

International Guidelines for the Selection of Lung Transplant Candidates

THIS JOINT STATEMENT OF THE AMERICAN SOCIETY FOR TRANSPLANT PHYSICIANS (ASTP)/AMERICAN THORACIC SOCIETY (ATS)/EUROPEAN RESPIRATORY SOCIETY (ERS)/INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION (ISHLT) WAS APPROVED BY THE ATS BOARD OF DIRECTORS FEBRUARY, 1998

More than 6,400 lung transplants have been performed since the first successful operations in the early 1980s (1). Lung transplant programs now exist in many countries. Internationally, the number of donor organs available is far fewer than the number of patients with end-stage lung disease. Because of this, many candidates die on the waiting list, and the average wait to receive a donor organ may approach 2 yr (2). Overall survivals are between 60 and 65% at 2 yr and approximately 40% at 5 yr (1). Considering the resource limitations and the importance of assuring optimum outcomes, we believe that international guidelines for selection of appropriate candidates for lung transplant will ensure a fair distribution of donor organs. Transplant physicians and surgeons representing the International Society of Heart and Lung Transplantation, the American Society of Transplant Physicians, the American Thoracic Society, the European Respiratory Society, and the Thoracic Society of Australia and New Zealand have agreed on the information in the following document as acceptable guidelines for candidates for lung transplantation. Our aim is that this document will assist physicians throughout the world who are treating patients with pulmonary diseases to identify potential candidates for lung transplantation.

This document is divided into two sections. The first describes general health guidelines that all candidates for lung transplantation should meet; the second describes disease-specific exercise or lung function criteria that are generally felt to identify patients whose poor prognosis from their underlying diseases justify transplantation. Candidates for either live donor organs or cadaver donor organs should meet the same selection criteria. In all cases it must be remembered that these guidelines are a general statement and that individual patients might have specific circumstances that do not meet all guidelines yet would be acceptable transplant candidates.

Lung transplantation remains a developing field within pulmonary medicine and thoracic surgery. It is anticipated that with increasing experience and knowledge the state of the art will change and these guidelines will require review and modification.

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GENERAL GUIDANCE FOR CANDIDATE SELECTION FOR LUNG TRANSPLANTATION

Physicians evaluating patients for lung transplantation should ensure that the patient has received or is receiving maximum, optimal medical therapy for his disease but nevertheless has declining function. In general, candidates should have chronic disease for which no further medical or surgical therapy is available and survival is limited; lung transplantation is rarely an option for acutely, critically ill patients. Comorbid medical conditions should also be optimally treated in transplant candidates, and routine preventive medicine measures (such as mammograms, Pap smears, and colon cancer screening) should be completed where appropriate.

Older patients have a significantly worse survival rate than younger patients (1). The following guidelines are suggested.

Age limits.

- Heart-lung transplants ~ 55 years
- Single lung transplants ~ 65 years
- Bilateral lung transplants ~ 60 years

GENERAL MEDICAL CONDITIONS THAT IMPACT ON ELIGIBILITY FOR LUNG TRANSPLANTATION

The following are a list of general medical conditions that are felt to impact on the long-term outcome of lung transplant recipients. Medical or psychosocial treatment to address these issues should be instituted when appropriate in patients who do not currently, but may ultimately, meet the criteria for lung transplantation. However, in most cases, referral should not be delayed while patients are undergoing corrective treatment. Other medical conditions which, when they have not resulted in organ damage, are generally acceptable in candidates for lung transplantation—e.g., systemic hypertension, diabetes mellitus, peptic ulcer disease, should also be optimally treated and well controlled. In the presence of any comorbid medical condition with the potential for end organ damage, a careful search should be made for evidence of organ dysfunction.

- *Symptomatic osteoporosis* is a relative contraindication to transplantation and the potential risk to acceptable long term outcome should be assessed on a case by case basis (3). Both symptomatic and asymptomatic significant disease requires treatment that should be initiated prior to transplant. Patients should be fully investigated and followed by appropriate objective measures, i.e., bone densitometry.
- *Severe musculoskeletal disease* affecting the thorax, e.g., kyphoscoliosis, is a relative contraindication, and progressive neuromuscular disease is an absolute contraindication to lung transplantation.
- *Current use of corticosteroids* is not a contraindication to transplantation; however, all attempts to discontinue these

- drugs or at least reduce the dose to ≤ 20 mg/d prednisolone or prednisone should be made (4).
- *Nutritional issues* are an important predictor of surgical outcome (5, 6). Patients with an ideal body weight (IBW) $< 70\%$ or $> 130\%$ percent require either weight gain or weight loss to become eligible for transplant.
 - Candidates for lung transplantation must have been *free of substance addiction*, e.g., alcohol, tobacco, narcotics, for at least 6 mo. Appropriate preoperative biochemical monitoring is recommended in at-risk patients.
 - *Psychosocial problems* that are unable to be resolved and that have a high likelihood of impacting negatively on the patient's outcome, e.g., poorly controlled major psycho-affective disorder, inability to comply with complex medication regimen, are a relative contraindication. A documented history of *noncompliance* with medical care or treatment plans even in the absence of documented psychiatric problem is a relative contraindication.
 - *Requirement for invasive ventilation* is a relative contraindication to transplant. Patients receiving noninvasive ventilatory support who meet all other criteria are eligible for lung transplantation.
 - *Colonization with fungi or atypical mycobacteria* is not an absolute contraindication to transplantation. Cases should be considered on an individual basis, and special care should be taken when a unilateral transplant is considered. When possible, attempts preoperatively to eradicate colonization with antibiotic therapy are appropriate.
 - Adequately treated *M. tuberculosis* is not a contraindication to lung transplantation.

Current Contraindications

- Dysfunction of major organs other than the lung is a contraindication, particularly renal dysfunction—*creatinine clearance of < 50 mg/ml/min*—because of the impact of immunosuppressive drugs on renal function (7). Patients with significant untreatable coronary artery disease or left ventricular dysfunction warrant consideration for heart–lung transplant.
- Infection with *HIV*.
- Active *malignancy* within the past two years with the exception of basal cell and squamous cell carcinoma of skin. In addition, recent data on recurrence of tumors posttransplant suggest that a waiting period of at least 5 yr is prudent for extracapsular renal cell tumors, breast cancer stage 2 or higher, colon cancer staged higher than Dukes A, and melanoma, level III or higher (8).
- *Hepatitis B* antigen positivity.
- *Hepatitis C* with biopsy-proven histologic evidence of liver disease.

Lung transplant is not contraindicated per se in patients with systemic disease, e.g., collagen vascular processes, diabetes mellitus (9). Each potential candidate should be considered on an individual basis with particular attention paid to the presence of any target organ damage outside the lung that might affect long-term outcome. This would constitute a relative or absolute contraindication.

Diagnostic and Prognostic Investigations before Referral

The following list of studies are considered useful by most transplant centers in assessing potential candidates. Queries regarding specific center requirements should be directed to that center and, when possible, efforts should be made to avoid duplicate studies.

- Full lung function tests

- Exercise performance measured by a standardized test, e.g., six-minute walk
- Electrocardiogram
- Echocardiogram
- High resolution computed tomography (HRCT) of the thorax in patients with parenchymal disease, pleural disease, or previous thoracic surgical procedures
- Stress echocardiogram—e.g., dobutamine, dobutamine PET, sestamibi, etc.—and/or coronary angiograms in patients at high risk for coronary artery disease
- 24-hour creatinine clearance
- Liver function studies

DISEASE SPECIFIC GUIDELINES

1. Nonbronchiectatic Chronic Obstructive Lung Disease

This disease category encompasses a number of diagnoses of which the most common are emphysema, chronic bronchitis, and bronchiolitis obliterans. Every effort should be made to exclude asthma and to maximally treat any reversible component of the airways disease prior to referral for transplant workup. Pulmonary rehabilitation and long-term oxygen therapy should also be included in medical management prior to referral to a transplant center. Other treatment options such as volume reduction surgery for emphysema patients may also be considered in appropriate candidates (10–12). It is inherently difficult to accurately predict survival in many patients with advanced obstructive disease (13–15). In terms of transplant outcome, therefore, some of these patients may experience improved functional capacity but not necessarily improved survival.

Guideline:

COPD patients are considered potentially to be in the transplant window if they meet the following criteria (16, 17):

- $FEV_1 < 25\%$ of predicted (without reversibility)
- and/or $Pa_{CO_2} \geq 55$ mm Hg (7.3 kPa) and/or elevated pulmonary artery pressures with progressive deterioration, e.g., cor pulmonale.
- Preference should be given to those patients with elevated Pa_{CO_2} with progressive deterioration who require long-term oxygen therapy, as they have the poorest prognosis (18).

2. Cystic Fibrosis and other Bronchiectatic Diseases

Patients with cystic fibrosis have special problems related to the microbiology of their pulmonary secretions, particularly with respect to resistant organisms (19, 20). Controversy exists as to the outcome of patients colonized with multiply resistant *P. aeruginosa* and *B. cepacia* (biologically, *B. cepacia* is inherently multiply resistant). The following definitions may be used to categorize the resistance of pseudomonas and related organisms (21):

—A *multiple resistant* organism is resistant to all agents in two of the following classes of antibiotics: the beta-lactams, aminoglycosides and/or quinolones.

—A *pan-resistant* organism is resistant *in vitro* to all groups of antibiotics.

A substantial number of patients will have organisms that are pan resistant *in vitro*. However, *in vitro* resistance does not equate with *in vivo* resistance. Different combinations of antibiotics may function synergistically *in vivo*. Thus *multiple resistance* is not a contraindication to transplantation in this group of patients. Colonization with *pan-resistant* organisms should be considered a relative contraindication to transplantation because of concern about long-term outcomes in these

patients. Occasionally, specialized testing of different combinations of antibiotics against organisms considered to be pan-resistant to the usual antibiotic regimens may demonstrate sensitivity to the new drug combinations (synergy testing). Patients with presumed pan-resistant organisms should be referred to a transplant center capable of this type of antibiotic sensitivity testing, and each patient should be assessed on an individual basis. Listing of such patients should be determined based on individual center experience.

Microbiologic review of the sputum of listed patients should be done on a periodic basis, e.g., every 3 mo, or if inter-current antibiotic treatment has been necessary. The following criteria identify patients potentially within the transplant window.

Guideline:

- $FEV_1 \leq 30\%$ predicted or rapid progressive respiratory deterioration with $FEV_1 > 30\%$ predicted, e.g., increasing numbers of hospitalizations, rapid fall in FEV_1 , massive hemoptysis and increasing cachexia despite optimal medical management.
- Resting arterial blood gases obtained while patient is breathing room air— $Pa_{CO_2} > 6.7$ kPa (50 mm Hg); $Pa_{O_2} < 7.3$ kPa (55 mm Hg)—are useful criteria and are associated with a prognosis of $< 50\%$ survival in 2 yr; however, patients should be considered candidates for transplant if they meet FEV_1 criteria even though they may not yet be markedly hypercapnic or hypoxemic (22).
- Young female cystic fibrosis patients who deteriorate rapidly have a particularly poor prognosis (23). These patients should be evaluated on an individual basis regardless of physiologic criteria.

Patients may present for transplant consideration with bronchiectasis from other causes—immunodeficiency syndromes, immotile or dysfunctional cilia syndromes, post-infection, etc. Few data are available regarding projected survivals in such patients with advanced disease, and that makes it more difficult to formulate guidelines for selection. In general, the lung transplant community has followed the guidelines listed above for cystic fibrosis patients.

3. Idiopathic Pulmonary Fibrosis (Cryptogenic Fibrosing Alveolitis)

Idiopathic pulmonary fibrosis (IPF) refers to patients without evidence of other systemic disease who present with diffuse fibrotic changes in the lung. The rapid progression of this disease and the high mortality mandates early referral (24–27). It is recognized that this is a disease that is more common among older people, and therefore coexistent pulmonary and non-pulmonary morbidities that may contraindicate transplant are common. Pulmonary conditions for which the patient should be evaluated prior to referral are bronchogenic carcinoma, pulmonary tuberculosis, and bronchiectatic areas colonized with pathogenic organisms. A CT scan with high resolution images is useful in assessing these issues as well as highlighting atypical features of a patient's disease that may suggest an alternative diagnosis. Other frequent medical problems mandating careful evaluation are steroid-related morbidities and symptoms of coronary artery disease. Medical therapy, and especially oxygen therapy, should be optimized and frequently reassessed in these patients. Testing should be done both at rest and during exercise. Optimization of therapy may include the withdrawal of steroids or other cytotoxic agents where no meaningful benefit has been achieved.

Patients who meet the following criteria are considered to be potentially within the transplant window.

Guideline:

- Symptomatic (including rest or exercise oxygen desaturation), progressive disease with failure to improve or maintain lung function while being treated with steroids or other immunosuppressive drug therapy. Clinical assessment at frequent intervals, e.g., every 3 mo, is extremely useful in evaluating the progression of disease or failure to improve on drug therapy.
- If (when) pulmonary function is (becomes) abnormal, even though the patient may be minimally symptomatic, serious consideration should be given to referral to a transplant center for initial evaluation.
- Patients are often symptomatic and have advanced disease when the vital capacity falls below 60 to 70% predicted and/or the diffusing capacity (corrected for alveolar volume) falls below 50 to 60% predicted.

Systemic Disease with Pulmonary Fibrosis

Pulmonary fibrosis is a common lung pathology in a number of systemic diseases, e.g., scleroderma, rheumatoid arthritis, sarcoidosis, post-chemotherapy. In patients with these diagnoses, the manifestations of the underlying process are highly variable and each patient should be considered on an individual basis. In general, evidence of quiescent systemic disease is required. It is necessary for all patients to meet general selection criteria and to have failed optimum medical therapy to be considered for lung transplantation. The criteria for timing of selection for transplant listed above should be followed.

4. Pulmonary Hypertension without Congenital Heart Disease

Severe pulmonary hypertension occurs as a primary process or as a secondary manifestation of another disease. Typical causes of secondary pulmonary hypertension include thromboembolic disease, venoocclusive disease, capillary hemangiomatosis, medication-related, and collagen vascular disease. Patients with these diagnoses generally have a poor prognosis (28).

Significant advances in long-term vasodilator therapy have recently shown encouraging results in patients with primary pulmonary hypertension (29). Less information is available in patients with pulmonary hypertension as a secondary manifestation of other disease; however, studies in selected patients are ongoing. In some cases surgical therapy—either atrial septostomy or thromboendarterectomy depending on the underlying primary diagnosis—has been reported to improve symptoms and possibly survival (30, 31).

Potential candidates for lung transplant with a diagnoses of primary pulmonary hypertension should be evaluated by a center with experience in vasodilator therapy, and all patients should be evaluated for vasodilator therapy and other medical or surgical interventions prior to transplant consideration. The following criteria should be met to consider a patient within the transplant window.

Guideline:

- Symptomatic, progressive disease which, despite optimal medical and/or surgical treatment, leaves the patient in NYHA III or NYHA IV. Where available prostacyclin should be considered the gold standard for medical vasodilator therapy if there is no objective indication that calcium channel blockers may be useful.
- Useful hemodynamic parameters in assessing the failure of optimal pre-transplant therapy include a cardiac index of

less than 2 L/min/m², a right atrial pressure of more than 15 mm Hg, and a mean pulmonary artery pressure greater than 55 mm Hg (28).

5. Pulmonary Hypertension Secondary to Congenital Heart Disease (Eisenmenger's Syndrome)

Pulmonary hypertension in patients with congenital heart disease behaves differently prognostically than in patients with other types of pulmonary hypertension. Hemodynamically, similar pulmonary artery pressures are associated with better cardiac function and lower right atrial pressures and a somewhat better prognosis (32). Predictors of survival are less reliable. The role of vasodilator therapy in pre-transplant management of these patients is not yet clear.

Guideline:

- Severe, progressive symptoms with function at NYHA III or NYHA IV level despite optimal medical management

6. Combined Pulmonary and Other Organ Failure

Patients presenting with failure of more than one organ have occasionally been considered candidates for multiorgan transplantation. Advanced liver disease, for example, can be associated with pulmonary hypertension (33). Selected patients with liver and lung disease may be candidates for liver-lung transplants (34). Similarly, patients with heart and lung disease or kidney and lung disease or some other organ failure combination might occasionally be candidates for a multiorgan transplant. In each case the candidate should meet all the criteria for selection for the individual transplant. Furthermore, since experience in this area is limited and outcomes not well studied, only well established centers with transplant programs in each of the organ systems involved should consider such procedures.

PEDIATRIC LUNG TRANSPLANTATION

Cardiopulmonary Vascular Disease

Lung transplantation in children is evolving (35). Diseases that are potentially amenable to lung transplantation include primary pulmonary hypertension, pulmonary hypertension associated with structural heart disease, pulmonary vein stenosis, pulmonary hypertension associated with parenchymal lung disease, and congenital abnormalities of lung development or of lung adaptation to extrauterine life. As in adults, maximal medical therapy including vasodilators and supplemental oxygen should be instituted before children are considered for transplantation. Since the diagnoses are varied and the disease spectra diverse, prognostic indicators have been difficult to develop; thus empirical criteria are the primary means of selecting candidates.

Guideline:

- Disease no longer responding to maximum medical and surgical treatment
- Moderately severe or severe functional impairment (NYHA Class III or IV)
- Right ventricular failure, severe cyanosis, and low cardiac output

In order to arrive at appropriate decisions it is necessary to follow up these patients with great care in centers that specialize in pediatric work. Careful assessment of all these patients is vital to exclude other correctable cardiac defects contributing to pulmonary hypertension.

Pulmonary hypertension with parenchymal lung disease or abnormalities of development or adaptation need to be indi-

vidually assessed as only single cases of patients receiving transplants have been described. These diseases include: congenital diaphragmatic hernia, congenital surfactant protein B deficiency, and congenital cystic emphysematous lung disease.

Other Diseases

Other diseases presenting in advanced stages in children include among others cystic fibrosis, bronchiolitis obliterans, pulmonary fibrosis and bronchopulmonary dysplasia. It is often difficult, because of the limited available historical data, to make accurate predictions regarding survival. As in the case of the cardiopulmonary diseases, patients may be considered candidates for transplant when progressive disability occurs (NYHA III or IV) despite optimal medical therapy. In the case of cystic fibrosis patients, guidelines for adult patients can be generally adapted to the pediatric population.

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