REVIEW ARTICLE

Lung Transplantation in Spain: an Update

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Introduction

The first Spanish work on lung transplantation was published in 1963,[1] but almost 30 years passed until the first heart-lung transplant with long-term survival of the recipient was performed in Spain in February of 1990.[2] In fact, the recipient of that transplant is still alive today. The first single-lung transplant was performed in 1990[3] and the first double-lung transplant in 1992.[4] The first transplant in a patient with cystic fibrosis was performed in 1993 and first lung transplant with a child recipient was performed in February, 1994.[5] Both operations took place in Valencia and both patients are alive at the time of writing.

Since this initial period of occasional transplants in Valencia,[6] the number of hospitals that perform such operations has steadily increased.[7] The hospitals that offer lung transplants have faced a steep learning curve and, with varying degrees of success, have joined the group of hospitals that perform 20 transplant operations a year, the threshold for better outcomes according to the international registry.[8] Subsequent programs have made use of the experience of surgeons from other groups that are already operational to provide support in the early stages and accelerate the learning process.[9]

Lung transplant programs have usually been initiated thanks to the efforts hospital management boards and to the personal stimulus of interested surgeons. This pattern has led to a distribution of transplant programs that, although able to cover needs, has also created clear differences from one Spanish autonomous community to another with respect to organ donors and recipients (Table 1).

Activity has increased sharply over the last 14 years, and transplantation practice has undergone important changes in aspects ranging from donation to long-term follow-up. Transplant programs with experienced surgeons have an early postoperative mortality rate below 10% and a survival rate of approximately 80% in the first year, with a large improvement in the quality of life of the patients.[8] This has been achieved thanks to an improvement in preservation, surgical technique, anesthetic management, and postoperative monitoring of the patients. Bronchiolitis obliterans syndrome (BOS) remains the main cause of death and the main obstacle to better long-term results.

An international registry has published the outcomes of 3047 heart-lung transplants and 17 128 lung transplants,[8] though more transplant operations are clearly performed given that many groups do not send

TABLE 1
Indication and Lung Transplants per Million Inhabitants in Each Spanish Autonomous Community, 2003*

Spanish Autonomous Community of Origin of Recipient	Indication/Transplant	
	Total No.	Percentage
Andalusia	36/22	61
Aragon	2/1	50
Asturias	7/2	29
Balearics	5/–	
Canaries	9/5	56
Cantabria	10/4	40
Castile-La Mancha	10/2	20
Castile-Leon	28/13	46
Catalonia	78/21	27
Valencia	32/15	47
Extremadura	5/2	40
Galicia	40/29	73
La Rioja	5/2	40
Madrid	37/17	46
Murcia	6/3	50
Navarre	6/4	67
Basque Country	15/6	40
Outside Spain	3/1	33
Total State	306/161	52.6

*Source: Spanish National Transplantation Organization.

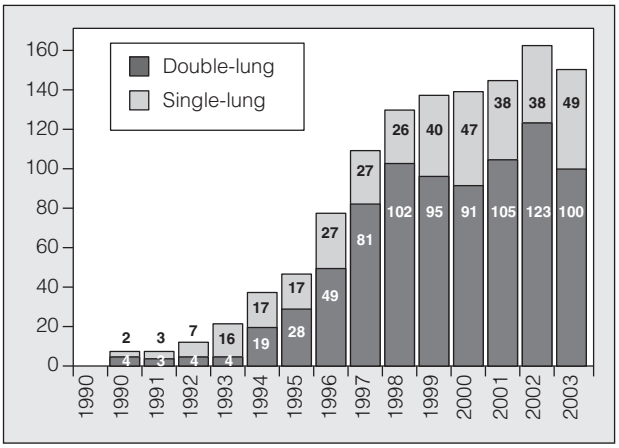

Figure 1. Lung transplants by years in Spain. Source: Spanish National Transplantation Organization.

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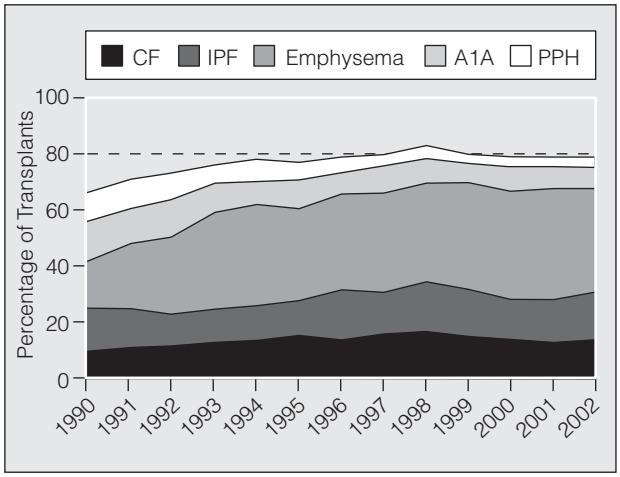
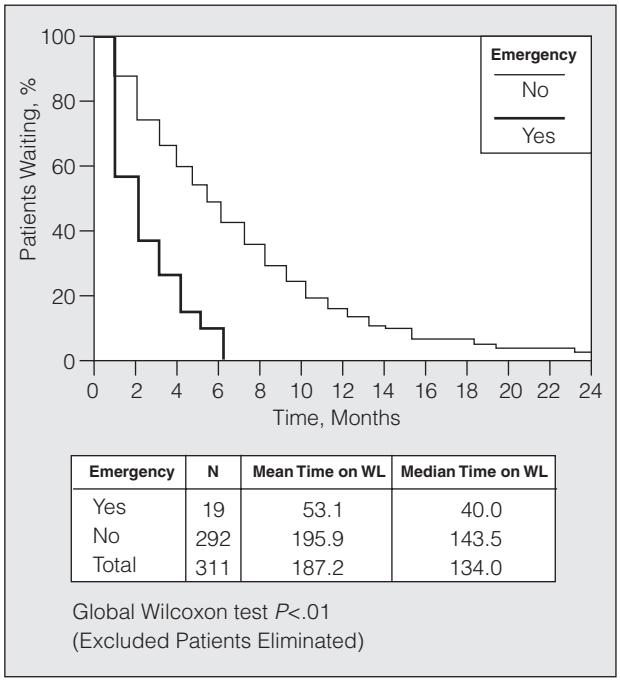


Figure 2. Change in type of lung disease leading to transplantation, by year. Source: international registry. CF indicates cystic fibrosis; IPF, idiopathic pulmonary fibrosis; A1A, alpha-1-antitrypsin deficiency; PPH, primary pulmonary hypertension.



Emergency	N	Mean Time on WL	Median Time on WL
Yes	19	53.1	40.0
No	292	195.9	143.5
Total	311	187.2	134.0

Figure 3. Time on emergency and nonemergency waiting list (WL). Source: Spanish National Transplantation Organization.

information to this registry. In Spain, 1162 transplants have been performed (808 double-lung procedures, including heart-lung transplants, and 354 single-lung procedures) in the last 14 years (Figure 1). The number of transplants increased steadily during the first 10 years of this period but has remained stable at around 150 per year over the last 4 years.

Recipients

The recipient of a lung transplant is usually a patient with long-standing disease and very limited quality of life. When a recipient is referred for assessment for transplantation, a period of uncertainty and insecurity ensues for reasons that include being wait listed, the possibility of dying while waiting or during the transplant operation, and the need to overcome a difficult postoperative period with high risk of complications. These uncertainties should be balanced against the chance to lead a normal life when assessing potential candidates.

Selection Process for Potential Candidates

Patients are considered for transplantation if they have advanced end-stage lung disease refractory to alternative treatments and a high chance of survival.[10,11]

The list of indications has been growing ever since lung transplantation became part of clinical practice. In present general clinical practice, the only absolute contraindications are malignant neoplastic diseases and those that irreversibly affect vital organs that cannot be transplanted. Patients are also currently considered inappropriate candidates if they have diseases which alter immune response and which are supposedly associated with a short life expectancy. Examples are hepatitis B, human immunodeficiency virus infection, or some types of collagen disease. The maximum age of recipients is currently between 65 and 70 years, and biological rather than chronological age should be used for guidance.

Indications

The most common indications are obstructive diseases,[12] suppurative diseases,[13,14] interstitial diseases,[15,16] and vascular diseases. The international registry (Figure 2) shows a progressive increase in the indication of emphysema for transplantation,[8] whereas the indications for vascular diseases have decreased due mainly to more effective medical treatments[17-20] and septostomy.[21]

Consensus statements have established criteria that are normally used for selecting recipients.[22] An excellent reference source is the international guidelines published in 1988 by Maurer et al.[23] Recently, the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) has published its own guidelines, which represent the opinion of most of the Spanish groups.[24]

There is no evidence that various preoperative risk factors can actually contraindicate lung transplantation, and so surgical teams accept more complex cases or patients at greater risk in accordance with factors such as their experience or the pressure of the waiting list.[25]

Some reports of isolated transplants have been published (bronchioloalveolar carcinoma,[26] agammaglobulinemia,[27] or leiomyosarcoma[28]) that confirm the ever broadening indications. For the time being, however, these new indications should be considered with caution and only for selected cases.

When the patient is referred, the benefit of transplantation should be weighed against the risks of surgery and subsequent immunosuppression. Patients with primary pulmonary hypertension or idiopathic

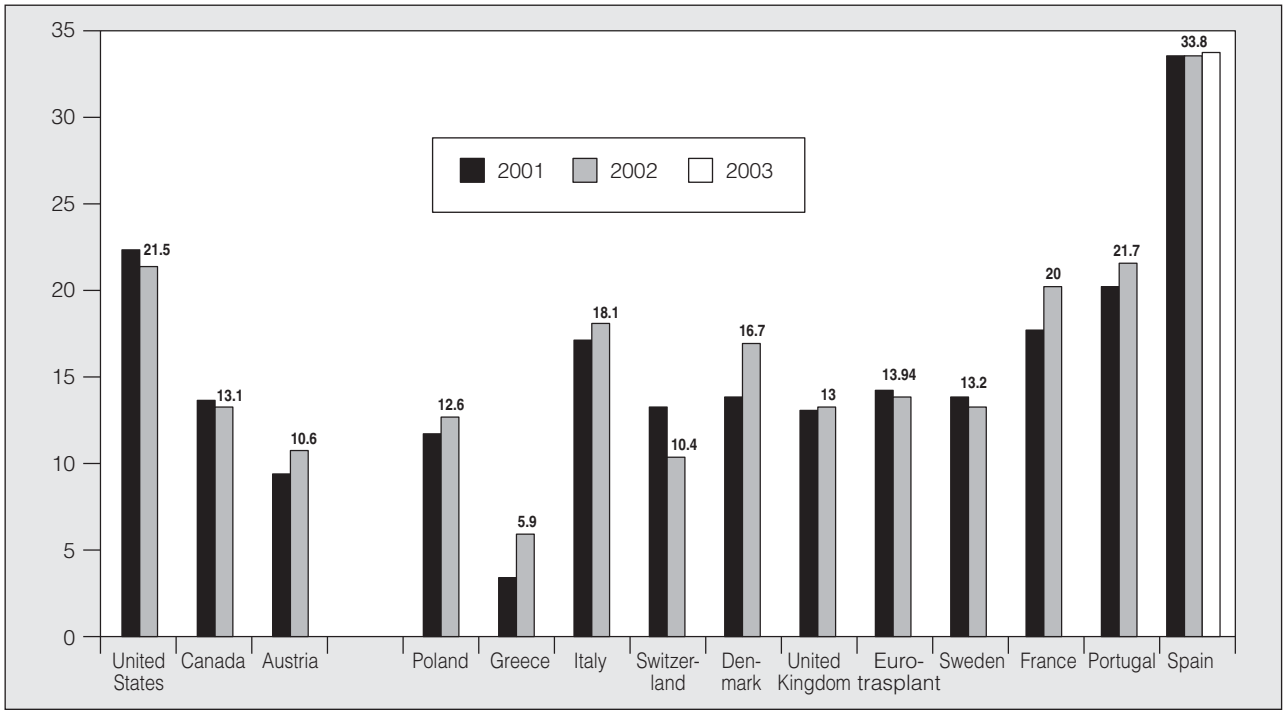


Figure 4. Organ donors by country. Annual rate per million inhabitants. Source: Spanish National Transplantation Organization.

pulmonary fibrosis should be referred for evaluation as soon as possible because disease progression is rapid and because early referral makes it easier to treat possible complications or concurrent diseases. Spanish groups are privileged in that the median waiting time is 180 days (Figure 3). In the Complejo Hospitalario Juan Canalejo, median waiting time was 60 days in 2003. With such short waits, the moment when a patient is wait listed is flexible and a patient who meets criteria for preference or whose case is considered relatively urgent can be promoted without increasing preoperative mortality.

Prioritization of Recipients—The Spanish "Emergency 0" Concept

In Spain, patients who are in imminent mortal danger are given priority as "Emergency 0" (E0) cases, unlike in transplant programs in other countries, where such an approach is not widely practiced. When lung transplantation first became available in Spain, patients were considered as E0 if they needed invasive mechanical ventilation.[29] Subsequently, this criterion changed to allow each group to apply its own E0 definition. Access is thus guaranteed to the first available organ without assigning the patient a national priority listing.

With the E0 system, Spanish patients who have entered a terminal phase due to rapid disease progression and who would otherwise have had to wait their turn have been saved.

Analysis of the outcomes for patients who received an E0 transplant shows that short-term survival is somewhat worse than in nonurgent cases, but after the initial period, survival for both types follows a similar pattern.[30]

Donors

Lung transplantation is limited by the shortage of donors, and transplant teams are responsible for optimizing the use of the limited donor organs available. A strong regulatory system and strict organization of organ distribution and logistics are essential to ensure widespread social acceptance of donation. Spain is among the leaders in this field thanks to the Spanish National Transplantation Organization.

Spain has by far the highest rate of organ donation —approximately 34 per 1 000 000 inhabitants (Figure 4)

TABLE 2
Cause of Death of the Donor, by Years*

	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
Head trauma, car accident	43	35	28	29	25.6	23.4	24.9	23.0	20.7	20.2	17.6	20.3
Head trauma, not car accident	9	10	13	12	11.3	10.7	11.9	11.0	11.3	10	11.5	11.1
Stroke	39	46	48	49	51	55.3	53.5	55.4	56.3	59.9	59.9	56.4
Others	9	9	11	10	12.1	10.6	9.7	10.6	11.6	9.9	11	12.2

*Data are given in percentages. Source: Spanish National Transplantation Organization.

become donors thanks to the excellent network of coordinators and the understanding and solidarity shown by the general population.

The profile of donors has changed over the years. In the past, most donors were young people who died of traumatic brain injury, but currently, most are older people who have died of heart attacks or strokes. For the moment, this change does not seem to have affected medium-term outcomes[31,32] (Table 2).

Lung donation accounts for only a small percentage of all organ donations. We should therefore insist on the need to consider lung donation by multiorgan donors.

Selection Criteria

The selection criteria for donors are common to all types of transplantation and have been reviewed recently.[33,34] Criteria include maximum age of 55 years, blood group compatibility, normal chest x-ray of the lung prior to transplantation, PaO_2 greater than 300 mm Hg with inspiratory oxygen fraction of 1 cm H_2O and positive end expiratory pressure of 5 cm H_2O, smokers of less than 20 pack-years, negative culture of bronchial secretions, and absence of trauma, aspiration, and infection of the lung prior to transplantation.

The best way to increase the number of donors has been subject to prolonged debate.

When considering the ethics of transplantation, the transplant team should bear in mind that the decision to use a suboptimal donor may compromise an often-complicated postoperative period and that mortality is high with lung retransplantation in such conditions. We should thus always try to transplant an organ that maximizes the chances of success.

Acceptance of a donated lung is always considered individually, taking into account both the donor and the recipient. Some suboptimal characteristics of the donors, for example focal lesions, atelectasia, or contusions, or age close to the accepted maximum may have slight repercussion during the postoperative period. More problematic are donors over the age of 60 years or whose bronchial aspirate culture is suspicious or Gram positive even if the findings are clinically or analytically silent or bronchoscopic inspection of the lung to be transplanted is normal. Ethically, these donors are acceptable, particularly for emergency patients or those with fast disease progression. Finally, it is ethically questionable whether to accept donors whose conditions may have important clinical or analytical repercussion, that is, those who have smoked more than 30 pack-years, those with purulent secretions, or those with PaO_2 below 300 mm Hg after correct medical treatment.[35] One approach to optimize outcomes is to use suboptimal donors preferably in double-lung transplantation and, if possible, in surgically less complex diseases.[8]

The lack of clinical evidence for many aspects of transplantation often forces the transplantation team to make decisions based on the experience of the attending surgeon and on the individual progression or response in each case, and decisions about donor selection are no exception.

It is important to optimize the use of organs by using both lungs when single-lung transplants are performed.[36] Thus, the local group should extract both lungs at the same time if necessary[37] and a single-lung transplant should be preferred if acceptable quality of life can be achieved. According to the international registry, single-lung transplants represent around 50% of all lung transplants in recent years. In Spain, however, single-lung transplants account for 25% to 30%.

The use of nonheart-beating donors is an excellent approach if the emergency service can take decisions quickly in and outside the hospital.[38] Outcomes have been good for the first of such transplants performed by the group at the Clínica Puerta de Hierro in Madrid, so this strategy should be encouraged.[39]

The outcomes obtained with living donors are also encouraging.[40] In particular, living donors are an option in children whose disease is progressing rapidly and for whom it is hard to find an acceptable donor. Split-lung transplantation is also another possibility to be considered in children or patients with a small chest volume.[41]

Preservation

Methods for preserving organs have changed over the years. The first positive results were obtained with topical cooling of the lungs as the only preservation mechanism, but it was soon found that lung perfusion minimizes the effects of ischemia, thereby maintaining the morphological and functional integrity of the organ. One recent article provided a clear review of the guidelines for caring for the organ donor and the method normally used for lung preservation.[42] Lung care should include correct ventilation and cleaning of the airways to avoid atelectasia and a negative fluid balance to prevent neurogenic pulmonary edema, which is common after brain death. For lung perfusion, solutions with low potassium content tend to be used at 4ºC to 8ºC and at a flow of 60 mL/kg with anterograde circulation. Before implantation, anterograde circulation is usually 15 mL/kg, administered at a pressure of 10 to 15 mm Hg, while maintaining an inspiratory oxygen fraction of approximately 40% and a tidal volume of 10 mL/kg. The organs should be transported at 4ºC to 8ºC with an insufflation pressure below 20 cm H_2O. A review of the different preservation solutions and their mechanisms of action has been published recently in this journal.[43] According to this review, much experimental data are available on various aspects of lung preservation and reperfusion but few prospective clinical studies have been conducted to provide firm clinical evidence of outcomes.

Modified Euro-Collins solution was the most widely used during the first 10 years of lung transplantation in Spain. Several experimental studies showed that solutions with low potassium concentrations provided the best lung preservation.[44-46] Use of solutions low in potassium in clinical practice has lowered the number

of clinical complications such as arrhythmias and occasional cardiac arrests due to hyperpotassemia caused by Euro-Collins solution. Fewer reperfusion disorders have also been reported with low potassium solutions. Most Spanish groups therefore now use this type of solution instead of the Euro-Collins solution. Results with the Celsior solution, also low in potassium, seem to be good in a study with few clinical cases, so further studies should be done to confirm these preliminary findings.[47]

Preservation technique has also been changed by the introduction of retrograde preservation.[48,49] The Clínica Puerta de Hierro was the first Spanish group to adopt this technique of retrograde circulation, which in particular improves preservation of the donor bronchus.[50] Often, mixed preservation is practiced, that is, anterograde circulation at the moment of extraction and retrograde circulation at the back table before transplantation.[51-53]

Although consensus is that cold ischemia time should be less than 7 hours for a good outcome, all groups have experience of good outcomes after longer preservation times.

Type of Intervention (Single-Lung, Double-Lung, or Heart-Lung)

Some reviews suggest that long-term outcomes are significantly better with double-lung transplants compared to single-lung procedures.[54,55] Single-lung transplants have usually been performed in elderly high-risk patients, and so the final analysis of the data could be substantially biased. Moreover, most single-lung transplants are performed in patients with pulmonary fibrosis, who have a poorer long-term survival than those with diseases such as emphysema, cystic fibrosis, or bronchiectasia who normally receive double-lung transplants. This prior selection could also influence the findings of these analyses.

Single-lung transplantation in noninfectious diseases has been the subject of much discussion. Single-lung transplants would be preferred in infectious diseases if we accept that such procedures have lower operative morbidity and mortality and provide good quality of life, and given that studies suggest that native lung pathology is not a particularly important factor in the course of the transplanted lung.[56,57]

In the Complejo Hospitalario Juan Canalejo, 30 transplants were performed (19 single-lung ones, 9 of which were for emphysema, and 11 double-lung procedures), with an in-hospital mortality of 10% (2 double-lung transplants for emphysema and 1 single-lung procedure) in 2003. After 6 months, 2 patients had died, 1 with a double-lung transplant for collagen disease and 1 with a single-lung transplant for idiopathic pulmonary fibrosis. These findings suggest that good medium-term outcomes are possible to attain with single-lung transplantations. Careful selection of donor and recipient is particularly important for a good outcome in single-lung transplantation for emphysema. Volume reduction of the native lung is a good way to recover lung function in patients with severe overdistension.[58-63]

Single-lung transplantation for primary pulmonary hypertension has proved possible when performed by experienced groups.[64] The number of patients with primary pulmonary hypertension put on the waiting list is currently decreasing, so it is difficult to find groups with broad experience in this type of patient. Spanish groups tend to prefer double-lung transplantation.

The number of indications for heart-lung transplantation has decreased because hospitals are now more experienced at saving the least compromised organ. This type of transplantation is further discouraged by the greater need for organs, and the high rate of short and medium-term complications and side effects.[65]

Surgical Technique

Studies by Veith et al,[66] Pearson,[67] Cooper et al,[68] and Patterson et al[69] in the 1980s established the techniques on which clinical transplantation would be based. Since then, these techniques have been modified and refined.[70]

Thanks to the accumulated experience of these early years, lung transplantation is rarely contraindicated on grounds of surgical difficulty. Operations involving patients with prior interventions, pachypleuritis, or hilar masses require surgeons with greater experience, but these conditions should not be considered as contraindications for transplantation. It should be remembered that pleurectomy and talc pleurodesis are usually unnecessary in surgery for benign processes such as pneumothorax, volume reduction, or bullae formation. These procedures should therefore be avoided in patients who, later on, might need any type of chest surgery, including lung transplantation, because subsequent surgery is made more difficult.

Occasionally, transplantation can be considered even in patients with clear criteria for contraindication such as thoracoplasty, plombage, or phrenectomy and parietal conditions caused by fungal diseases.

The improvements in preservation and surgical techniques (particularly through the shortening of the donor bronchus), early extubation, and prophylaxis for infectious diseases have improved healing of the bronchial anastomoses without having to wrap them in the omentum or revascularize them. In the past, telescoping was essential to ensure a good outcome but, nowadays, it has become a technical resource to facilitate anastomosis of bronchi of different sizes.

In patients with cardiomegalia and extensive tissue adhesion, rotation of the heart to a vertical position facilitates access to the left hilum, and particularly to the inferior pulmonary vein and left triangular ligament. Repeat lung transplantation, if needed, is made easier if the pericardium has been closed.

In my experience, problems of sternal wound healing are very uncommon (less than 2% of the cases). Nevertheless a group decided to perform double-lung

transplants through bilateral anterolateral thoracotomies rather than through an anterolateral thoracosternotomy to avoid this potential complication.[71] The results showed that this approach is possible even if extracorporeal circulation is necessary.[72]

Early Postoperative Complications

Surgical complications have become less common, but they continue to be a risk factor for postoperative morbidity and mortality.[73]

Primary Graft Dysfunction

The main cause of early postoperative morbidity and mortality is primary dysfunction of the transplanted organ,[8] due mainly to ischemia-reperfusion injury in which potent mediators and different cell groups are implicated.[42,74,75] This journal has recently published a complete update on this topic.[43] A variety of studies confirm that use of better preservation solutions, decreased ischemic times, and better selection and care of donor organs have reduced the number of patients with primary graft dysfunction.[76-78] Mortality as a result of such dysfunction has therefore been greatly reduced.[8] Experimental findings show that antithrombin III prevents the development of ischemia-reperfusion injury through increased production of prostacyclin.[79]

Better lung preservation[47] and correct use of nitric oxide, prostaglandins, and other vasoactive drugs have reduced the need for extracorporeal circulation in lung transplantation. Extracorporeal circulation is no longer used systematically in patients with pulmonary hypertension. Furthermore, extracorporeal circulation is required only rarely in single-lung transplants and not often in double-lung procedures because dysfunction of the first graft, the most common reason for extracorporeal circulation in double-lung transplantation, is rare nowadays.[8]

Complications Involving Bronchial Anastomosis

Complications resulting from bronchial anastomosis used to be the main cause of mortality in the period before clinical development of lung transplantation and the main factor that delayed development of the technique. During the 1980s and the early part of the 1990s, it was one of the main causes of morbidity and mortality. Then a number of studies, in particular those published by Couraud et al,[80] contributed to an understanding of the pathogenesis, allowed diagnosis and classification of the lesions, and pointed to appropriate treatments.

Such complications are currently much rarer due to better preservation, surgical technique, and postoperative management of the patients.[81] They are diagnosed early by spirometry, bronchoscopy, and radiology and are treated effectively using dilatation, lasers, and expandable stents. Such management has therefore lessened the importance of these complications and mortality due to problems of bronchial wound healing is now very low. In the Complejo Hospitalario Juan Canalejo, we had no complications involving bronchial anastomosis in the first 70 transplants and the current incidence is 3% without any corresponding deaths.

Nonanastomotic bronchial stenosis is a rare problem.[82] The process may be caused by poor bronchial vascularization, and it presents more often in the intermediate bronchus. Early diagnosis is necessary to prevent occlusion of the bronchial airway.

Acute Rejection

Acute rejection is a common problem during the early posttransplant period.[83] Only 24% of lung transplants do not show any histological evidence of acute rejection in the first year after transplantation. The high rate of rejection may be due to the intricate vascular architecture and the extensive lymphatic system of the lung, and also to continuous exposure to pathogens and external irritants.[84]

The most valid diagnostic test is lung biopsy by fiberoptic bronchoscopy, in which at least 6 samples are taken, preferably from the inferior lobes.[85]

Histological classification has standardized the descriptions for diagnosis and treatment of these patients. Perivascular and peribronchial involvement should be included in such a classification. Lymphocytic bronchiolitis may play a special role in the development of BOS.[86]

The results from various experiments with cellular or molecular analysis of lymphocyte activation in bronchoalveolar lavage fluid have not been good enough to justify incorporation of this technique into normal clinical practice as a diagnostic marker of rejection.[87] In the future, it would be desirable to be able to analyze biomarkers in exhaled air to at least identify a group of patients with a strong chance of receiving a diagnosis of rejection.[88]

The use of biopsies to monitor transplant patients for rejection has been subject to debate since the earliest procedures were performed. Between 15% and 40% of biopsies have been reported to be positive, which implies progression from these clinical states to BOS is possible.[84] On the other hand, in most cases, these biopsies detect early-stage rejection, which often resolves spontaneously.[89] This raises the question of whether to treat these early asymptomatic stages and how often should these monitoring biopsies be taken.[90] The recommendation most often made is to treat even initial stages and extend monitoring for at least a year.

Acute rejection is the only variable consistently associated with developing BOS,[91] particularly when rejections occur repeatedly and late.[84,92]

Different therapeutic regimens with Neoral cyclosporine/tacrolimus or azathioprine/mycophenolate mofetil have not significantly affected the incidence of rejection.[93-95] Ongoing multicenter studies, with strong

participation from Spanish groups, should clarify whether such regimens do in fact affect the incidence of rejection.

Evidence suggests that induction therapy significantly reduces the number of rejections.[96-98] A Spanish-Canadian study using basiliximab for induction should confirm the current evidence available.

Opinion is unanimous regarding treatment of rejection with corticosteroid boluses. However, several approaches have been used to treat refractory rejection (OKT3, total radiation, methotrexate, extracorporeal photophoresis), without any conclusive results, partly because of the small sample sizes in the studies.[84] A recent prospective study with inhaled cyclosporine shows a significant reduction in the rate of acute rejection and development of BOS.[99]

Acute rejection remains an important postoperative problem immediately after lung transplantation. We should aim to prevent rejection because of its strong association with the development of BOS.

Bacterial Infection

The most common complication in the first few months after transplantation is bacterial infection,[100] which is often associated with other complications and represents the most common cause of death during this period.[8] The usual approach for protecting the transplant patient during the first few days after transplantation involves early extubation and prophylaxis with an antibiotic active against the bacteria most commonly isolated in critical care units or a combination of antibiotics active against bacteria commonly found in donors and recipients until the results from the first cultures taken during surgery are available.[101] Outcomes are similar even in the presence of panresistant bacteria, except for *Burkholderia cepacia* genomovar III, which is considered by some to be a contraindication to transplantation because of the poor outcomes obtained.[102,103]

Viral Infection

The most important viral infection in lung transplant operations is that caused by cytomegalovirus (CMV), not only because of associated morbidity and mortality in the postoperative period, but also because of its relationship with the development of BOS. A recent review did not find that CMV compatibility influences the development of BOS or survival provided infection is correctly diagnosed and appropriate prophylaxis and treatment are administered.[104] In Spain, most groups opt for prophylaxis with ganciclovir instead of starting early treatment and monitoring once the CMV antigen is detected in blood. This approach, along with immunosuppression and the poor bioavailability of oral ganciclovir, could be why relapses and resistance to treatment have become more common in recent years. Outcomes will hopefully be better with widespread use of valganciclovir, which has recently become available, thanks to its better absorption. Treatment with specific antibodies has been indicated for prophylaxis in CMV-seronegative recipients of a lung from a CMV-seropositive donor and in treatment of relapses, but always in association with ganciclovir.[105]

Fungal Colonization

Fungal colonization by different species of *Candida* and *Aspergillus* is common during the entire posttransplant period. Prophylaxis with amphotericin aerosols,[106,107] possibly associated with fluconazole or itraconazole, has been shown to be every effective at preventing the development of fungal infections in patients progressing satisfactorily after transplantation.[108] The native lung can be a fungal reservoir in single-lung transplantation, and so if infection is detected before the operation, a double-lung procedure is recommended. Fungal infection is also associated with increased immunodepression due to acute or chronic rejection, prolonged need for intubation, and relapses of bacterial infections. Prophylaxis should be maintained in such cases.

Treatment of these infections is limited by the susceptibility of the fungus to the drug and nephrotoxicity, and by competition from calcineurin inhibitors in hepatic metabolism. Frequent monitoring of blood levels of calcineurin inhibitors, creatinine, and urea are therefore required. The new drugs voriconazole and caspofungin, and their possible association with liposomal amphotericins provide hope for better outcomes in the treatment of pulmonary fungal infections in immunodepressed patients.

Infection by Pneumocystis carinii

Infection by *P carinii* has become rare since the widespread availability of prophylaxis with trimethoprim-sulfamethoxazole. However, clinicians should remember to maintain prophylaxis when immunodepression is increased to treat episodes of acute or chronic rejection.

Pleural Complications

Pleural complications are also fairly common and may be partly responsible for loss of function of the transplanted organ.[109]

Late Posttransplant Complications

BOS is diagnosed clinically when progressive loss of lung function of an obstructive nature occurs, provided acute rejection, infection, and airway obstruction have been ruled out. Normally, the forced expiratory volume in 1 second (FEV_1) is used to quantify loss of lung function, although a recent review also included forced expiratory flow between 25% and 75% of the forced vital capacity (FEV_{25-75}) among variables recorded for that purpose because it can detect the onset of BOS earlier. The concept of potential BOS has been established as when there is a 10% decrease in FEV_1 and a 25% decrease in FEV_{25-75}.

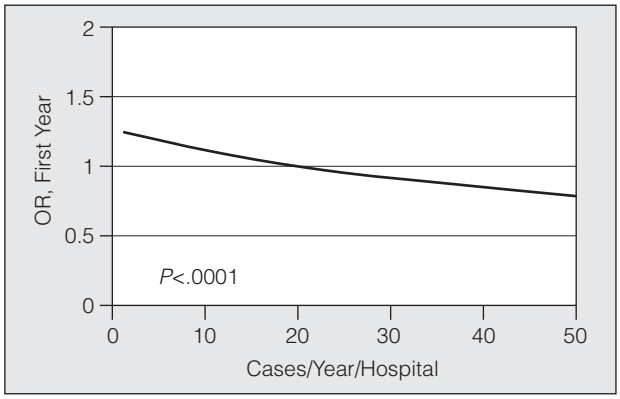


Figure 5. Number of transplants performed per hospital. Source: International Transplantation Organization. OR indicates odds ratio.

In 1993, a classification system was set up to establish the clinical and histological staging of lung dysfunction.[110] The classifications have been revised recently by the International Society for Heart and Lung Transplantation.[111]

When a patient presents with clinical signs of BOS, the fibroproliferative process in the epithelial lining of the bronchi is usually well advanced and so the loss of lung function may be irreversible. For many years, the development of BOS has been associated with immunological mechanisms, but recently, other factors such as bronchial aspiration in gastroesophageal reflux disease have been shown to significantly correlate with BOS.[112,113] This suggests that BOS is the result of repair of lung damage caused by immunological disorders (clinical or subclinical rejection), which may be favored or provoked by nonimmunological mechanisms. According to this suggestion, a range of inflammatory processes may trigger immunological disorders that contribute to the development of BOS.

Doubts about the etiology and the current lack of knowledge on the pathogenesis of BOS explain why the response to treatment is often not as good as hoped. Clearly, it is recommendable to prevent BOS from developing by controlling factors believed to be implicated in its pathogenesis. Measurement of levels of nitric oxide in exhaled air could provide an early diagnosis by noninvasive testing to select patients for further diagnostic confirmation.[114,115] A patient with a biopsy positive for lymphocytic bronchiolitis should also be treated for rejection or at least be given inhaled corticosteroids because such a finding is significantly associated with the development of BOS.

Induction therapy reduces the number of rejections, and so it is possible to reduce or delay the development of BOS. We are therefore awaiting the results of the prospective multicenter study whose primary objective is to assess the influence of anti-interleukin 2 antibodies on the development of BOS.

BOS can sometimes be stabilized by changing cyclosporine for tacrolimus or azathioprine for mycophenolate mofetil, but the value of this approach should be confirmed by extensive multicenter studies that are currently being conducted.

Cytolytic therapy does not seem to significantly affect the course of BOS. Methotrexate, cyclophosphamide, extracorporeal photophoresis, whole-body irradiation, or rapamycin have been used in small groups of patients with varying success.[116]

Effective treatments to prevent BOS can only be developed if studies are done to clarify its pathogenesis.

Other long-term complications such as tumors, renal impairment, hypertension, hyperlipemia, or diabetes are mainly caused by side effects of the immunosuppressant therapy and are common to other types of transplantation.

Outcomes

It is difficult to evaluate the outcomes in Spain as there is no national registry for lung transplants and, moreover, the indications and complexity of cases taken on by different groups vary greatly.

Survival published by the international registry for 15 267 transplant patients, collected from many groups between 1990 and 2002, was 84% at 3 months, 74% at 1 year, 58% at 3 years, and 47% at 5 years.[8] The recent clear increase in immediate posttransplant survival stands out in comparison with earlier periods. The main factors that influence survival are underlying disease (outcomes are better for emphysema[12] and cystic fibrosis[5,14,117,118]) and the clinical state of the patient at the time of transplantation.[25] Of particular note is the strong influence on 1-year survival of the number of transplants performed per year by the hospital (Figure 5).[8] Reviews of the only center with prolonged experience report survival of 84% in the first year and 55% at 5 years.[8] The experience in the Complejo Hospitalario Juan Canalejo in the first 90 transplants shows an actuarial survival of 78% in the first year and 53% at 5 years. Survival is higher, 90% and 68%, respectively, if we take into account only patients with emphysema.

The improvement in quality of life of patients who have received transplants is beyond question.[119,120] The international registry reflects this improvement: more than 83% of survivors lead normal lives after both 1 year and 5 years.[8]

It can be concluded that lung transplantation has become a clinical reality in Spain in the last 15 years, with broader indications and better outcomes, particularly in the first year posttransplantation. The faster growth of the list of recipients compared to donors has to be addressed. The main challenge is to understand why BOS arises in order to develop preventative treatments and improve long-term outcomes.

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