Management of End-Stage Lung Disease

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For a number of years the Spanish health care system has been witnessing an increasing number of treatments available to patients with end-stage lung disease. The 7 Spanish hospitals with lung transplant programs receive patients who are sometimes in less than ideal condition to cope with surgery or the complicated postoperative period entailed by lung transplantation. In fact, among solid organ transplantations, lung operations give the least favorable outcome at 5 years, with a mean survival of 3.7 years,[1] and although lung transplant survival has improved somewhat in the past decade, there are still impediments to achieving survival figures similar to those of other organ transplants. The major impediments to better lung transplant survival are serious primary graft failure, infection, chronic rejection, and complications of the long-term use of immunosuppressants. If lung transplant survival figures were excellent, it follows that waiting lists would receive patients as soon as it was clear that their disease had not responded to medical treatment. Such patients would, therefore, present minimal clinical deterioration resulting from either disease or medication. In reality, though, hospitals receiving patients with end-stage lung disease are caught in a predicament: they must accept patients whose only hope is lung transplantation, but they also need for the patients to present in the best possible state of health. At present another factor weighs against hastily scheduling lung transplants. For the past 3 years Spain has seen the number of organ donations level off at approximately 33 donors per 1 000 000 people. Consequently, it behooves us to optimize criteria for scheduling lung transplantations so as not to prolong waiting list time excessively.

End-stage lung disease develops from a variety of pulmonary processes. The end stage is marked by severe dyspnea, with or without associated symptoms such as cough, production of sputum, wheezing, and hemoptysis. Lung transplantation for end-stage lung disease represents the last therapeutic option—an attempt to reverse the irreversible. In general, a patient should be sent to a unit specializing in end-stage patients when the prognosis is death within 2 or 3 years due to disease progression despite optimal medical treatment. The poor quality of life of the lung transplant candidate is a significant factor favoring transplantation; however, the disease prognosis should prevail. A transplant should not be proposed as a response solely to the desperation of the patient's circumstance if there is little hope of success as, for example, for patients under treatment with invasive mechanical ventilation, who comprise a group with a high rate of post-transplant mortality.[2] However, one of the major problems the transplant candidate faces is the long-term multiple drug therapy after surgery since it creates unfavorable conditions that often lead to an unsuccessful outcome. During the first pre-transplant contact with an end-stage patient, standard practice is to set the dosage of corticosteroids and other immunosuppressants, treat possible osteoporosis and weight excess or deficit, evaluate the patient's psychological state, and seek effective support from the patient's family—given the complexity of the post-transplantation medical regimen and the need for total adherence to it. Dependency on tobacco, alcohol, and psychotropic drugs must stop at least 6 months prior to transplantation. This first contact, however, should not be understood as taking place immediately preceding a transplantation but as laying the foundation for the entire lung transplant process, which will include the ideal moment for the transplant, called the "transplant window," one of the most complex decisions in respiratory medicine.

Guidelines for screening transplant candidates list numerous absolute and relative contraindications aimed at optimizing the selection of patients with the greatest chance of success.[3] The ideal transplant patient should not be over 60 to 65 years of age, should have an appropriate body mass index (between 20 and 30 kg/m^2), and should not present significant nonpulmonary problems, except severe cardiac involvement when a heart-lung transplant may be under consideration. In special cases involving severe functional impairment of a lung and another organ, such as the liver or kidney, a dual transplant is an option. In general, thinking of the immunosuppression to come, positive serology for human immunodeficient virus, hepatitis B antigen, or a malignant disease active during the preceding 2 to 5 years must be ruled out. Such patients are not viable candidates for a lung transplant. Once past this first screening, if the patient has severe dyspnea despite optimal medical treatment, contact must be made with a unit specializing in end-stage patients in order to initiate assessment regarding the ideal moment for the transplant, which in some cases may be months away. Close collaboration with the patient's referring physicians must

always be maintained. To manage a candidate for transplantation, a unit should have at least 5 options available for treatment besides lung transplantation itself: rehabilitation, ventilator therapy, hemodynamic support, psychological support, and other surgical treatments such as lung volume reduction. The decision about the transplant window—that is, the ideal moment for the transplant—should be taken by the unit that performs the transplant. However, the moment at which the patient must be referred to physicians at the end-stage respiratory unit as a candidate for a lung transplant should be common knowledge among all the respiratory medicine specialists. Our aim is to clarify this last point.

For end-stage patients with chronic obstructive pulmonary disease (COPD), there are currently 2 nonsurgical therapeutic options (rehabilitation and ventilator therapy) and 2 surgical options (lung volume reduction and lung transplantation). Patients with end-stage COPD—for example, homogeneous emphysema—suffer intense dyspnea, which renders medication ineffective since what has been destroyed cannot be recovered.[4] Owing to this irreversibility, end-stage COPD patients often insist on lung transplantation in spite of the fact that they compose the group with the longest survival rate of all patients on transplant waiting lists. Respiratory rehabilitation is nowadays considered a basic component of holistic treatment of the COPD patient and should be performed indefinitely since it improves physical and social coping and personal autonomy.[5] Nevertheless, since rehabilitation has a bearing on exercise tolerance and quality of life, a patient's life expectancy should be considered when planning the feasibility of rehabilitation. Survival is best predicted by forced expiratory volume in 1 second after bronchial challenge testing (less than 25% of predicted) and by progressive deterioration of lung function due to frequent exacerbations.[6] Invasive mechanical ventilation should be used to treat acute respiratory failure in lung transplant candidates. In Spain such patients are given the highest priority—Emergency 0—in the consensus statement issued by the Spanish *Organización Nacional de Trasplante*. That is to say, the patient has immediate need of a compatible lung that becomes available anywhere in the entire national hospital network. In transplantation, as we have mentioned, patients under treatment with invasive mechanical ventilation are at greater perioperative risk. The condition for accepting such a patient onto a lung transplant waiting list is that the patient be on the roster of the transplant unit.[7] Noninvasive mechanical ventilation is considered in COPD after oxygen therapy, bronchodilators, and antibiotics have been used in the stable patient who presents at least 2 of the following 3 criteria: moderate to severe acidosis with hypercapnia, moderate to severe dyspnea, or respiratory rate of more than 25 breaths per minute,[8] but if the patient also presents significant hemodynamic compromise he or she should be sent to a unit specializing in end-stage patients for evaluation as soon as possible. Non-invasive mechanical ventilation is frequently used to treat idiopathic pulmonary fibrosis and pulmonary hypertension when supplementary oxygen therapy fails to maintain sufficient oxygenation.

However, the option of treatment by non-invasive mechanical ventilation is debatable if the patient presents no concomitant hypercapnia or chronic airway obstruction.[9] If therapy by medical treatment, rehabilitation, and ventilation have failed, the option of treatment by lung volume reduction for emphysema type COPD is an alternative and even a bridge to a lung transplant for carefully selected patients who present severe dyspnea with upper lobe predominant emphysema and absence of hypercapnia. Lung volume reduction has advantages and drawbacks. On the positive side, such surgery spares the patient the immunosuppression inherent in the transplant process. On the other hand, it is debatable whether long-term benefits result from lung volume reduction owing to a significant mortality risk and the fact that improved forced expiration volume in 1 second lasts no longer than 2 years. *The New England Journal of Medicine* recently published the much-awaited results of the Emphysema Treatment Trial, a 4-year study of 1218 rehabilitation patients in the United States of America with severe emphysema who were randomly assigned either lung volume reduction or continuous medication. The conclusions were clear. Lung volume reduction benefits emphysema patients who simultaneously present the following 2 conditions: upper lobe predominant emphysema and low exercise capacity. This was the group that most benefited from lung volume reduction in terms of survival and quality of life compared to the continuous medication group.[10]

The treatment of patients with interstitial lung disease —idiopathic pulmonary fibrosis and usual interstitial pneumonia being the most common types once asbestos- and medication-associated forms or collagenosis have been disregarded—has recently been reviewed in an international consensus statement from respiratory societies in Europe and the United States.[11] One problem regarding lung transplantation for treating interstitial lung disease is that 2 out of every 3 patients are more than 60 years of age—an age group for which transplantation begins to be regarded as questionable therapy. Consequently, clear criteria are required for diagnosis and treatment, perhaps more so than for other diseases treated by lung transplantation. The rapid deterioration of the patient in idiopathic pulmonary fibrosis and severe primary pulmonary hypertension will also mean that a transplant will usually be required urgently. A factor contributing to poor prognosis that should be kept in mind from the beginning of the evolution of idiopathic pulmonary fibrosis is the sharp decline in a patient's carbon monoxide transfer factor.[12] Furthermore, in the last stages of idiopathic pulmonary fibrosis secondary pulmonary hypertension often appears, as do bronchopulmonary infections by multidrug resistant germs owing to treatment with a variety of drugs, thus complicating lung transplant surgery and the post-operative period. Early treatment of interstitial lung diseases can be aided by the conclusions of a recent review of the correlations between computed tomography, histology findings, and prognosis of idiopathic pulmonary fibrosis.[13] The typical appearance of usual interstitial

pneumonia is described as a basilar-subpleural distribution with honeycombing. Other radiological patterns, such as ground glass opacities, septal lines, or diffuse distribution of lesions, point in the direction of a less pessimistic diagnosis: nonspecific interstitial pneumonia.[13] Mean survival for usual interstitial pneumonias overall—about 2 years despite medical treatment—differs significantly from the 5-year mean survival of nonspecific interstitial pneumonias.[13] According to the cited European-United States consensus, medical treatment of usual interstitial pneumonia should begin as early as possible, with a combination of corticosteroids and azathioprine or cyclophosphamide, and continue for at least 6 months. If, however, no improvement or stabilization is evident at the end of this period, certain clinical parameters are well established as indicators of when the patient should be sent to an end-stage unit for assessment and a possible lung transplant, thus terminating immunosuppressant therapy, such as corticosteroids, which have severe repercussions on the organism in the long term.

In pulmonary vascular disease, pulmonary hypertension is produced as either a primary process or as one that is secondary to other diseases. A diagnosis of primary pulmonary hypertension can be made once the effects of pulmonary ventilation, diseases of the pulmonary parenchyma, collagenosis, congenital heart disease, or chronic pulmonary embolism have been ruled out. Lung transplant candidates with a diagnosis of pulmonary hypertension should be evaluated in a center with experience in vasodilator therapy since a unit with expertise in hemodynamics is required. A positive vasodilation test (decrease of more than 10% in pulmonary vascular resistance) indicates effective treatment with calcium channel blockers, although a negative test does not contraindicate the utilization of other medication such as epoprostenol or new agents such as iloprost, sildenafil, or endothelin receptor antagonists.[14] Depending on the severity of hypertension and the clinical picture, medical options and even other surgical ones such as thromboendarterectomy and interauricular septostomy may, for certain patients, be viable alternatives to lung transplantation or heart-lung transplantation.[15]

Given the complexity of cystic fibrosis, specialized units are available for the integrated treatment of patients with this disease, and normally contact is made with a lung transplantation unit when patients begin to suffer rapid decline.[16] Experts in cystic fibrosis also know that patients should be sent to a unit for initiation of the pretransplant assessment whenever forced expiratory volume in 1 second is less than or equal to 30% of predicted, normal PaO_2 is below 55 mm Hg, or they are suffering life-threatening hemoptysis—criteria that also hold true in other chronic suppurative diseases, such as diffuse bronchiectasis.[3]

In summary, if medical therapy and rehabilitation are no longer effective, if dyspnea is severe, and if the course of the disease progressive, there should be no delay in contacting a unit specializing in end-stage respiratory patients. Nevertheless, an individualized risk-benefit assessment should be carried out, especially regarding the continuation of medication that has severe side effects and that frequently does no more than worsen the condition of a patient who almost inevitably will have to undergo lung transplantation, a solution that is still less than ideal in the long term. In end-stage lung disease units, not only can patients be offered alternatives to lung transplantation, but they are also prepared through optimal rehabilitation and exhaustive information on the transplant process aimed at obtaining their full psychological acceptance. Furthermore, steps are taken to ensure that strong family support is forthcoming. The challenge is still enormous. Nevertheless, we hope that with the improved effectiveness of new immunosuppressants, techniques of organ preservation, and early detection of rejection and infection, the future will provide us with the ability to offer lung transplantation with better survival rates for certain patients, who in turn should present for surgery in the best possible overall state of health.

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