbidities does not necessarily compromise successful transplant outcomes), the presence of several relative contraindications can combine to increase the risks of transplantation above a safe threshold.

- Critical or unstable clinical condition (e.g., shock, mechanical ventilation or extra-corporeal membrane oxygenation).
- Severely limited functional status with poor rehabilitation potential.
- Colonization with highly resistant or highly virulent bacteria, fungi, or mycobacteria.
- Severe obesity defined as a body mass index (BMI) exceeding 30 kg/m^2.[12]
- Severe or symptomatic osteoporosis.
- Mechanical ventilation. Carefully selected candidates on mechanical ventilation without other acute or chronic organ dysfunction, who are able to actively participate in a meaningful rehabilitation program, may be successfully transplanted.
- Other medical conditions that have not resulted in end-stage organ damage, such as diabetes mellitus, systemic hypertension, peptic ulcer disease, or gastroesophageal reflux should be optimally treated before transplantation. Patients with coronary artery disease may undergo percutaneous intervention before transplantation or coronary artery bypass grafting concurrent with the procedure.[13]

3. Timing of Referral

In general, referral for transplantation assessment is advisable when patients have a less than 50%, 2- to 3-year predicted survival or New York Heart Association (NYHA) class III or IV level of function, or both. The chance of surviving the waiting period will depend on the waiting time, underlying disease, and the existing system for allocation of donor organs. Waiting time tends to be variable and based on many factors such as height and blood group. It tends to be longer for small women compared with taller patients and for recipients with blood groups other than AB. Patients who have idiopathic pulmonary fibrosis, cystic fibrosis, or primary pulmonary hypertension experience lower survival rates while awaiting lung transplantation compared with patients who have emphysema or Eisenmenger's syndrome.[4]

Early referral for consideration of transplant is highly desirable. It allows an orderly process for assessment, management of areas of concern, and patient education before active listing. An experienced multidisciplinary team, attending to the details of the underlying disease and any associated comorbidity, can lead to improved patient outcomes regardless of whether the patient receives a transplant. *It is important to stress that the decision to refer should not be based on a single factor, because no simple, single-point determinant is sufficiently predictive of early mortality.* Rather, it is recommended to rely on a variety of clinical (e.g., rate of infection, intensive care unit [ICU] hospitalization, oxygen need, weight loss, etc.), laboratory (e.g., Pao_2 and $Paco_2$), and functional findings (e.g., pulmonary function tests, echocardiography, exercise capacity, etc).

DISEASE-SPECIFIC LUNG TRANSPLANTATION CONSIDERATIONS

There are no prospective, randomized, well-powered studies in lung transplantation to support the recommendations in this report. Therefore, the guidelines for referral and transplantation proposed hereafter are, for the most part, a combination of recommendations based on small and/or retrospective and/or registry studies, and expert opinion consensus. In the bulleted list of criteria given at the end of each section, unless otherwise specified, any one of the bullets suffices to recommend referral or transplantation, but the need increases with the number of criteria met by the patient.

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is the most common indication for which lung transplantation is performed.[2] Referral for transplantation in COPD patients should only be considered in patients who continue to deteriorate despite optimal medical and surgical therapy, including smoking cessation, maximal bronchodilating treatment, rehabilitation, long-term oxygen therapy, and endoscopic or surgical lung volume reduction where feasible. The definition of the appropriate timing for transplantation is complicated because very symptomatic COPD patients may have a relatively good prognosis; so, the question of whether it may be justified to perform a transplant primarily for quality of life purposes arises frequently in these patients.

Hospitalization for an acute exacerbation associated with hypercapnia carries a poor prognosis, with a 49% 2-year survival.[14] Survival rates without transplantation decrease as age, the degree of hypoxemia and hypercapnia, and pulmonary artery pressure increase and as forced expiratory volume in 1 second (FEV_1), diffusing capacity for carbon monoxide (DLCO), and BMI decrease.[14,15]

In addition, measures of health-related quality of life are independent predictors of mortality.[15] Several of these factors are captured by the recently proposed BODE index which includes the BMI, the degree of airflow obstruction (assessed by percent predicted FEV_1), the degree of dyspnea (assessed by the modified Medical Research Council [MMRC] dyspnea scale), and the exercise capacity (assessed by the 6-minute walk distance [6-MWD]); the index increases as BMI, FEV_1, and distance walked decrease and as the MMRC scale increases.[16] In a prospective study of 625 COPD patients, a BODE index of 7 to 10 (on a scale from 0 to 10) was associated with a median survival of about 3 years,

which is less than would be expected after transplantation. Patients with a BODE score of 5 to 6 would likely not derive a survival benefit from transplantation but may be candidates for early referral.

The National Emphysema Treatment Trial study of lung volume reduction surgery has also identified a high-risk group of patients with a median survival of about 3 years with medical therapy, which is less than the expected survival after transplantation. These are patients with an FEV_1 of less than 20% and either a DLCO of less than 20% or homogeneously distributed emphysema.[17]

Guidelines for Referral

- BODE index exceeding 5.[16]

Guidelines for Transplantation

- Patients with a BODE index* of 7 to 10[16] or at least 1 of the following:
- History of hospitalization for exacerbation associated with acute hypercapnia (P_{CO_2} exceeding 50 mm Hg).[14]
- Pulmonary hypertension or cor pulmonale, or both, despite oxygen therapy.[18]
- FEV_1 of less than 20% and either DLCO of less than 20% or homogenous distribution of emphysema.[17]

Cystic Fibrosis and Other Causes of Bronchiectasis

Cystic fibrosis (CF) is the third most common indication for which lung transplantation is performed.[2] CF patients are often chronically infected with antibiotic-resistant organisms that remain in the large airways, upper respiratory tract, and sinuses after transplantation, posing potential risks for pulmonary infection in the context of immune suppression. In addition, the multisystem nature of CF poses extra challenges for the selection of transplant candidates. Yet, post-transplant survival of patients with CF is similar or even greater than survival of patients with other conditions.[4,5,8,19–21]

This section focuses specifically on CF patients because no specific recommendation can be made for the selection of patients with non-CF related bronchiectasis (e.g., secondary to immunodeficiency syndromes, primary cilia dyskinesia syndromes, infections, etc.) given the limited amount of data for the latter. In general, the lung transplant community has followed the guidelines used for CF patients for these other diseases.

*The expert panel recognizes that the BODE index has not been validated in the group of patients listed for lung transplantation; however, at the time of this report, it appears to be the most comprehensive model to predict survival in patients with COPD. Hence, it is the belief of the group that the index should be utilized to help guide the selection of candidates with COPD, unless new data prove that the tool is not valuable in this specific patient population.

Special Considerations

Infection. Certain resistant pathogens may increase the risk of poor outcome in the short or long term after transplantation, but it is not possible currently to identify absolute contraindications based on either the type of organisms or the pattern of antibiotic resistance. The decision to not list a CF patient colonized by resistant pathogens should be based on a comprehensive evaluation of all other comorbidities, which when combined may increase the risk of transplantation above a safe threshold.

Overt sepsis is an absolute contraindication. The presence of an increased white cell count and pyrexia immediately before surgery tends to increase the risk of death due to peri-operative sepsis, but only with a modest positive predictive value.[22]

Pre-transplant colonization with multidrug or pan-resistant *Pseudomonas aeruginosa* is not a contraindication to transplantation because it has no significant influence on short-term survival outcome.[22–24] Although specific data are not available, pre-transplant colonization with methicillin-resistant *Staphylococcus aureus*, multi- or pan-resistant non-fermenting gram-negative rods such as *Stenotrophomonas maltophilia* and *Alcaligenes xylosoxidans*, and *Aspergillus fumigatus* is not considered a contraindication. Specific therapy regimens are required.

Single-center reports and registry studies indicate a 30% to 40% increase in 1-, 3-, and 5-year mortality rates among CF patients infected with *Burkholderia cepacia* complex,[20,22,25–27] in particular in case of *Burkholderia cepacia* genomovar III.[26,28] Although patients colonized with this organism have had successful transplantations in some centers, many centers currently refuse to offer transplantation to such patients.[29] It is important, however, to emphasize that great care should be taken when identifying species within the *B cepacia* complex because of the high rate of misidentification[30] and the potential impact of such error for the patient.

Antibiotic susceptibility testing should be repeated at regular intervals while patients are on the waiting list to ensure that a recently tested antibiotic combination is administered at the time of transplant surgery. The possibility of utilizing in vitro synergy testing to identify the optimum antibiotic combination in patients with pan-resistant organisms holds promise to improve survival[25] but it is not yet widely available.

Liver disease. Lung transplantation without liver transplantation has been safely performed in patients with controlled portal hypertension and preserved hepatic function.[31] The precise guidelines to define "preserved hepatic function" in the context of CF are not currently available, however. In the non-CF population, a score

higher than 24 on the model of end-stage liver disease indicates severe hepatic dysfunction and need for liver transplantation, but this threshold has not been validated in CF patients.

Ventilator use. The question of whether lung transplantation should be performed in CF patients requiring invasive mechanical ventilation is debated, and there is no consensus among transplant centers. Although the ISHLT database[2] indicates that pre-transplant invasive mechanical ventilation is a risk factor for post-transplant mortality in the lung transplant population as a whole, small single-center studies[32,33] and the United Network for Organ Sharing database[20,34] suggest that this may not apply to CF patients. Yet, progression to intubation in these patients is often associated with deterioration in the function of other organs and sepsis. Moreover and importantly, the decision to proceed to intubation and mechanical ventilation poses a difficult ethical dilemma in that it may interfere with the appropriate introduction of terminal care. So, lung transplantation in CF patients who require invasive ventilation should only be considered if (1) they have been evaluated and listed before the onset of ventilatory assistance, (2) they have been informed that worsening of their clinical situation after intubation may eventually contraindicate transplantation, (3) they have no other significant organ dysfunction, and (4) they agree to proceed to intubation.

Several nonpulmonary problems that are frequently associated with CF should be treated optimally before, or as soon as possible after surgery; for example, diabetes mellitus, osteoporosis, sinus disease, and gastroesophageal reflux disease. If well controlled, these problems are not contraindications for transplant.

Prognostic factors. The guidelines proposed in the original international consensus document were primarily based on the single-center study by Kerem et al,[35] who identified a FEV_1 of less than 30% predicted (and to a lesser extent, a $Paco_2 > 55$ mm Hg, a $Pao_2 <$ 50 mm Hg, age <18 years, and female gender) as useful markers for predicting survival. However, more recent studies based on data from national[36–38] or single-center[39,40] CF registries and including a variety of anthropometric, clinical, physiologic, and laboratory characteristics failed to identify a consistent combination of predictors of survival.

Two large cohort studies that used data from the US Cystic Fibrosis Foundation Registry to compute multivariable models predicting 2- and 5-year survival provided discrepant results.[21,27,36,38] Both models adequately fitted observed data but in 1 study,[38] the ability of the model to predict mortality was only modest (about 30%) and did not exceed that of a FEV_1 of less than 30% predicted.[38] Defining predictors of mortality and their thresholds is difficult because the course and prognosis of the disease are highly variable between individuals, which relates to the heterogenous, multisystem nature of CF.

In practice, transplantation should be discussed with the patient and family, and consideration of referral to a transplant center should occur when FEV_1 decreases to about 30% of predicted, or when there is a rapid decline in FEV_1.[41,42] Early referral is recommended in female patients younger than 20 years who deteriorate rapidly, because they have a particularly poor prognosis.[43] Referral should also be advised in patients who have been hospitalized for a pulmonary exacerbation that was severe enough to require treatment in the ICU.[41] The decision of transplantation will eventually derive from 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 (e.g., 6-MWD), and pulmonary hypertension.[44]

Guidelines for Referral

- FEV_1 below 30% predicted or a rapid decline in FEV_1—in particular in young female patients.[41–43]
- Exacerbation of pulmonary disease requiring ICU stay.[41]
- Increasing frequency of exacerbations requiring antibiotic therapy.
- Refractory and/or recurrent pneumothorax.
- Recurrent hemoptysis not controlled by embolization.

Guideline for Transplantation

- Oxygen-dependent respiratory failure.
- Hypercapnia.
- Pulmonary hypertension.[44]

Idiopathic Pulmonary Fibrosis And Non-Specific Interstitial Pneumonia

Idiopathic pulmonary fibrosis, also known as usual interstitial pneumonia (UIP), is the most common and most serious of the idiopathic interstitial pneumonias (IIPs) and is the second most frequent disease for which lung transplantation is performed.[2,45] Because patients with IPF die without transplantation (median survival time from diagnosis, 2.5 to 3.5 years), it is important to distinguish UIP from other interstitial lung disorders that have a more favorable prognosis. Importantly, patients with idiopathic pulmonary fibrosis (irrespective of the fact that registry data do not discriminate underlying types of IIPs) have the highest mortality on the transplant waiting list.[2] The dismal survival rates of IPF patients awaiting lung transplantation around the world indicate that the pulmonary community should

promote the early referral of IPF patients for transplantation to a greater degree.

Prognostic Factors

Histology. Numerous investigators have demonstrated that the histologic diagnosis in a patient with an IIP strongly influences survival. The presence of UIP-like changes on any surgical biopsy from patients with IIP identifies a patient with poorer survival.[46-48] Compared with UIP, the prognosis of nonspecific interstitial pneumonia (NSIP) is more variable and tends to decrease with the extent of fibrosis.[49,50] Overall survival is lower in UIP than in fibrotic NSIP, but studies showed that a subset of patients with fibrotic NSIP have a 2-year survival, which is similar to that of patients with UIP. This subset is characterized by a severe functional impairment at presentation and/or a decline in functional indices, in particular the DLCO at 6 to 12 months, despite treatment.[51,52]

Pulmonary function and exercise capacity. Several investigators have used spirometry as a prognostic marker, with varying results.[53] These studies suggest that a forced vital capacity (FVC) of less than 60% of predicted is associated with increased mortality. However, more recent data from a large prospectively followed cohort of patients with IPF indicate that that patients with relatively well preserved lung volumes are at similar risk of mortality, as are those patients with lower levels of lung function.[54] It appears, therefore, that well preserved spirometry should not preclude referral for transplantation.

Serial measurement of spirometry provides added prognostic value in IIP patients. Five recent studies demonstrated remarkable consistency in their findings demonstrating that a fall in FVC or other pulmonary function parameters, or oxygen saturation/p (A–a) O_2 is associated with a higher mortality.[51,52,54-56] These data suggest that a 10% or greater decrement in FVC during 6 months of follow-up identifies patients at significantly increased risk of mortality, although the positive predictive value of such a change is 31% and the negative predictive value is 91%.[54] This, in part, relates to the occurrence of rapid deterioration and death that may occur in IPF patients.[57]

Similar data have been suggested in serial measurements in patients with fibrotic NSIP.[46,51,58] The DLCO has proven a more dependable measure in predicting survival in patients with UIP or fibrotic NSIP[51,59] with a DLCO of less than 35% to 39% predicted identifying patients that are at higher risk of mortality. Serial measurement of spirometry can estimate disease progression in patients with limited disease (DLCO $>$ 40% predicted).[51] These data suggest that a 10% decrement in FVC during 6 months of follow-up identifies patients at significantly increased risk of mortality.[46,51,58]

In addition, measurement of exercise capacity is of value to estimate survival in IIP patients.[60] Data concerning formal cardiopulmonary exercise testing are contradictory,[61-63] but oxygen saturation during a 6-minute walk test (6-MWT) was recently demonstrated to have considerable prognostic value.[64] An oxygen saturation of less than 88% during a 6-MWT identified a group of patients at particularly high risk of mortality.

Radiology. High-resolution computed tomography (HRCT) findings have also demonstrated significant prognostic value. IIP patients with a typical HRCT picture of UIP (i.e., honeycombing) exhibit a shorter period of survival than patients with an atypical HRCT appearance— even in the presence of a histologic UIP. This supports previous data from 2 groups that suggested a higher HRCT fibrotic score is associated with impaired survival[48,59]

Trials of therapy. Failure of corticosteroid therapy was considered an important factor in guiding the timing for transplantation in the previous guideline report.[1] Since then, extensive data have been published suggesting only a limited benefit to current therapies.[65-67] Therefore, waiting for IPF patients to respond to therapy will likely delay referral inappropriately. Whether this same recommendation applies to patients with other forms of interstitial lung disease such as NSIP requires additional prospective study, as these patients may experience a more favorable response to immunosuppressive therapy.[46,48]

Guideline for Referral

- Histologic or radiographic evidence of UIP irrespective of vital capacity.
- Histologic evidence of fibrotic NSIP.

Guideline for Transplantation

- Histologic or radiographic evidence of UIP and any of the following:
  - A DLCO of less than 39% predicted.
  - A 10% or greater decrement in FVC during 6 months of follow-up.
  - A decrease in pulse oximetry below 88% during a 6-MWT.
  - Honeycombing on HRCT (fibrosis score of $>$ 2).
- Histologic evidence of NSIP and any of the following:
  - A DLCO of less than 35% predicted.
  - A 10% or greater decrement in FVC or 15% decrease in DLCO during 6 months of follow-up.

Pulmonary Fibrosis Associated With Collagen Vascular Disease

Diffuse parenchymal lung diseases and/or pulmonary hypertension associated with collagen vascular disease

(CVD) are rare indications (0.5%) for lung transplantation.[2] Pulmonary fibrosis (either UIP or NSIP) is common in scleroderma, rheumatoid arthritis, and mixed connective tissue disease. The manifestations of the CVD are highly variable, and each patient should have individual consideration. In general, evidence of quiescent systemic disease is recommended, and any evidence of active vasculitis should preclude referral.

Data regarding estimation of prognosis of patients with CVD from a pulmonary perspective come predominantly from scleroderma. Age older than 60 years at diagnosis is an independent poor prognostic factor.[68] A FVC below 70% to 80% predicted at the time of diagnosis (and within 5 years of disease onset if the diagnosis was delayed) is predictive of decreased survival and/or end-stage lung disease.[68,69] Although patients with scleroderma have had successful lung transplantations, current data are insufficient to support specific guidelines for patients with this or other collagen vascular diseases.[70]

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a progressive and severely disabling disorder induced by an increase in pulmonary vascular resistance ultimately leading to right heart failure and death. The natural history of idiopathic PAH (iPAH) is dismal, with a reported median survival rate of 2.8 years when untreated.[71] Over the past decade, advances in medical therapy considerably changed the prognosis of the disease.[72] Most expert centers discuss the notion of transplantation early after diagnosis and closely follow patients' symptoms, functional status, including 6-MWT distance, and hemodynamics. The decision to list for transplant is made when functional status and hemodynamics decline to the point where survival without transplantation is likely to be compromised.

When considering outcome predictors in PAH, one should bear in mind the following issues: (1) most of the knowledge is derived from iPAH, and few reports provide robust information regarding other causes of PAH; (2) data on large-scale clinical trials encompassing the broad range of PAH are scarce and usually refer to short- to mid-term observations; (3) although long-term survival data are available for patients treated with intravenous epoprostenol, the effects of new therapeutic modalities on long-term outcome are still unknown; and (4) most factors associated with a poor prognosis are linked to the degree of right ventricular dysfunction.[72]

Prognostic Factors

Etiology. PAH associated with systemic sclerosis carries a worse outcome than iPAH, even with epoprostenol therapy.[73,74] At the other end of the spectrum, patients with PAH due to congenital left-to-right shunt appear to fare better than those with iPAH while awaiting transplantation (97% vs 77%, 89% vs 69%, and 77% vs 35% at 1, 2, and 3 years, respectively).[72] Pulmonary venoocclusive disease and pulmonary capillary hemangiomatosis have the worst overall prognosis due to the lack of disease-specific medical therapy.

Functional status. Overall functional status assessed by symptoms (NYHA functional class/World Health Organization functional class)[75] and functional capacity assessed primarily by the 6-MWT correlates with survival in iPAH.[75] Idiopathic PAH patients with functional class III to IV symptoms are at higher risk of dying.[76–78] The 6-MWT has been the cornerstone functional test to evaluate treatment efficacy both in clinical trials and in daily clinical practice. In unselected patients (treated or not), a 6-MWT of less than 332 meters is associated with a worse prognosis.[75]

Hemodynamics. Only a minority of patients respond to acute reversibility testing. Recent data suggest that 12% of patients with iPAH experience a decrease in pulmonary pressure during testing, with only 6% responding to long-term therapy with a calcium-channel blocker.[76] Although patients with PAH due to congenital shunts are rarely responders, these patients fare better than those with iPAH. Therefore, acute response to vasoreactive testing should not be considered as an outcome predictor per se.

D'Alonzo et al[71] demonstrated from the National Institutes of Health Registry of Pulmonary Hypertension that survival was markedly diminished in untreated patients who had a cardiac index of less than 2 liters/min/m^2 vs a cardiac index of 4 liters/min/m^2 or more, a right atrial pressure of 20 mm Hg or more vs less than 10 mm Hg, or a mean systolic pulmonary artery pressure of 85 mm Hg or more vs less than 55 mm Hg. A more recent analysis continues to show the impact of hemodynamic parameters on survival, with a right atrial pressure of 12 mm Hg or more as a predictor of mortality.[76] However, although associated with a worse immediate outcome, severely disturbed hemodynamics (low cardiac index, elevated right atrial pressure, low mixed venous oxygen saturation or high vascular resistance) do not predict the lack of a potential response to medical therapy.

Impact of medical therapy. Continuous epoprostenol therapy improves outcome in iPAH, including survival.[76,77] However, this survival benefit was not confirmed in other forms of PAH, including scleroderma, in 1 large randomized controlled trial.[73] Long-term observations with other medical treatments (bosentan or treprostinil) suggest that newer drugs may have com-

parable effects on a larger population of patients with PAH. Although single-center experiences are encouraging, no study to date supports the hypothesis that combination therapy will improve prognosis in PAH.

Guideline for Referral

- NYHA functional class III or IV, irrespective of ongoing therapy.
- Rapidly progressive disease.

Guideline for Transplantation

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

Sarcoidosis

Sarcoidosis represents 2.6% of indications for adult lung transplantation.[2] The potential for significant extrapulmonary involvement, such as cardiac-, hepatic- or neurosarcoidosis should be considered. Furthermore, significant bronchiectasis with bacterial colonization and aspergilloma(s) are more prevalent in such patients. Because sarcoidosis tends to have a chronic and variable natural course, the optimum timing to refer a patient for transplantation is difficult to define. Factors indicating poor prognosis include African-American ethnicity, presence of hypoxemia, pulmonary hypertension, diminished cardiac index, and elevated right atrial pressure.[79-81] An elevated right atrial pressure indicates severe right ventricular dysfunction and is an ominous prognostic factor associated with high short-term mortality.[80] Recent studies have revealed high mortality rates from 30% to 50% in sarcoid patients on a lung transplant waiting list, not unlike mortality rates observed in patients with pulmonary fibrosis.[79-81]

Guideline for Referral

- NYHA functional class III or IV.

Guideline for Transplantation

- Impairment of exercise tolerance (NYHA functional class III or IV) and any of the following:
- Hypoxemia at rest.
- Pulmonary hypertension.
- Elevated right atrial pressure exceeding 15 mm Hg.

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is a rare disorder, and these patients account for only 1.1% of all transplant recipients.[2] Early studies suggested that almost all LAM patients died within 10 years of onset of symptoms, but more recent studies have documented a more favorable prognosis, with 10-year survival rates of between 40% and 78%.[82,83] The mean annual rate of decline in FEV_1 approximates 120 ml, and there is a trend toward lower rates of decline among patients receiving progesterone and among those who are postmenopausal.[84] A study focusing exclusively on LAM patients undergoing lung transplantation documented an average interval of 11 years (range, 3–24 years) from symptom onset to transplantation.[85] Factors associated with a poorer prognosis include a reduction in the FEV_1/FVC ratio, increased total lung capacity, and a predominance of cystic lesions rather than smooth muscle proliferation on histologic examination of the lung.[82]

Guideline for Referral

- NYHA functional class III or IV.

Guideline for Transplantation

- Severe impairment in lung function and exercise capacity (e.g., VO_2 max < 50% predicted).
- Hypoxemia at rest.

Pulmonary Langerhans Cell Histiocytosis (Eosinophilic Granuloma)

Pulmonary Langerhans cell histiocytosis (LCH) accounts for only 0.2% of all lung transplants,[2] reflecting the rarity of the disease and that only a few patients progress to a state of advanced functional impairment. Severe secondary pulmonary hypertension often develops in these patients due to intrinsic pulmonary vascular disease in which the pulmonary circulation is involved independently of the small airway and the lung parenchymal injury.[60] The median survival of patients with pulmonary LCH is approximately 13 years.[86,87] Factors portending a poorer prognosis include older age at the time of diagnosis, the severity of reduced FEV_1 and FEV_1/FVC ratio, increased residual volume and residual volume/total lung capacity ratio, reduced diffusing capacity,[86,87] and pulmonary hypertension.

Guideline for Referral

- NYHA functional class III or IV.

Guidelines for Transplantation

- Severe impairment in lung function and exercise capacity.
- Hypoxemia at rest.

SUMMARY

Since the writing of the 1998 guidelines for the selection of candidates for lung transplantation, there has been an increased understanding of the natural history

of various lung diseases as well as new treatment strategies developed that may forestall the need for transplantation for certain disorders. This has resulted in several changes to the current strategy for selecting patients for this procedure.

The primary goal of this document is to provide up-to-date guidelines to help physicians in the referral and selection process of candidates for lung transplantation. With limited prospective randomized studies to support the recommendations outlined in this document, this update to the international guidelines is based primarily on a consensus of opinion rendered by experts in the field. The bulleted guidelines should therefore not be considered to be hard and fast rules. Because of the potential for long waiting times to transplantation, physicians should err on the side of early referral of their patients to a lung transplant center.

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