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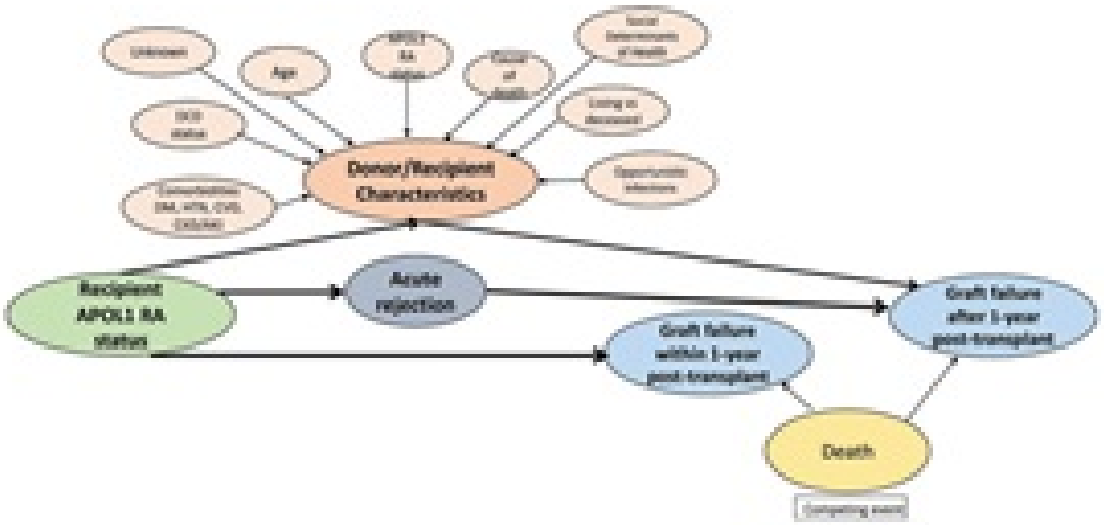

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INTERNATIONAL GUIDELINES FOR THE SELECTION OF LUNG TRANSPLANT CANDIDATES

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More than 6400 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 two years. (2) Overall survivals are between 60 and 65 per cent at two years and approximately 40 per cent at five years. (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 which all candidates for lung transplantation should meet; the second describes disease specific exercise or lung function criteria which are generally felt to identify patients whose poor prognosis from their underlying disease 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

which 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) be completed where appropriate.

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

Age limits:

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GENERAL MEDICAL CONDITIONS WHICH IMPACT ON ELIGIBILITY FOR LUNG TRANSPLANTATION

The following are a list of general medical conditions which 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.

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Current Contraindications

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Diagnostic and Prognostic investigations before referral

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

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DISEASE SPECIFIC GUIDELINES

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1. Non-bronchiectatic 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 work up. 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)

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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 Ps. aeruginosa and B. cepacia (biologically B. cepacia is inherently multiply resistant). The following definitions may be used to categorize the resistance of pseudomonal and related organisms: (21)

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 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 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 three months, or if intercurrent antibiotic treatment has been necessary. The following criteria identify patients potentially within the transplant window.

Guideline:

Patients may present for transplant consideration with bronchiectasis from other causes-immunodeficiency syndromes, immotile or dysfunctional cilia syndromes, postinfection, 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.

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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 which 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 which 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:

Systemic Disease with Pulmonary Fibrosis: Pulmonary fibrosis is a common lung pathology in a number of systemic diseases, e.g., scleroderma, rheumatoid arthritis, sarcoidosis, postchemotherapy. 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.

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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-have 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:

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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 pretransplant management of these patients is not yet clear.

Guideline:

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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.

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PEDIATRIC LUNG TRANSPLANTATION

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Cardiopulmonary vascular disease

Lung transplantation in children is evolving. (35) Diseases which 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:

In order to arrive at appropriate decisions it is necessary to follow up these patients with great care in centers which 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 individually assessed as only single cases of patients receiving transplants have been described. These diseases include: congenital diaphrgmatic hernia, congenital surfactant protein B deficiency and congenital cystic emphysematous lung disease.

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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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