ORIGINAL ARTICLES

Lung Transplant Therapy for Suppurative Diseases

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OBJECTIVE: Lung transplantation is a valid therapeutic approach for patients with bronchiectasis. The objective of the present study was to evaluate our experience with bronchiectasis patients and compare the results in patients with cystic fibrosis to results in those with bronchiectasis caused by other processes.

PATIENTS AND METHOD: We carried out a retrospective study of bronchiectasis patients treated by lung transplantation in order to analyze demographic, functional and microbiological characteristics before and after transplantation, and survival.

RESULTS: From 1991 to 2002 lung transplants were performed on 171 patients, 44 of whom had suppurative lung disease (27 had cystic fibrosis and 17 had bronchiectasis caused by other processes). There were no significant differences in the demographic variables between the 2 groups. At transplantation, lung function variables showed severe bronchial obstruction (mean [SD] forced expiratory volume in 1 second of 808 [342] mL and forced vital capacity of 1390 [611] mL) and respiratory insufficiency (PaO_2 at 52 [10] mm Hg and $PaCO_2$ at 48 [9] mm Hg). Only PaO_2 was significantly lower in patients with bronchiectasis from causes other than cystic fibrosis. Airway colonization was present in 91% of the patients; *Pseudomonas* spp germs were detected in 64% of the cases and were multiresistant in 9%. In the early postoperative period germs were isolated in 59% of the cases, half of which involved the same germ as had been isolated before transplantation. One year after lung transplantation, 34% of the patients continued to have bronchial colonization. Survival at 1 year was 79% and at 5 years, 49%, with no significant difference between the patients with cystic fibrosis and those with other suppurative diseases, nor between the patients with and without *Pseudomonas* colonization. Only 2 patients had died of bacterial pneumonia at 1 month after transplantation.

CONCLUSIONS: Although airway colonization in patients with suppurative diseases complicates postoperative management, the results in terms of survival are good.

Key words: *Lung transplantation. Bronchiectasis. Cystic fibrosis.* Pseudomonas. *Suppurative lung disease.*

Trasplante pulmonar en enfermedades supurativas

OBJETIVO: El trasplante pulmonar es una opción terapéutica válida para pacientes con bronquiectasias. El objetivo de nuestro trabajo ha sido analizar nuestra experiencia en estos pacientes y comparar los resultados entre los pacientes con fibrosis quística y bronquiectasias de otra etiología.

PACIENTES Y MÉTODO: Se ha realizado un estudio retrospectivo de los pacientes trasplantados por bronquiectasias para analizar las características demográficas, funcionales y aspectos microbiológicos antes y después del trasplante, así como la supervivencia.

RESULTADOS: Entre 1991 y 2002 trasplantamos a 171 pacientes, de los cuales 44 presentaban enfermedad pulmonar supurativa (27 fibrosis quística y 17 bronquiectasias de otras etiologías). No había diferencias significativas en las variables demográficas entre ambos grupos. En el momento del trasplante la función pulmonar mostraba grave obstrucción bronquial (volumen espiratorio forzado en el primer segundo: 808 ± 342 ml; capacidad vital forzada: 1.390 ± 611 ml) e insuficiencia respiratoria (presión arterial de oxígeno: 52 ± 10 mmHg; presión arterial de anhídrido carbónico: 48 ± 9 mmHg). Sólo la presión arterial de oxígeno fue significativamente inferior en los pacientes con bronquiectasias de etiología diferente de la fibrosis quística. El 91% de los pacientes presentaba colonización de la vía aérea; el germen más frecuente fue *Pseudomona* spp. (64%), que en un 9% de los casos fue multirresistente. En el postoperatorio inmediato se aislaron gérmenes en el 59% de los casos; la mitad de ellos eran los mismos que se habían aislado antes del trasplante. Un año después del trasplante pulmonar, un 34% de los pacientes seguían mostrando colonización bronquial. La supervivencia al año fue del 79% y a los 5 años del 49%, sin diferencias significativas entre los pacientes con fibrosis quística y el resto de las enfermedades supurativas, ni entre los pacientes con o sin colonización por *Pseudomonas* spp. Sólo 2 pacientes fallecieron por neumonía bacteriana en el primer mes del trasplante pulmonar.

CONCLUSIONES: A pesar de que la colonización de la vía aérea de los pacientes con enfermedad supurativa complica el manejo tras el trasplante pulmonar, los resultados en términos de supervivencia son buenos.

Palabras clave: *Trasplante pulmonar. Bronquiectasias. Fibrosis quística.* Pseudomonas. *Enfermedad supurativa.*

Introduction

Bronchiectasis, regardless of etiology, is characterized by chronic suppuration, lung infection, and decreased lung function. Bronchiectasis can lead to respiratory

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insufficiency and poor quality of life Mortality is high. In the advanced stages of the disease, regardless of etiology, lung transplantation therapy is considered. However, cystic fibrosis patients must be distinguished from those with other types of suppurative disease because cystic fibrosis is a systemic condition that affects very young patients who may have been colonized by infectious germs for years, prescribed diverse combinations of antibiotics, and treated with physiotherapy. All those factors can affect the evolution of a transplant.

The objective of the present study was to analyze our experience with lung transplantation therapy for patients with suppurative diseases, compare the results for survival and mortality between cystic fibrosis patients and patients with other types of bronchiectasis, and evaluate causes of death in both groups.

Patients and Method

We carried out a retrospective study using a set protocol to review the clinical records of all patients in our department who received lung transplantation therapy for bronchiectasis from any cause.

All the transplant patients received induction immunosuppression with antilymphocyte globulin, prednisone, cyclosporine, and azathioprine—the last 3 of which were administered indefinitely. Only in cases where patients showed side effects to one of the pharmaceuticals was tacrolimus or mycophenolate used instead.

Infection prophylaxis administered in the early postoperative period was composed of bactericidal antibiotics chosen according to cultures and antibiograms of pretransplant sputum, and specimens obtained on the day of surgery. The antiviral agent ganciclovir was administered intravenously for the first 15 days and then orally for the remainder of the first 3 months—except in cases where the donor and recipient were serologically negative, in which case no prophylaxis was prescribed. In the early postoperative period, all patients were given nebulized amphotericin for antifungal prophylaxis.

We analyzed demographic data, lung function, and arterial blood gas measurements at registration on the waiting list, microbiological data, susceptibility of the pretransplant sputum cultures to antibiotics, culture of donor and recipient bronchial aspirates at surgery, respiratory samples obtained by bronchoscopy or from sputum at intervals during posttransplant evolution, complications due to infection, and date and cause of death. Routine bronchoscopy procedures with collection of bronchial aspirates and bronchoalveolar washings were performed in the early posttransplant period and again at 15 days, without antibiotic therapy. Other bronchoscopic inspections were performed as a response to radiographic or clinical changes suggestive of infection or lung rejection.

Posttransplantation complications related to infection were classified as colonization if positive microbiology cultures did not coincide with symptoms of infection; as bronchitis if symptoms of infection (fever, leukocytosis, or functional deterioration once rejection was ruled out) and/or inflammation of the bronchial mucosa were present or if there were bronchoscopy findings of suppurative secretions but no indication of infiltrates on x-ray images; and as pneumonia if microbiology cultures coincided with x-ray images of infiltration that resolved with antibiotic treatment or if there was histological confirmation. Susceptibility to antibiotics was analyzed for all microbiology cultures.

The results for cystic fibrosis patients and patients with other types of bronchiectasis were compared.

Statistics software SPSS, version 8.0 was used to analyze the data. Quantitative variables were compared using the Student *t* test and qualitative variables were analyzed using the χ^2 test or the Fisher test, as appropriate. Survival was analyzed using the Kaplan-Meier procedure.

TABLE 1
Characteristics of Patients With Suppurative Lung Diseases*

	Disease			
	Suppurative	Cystic Fibrosis	Bronchiestasis	*P*
Number of patients	44	27	17	
Mean (SD) age, years	28 (13)	21 (5)	41 (10)	<.01
Mean weight (SD), kg	52 (13)	47 (11)	62 (11)	<.01
Mean height (SD), cm	163 (10)	160 (10)	168 (8)	<.05
Sex, men/women	23/21	11/16	12/5	NS

*NS indicates not significant.

Results

Between January 1991 and December 2002 lung transplants were performed on 171 patients, of whom 33% were diagnosed with obstructive disease, 29% with restrictive disease, and 26% with suppurative disease. Of the 44 patients with suppurative disease, 27 were diagnosed with cystic fibrosis (61%) and 17 (39%) with other types of bronchiectasis.

Table 1 shows the demographic data of patients with suppurative disease and Figure 1 gives those patients' lung function data. At transplantation, the patients presented severe obstruction and respiratory insufficiency, with a mean (SD) forced expiratory volume in the first second (FEV_1) of 808 (342) mL (25%); forced vital capacity, 1390 (611) mL (36%); PaO_2, 52 (10) mm Hg; and $PaCO_2$, 48 (9) mm Hg. No between-group differences were found other than for PaO_2, which was significantly lower in the group with bronchiectasis caused by processes other than cystic fibrosis.

In the walk test patients covered a mean 297 (117) meters, over a broad range of 45 to 550 meters. Cystic fibrosis patients tended to walk a greater distance (mean 310 [127] meters), although the difference was not significant.

Prior to transplantation 91% of the patients were colonized. The predominant microorganisms were of the genuses *Pseudomonas* (64%), *Staphylococcus* (25%), and *Aspergillus* (18%). Three specific isolates were more commonly found in cystic fibrosis patients (Figure 2). Nine percent of the *Pseudomonas* isolates

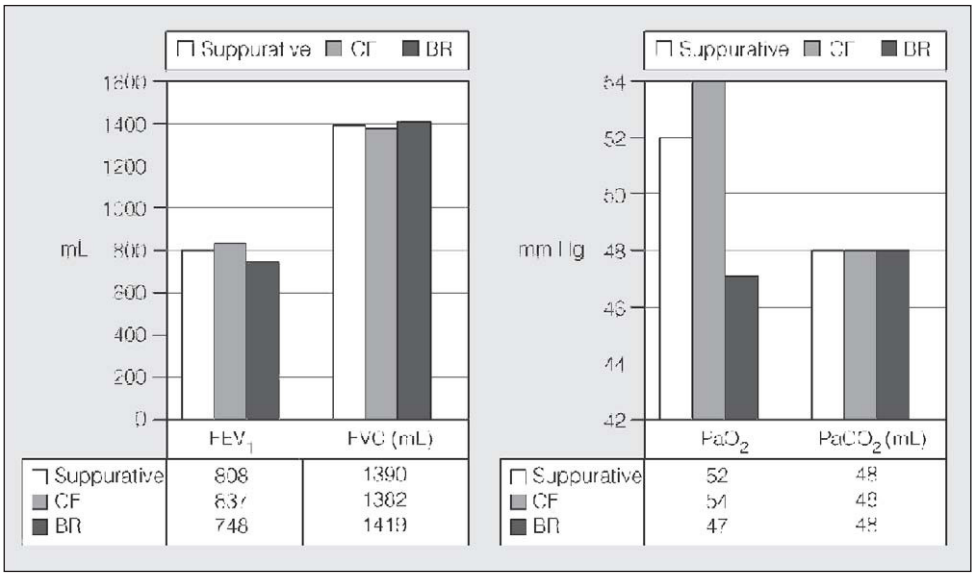

Figure 1. Patient lung function and blood gas measurements at time of registration on the waiting list. CF indicates cystic fibrosis; BR, bronchiectasis; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity.

were multiresistant and in only 1 case were they panresistant.

Figure 3 shows the microbiology results for respiratory samples taken from recipients and donors during surgery. At early posttransplantation, isolates were obtained from 26 patients (59%); half of the germs (14 of 26; 54%) were the same as those isolated prior to transplantation and the rest (46%) were acquired while hospitalized—especially *Staphylococcus* bacteria, which probably came from the donor. During this period 27% of the patients developed pneumonia; 16% developed bronchitis; and another 16% were diagnosed with bronchial infection.

At the first posttransplant year 34% of the patients were still colonized. The majority (62%) were colonized by the same germs as prior to transplantation although half of them showed greater resistance. The rest of the patients (38%) were colonized by newly acquired germs. In this period 15% of patients developed pneumonia, 9% developed bronchitis, and 6% were interpreted as having simple colonization.

Overall mortality in these patients was 43% (19 cases). Of these, 6 (14%) died in the first month.

Survival of patients who received transplants to treat suppurative diseases was 79% at 1 year and 49% at 5 years. Survival of cystic fibrosis patients (85% at 1 year and 45% at 5 years) compared with that of bronchiectasis patients (70% at 1 year and 54% at 5 years) revealed higher initial mortality for the bronchiectasis group but no significant long-term difference (Figure 4). Nor was there a significant difference in survival rate according to whether or not the patients were colonized by *Pseudomonas* bacteria (Figure 5).

Table 2 shows the different causes of death in each period. It is noteworthy that only 2 patients died of bacterial pneumonia (4%). One case involved *Pseudomonas* species that had colonized the patient prior to lung transplantation; the other case involved a nosocomial *Staphylococcus* infection. The most frequent cause of late death was chronic rejection, which caused the death of 8 patients.

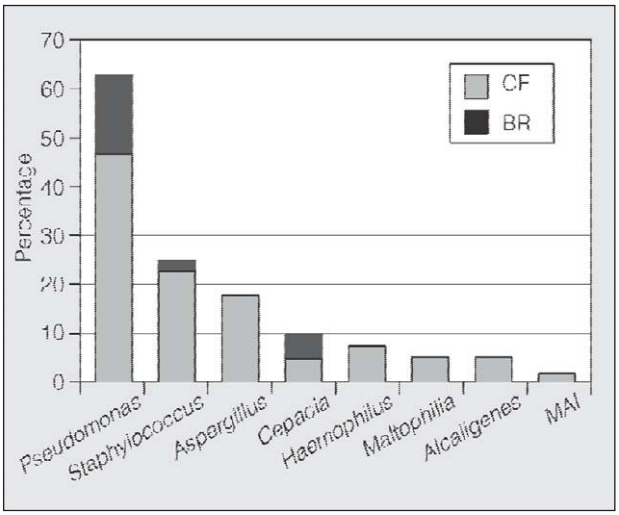

Figure 2. Isolates of sputum bacteria from patients with suppurative disease used for pretransplant evaluation. MAI indicates *Mycobacterium avium* complex.

Discussion

According to an international registry,[1] the diseases that most frequently require transplantation are obstructive disease (48%), suppurative disease (18%), and pulmonary fibrosis (17%). In Spain lung transplants are performed most frequently in patients with suppurative disease (31%), followed by chronic obstructive pulmonary disease (27%), and pulmonary fibrosis (25%).[2] Of the patients with suppurative diseases, cystic fibrosis patients are the most common, despite the extrapulmonary involvement characteristic of the disease and bronchial

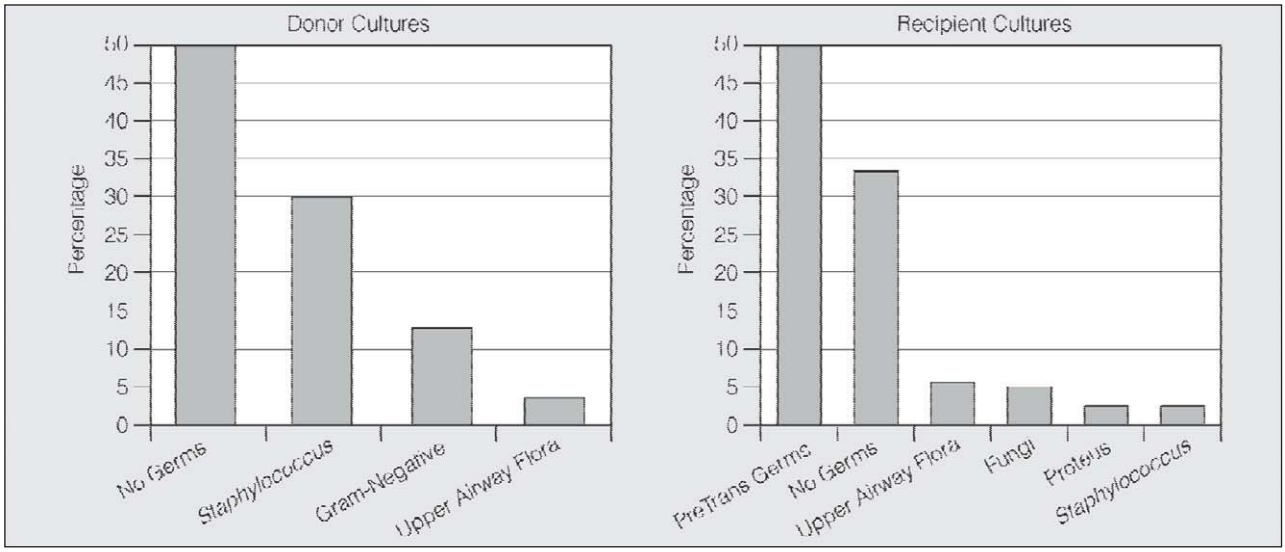

Figure 3. Isolates of bronchial aspirates from donors and recipients taken at surgery. PreTrans germs indicates the isolate was the same microorganism that colonized the patient prior to lung transplantation.

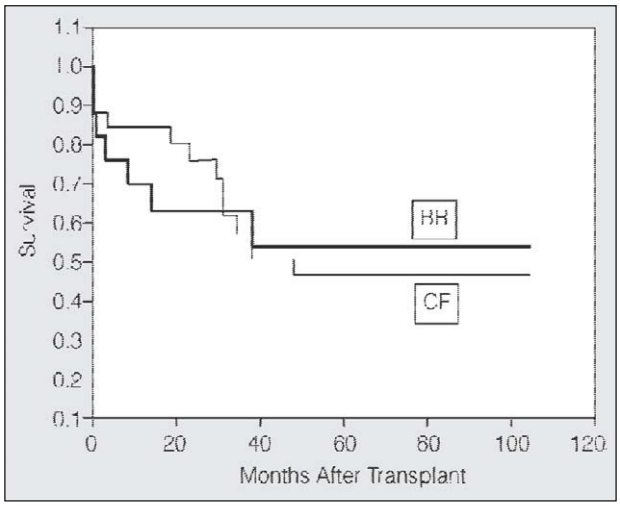

Figure 4. Survival of transplant patients with suppurative disease: comparison between cystic fibrosis (CF) patients and those with other types of bronchiectasis (BR).

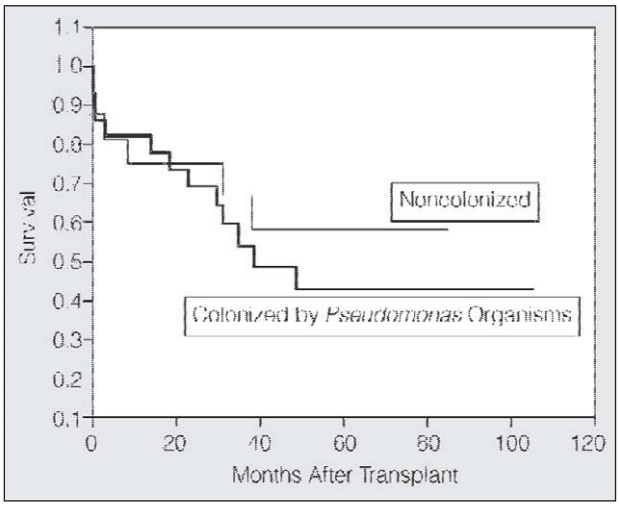

Figure 5. Survival rates of noncolonized patients and those colonized by *Pseudomonas* organisms.

colonization, which could suggest that such patients would be poor candidates for transplantation.

Colonizing germs in cystic fibrosis vary depending on the age of the patient. The majority of patients from 15 to 30 years of age who are referred for transplantation are colonized by *Pseudomonas* species (80%), almost half are colonized by *Staphylococcus* species, and a small percentage (10%) are colonized by *Burkholderia cepacia*.[3] Although colonization with germs that are resistant to antibiotics might be expected to worsen transplantation outcome, this has not been demonstrated.[4]

The results of the present study showed that bronchial colonization decreased over time and, despite frequent infectious complications, we observed a lower incidence of bacterial infection as a cause of early death (4%) than that reported by other studies (mortality due to sepsis, 10%).[5,6] This difference may be attributable to differences in the antibiotic therapies used by each group. Although it is recommended to prescribe 2 sensitive antibiotics to treat *Pseudomonas* infection in cystic fibrosis patients, reserving the use of 3 or even 4

TABLE 2
Transplantation for Suppurative Diseases: Causes of Early and Late Death

Cause of Death	Deaths in the First Month	Late Deaths
Bacterial infection	2	
Fungal infection	1	4
Graft failure	1	
Postoperative bleeding	1	
Kidney failure	1	
Chronic rejection		8
Hemoptysis		1

antibiotics for cases of severe infection or for *B cepacia* infection,[7] we prescribed a combination of 3 antibiotics to treat patients with suppurative disease showing any demonstrated early-postoperative colonization of resistant *Pseudomonas* bacteria. In this, we acted differently from other groups, who used much less aggressive protocols.[5] We adopted a 3-antibiotic protocol based on high mortality related to early postoperative infection.

Transplantation in patients colonized by *B cepacia* is another debated issue. Initially the Toronto group observed a poorer survival rate at the first year (67%) in transplant patients colonized by *B cepacia* compared with 92% survival in the rest of the patients in their study.[7] However, not all groups had such outcomes,[8,9] leaving it unclear whether *B cepacia* colonization should be considered an absolute contraindication. The fact that we had few patients colonized by *B cepacia* has prevented us from drawing conclusions on this issue based on the present study. The disparity in outcomes may also be related to the greater virulence of *B cepacia* type III, which was prevalent in Toronto but less common in other countries.[10] In fact, it has been shown that all transplant patients colonized by *B cepacia* type III died, while those colonized by other types of *B cepacia* infection survived.[11,12]

Estimating the right moment to schedule a lung transplant requires careful consideration. Based on a study by Kerem et al,[13] it has been considered timely to refer cystic fibrosis patients to the transplant department when figures for FEV_1 are less than 30% since those authors observed a mortality rate of more than 40% at 2 years. Later it was shown that FEV_1 alone was insufficient for offering cystic fibrosis patients a high chance of survival with transplantation therapy.[14] Other factors should also be taken into account—such as age, sex, weight, pancreatic function, presence of diabetes, infection by *B cepacia*, and number of exacerbations.[15,16]

Following the guidelines of various medical societies,[17,18] our department recommends transplantation for cystic fibrosis patients after evaluating lung function changes and, above all, when there are findings of progressive deterioration, hypoxemia, and hypercapnia; we also take into consideration the number of exacerbations, evidence of markedly lower nutritional status, and female sex (Table 1). Our decisions on transplantation therapy for patients with bronchiectasis other than cystic fibrosis are conditioned by information on patient lung function deterioration, since prospective studies on mortality in such patients are unavailable. Our comparison of cystic fibrosis patients and patients with bronchiectasis caused by other processes showed that the latter arrived at lung transplantation with poorer lung function and walk test results.

In summary, our experience leads us to conclude that transplantation therapy for patients with suppurative disease offers advantages in terms of survival. Colonized airways prior to transplantation can lead to problems in early postoperative management, but combined antibiotic treatment guided by antibiograms of pretransplant isolates prevents severe complications due to infection. We therefore consider that patients with suppurative disease are suitable candidates for lung transplantation.

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