Review Article　　　　　　　　　　　　　　　　　　　　　　　　　　　　　　**Open Access**

Spanish Society of Caridiorespiratory Rehabilitation. Recommendations in Lung Transplantation

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Abstract

Lung transplantation is considered for those patients with severe pulmonary disease who do not respond to specific treatments and whose life expectancy is very greatly reduced. It is a multidisciplinary intervention which extends from the selection and follow-up of candidates, up until the time of the surgery itself and which also includes the on-going treatments that these patients will require for the remainder of their lives.

The Spanish Society of Cardiorespiratory Rehabilitation (SORECAR) appointed an expert committee to review the current scientific evidence with regards to the management of these patients by our medical specialty and to produce a consensus document of interventions in lung transplantation.

In this article we provide an update on the management of patients leading up to and following lung transplantation from the point of view of the Physical Medicine and Rehabilitation specialty.

We describe how to carry out the functional assessment, rehabilitation treatment and follow-up during both the pre and post-transplant stages; together with the diagnosis and treatment of common musculoskeletal pathologies related to their underlying disease process.

Furthermore, we highlight the importance of potential complications arising in the immediate post-transplant period, as well as those also occurring in both the middle and the long-term. The ability to recognise them in a timely fashion and implement appropriate treatment within the remit of Physical Medicine and Rehabilitation can help to improve survival and the quality of life of these patients.

Introduction

In 2010, Spain carried out some 235 lung transplants (LT) and this has now increased to 307 per annum in 2016. These are performed amongst patients with chronic, progressive, end-stage respiratory disease and with a limited survival in order to improve their survival and quality of life (QoL). This option is offered to selected candidates who are capable of understanding and enduring this lengthy process and who are able to maintain an acceptable physical condition whilst on the waiting list [1]. A greater disease severity at the time of LT does not necessarily imply a poorer survival rate.

The goal of lung transplant units is to provide a greater survival and QoL following the transplant, one which exceeds the foreseeable course of the disease. It is, therefore, very important to assess and list candidates at the appropriate time. This is recommended in patients whose 2-3 year predicted survival is ≤ 50% and who have a III-IV

functional capacity according to the New York Heart Association (NYHA). Conversely, patients should be removed from the waiting list if it is predicted that the LT will not benefit them, having taken into account the potential risks of surgery, drug toxicities and the frequent complications affecting these patients [2]. Alongside lung function tests, other parameters of disease progression are also assessed: frequency of respiratory exacerbations and hospitalizations, oxygen requirements, hypercapnia, weight loss, exercise capacity and the patient´s own opinion [1].

Both the previous clinical guidelines [2] as well as the latest conclusions drawn by an expert committee of the International Society for Heart and Lung Transplantation (ISHLT) in 2014 [3] maintain that, in the absence of data from controlled clinical trials which may help establish a set of guidelines for the candidate selection process, the current recommendations are based on expert opinion, consensus documents, retrospective studies, national and international registers, together with the clinical experience of each team.

Mortality on the lung transplant waiting list

Due to a dearth of organs, once listed for transplant, patients with idiopathic pulmonary fibrosis (IPF), cystic fibrosis (CF) or pulmonary arterial hypertension (PAH) have a lower survival rate than those with emphysema if the LT is delayed. The Lung Allocation Score (LAS) has been applied in the USA since 2005, in order to prioritize waiting candidates based on the gravity of their situation, risk of mortality and estimated post-transplant survival [4-7]. Its implementation has led to a reduction in waiting list mortality, with the exception of those patients with PAH [4]. For this reason, we observe a slight increase in survival at one year, together with a variation in the diagnostic profile of transplanted patients relative to previous years; patients are getting older and cases of IPF are more frequently encountered [5]. The LAS includes a variety of items, such as functional classification (NYHA), distance covered in the six-minute walking test (6 MWT), hemodynamic values (pulmonary arterial pressure -PAP-, systolic, mean and pulmonary capillary wedge pressures -PCWP-). The scale ranges from 0 to 100, with higher LAS indicating a greater transplant priority [8].

Its usefulness has also been criticised as it prioritises patients whose situation is more critical (LAS>70) and who have a 1-year post-transplant survival rate of 68%. It was determined that by transplanting patients with a lower LAS scores, survival rates increased to over 80%, which raises the important issue of LT suitability in the long-term [2].

At present, in Spain, the National Transplant Organization (NTO) requests the LAS for inclusion on to the LT waiting list. Subsequent revisions pertaining to the application of LAS have explicitly proven its usefulness, reducing waiting list mortality of CF patients from 15% to 10% without increasing the mortality of other groups such as those with interstitial pulmonary fibrosis (IPF). Furthermore, its application has altered the profile of recipients, increasing the number of lung transplants in the IPF group and reducing those in the chronic obstructive pulmonary disease (COPD) group.

In countries with a large surface area, local LAS lists are used in place of a national list, due to the fact that ischemia time would make such a list unfeasible. The LAS for those on the transplant waiting list must be recalculated every three months and, in the case of those whose condition is deemed critical, every two weeks .

Referral to the lung transplant unit

It is recommended that potential candidates be referred as soon as possible when there is an objective decline despite an optimum medical treatment. This way, a comprehensive assessment of both the patient and their environment can be carried out and, at times, appropriate further follow-up may be required to reach a decision.

There is an established general consensus both as to the appropriate time to refer, which does not necessarily imply inclusion on the waiting list, as well as the ideal time for inclusion with relation to the different pathologies [1-3,8-10] .

Chronic obstructive pulmonary disease (COPD)

The referral of these patients is complex because some may be very symptomatic with intense dyspnea but with a good prognosis based on their forced expiratory volume in one second (FEV_1), whilst others may present with severely diminished spirometric values but with an acceptable QoL. The measurement of health-related quality of life (HRQoL) is capable of predicting mortality which, in turn, is also associated with a reduction in body mass or loss of inspiratory muscle strength. These predictive values for mortality are gathered up in the BODE index (for Body mass index-BMI-, airflow Obstruction, Dyspnea and Exercise capacity).

The controversy arises in the presence of a doubtful increase in post-transplant survival based on FEV1. In patients transplanted with an FEV1>25% (predicted), only 11% are predicted to gain one year of life relative to the natural progression of their COPD. On the other hand, survival rates increase up to 80% in patients with an FEV1<16% (predicted) [2].

COPD patients should be referred to the lung transplant unit for assessment if they have a BODE score>5, following completion of a pulmonary rehabilitation program and having received oxygen supplementation if they have a PCO_2>50 mmHg and/or a PaO_2<60 mmHg, or a FEV_1<25% predicted) [8].

COPD- Indications for inclusion on the lung transplant list

According to the recommendations of the Spanish Respiratory and Thoracic Surgery Society (SEPAR) [1], the patient must have a BODE score of between 7 and 10 (80% mortality at 4 years) and at least one of the following:

Hospital admission for exacerbation with hypercapnia (pCO_2>50 mmHg, 49% survival at 2 years)

FEV_1<20% (predicted) and DLCO (diffusion capacity of the lung for carbon monoxide) <20% (predicted) or diffuse homogenous emphysema (mean survival of 3 years).

Pulmonary hypertension, right heart failure or both.

Alpha-1 antitrypsin deficit.

The latest recommendations require the presence of only one of the criteria mentioned, adding to these having presented with three or more severe pulmonary exacerbations in the previous year or a single one with respiratory failure [3,8].

Pulmonary fibrosis (PF)-Interstitial lung disease (ILD)

Includes numerous conditions such as IPF or usual interstitial pneumonia (UIP). Patients with IPF usually live for between 2 and 4 years from the time the histological diagnosis is made. They are the group with the highest mortality rate on the LT waiting list as there are no effective pharmacological interventions to adequately control the disease [11], though Pirfenidone may help slow its progression [12]. DLCO and the extent of lesions observed on high-resolution computed tomography (HRCT), as independent prognostic factors, offer the most accurate prediction of 2 year survival. Mortality has been associated with a forced vital capacity (FVC) <60% (predicted), a reduction in exercise capacity (6 MWT<207 m is linked to a fourfold increase in mortality) and a pulmonary artery systolic pressure (PASP) >50 mmHg. Older patients and those with more dyspnea at the time of lung transplantation are also associated with a lower survival rate.

They should be referred to the lung transplant unit as soon as possible in the presence of altered lung capacity and diffusion parameters (FVC<80%, DLCO<40% predicted), radiological or histological suspicion of fibrosis, dyspnea or need for oxygen supplementation during exercise [3]. Serial measurements are recommended in order to establish the prognosis and evolution of the illness, as some patients present with a very rapid deterioration.

Patients with systemic connective tissue diseases (scleroderma, rheumatoid arthritis or mixed connective tissue disease) and pulmonary involvement usually have a presentation similar to that of the fibrotic form of non-specific interstitial pneumonia (NSIP). The indication for LT has been debated due to the possible negative impact of the systemic involvement in the evolution of the patient following lung transplantation [2]. Additional contraindications to LT in these patients would be the presence of associated co-morbidities: gastrointestinal and cardiac affectations.

Indications for inclusion on the lung transplant waiting list modified by the ISHLT [3]

a. Histological or radiological evidence of UIP or fibrotic NSIP and one of the following criteria:

DLCO <40% (predicted) with a fall in DLCO ≥ 15% (predicted) over a 6-month period

Fall in FVC ≥ 10% (predicted) in 6 months (even a drop of 5% implies a poorer prognosis).

Drop in 6 MWT exercise capacity with a fall in SaO_2<88% on room air (survival of 35% at 4 years), distance<250 m or a reduction of 50 m in 6 months.

PAH

Hospital admission for respiratory exacerbation.

In the current guidelines, the presence of honeycombing (fibrosis score>2) on chest HRCT is no longer deemed a necessary criteria [12]. The histological diagnosis is important, however, as the forms of ILD which differ from UIP, such as NSIP, have a better prognosis but these worsen over time when NSIP begin to take on traits of UIP.

b. Histological evidence of NSIP and one of the following:

DLCO<35% (predicted)

Fall in FVC ≥ 10% (predicted) or a fall of 15% (predicted) in DLCO over a 6 month period

Cystic fibrosis

Cystic fibrosis (CF) is one of the three most common indications for LT. Despite the multi-systemic nature of the disease and the recurrent infections by antibiotic-resistant microorganisms, the survival of transplanted CF patients is very good, both in adults and in children [1]. Chronic colonization is common in these patients and usually involves multi-resistant *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus*, *Alcaligenes xylosoxidans* or *Aspergillus fumigatus*, though this does not influence LT outcomes in the short-term. Colonization by *Burkholderia cenocepacia* (genomovar III) does, however, have a negative effect on mortality during the post-operative period [1]. Liver disease does not tend to be sufficiently advanced to contraindicate LT and does not usually affect survival. Similarly, the need for mechanical ventilation by those patients already on the waiting list is not an absolute contraindication to LT either.

Patients will be referred for transplant assessment, particularly young women <18 years (worse prognosis), when they present with an FEV1<30% (predicted) or a rapid decline in lung function; altered arterial blood gases (PCO_2>50, PO_2<55 mmHg); respiratory exacerbation with admission to the ICU (Intensive Care Unit); greater antibiotic requirements; recurrent or persistent pneumothorax or recurrent haemoptysis despite bronchial artery embolization's.

Similarly, referral should be made in the presence of uncontrollable malnutrition with no other cause than chronic bronchial infection [1].

The ISHLT committee has added some further criteria [3]: Infection by non-tuberculous mycobacteria or *Burkholderia cepacia*, due to the rapid progression of the disease which they bring about

Distance covered on 6 MWT<400 m

Presence of PAH (systolic PAH >35 mmHg or mean PAH >25 mmHg)

Increase in the frequency of exacerbations and respiratory failure requiring non-invasive mechanical ventilation (NIV) or poor control of these

Indications for inclusion on the lung transplant waiting list

The recommendations are complex due to the wide variability between individuals with CF and its multi-systemic involvement, which lead to a high mortality on the list. Factors that are associated with said mortality include PCO_2, resting heart rate, mean pulmonary arterial pressure, as well as raised vascular resistance or cardiac indexes. It has also been linked to QoL as perceived by the patient [13].

Common indications [12]: FEV1<30% (predicted) or rapid, progressive drop in females <18 years of age and one of the following:

Respiratory failure requiring continuous oxygen therapy due to PaO_2<60 mmHg.

Presence of resting hypercapnia. Need for NIV Presence of PAH.

Further indications include frequent hospitalizations, a rapid decline in lung function and functional class IV according to the NYHA [3]. Other aspects to be taken into account would comprise the measurement of exercise capacity using the 6 MWT, the 3-min step test in children or the presence of severe diffusion impairments (predictor of mortality) [10].

Pulmonary arterial hypertension

Severe, clinically progressive condition brought about by right ventricular failure, this being the main cause of death in these patients and which, in the absence of medical treatment, carries a mean survival of 2.8 years. Prognosis is even poorer for PAH associated with scleroderma than for idiopathic PAH or that secondary to congenital heart disease. Current pharmacological management has improved life expectancy and for this reason the indication for LT in PAH has been reduced from 10% of all lung transplants to the current level of 3%. The opportunity of LT or heart-lung transplant still remains a viable treatment option for those patients who, despite maximal medical management, inexorably deteriorate [11].

Patients in functional class III or IV (NYHA) who respond badly to treatment, with a rapidly progressive disease requiring intravenous prostacyclin's and a significant reduction in their exercise capacity (6 MWT<350 m) should be referred for assessment1. To this, the most recent guidelines add the suspicion of pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis [3].

Indications for inclusion on the lung transplant list: Persistence of class III or IV (NYHA) despite maximal medical treatment.

Reduced 6 MWT (<350 m) or progressively worse exercise capacity (predictor of mortality)

Absent response to epoprostenol or equivalent

Hemodynamic measurements signaling poor prognosis (cardiac index <2 l/min/m^2 and mean right atrial pressure >15-20 mmHg.

Other types of pulmonary disease

Less frequently, patients with histiocytosis X, lymphangioleiomyomatosis, bronchiectasis or sarcoidosis may require a LT if they present with:

NYHA class III or IV and one of the following.

Pulmonary decline

Resting hypoxemia requiring continuous oxygen supplementation

PAH

Mean right atrial pressure >15-20 mmHg (sarcoidosis)

Severe, rapid decline in exercise capacity (oxygen consumption VO$_2$<50%) in lymphangioleiomyomatosis

Contraindications to LT

There is a general consensus [1-3,14] regarding which pathologies would exclude an individual from receiving a LT. Most of these continue to be upheld, though some nuances have been added in the latest ISHLT revision [3] and Up to date resources in 2016 [8].

Absolute contraindications: Recent history of malignancy. A 2-year disease-free interval with a low predicted risk of recurrence after LT could be considered (e.g. non-melanoma localized skin cancer treated appropriately). However, a 5-year disease-free interval is recommended in most cases.

Untreatable or irreversible cardiac, renal or liver dysfunction unless a multi-organ transplant is deemed viable.

Acute medical instability due to sepsis, acute myocardial infarction or liver failure. Untreatable haemorrhagic diathesis.

Poorly controlled chronic infection pre-transplant.

Active tuberculosis.

Significant chest wall or spinal deformities which may lead to restriction post-LT.

Class II or III obesity (BMI ≥ 35 kg/m^2).

Anticipated risk of non-adherence to treatment following LT.

Significant psychiatric disorder or lack of stability with an absence of an adequate social support system which may affect their cooperation with the team.

Severe, functional limitations with little rehabilitation potential.

Current smoker.

Substance abuse or dependence (alcohol, drugs, etc.). Will require a sufficiently long period of abstinence to reduce the risk of relapse, which must be verified by appropriate blood and urine sample testing.

Relative contraindications to LT: Age>65 years in association with comorbidities and overall physical condition.

Class I obesity (BMI 30-34.9 kg/m^2), malnutrition, severe osteoporosis. Malnutrition with a BMI<18 may be associated with a greater post-operative mortality.

Prior chest surgery with lung resection. Previous thoracic cage surgery or pleurodesis increase the risk of intra-operative bleeding should extracorporeal circulation be required.

Worsening clinical status requiring mechanical ventilation or extracorporeal life support in a patient not previously assessed. Neither would necessarily preclude a successful LT in carefully selected candidates.

Colonization with multi-resistant or virulent bacteria, fungi or mycobacteria receiving adequate pre-operative treatment.

Other medical conditions such as peptic ulcer disease, gastroesophageal reflux, coronary artery disease or osteoporosis should be optimally treated prior to LT, and bearing in mind that aortocoronary bypass may be simultaneously carried out at the time of LT.

More recently, patients with human immunodeficiency virus (HIV) may be considered for LT, providing they have an undetectable viral load and are receiving anti-retroviral treatment. Similarly, those affected by hepatitis B and/or C without liver cirrhosis or portal hypertension that is under appropriate treatment may also be considered [3].

Rehabilitation in lung transplantation/pre-operative program and treatment in ICU

Functional assessment pre-transplant: Physical Medicine and Rehabilitation physicians, as an integral part of LT teams, should carry out the functional assessment that is particular to their specialty. In contributing their opinion they will help to determine, together with the rest of the multidisciplinary team (MDT) members, the suitability of candidates to be included on the LT waiting list.

The aforementioned assessment will include:

Musculoskeletal examination: joint range of motion (ROM), muscle strength, spinal assessment and evaluation of bone density.

Neurological examination to detect associated pathologies which may influence recovery.

Assessment of exercise tolerance: 6 MWT.

QoL: assesment of an individual´s level of independence in activities of daily living (generic and specific QoL questionnaires and scales).

Social, family and work situation.

The prevention and treatment of osteoporosis merits special attention. Many candidates who commence the assessment for LT already present with a low bone mineral density (BMD) prior to transplant. Pulmonary disease leading to a LT will usually require the prolonged use of steroids and immunosuppressors, resulting in a sharp drop in BMD which will affect their future QoL [15-18].

Preoperative programs

The goals of these programs are to: Teach techniques that can improve pulmonary compliance and thoracic expansion, together with good pain control in the postoperative period.

Achieve an adequate respiratory pattern.

Improve inspiratory muscle strength.

Ensure an adequate level of airway clearance and adherence to it.

Improve exercise capacity through a specific training program and prior strength conditioning.

Pre-operative treatment

If the patient has been admitted on to the LT waiting list, they will take part in a personalised rehabilitation program, for which it is recommended they sign an informed consent form. The aim is to prepare the patient to face the surgery in the best physical condition possible, both in terms of their respiratory and general physical condition. The reasons and importance for this preparation prior to surgery is discussed with the patient, informing them of the respiratory changes which may occur and how these can be prevented. The patient must also understand the nature of their illness and the benefits, together with the potential adverse effects of the transplant; the correct use of oxygen and their medication, symptom management and how to recognise exacerbations.

Pulmonary rehabilitation also allows for the identification of patients who are potential candidates for surgery but whose physical condition is suboptimal, thereby enabling them to improve their fitness prior to LT.

Respiratory physical therapy

As mentioned previously, basic respiratory physical therapy (PT) techniques will be taught in order to achieve an efficient respiratory pattern, revising and optimizing these techniques to ensure optimum airway clearance, correct thoracic expansion and ways of improving these with adequate pain control. Teaching these prior to surgery minimizes fear and pain, both of which may favour respiratory complications in these patients and may add to the workload of physical therapists in the intensive care units.

Treatment

The program will basically consist of

Guided diaphragmatic breathing: Prior respiratory assessment, anomalous or dysfunctional breathing patterns are corrected. Positions that the patient can easily employ whilst in bed will be used, namely supine and alternate side lying. The sessions will be carried with attention to the patient´s comfort and in line with their preoperative condition, taking care to avoid the appearance of dyspnea and monitoring heart rate and oxygen saturations throughout. It is extremely important to teach patients to breathe with a relaxed chest wall with the aim of reducing pain whilst at the same time ventilating all the pulmonary segments to avoid areas of atelectasis. Breathing with a low frequency but utilizing larger than normal tidal volumes will be carried out.

Teaching thoracic expansion exercises, working each hemithorax individually. The correct use of volumetric in spirometers can also be taught, seeking to avoid rapid inspiratory manouvres in the immediate post-operative period which may aggravate the pain and further reduce tidal volumes.

Learning and optimizing airway clearance techniques, teaching slow expiratory techniques, together with directed huffing and supported coughing.

Finally, in the event of identifying postural abnormalities, specific postural exercises aimed at raising self-awareness and improving said posture will be taught.

Respiratory muscle training

Inspiratory muscle strength is one of the main factors that determine functional capacity post-operatively and it is precisely the efficiency of the respiratory muscles which is compromised following thoracotomy. Once respiratory muscle strength has been assessed, a training program will be appropriately adapted to reflect the clinical situation of the patient. In this way, it is recommended that individuals train at 30% of their maximum inspiratory pressure (MIP), with increments of 5% according to the Borg scale [19]. The aim is to improve both strength and endurance. This type of training has been found to reduce respiratory complications in the post-operative period, as well as the mean hospital stay of patients undergoing thoracotomy for cardiac surgery [20].

Peripheral muscle training

The reduction in exercise capacity of patients with advanced pulmonary disease is an important predictor of survival and of thoracic surgery success. An increase in exercise capacity and exercise tolerance acquired through a rehabilitation program can improve survival. Pre-transplant rehabilitation can reduce the risk of peri-operative respiratory complications and even help reduce the mean hospital stay post-LT. The patients awaiting LT are typically those with the most severe lung disease. Therefore, the intensity of the exercises must be reduced.

In those patients who are practically housebound, daily treatment will be carried out until they reach their maximum functional capacity and this can be aided by the use of electrical muscle stimulation. Patients who have a greater limitation and who are unable to walk will carry out an 8-week program stimulating lower limb muscle groups with symmetrical biphasic currents (50 Hz, 2/6 s of stimulation–rest), these programs having demonstrated that they help to improve both parameters of strength as well as QoL [21,22]. These patients will subsequently benefit from an interval training program.

Training to improve exercise tolerance is carried out on a treadmill or exercise bike, monitoring oxygen saturations and heart rate. In the event of desaturations, supplemental oxygen is administered to maintain oxygen saturations>85%. Speed and resistance are increased to maintain a Borg of 12-13. The patient will be taught to control the level of effort required so that they can continue to exercise at home under the same conditions.

The upper limbs are exercised, first against gravity alone and then with light weights. Improving shoulder girdle strength helps to improve exercise capacity in relation to activities of daily living (ADLs). Patients with IPF will require a greater degree of supervision during training, due to marked desaturations with exercise and, for this reason, increases in resistance or exercise duration will be done gradually. Those patients with severe PAH will require a lower exercise intensity and will be monitored to control hemodynamic stability, avoiding manouvres that may increase intra-thoracic pressure. Exercise will be supervised to ensure that the prescribed workload can be safely tolerated whilst at the same time having sufficient intensity to reap benefits.

If there is an abrupt deterioration during the training sessions, especially in cases of fibrosis, the transplant team will have to be informed. Educational talks for both the patient and their family will also be included during this period. Other pulmonary pathologies only

require monitoring of their oxygen saturations and arterial blood pressure.

The patient must maintain the same intensity acquired during the rehabilitation program up until the time of surgery, preferably continuing with exercise in a pulmonary rehabilitation center and complemented by a domiciliary program. Alternatively, patients may require repeated admissions to rehabilitation centers and must keep in contact with the MDT members. Whilst awaiting lung transplantation, pulmonary disease will undoubtedly progress, thus requiring periodic re-assessment and modifications to the rehabilitation program, medication and exercise prescription.

The program will generally last 6 weeks, three days per week and, at the end of which, the patient should be capable of carrying it out at home. It is revised every 2 or 3 months, save in the event of complications.

Successive consultations

The follow-up in Rehabilitation Units of a maintenance program and a review of the exercises that the patient carries out in their home is fundamental, as it allows the program to be re-evaluated. Serialized 6 MWT every 4-6 months are extremely useful, as well as the assessment of sit-to-stand without the use of upper limbs. With this simple data it is possible to re-adapt the program, boost participation and minimize the severity of pre-transplant complications. This is especially important in light of the long delays endured on the waiting list, which at times exceed a year, until they are transplanted.

In paediatric patients, specifically in those identified as having postural abnormalities, follow-up appointments will be carried out at 6 months and annually thereafter until they reach the end of puberty, applying orthopedic treatment where it is required.

Treatment in critical care units

ICU immediate post-operative period: This phase corresponds to the first 8 days following the intervention. At this moment in time the patients being treated have a high risk of mortality and of developing future pulmonary complications. Once hemodynamically stable, the assessment by the rehabilitation team must decide when to initiate the rehabilitation treatment, carefully weighing up the risks and benefits to ensure that input at that stage will contribute to the patient´s recovery.

A respiratory assessment is carried out, regardless of whether or not a swift extubation is achieved, together with en evaluation of the need for ventilatory support. In the case of an intubated patient requiring invasive mechanical ventilation (IMV), the action of the mucociliary escalator is impaired due to the patient´s own baseline pathology and, on the other hand, the intubation process itself and the ventilator´s characteristics [23]. Nowadays, many of the problems derived from ventilation have been corrected thanks to an adequate temperature and level of humidification of inspired gases. In any case, for however long the patient requires ventilatory support of any kind, if we fail to manage secretions correctly, respiratory failure will ensue. Our interventions will focus on preventing this from occurring and on reducing ventilator dependence. To this end we have two main therapeutic options: respiratory PT and technology applied to secretion management.

Respiratory physical therapy in the non-cooperative patient

It is crucial to acknowledge that the most appropriate technique will greatly depend on the patient´s baseline pathology, their degree of cooperation and the presence of an artificial airway. A review of the current literature on this subject reveals that the application of conventional PT techniques does not influence the evolution of the dependent, intubated patient [24,25]. The use of classic postural drainage positions is no longer considered useful [26] and the application of more strenuous physical therapy techniques, such as thoracic cage compressions, do not improve bronchial hygiene, nor oxygenation or ventilation. Moreover, it has been documented that these techniques, when applied to patients on IMV, can induce desaturations and worsen thoracic distensibility, thus favoring atelectasis, especially amongst paediatric patients [27]. These publications may cause us to think that mechanically ventilated patients should not be treated, but one should not generalize the indication for treatment nor the type of treatment itself. Each case must be considered individually in order to decide whether there is an indication for treatment and which particular technique may be suitable. Even in the event of a clear indication for treatment, both the correct timing of the technique as well as the expertise of the PT is essential [28].

In neonatal intensive care units, where patients require prolonged ventilatory assistance, the benefits of their application have yet to be demonstrated whilst, so far, a worsening in parameters such as heart rate, respiratory rate and oxygen saturations, amongst others, has been found to occur. In summary, there is currently no scientific evidence to support the idea that respiratory PT in dependent, intubated patients alters their evolution but that complications arising from its use, such as a higher incidence of atelectasis, gastroesophageal reflux, increase in intracranial pressure or increased risk of brain haemorrhage in paediatric patients has been documented [29,30]. This indicates that both patients and the techniques employed must be carefully selected, always evaluating the risks and benefits of the same.

Respiratory physical therapy: peri-extubation in cooperative patients on IMV

Historically, following the publication of the work by Finner in 1979, which explained the benefits of respiratory PT in the intubated patient, its application became a routine treatment in all critical care units. Over time, however, other publications appeared that started to question the risks and benefits of these techniques. In the Cochrane revision [31], with regards to pediatric patients, we find some published studies in which no appreciable change, neither with regards to time spent intubated nor subsequent respiratory improvements, were found. Conversely, other studies noted a reduction in the risk of reintubation. They concluded that these results should be interpreted with caution and that the potential risks and benefits be evaluated beforehand. Therefore, in cases where the ventilatory support is being reduced, we must assess each patient individually, noting the presence or absence of secretions, their ability to cooperate, improve ventilation or undertake training and whether a patient´s particular situation may deteriorate as a result of our treatments.

Respiratory physical therapy: immediately post-extubation

A careful assessment must be carried out in each particular case. Treatments cannot be generalized, as revisions on this subject have found no additional benefits when compared to other post-extubation

protocols such as CPAP (continuous positive airway pressure) or nasal positive pressure ventilation. They have, however, found increased risks [32]. We should, therefore, re-assess the patient, noting their overall condition, level of cooperation, whether more secretions are present, if they are unable to clear them even with suction and whether they require respiratory muscle training and/or help to stimulate ventilation [33].

In any event, each patient should always be assessed on an individual basis and the decision made to prescribe or not PT treatment and advice regarding specific techniques; the indiscriminate application of PT in in the ICU has not been found to be effective but does increase costs. Therefore, these patients should be rigorously followed up.

Respiratory muscle training

Recent published studies have described respiratory muscle training in patients during the weaning process, with good results so far [34]. This can be carried out in patients with a tracheostomy, making use of the artificial airway and disconnecting them from the ventilator for short periods of time. At present, it is not a routine part of LT programs.

Peripheral muscle training

This can be carried out in conscious patients on IMV, using adapted pedals and other equipment such as dumbell's and elasticated exercise bands. It has been linked to improvements in weaning, survival and ADLs [35].

If there is good progress with an early extubation, free of ventilatory changes or an altered respiratory pattern, the patient will then start to carry out the techniques they were previously taught. This will be encouraged by the nursing staff, being directed and supervised by the PT personnel. Physical therapy treatment will be performed a minimum of twice daily, as it involves a patient with a denervated lung who lacks a cough reflex. Mobilizations and postural changes are also part of the treatment. A medical follow-up will be carried out to detect the possible appearance of respiratory, musculoskeletal and neurological complications derived from the surgical procedure itself or medication.

Technology applied to secretion management

These devices will be adapted by the physician responsible for the rehabilitation of the patient. Once the optimum treatment parameters have been set, these can then be applied by the PT and nursing staff. There are various devices available, but the one which is often most useful for the transplanted patient during their ICU stay is intrapulmonary percussive ventilation (IPV).

Essentially, it is an instrumental technique used to help clear secretions from the airways [36]. Its effectiveness as a means of airway clearance has been demonstrated but its main problem lies in that it is not always well tolerated by the patient.

It consists in administering successive subtidal volumes to the upper airways of the patient using an open respiratory circuit called the Phasitron. Peripheral secretions are mobilized by means of the vibrations generated, which are then evacuated along the upper airways, improving pulmonary compliance and the resolution of atelectatic regions.

This device must be adapted with relation to the patient´s baseline pathology, specific respiratory changes, clinical situation and age. The parameters requiring adjustment are the following: driving pressure, percussion frequency and I/E (inspiratory/expiratory time) ratio.

Its effects include the mobilization of peripheral secretions from the bronchi and lungs through the use of vibration and constant airflow, the recruitment of alveoli (resolving atelectasis), improvements in gas exchange due to high flow rates and increased alveolar movement with greater contact between oxygen molecules and alveolar-capillary membranes, as well as improvements in lung compliance.

The main indication for its use is the presence of excessive secretions, both in restrictive as well as obstructive lung pathology. The presence of an undrained pnemothorax is an absolute contraindication, whilst relative contraindications include Lyell´s syndrome, severe hemoptysis, clotting disorders and current anticoagulation therapy (depending on extent of the same).

It can be used with a mouthpiece or, in the case of less-cooperative patients, a cushioned facemask. Similarly, patients on IMV can benefit from its use but we must first modify the pressures and the PEEP (positive end-expiratory pressure) of the ventilator when we apply IPV [37,38]. In tracheostomized patients, it has been shown to improve gas exchange, expiratory muscle function and reduce the incidence of pnemonia [39].

Treatment with the IPV should be followed by an effective cough from the patient and, if they are unable, will require the assistance of the PT or the use of mechanical aids of cough augmentation: insufflator-exufflator devices or airway suction to clear secretions. Treatment sessions generally last 7 to 10 min and can be carried out once or twice daily.

Respiratory complications in the immediate post-operative period

In the event of a fully conscious and cooperative patient requiring re-intubation, assisted ventilation can be carried out. The PT will ask the patient to carry out one or two deep breaths, followed by assistance during passive expiration. This can also be carried out with the help of an Ambu bag connected to the ventilatory circuit for short time periods throughout the day. Similarly, the ventilatory modes and parameters can be modified during treatment times in order to help increase lung volumes or, in the case of reducing ventilatory assistance, to increase the patient´s respiratory effort, depending on the patient´s current clinical situation. Treatment at this point in time will help reduce the incidence of atelectasis post-extubation.

Hypoxemia: If the patient is able to cooperate, directed diaphragmatic breathing can initially be carried out in supine. 24 h after surgery, this can be attempted in side-lying with the head of the bed raised 30°C above the horizontal plane. After 48 h, the same can be tried in a half-sitting position in bed. On the third day post-op this can be carried out in full side-lying and upright sitting. In paediatric patients and uncooperative adults, passive expiratory techniques will be applied.

Increased bronchial secretions: Airway clearance techniques will be carried out depending on the age and clinical situation of the patient. Neither manual percussion nor forced expiratory manouvers should be employed in very small children or in the immediate post-operative period due to the increased risk of atelectasis and pain. Gentle thoracic compression during exhalation, with the object of increasing

expiratory airflow, may be performed with caution. Systemic hydration and the use of direct humidification with nebulizers are essential prior to carrying out PT treatment.

Atelectasis: Treatment will seek to re-expand the affected area, making use of thoracic expansion exercises and keeping the atelectic region uppermost. It is worth remembering that percussion is not indicated in post-operative atelectasis, not even in the case of adult patients [40,41].

Historically, the use of incentive spirometers following a surgical intervention has always been recommended. However, its routine use has not been proven to reduce post-operative respiratory complications, whilst a poor use of the same may even increase these due to greater pain on inspiration and a subsequent reduction in tidal volumes [42-44]. On the other hand, the use of volumetric incentive spirometers (devices which encourage gradual inspiration and lower flow rates) or end-inspiratory breath holds following maximal inspiration have been shown to be effective in reducing said complications [45].

Diaphragmatic paralysis: Exercises aimed at improving ventilation and diaphragmatic activity of the affected hemidiaphragm during tidal breathing will be carried out. This will be followed by airway clearance techniques.

Pneumonia: There is currently no scientific evidence to suggest that respiratory PT should be applied in cases of pneumonia whilst, however, some studies have found that its use may prolong the febrile period. For this reason, it is recommended that PT only be performed once the pneumonia begins to resolve, the patient is afebrile and in the presence of increased bronchial secretions which are difficult for the patient to clear [46].

Pneumothorax: Where required, the use of intercostal drains usually leads to a satisfactory resolution of the same.

Pleural effusion: When it is of moderate volume, this usually resolves of its own accord over the course of a couple of weeks. Occasionally, a chylothorax may develop, requiring the use of an intercostal drain and a specific diet. In more persistant cases, a surgical intervention may be required [47-50].

Complications associated with the implanted organ

Acute rejection (AR), lung ischemia-reperfusion injury, complications related to the airways (stenosis, bronchial suture dehiscence) and vascular problems such as arterial stenosis or venous thrombosis may present during this period. Following their diagnosis and appropriate treatment, the rehabilitation program will be modified accordingly to reflect the patient´s new clinical condition [51-54].

Complications related to surgery

Due to the surgical approach, certain complications may arise, such as infection or wound dehiscence, which may lead to lung herniation. Lung transplantation is a high-risk surgical procedure, with extended intervention times and occasionally requiring extracorporeal circulation, both of which may result in damage to the central or peripheral nervous system. All these pathologies will lead to modifications in the rehabilitation program post-LT as required.

Complications arising from a prolonged time in critical care

The persistence of a patient in a critical situation, associated with the required pharmacological support (neuromuscular blocking agents, high-dose steroids, etc.) can condition the response of the peripheral nervous system with the development of polyneuropathies or polymyoneuropathies, resulting in respiratory muscle failure and a very difficult weaning process.

The possibility that the phrenic nerve may be compromised, which in this context is very high, together with the possibility of it being damaged during the surgical intervention itself (a reported 3 to 30% incidence, depending on the series) will substantially increase the complexity of the rehabilitation process [55,56].

During the follow-up in the ICU it is important to detect AR and/or infection, which at times may require a fibrobronchoscopy (FBS) and transbronchial biopsy (TBB). After carrying out a TBB it is advisable to suspend active respiratory PT for at least 24 h in order to prevent the development of a pneumothorax or pulmonary hemorrhage.

Two to three sessions of respiratory PT treatment will be carried out each day whilst the patient remains in the ICU. This is vital, as the transplanted lung is a denervated organ and, as such, lacks the appropriate cough reflex, which makes expectorating secretions more difficult. Active-assisted mobilizations of both upper and lower limbs will be carried out, together with routine postural changes. As soon as their clinical condition allows, the patient can raise the headrest of their bed, then progressing to sitting on the side of the bed, followed by sitting in an armchair. Similarly, they will progress to standing and marching on the spot in the ICU itself as their condition allows.

Digestive system complications following lung transplantation

Swallowing difficulties, the presence of gastro-esophageal reflux and gastroparesis following LT are frequent. Their pathogenesis is multifactorial and, in many cases, often involves phrenic, recurrent and vagus nerve injuries due to the surgery itself or as a result of pre-existing pathology [57].

Oropharyngeal dysphagia, especially in the form of silent aspiration, has been shown to be a very frequent dysfunction amongst LT patients [58] and carries a very serious risk of aspiration pneumonias and bronchiolitis obliterans syndrome (BOS). Once again, its causes are multifactorial, amongst them gastro-esophageal reflux, lesions of the recurrent and superior laryngeal nerves and localized trauma secondary to intubation and transesophageal echocardiograms.

It is known that patients with end-stage pulmonary disease often suffer from gastroesophageal reflux, which can negatively affect them in an important way during the immediate post-transplant period, leading to a reduction in FEV_1 and survival compared to patients who do not share this problem [59]. Some authors have suggested that anti-reflux surgery prior to LT or within the first six months following it may be an important step in preventing early damage to the graft [60].

Delayed gastric emptying is another frequent finding both in LT waiting list patients, in some 50% of these, as well as in LT recipients, with a 74% incidence at 3 months and 63% at 12 months following transplantation [61]. Gastroparesis itself can further accentuate gastroesophageal reflux and silent aspiration.

We must be acknowledge the importance of these processes in order to adequately assess, diagnose and treat them in a proactive fashion.

Post-surgical ICUs are becoming increasingly aware of the significance of dysphagia and MDT members should be adequately trained in the prevention of food aspiration, insisting on basic preventive measures during food intake (posture, attention, consistency of foodstuff, avoid mixing textures, etc.). Even if there is the slightest doubt of dysphagia, a request for assessment and, where appropriate, treatment must be made to the MDT members whose remit it is to do so. A targeted swallow assessment will then be carried out, together with a volume-viscosity test as a means of screening in the first instance and, afterwards, where necessary and possible, a bronchoscopy and/or a videofluoroscopic. With tracheostomized patients, assessment with a methylene blue test can be performed at the bedside. In the event of a positive diagnosis and, in addition to the general measures described, treatment with a speech therapist to teach the patient to carry out orolingual-facial and swallowing exercises can be implemented [62]. In a limited number of tracheostomized patients with persistant dysphagia, the option of a percutaneous gastrostomy must be considered.

The treatment of gastroparesis may range from appropriate pharmacological management and changes in eating habits to, in more severe cases, the need to carry out a jejunostomy for enteral feeding. In chronic, refractory cases the possibility of implanting a gastric electrical stimulator device may be considered, though this carries its own risks and complications [63]. There are currently positive, preliminary studies for the treatment of severe drug-related refractory gastroparesis using a non-invasive external device to stimulate the vagus nerve at the cervical level [64].

Rehabilitation in patients on ecmo treatment

Extracorporeal membrane oxygenation (ECMO) is an artifical system capable of providing circulatory and ventilatory support. It is indicated in cases of severe respiratory failure or cardirespiratory insufficiency despite maximal conventional therapy, including the use of intra-aortic balloon pump counterpulsation.

Its indications have grown in recent years. At its outset in the 1970s, it was exclusively used to manage untreatable respiratory insufficiency. It is currently a therapeutic alternative to conventional treatment techniques when these are deemed insufficient, both in respiratory as well as cardiac failure.

In lung transplant units, ECMO is used as both a bridge to transplant as well as a means of treating post –transplant complications which may entail severe respiratory failure despite the use of IMV. Its setup can be carried out in such a way that the patient may remain awake and able to continue with a modified rehabilitation program whilst on ECMO.

Its risks are primarily associated with vascular cannulation, the need for appropriate anticoagulation therapy and potential accidents due to the complexity of the technique. There is currently sufficient evidence to affirm that its use improves survival without increasing the after-effects in critical situations where conventional treatment has failed.

Its advantages compared to other mechanical circulatory support systems include: rapid commencement of treatment thanks to peripheral cannulation; minimally-aggressive technique that is better tolerated by critically ill patients; as it does not require a thoracotomy, it allows cardiopulmonary resuscitation to be carried out in the event of a cardiac arrest; provides univentricular or biventricular pulmonary support and has been proven to be an effective intermediate step prior to long-term ventricular assistance or as a bridge to heart or lung transplant.

There are a number of ECMO systems currently in use, but a standard circuit entails a venous drainage cannula, a venous line, centrifugal pump, an oxygenator, arterial line and a second venous or arterial return cannula:

One cannula connects to the venous line of the circuit and carries deoxygenated venous blood, whilst the other cannula is connected to the arterial line of the circuit and returns oxygenated blood via an artery or a vein.

The venous line carries deoxygenated blood from the venous cannula to the centrifugal pump and from there to the oxygenator.

The arterial line transports the oxygenated blood from the oxygenator to an arterial cannula or a second venous one.

The centrifugal pump moves the blood along with the use of impeller blades or rotating plastic cones within its plastic housing. By rotating rapidly, the impellers generate a negative pressure at the inlet port of the pump, drawing the blood inwards and expelling it by the opposite effect via the outlet port.

The oxygenator is composed of a gaseous and a liquid film layer separated by a membrane, allowing for gas exchange and blood oxygenation according to the principle of Fick´s law of diffusion.

A literature review pertaining to the inclusion of these patients in rehabilitation programs carried out by Polastri [65] in 2016 found that, in most medical centers, non-sedated ECMO patients received a combination of both passive and active treatment modalities and that most of them reached an acceptable level of autonomy following its completion. Thus, initial evidence contributes to our knowledge that early mobilization and ambulation of these patients can be carried out safely. It must be noted, however, that those patients requiring ECMO pre or post-LT have a poorer functional status at the time of discharge from ICU than those not who do not require it [66].

In cases where ECMO has been used as a bridge to lung transplantation, there are studies such as that by Bain [67] in 2016 where the hospital costs of inclusion or non-inclusion of ECMO patients within a rehabilitation and ambulation program has been analysed. They found that the clinical benefit afforded by rehabilitation when compared to those not receiving it resulted in a reduction of 11% with regards to the total cost of the process, which translated into a 22% reduction in the total hospital cost and a 73% reduction in ICU costs alone post-LT.

Therefore, taking into account the logical precautions inherent to the presence and location of venous and arterial cannulas, it is safe to say that selected patients may be included within an early mobilization and ambulation program, which will then allow them to continue to progress with their rehabilitation both pre and post-LT as the case may be.

In-patient rehabilitation

As the rehabilitation treatment program progresses on from the previous phase, pain control becomes increasingly important as the level of sedation diminishes. If pain around the wound site makes respiratory PT difficult, transcutaneous electrical nerve stimulation (TENS) may be used to optimize this. Respiratory PT treatments will focus on slow, maximal inspiratory manouvers as well as on improving exercise capacity. Treatment will continue in the gymnasium as soon as

the clinical situation of the patient allows for it, monitoring oxygen saturations and heart rate throughtout with a pulse oximeter. In the event of desaturations during treatment sessions, supplementary oxygen will be used to keep saturations above 85% whilst maintaining a perceived level of exertion of 12-13 on the Borg scale. If musculoskeletal or neurological complications following LT are identified, these will also be treated accordingly [15,16].

Outpatient rehabilitation

In this phase, patients will continue to carry out directed diaphragmatic breathing and directed coughing (aimed at clearing any potential respiratory secretions) and will further progress their training to improve their exercise capacity. Patients will attend for pulmonary rehabilitation sessions 3 to 5 days per week for between one and three months, equipping them and encouraging them to continue to exercise independently as well carrying out their respiratory exercises. After 8-12 weeks have elapsed and, based on their individual clinical situation, it is recommended that they return to their usual ADLs, sex, leisure, sport and work activities. It is important to plan a maintenance exercise program which can be carried out in the domiciliary setting or within their local gym. Regular reviews in the outpatient clinics at three and 6 months post-LT and annually thereafter are required, barring complications, in which case the transplant team may be contacted immediately.

In following up a LT patient, it is essential to be able to detect AR, as it is the most frequent complication in the initial post-operative period, occurring in 26% of cases within the first month and in more than 50% in the first 3 months. Only 24% of LT recipients do not display histological evidence of AR in the first year post-LT and its appearance is a known risk factor for chronic rejection.

Rejection is much more frequent in lung transplantation than for other types of transplant as it is a highly vascularized organ, with a large lymphatic network and exposed to external pathogens and irritants. During the physical reconditioning process these patients may present with a greater degree of fatigue than usual or more marked desaturations which, if coupled with a low-grade fever, cough and a drop in FEV_1>10-12% (predicted) and/or FEF25-75% (predicted) should make us think of AR.

Diagnosis requires a bronchoscopy with transbronchial biopsy. The histopathological diagnosis of AR is based exclusively on the presence of perivascular and interstitial mononuclear cell infiltrates. The greater the degree of AR, the greater the chances of chronic rejection are. Clinically silent acute rejection may occur in up to 40% of cases.

In order to treat AR, methylpredinisolone boluses are prescribed for a 3 to 5 day period (10-15 mg/kg/day), followed by a tapering dose of the same over 2 to 3 weeks and/or optimization or changes to immunosupresion (IS) treatment levels. This treatment can occasionally bring about a setback in the rehabilitation process, relative to the previous levels of fitness that the patient had achieved. During AR exercise capacity training must be put on hold whilst respiratory PT exercises must be maintained: directed diaphragmatic breathing as well as airway clearance techniques to check for and expectorate unwanted secretions. Once the treatment for AR has finished, patients will have to re-start a physical reconditioning treatment program once again [68,69].

Chronic rejection (CR) may occur at any point in the post-LT period. This results in a lower exercise tolerance accompanied by an increase in dyspnea and a reduction in FEF25-75% (predicted),

sustained and irretrievable decline in FEV_1, represented by a fall >20% relative to their best FEV1 value post-LT. A positive diagnosis also requires FBS with TBB. The fibrotic lesions to the airways are irreversible and for this reason the only effective treatment for BOS is primary prevention and early detection.

An increase or change to their maintenance IS treatment is usually required and, in carefully selected cases, reassessment may be carried out with a view to re-transplantation. In most cases of CR, patients are encouraged to continue with their physical maintenance exercises as tolerated, generally with the aid of supplementary oxygen, in order to maintain the QoL achieved following LT.

Other possible complications to look out for during the physical rehabilitation of LT patients are those commonly associated with the IS drugs: infections, malignancy and the unwanted side-effects of the medications themselves.

Infections caused by cytomegalovirus, mycobacteria and fungi will be treated according to a specific pharmacological protocol. Rehabilitation treatment will be modified according to the clinical situation of the patient and PT airway clearance techniques will be carried out in order to keep the airways free of secretions [70,71].

The possibility of developing a malignancy during the post-LT period increases and becomes more frequent over time. We must remain alert to the presence of skin cancers and lymphomas, as these are the most prevalent forms of malignancy [72-75]. Arterial hypertension, renal insufficiency, dyslipidemia, cataracts, osteoporosis, avascular necrosis of the hip, polyneuropathies and gastro-intestinal problems such as gastroparesis are some of the more common side-effects of the immunosuppressive treatment which is required following lung transplantation [76,77].

Of the numerous complications associated with IS, it is important to note that it is vital to monitor and follow up bone density, which should have been initiated in the pre-LT period. There are a number of risk factors which may condition osteoporosis, steroids being the single most important one amongst these. *In vivo* studies looking at immunosuppressive therapy, including both ciclosporin and tacrolimus, show that they favor bone resorption over bone formation, leading to an imbalance in bone remodelling and an overall loss in BMD. Low BMI pre-LT, smoking history, reduced physical activity levels and vitamin D deficiency are also additional predisposing factors. In the case of CF, hypogonadism, malnutrution and malabsoption issues can further compound the problem [78].

The prevalence of osteoporosis in lung transplantation is higher than that of any other solid organ transplant. Its presence conditions, in no mean way, a significant rate of vertebral fractures which occur primarily during the first year post-LT and which understandably have a very negative impact on the recovery of these patients.

In LT treatment programs, the importance of bone health cannot be overstated as the prevalence of osteoporosis and combined osteopenia and osteoporosis exceeds 37% and 69%, respectively [79]. Treatment with high dose steroids and immunosuppressors as calcineurin inhibitors post-LT are asscociated with a rapid loss of BMD and a high risk of fractures [80-82].

Patient follow-up must be carried out based on a correct diagnosis and treatment leading up to transplant, as well as an exhaustive medical follow-up after LT. The first year following LT is considered a critical period, especially the immediate post-transplant period, during which a decoupling of the bone remodelling process occurs,

punctuated by an increase in biochemical markers of bone resorption and a reduction in those of bone formation. Clear evidence of a rapid loss in bone density, together with a high incidence of fragility fractures during the first year post-LT, is a well-established fact [83-85].

Pertinent studies prior to transplantation

Complementary tests at the time of the initial consultation: Full blood biochemistry analysis with bone remodelling markers [86]: PTH, 25-OH Vitamina D, Beta Cross-Laps and bone-specific alkaline-phosphatase. Twenty-four urine samples are used to measure creatinine clearance and calciuria.

Lumbar spine and femoral neck bone densitometry. These will be reviewed annually thereafter up until the time of LT in patients diagnosed with osteopenia or osteoporosis. In the event of osteoporosis being detected, potential secondary causes must be ruled out. The patient will be referred to the Department of Endocrinology in the face of persistent hyperparathyroidism despite correcting vitamin D and calcium levels, thyroid disturbances and hypogonadism.

Thoracic and lumbar spine X-ray with anteroposterior and lateral projections (T7 and L2 weighted).

Treatment is carried out with reference to baseline bone densitometry results [86]: T-score>-1.0: In this case, no further recommendations are made save for advice relating to diet and physical exercise. The use of oral or intravenous bisphoshonates in patients with normal BMD is not indicated.

T-score between -1.0 and -2.5: Osteopenic patients receive oral bisphosphonate treatment prior to LT. Intravenous zolendronic acid may be used in place of oral bisphosphonates, with a single 4 mg annual dose of given intravenously. Teriparide (PTH 1-34) injections may also be considered as a further treatment option.

T-score<-2.5: Treatment of osteoporotic patients with oral or intravenous bisphosphonates is indicated. Teriparide may be used in selected cases where there has been a poor response or proven intolerance to bisphosphonates.

Treatment with bisphosshonates is considered the most effective means of preventing and treating osteoporosis in solid organ transplant recipients [78,79,87]. A protocolized follow-up and treatment program, both pre and post-LT, will ensure that all patients have received a bone densitometry test as well as an adequate annual follow-up up until the time of LT, with the aim of achieving a stable and optimum BMD that will facilitate the best possible post-operative management.

If for some reason these tests were not carried out in the pre-LT period, they will be performed in the immediate post-LT window. The correct management of bone pathology post-LT implies both the optimization of bone health prior to transplantation as well as the prevention of accelerated bone loss following surgery [88].

Assessment and treatment of BMD post-transplantation at the time of hospital discharge

Radiological studies: Spinal X-ray, this will depend upon patient symptomatology. If there is a suspicion of vertebral fracture, anteroposterior and lateral spinal X-rays will be taken as described previously.

Full blood biochemistry analysis with bone remodelling markers immediately post-LT and at 3, 6 and 12 months during the first year, then every 6 months over the course of the second year, save in the event of complications that merit strict monitoring. Subsequent follow-up will depend upon the treatment that is being carried out.

Post-LT densitometry at 3 months will be carried out in all patients without fail and, in the case of osteopenia or osteoporosis, yearly for the first two years. After the second year, these follow-ups will be of an annual nature only for those who are osteopenia or osteoporotic.

In our clinical experience, we carry out preventive treatment in all recipients of solid organ transplants, independently of their pre-transplant BMD in order to mitigate the known accelerated loss of bone mass inherent in lung transplantation [89,90].

Inpatient treatment protocol in the immediate post-transplant period

Early treatment with calcium (1000-1500 mg/day) and vitamin D (400-800 IU/day) as soon as the patient can tolerate oral administration in order to ensure adequate circulating plasma levels of 25-OH vitamin D and calcium.

Administration of intravenous zolendronic acid (4 mg), once oral tolerance has been initiated. Following one week of treatment with oral calcium and vitamin D, we must confirm adequate levels of bone remodelling markers and that creatinine clearance is >35.

Initiate weight-bearing physical exercise and early deambulation on the ward with special attention to falls prevention.

Treatment of osteopenia and osteoporosis following hospital discharge

A 4 mg dose of IV zolendronic acid will be repeated at 6 months post-LT in patients diagnosed with osteopenia or osteoporosis at the 3 months post-transplant densitometry test. Calcium and vitamin D plasma levels, together with 24-h calciuria measurements and creatinine clearance must all be assessed prior to administering IV bisphosphonates [91].

Sucessive doses of IV zolendronic acid or oral bisphosphonates will be administered annually depending on the results of the bone densitometry checks.

In cases of severe osteoporosis or in the absence of an adequate response to bisphosphonates, the MDT team may opt to treat them with synthetic analog of PTH (Teriparide), whilst continuing with calcium and vitamin D supplements.

Long-term post-transplant physical rehabilitation treatment-sport, exercise and quality of life

Quality of life and physical activity: One of the main aims of lung transplantation is to improve the survival of selected patients with end-stage pulmonary disease where other therapeutic options have failed. According to the ISHLT (International Society of Heart and Lung Transplantation), current one year survival following lung transplantation is 80%, 65% at three years, 54% at 5 years and 32% at 10 years [92]. In addition to advances in survival, achieving improvements in the health-related quality of life (HRQoL) of these patients is also of paramount importance and is now considered as a specific goal of lung transplantation. Measurements of HRQoL are

increasingly relevant as a validated means of studying the health of a population and of analyzing the efficacy and effectiveness of health-related interventions. In this way, its assessment can provide valuable information, helping to identify which factors shape it and which of these, therefore, may be subject to change through interventions and, in doing so, aid the clinical decision-making process [93].

Taking into account a lower survival following LT compared to that of other solid organ transplant recipients, lung transplantation could be considered as an intervention to palliate symptoms and lead to improvements in QoL, even if a considerable increase in survival cannot be guaranteed [94].

Many validated questionnaires are currently available to help assess HRQoL and, amongst these, the most frequently used generic ones include the SF-36 (Short Form-36 health survey) and the EQ-5D (EuroQoL-5D), whilst aspects specific to respiratory disease may be assessed using the SGRQ (St George´s Respiratory Questionnaire). It is important to highlight that HRQoL must reflect the individual´s perspective and not that of interested third parties, such as family members, carers, or healthcare professionals, in order correctly appraise the patient´s own perception.

Despite the interest shown by clinicians, researchers and patients alike with regards to the analysis of HRQoL, future medical publications need to reflect a greater depth and quality in this growing field of research. Singer [94] manifests in their literature review that there is a heterogeneity in this matter and proposes, looking ahead, new directions in which to expand the study of HRQoL with relation to LT patients. The Cochrane Collaboration [95] has proposed carrying out a review with the aim of a analyzing the effects of training on functional capacity and HRQoL amongst LT patients.

Taking this into account, it should be emphasized that a number of studies have documented improvements in general QoL and HRQoL following LT. Once the initial difficulties have been overcome, most recipients who survive are capable of re-starting an active and independent new life. Despite the numeous difficulties that the process entails, most survivors are satisfied with their decision to undergo a transplant [96,97].

Having accepted that the LT itself has a positive impact on HRQoL, we must design new interventional strategies that will allow us to further improve these. To this end, it is useful to identify HRQoL predictive factors and the impact of different pulmonary rehabilitation programs, both on candidates as well as LT recipients [98].

Amongst the factors which have an adverse impact on a good clinical outcome, the most important one is that of BOS [99], considered to be one of the principal causes of mortality between the first and third year post-LT. Patients who go on to develop it will present with greater physical restrictions, as well as a greater risk of suffering depression and anxiety. Other factors which have a negative impact on HRQoL include the adverse effects related to immunosuppression (especially infections), episodes of AR, pain and dyspnea [100].

Exercise following transplantation

Even though physical exercise training plays a key role in the management of LT patients, there is still an on-going need to reach a consensus with regards to the ideal way in which these should be carried out, which specific techniques should be employed, both in the initial phases as well as the later stages of rehabilitation following LT, in

order to achieve even better results. This is due, largely, to the wide gamut of protocols described in the literature, the variety of definitions used to describe the training regimes with relation to intensity, frequency and duration of the exercise sessions, and with regards to the overall design of said programs, without forgetting the type of training to be carried out (aerobic, anaerobic or interval training) [96].

Exercise capacity following transplant remains quite limited in the early stages following LT despite significant improvements in lung function and this is largely due to cardiovascular and musculoskeletal deconditioning. It is for this reason that rehabilitation programs are essential for LT recipient's right from the very start as well as in the long-term [101,102].

Following transplantation, a lower exercise capacity is associated with a greater mortality, which may imply that an improved exercise capacity affords a protective role in LT patients. Some studies suggest that, in the long-term following LT, functional results may improve under both hospital and community-based supervised exercise programs, there being no differences or additional benefits between the two settings. The two, however, need to be structured with regards to the physical training program used and must be capable of engaging the patient [103]. Domiciliary training programs appear to be effective at improving exercise tolerance, muscle strength and QoL, especially in patients with moderate muscular dysfunction in the first years after transplantation. However, further multicentric, randomized controlled trials are necessary to confirm these benefits and clarify which treatment modalities are the most optimum [104]. Those patients who have had a prolonged ICU admission prior to LT often present a diminished exercise capacity, as measured by the 6 MWT, during at least the first year after transplant; for this reason, the exercise intensity during the rehabilitation program of these patients must be intensified so as to improve their results [105]. Though further studies aimed at quantifying the training potential of individuals in order to optimise positive, functional results and establishing optimum guidelines for effective exercise prescription are still required, we can confidently state that a structured exercise routine can improve maximal exercise capacity and function, muscle strength and lumbar BMD in LT patients [96,106-108]. Based on the results of studies published so far, these patients should be strongly encouraged to take part in regular exercise, as its benefits are more than justified and are capable of reducing cardiovascular morbidity, improving functional recovery and, ultimately, improving their QoL [105,109].

Despite the importance of physical activity for transplant recipients, the minimum recommendations of physical exercise are seldom met. A relatively inactive lifestyle leading up to transplantation has been proposed as one of the possible causes. Currently, however, the factors that may act as a barrier to developing adequate physical activity levels, as well as the mechanisms which may facilitate this amongst this particular population remain largely unknown. It has been suggested that obstacles to following exercise recommendations may include physical limitations, lower energy levels, fear and the appearance of comorbidities [110].

At the other end of the spectrum, however, there are also LT recipients who, with an adequate training program, have increased their exercise capacity to such an extent that they regularly take part in sporting events. The World Transplant Games, in which LT recipients also participate, have been held annually for over twenty years and are proof of this. However, further studies need to be carried out in order to establish optimum training guidelines and quantify the long-term benefits of exercise, together with a greater knowledge of how to best

minimize the potential risks that may affect these patients [110]. In any case, recommendations pertaining to physical activity in lung transplantation must be individualized and regularly modified to reflect the changing clinical condition of each patient.

Conclusion

Lung transplantation is a surgical procedure widely developed for patients with chronic respiratory failure, for whom all other therapeutic treatments options have run out and who meet all the required inclusion criteria in the absence of absolute contraindications.

Due to a dearth of organs, it is fundamental to determine the most appropiate time to list someone for lung transplantation. Waiting times once listed are, unfortunately, quite long in the majority of cases and it is essential to maintain and/or improve the functional status of candidates with appropriate rehabilitation programs.

Once the lung transplant has been carried out, it is extremely important to implement an optimal rehabilitation program in order to achieve the best functional results possible which, in turn, will lead to a better quality of life and a swifter return to personal, family, leisure and professional activities within their own environment.

Further research is required to help clarify which exercise training guidelines are the most appropriate for these patients, taking into account multiple variables such as speed, intensity, frequency and type of exercise amongst a myriad of available options.

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