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Feasibility, tolerability, and outcomes of nebulized liposomal amphotericin B for *Aspergillus* infection prevention in lung transplantation

Víctor Monforte, MD,[a,f] Piedad Ussetti, MD,[b] Joan Gavaldà, MD,[c] Carles Bravo, MD,[a,f] Rosalia Laporta, MD,[b] Oscar Len, MD,[c] Cristina López García-Gallo, MD,[b] Lluís Tenorio, MD,[d] Joan Solé, MD,[e] and Antonio Román, MD[a,f]

[a]*From the Respiratory,*
[c]*Infectious Disease,*
[d]*Intensive Care, and*
[e]*Thoracic Surgery Departments, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona; the*
[b]*Respiratory Department, Hospital Universitario Puerta de Hierro, Madrid; and*
[f]*Ciber Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain.*

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BACKGROUND: Nebulized amphotericin B deoxycholate (n-ABD) is used to prevent *Aspergillus* infection in lung transplantation. Nebulized liposomal amphotericin B (n-LAB) is another option; however, no clinical data are available on the results of n-LAB for this purpose.

METHODS: In an observational study performed in 2 centers to assess the feasibility, tolerability, and outcomes of n-LAB prophylaxis, 104 consecutive patients undergoing prophylaxis with n-LAB were compared with 49 historical controls who received n-ABD. Patient follow-up lasted 12 months. The n-LAB prophylaxis regimen was 25 mg thrice weekly starting on the first post-operative day and continuing to 60 days, 25 mg once weekly from 60 to 180 days, and the same dose once every 2 weeks thereafter.

RESULTS: *Aspergillus* infection developed in 8 of 104 patients (7.7%) with n-LAB prophylaxis (5 colonization, 1 simple tracheobronchitis, 1 ulcerative tracheobronchitis, and 1 invasive pulmonary infection). Ulcerative tracheobronchitis and invasive pulmonary aspergillosis were regarded as invasive disease; hence, the rate of invasive disease was 1.9% (2 patients). The control group had similar rates of *Aspergillus* infection (10.2%; $p = 0.6$) and invasive disease (4.1%; $p = 0.43$). In 3 patients (2.9%), n-LAB was withdrawn due to bronchospasm in 2 and nausea in 1. In the control group, prophylaxis was stopped in 2 patients (4.1%) because of bronchospasm ($p = 0.7$).

CONCLUSIONS: At the dose and frequency described, n-LAB seems effective, safe, and convenient for the prevention of *Aspergillus* infection in lung transplant patients.

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Lung transplant recipients are particularly susceptible to infection by *Aspergillus* spp.[1–4] Despite the development of several anti-fungal drug groups in recent years, *Aspergillus* infection is associated with a persistently high mortality rate in this population.[5–7] Prophylaxis with nebulized amphotericin B deoxycholate (n-ABD) has proven to be safe and efficacious in lung transplant patients[8–12] and is now used in many transplant centers.[13,14] Nebulized ABD produces an aerosol that evenly distributes the drug to reach the most distal areas of the bronchial tree.[15] Moreover, the absence of significant

Reprint requests: Víctor Monforte, MD, Servei de Pneumologia, Hospital Universitari Vall d'Hebron, Passeig Vall d'Hebron 119-129, 08035 Barcelona, Spain. Telephone: +34-93-2746157. Fax: +34-93-2746083.
E-mail address: vmonforte@vhebron.net

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systemic absorption of amphotericin B avoids potential nephrotoxicity.[12,15]

Other forms of amphotericin B, such as nebulized liposomal amphotericin B (n-LAB) could also be used as prophylaxis. In a previous pharmacokinetic study,[16] we found high concentrations of amphotericin B in the respiratory tract of lung transplant patients 14 days after a 25-mg dose of n-LAB. No significant systemic absorption of amphotericin B was detected, and no effect was observed on respiratory function measured by spirometry. In July 2003, n-ABD was switched to n-LAB as prophylaxis for *Aspergillus* infection in all patients because of a lack of supply of amphotericin B deoxycholate in our hospitals. The aim of this study was to assess feasibility, tolerability, and outcomes of n-LAB as prophylaxis for *Aspergillus* infection in lung transplant recipients.

Materials and methods

Study design

This observational study was performed in a consecutive cohort of patients undergoing lung transplantation in 2 centers. All patients were included in the Spanish Research Network for the Study of Infection in Transplantation (RESITRA, Red de Estudio de Infección en el Trasplante), an on-line database that includes all solid organ and hematopoietic stem cell transplant recipients from 16 Spanish transplant centers. RESITRA was approved by the Institutional Review Board at each center, and informed consent was obtained from all patients for participation in the study.

In July 2003, n-ABD was switched to n-LAB as prophylaxis for *Aspergillus* infection in all patients. The first consecutive new adult recipients receiving n-LAB in each center were included in the present study. The study group was compared with a historical control group of consecutive transplant recipients who received n-ABD as prophylaxis. The inclusion and exclusion criteria for both groups were patients aged older than 18 years who had survived for more than 24 hours after transplantation. All patients were followed up, and the 1-year post-transplantation data of both groups were used for the study. The analysis was based on intention-to-treat for prevention of *Aspergillus* infection.

Patients and *Aspergillus* infection prophylaxis

The n-LAB prophylaxis group comprised 104 consecutive patients who were enrolled from July 2003 to November 2005. Their characteristics are summarized in Table 1. The surgical procedure was essentially similar over time. Patients received 25 mg (6 ml) of n-LAB 3 times per week for the first 60 days after transplantation, 25 mg 1 time per week between 60 and 180 days, and 25 mg once every 2 weeks thereafter. Nebulized LAB was prepared for administration by dissolving 50 mg of liposomal amphotericin B for injection (Ambisome, Gilead Sciences S.L., Madrid, Spain) in 12 ml of sterile water. The solution remained stable for at least 7 days at 2° to 8°C.

Liposomal amphotericin B was nebulized mainly by a 1-jet nebulizer (Ventstream® or Sidestream®, Phillips Respironics, Murrysville, PA) with a CR60 compressor (air pressure, 27.2 psi; flow, 7.3 liters/min, Phillips Respironics) equipped with a disposable bacterial exhale filter. Patients were instructed by a trained staff nurse to inhale through a mouthpiece and exhale through the nose. The procedure took 10 to 15 minutes. To avoid contamination, the nebulizer was washed and brushed with soap and water after each administration; once rinsed, it was submerged in 1% sodium hypochlorite solution (Milton solution).

For the control group, data were recorded from the clinical reports of 49 consecutive patients who underwent lung transplantation between January 2000 and December 2001 and received n-ABD prophylaxis. Their characteristics are summarized in Table 1. Patients received 6 mg (6 ml) of nebulized amphotericin B every 8 hours starting on the first post-operative day and continuing to 120 days, and thereafter, 6 mg once daily for life. Nebulized ABD was prepared by dissolving 50 mg of amphotericin B desoxycholate for injection (Fungizone, Bristol-Myers Squibb S.L., Madrid, Spain) in 10 ml of sterile water to achieve a concentration of 5 mg/ml. This solution was then diluted in a total volume of 50 ml of sterile water to reach a final concentration of 1 mg/ml. The solution remained stable for at least 30 days at 4°C, as measured by high-pressure liquid chromatography.[17] The nebulization technique was similar to that of the study group.

Clinical definition

Aspergillus infection was categorized as:

1. Colonization: 2 or more positive respiratory cultures for *Aspergillus* spp in asymptomatics patients.
2. Simple tracheobronchitis: 2 or more positive respiratory samples (at least 1 of which was obtained by bronchoscopy) and clinical symptoms (eg, production of purulent sputum) plus bronchoscopy findings of red edematous mucosa and mucus plugging, with bacterial infection ruled out.
3. Ulcerative tracheobronchitis: diagnosed by bronchial biopsy and/or bronchoscopy findings of necrotic ulcers or pseudomembrane in the anastomosis or in the tracheobronchial tree that disappeared after treatment.
4. Invasive pulmonary aspergillosis: detection of *Aspergillus* spp with evidence of tissue damage on lung histopathology or radiological signs of invasive aspergillosis.

Ulcerative tracheobronchitis and invasive pulmonary aspergillosis were regarded as invasive disease.

Tissue-invasive cytomegalovirus (CMV) disease was defined as isolation of CMV from any tissue or body fluid plus consistent clinical signs or histologic findings.[18] The diagnosis of acute rejection was made on clinical signs and chest X-ray findings, with or without lung biopsy.[19] Bronchiolitis obliterans syndrome (BOS) was defined as a persistent

Table 1 Demographic Data and Patient Characteristics

Variable	n-LAB prophylaxis (study group)	n-ABD prophylaxis (control group)	*p*-value
Patients, No.	104	49	
Age, mean ± SD, years	48.3 ± 14.0	51.3 ± 9.5	0.18
Gender, No. (%)			
Male	67 (64.4)	33 (67)	0.72
Female	37 (35.6)	16 (32.75)	
Pre-Tx diagnosis, No. (%)			
COPD	39 (37.5)	27 (55.1)	0.04
Idiopathic pulmonary fibrosis	32 (30.8)	12 (24.5)	0.42
Cystic fibrosis	16 (15.4)	3 (4.1)	0.04
Lymphangioleiomyomatosis	8 (7.7)	1 (2.0)	0.17
Bronchiectasis	5 (4.8)	2 (4.1)	0.84
Primary pulmonary hypertension	2 (1.9)	3 (6.1)	0.17
Langerhans cell histiocytosis	1 (1.0)	1 (2.0)	0.58
Sarcoidosis	1 (1.0)	0 (0.0)	0.49
Aspergillus colonization pre-Tx, No. (%)	2 (1.9)	2 (4.1)	0.43
Transplant type			0.18
Single	29 (27.9)	19 (38.8)	
Double	71 (68.3)	30 (61.2)	
Heart-lung	4 (3.8)	0	
Ischemia time, mean ± SD, min			
First lung	255 ± 116	263 ± 78	0.73
Second lung	389 ± 117	404 ± 114	0.60
Acute rejections/patient, mean ± SD, No.	0.80 ± 0.69	0.70 ± 0.73	0.58
Chronic rejection, No. (%)	3 (2.9)	3 (6.1)	0.34
CMV pneumonitis, No. (%)	1 (1.0)	3 (6.1)	0.06
Deaths, No. (%)	23 (22.1)	15 (30.6)	0.26
Infection (not CMV).	9	6	
Technical	7	3	
Graft failure	2	3	
Cardiovascular	2	1	
CMV	0	0	
Bronchiolitis	0	0	
Other	3	2	

CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; n-ABD, nebulized amphotericin B deoxycholate; n-LAB, nebulized liposomal amphotericin B; SD, standard deviation; Tx, transplantation.

forced expiratory volume in 1 second (FEV_1) drop of 20% or more compared with baseline, with or without histologic findings of bronchiolitis obliterans, when other causes of pulmonary dysfunction were excluded.[20]

Immunosuppression and anti-microbial prophylaxis

All patients in both groups were under the same treatment protocol based on triple therapy with cyclosporine, azathioprine, and corticosteroids. Induction therapy with anti-thymocyte globulin or basiliximab was used according to the local protocol. Cyclosporine was started on Day 1 at a dose adjusted to trough blood levels (200 to 300 ng/ml). Azathioprine was started within 2 weeks after transplantation at a dose of 1 to 3 mg/kg/day depending on white cell count and avoiding a total leukocyte count of less than 4.0×10^9/liters. Methylprednisolone was started in the operating room at a dose of 10 mg/kg before graft reperfusion, followed by 375 mg/day the first day, and gradually tapering over the first year to reach a maintenance dose of 0.1 to 0.2 mg/kg/day for life.

Cyclosporine was replaced by tacrolimus in patients with cystic fibrosis, young women, and as rescue therapy in chronic and recurrent acute rejection in some patients. When tacrolimus was used, the dose was adjusted to a trough level of 5 to 15 ng/ml. Occasionally, azathioprine was substituted by mycophenolate mofetil at a dose of 1 to 3 g/day, with dose adjustment to maintain trough blood levels of 2 to 4 μg/ml and avoiding a total leukocyte count of less than 4.0×10^9/liters.

Rapamycin or everolimus was used in some patients as rescue therapy in BOS, recurrent acute rejection, or to substitute other immunosuppressive agents because of adverse effects. Acute rejection was treated with intravenous (IV) pulse administration of methylprednisolone at a dose of 5 to 10 mg/kg/day for 3 days or 1 mg/kg/day for 10 days, depending on the severity of the episode.

In the immediate post-operative period, patients without pre-operative septic disease received amoxicillin-clavulanate (2 g every 8 hours) plus aztreonam (1 g every 8 hours). Prophylaxis was modified according to the microorganisms isolated from the last cultures performed in recipients with an underlying septic disease. Duration of prophylaxis was set according to the results of recipient and donor intraoperative cultures.

In the study group, CMV prophylaxis consisted of IV ganciclovir (5 mg/kg every 12 hours) until oral intake was restarted, and subsequently, valganciclovir (900 mg/day) thereafter up to 120 days after transplantation in seropositive patients and to 240 days in seronegative patients. In the control group, patients received IV ganciclovir prophylaxis during the first 21 days (5 mg/kg every 12 hours) and 3 g/day of oral ganciclovir thereafter up to 120 days or to 240 days after transplantation in seropositive and seronegative patients, respectively.

The schedule of CMV antigenemia monitoring was similar in the 2 groups: every 1 to 4 weeks during prophylaxis, then every 1 to 2 weeks up to 180 days, followed by every 2 to 4 weeks up to 1 year. All patients received prophylaxis with cotrimoxazole (400 mg sulfamethoxazole plus 80 mg trimethoprim) once daily for life, starting when oral intake was possible. Prophylaxis against tuberculosis was prescribed in patients with tuberculosis infection (positive purified protein derivative [PPD] test).

Follow-up

Before transplantation, respiratory samples from recipient lungs were cultured for bacteria, mycobacteria, and fungi. On the day of the operation, respiratory samples from the donor and recipient were cultured in the same way. After hospital discharge, patients were regularly followed up in our outpatient clinic at maximum intervals of 4 to 6 weeks. Respiratory samples were obtained and cultured for bacteria, mycobacteria, and fungi when the patient had sputum production or bronchoscopy was indicated. Compliance and possible adverse effects of immunosuppressive treatment and prophylaxis, including n-LAB, were routinely investigated.

All patients underwent a single surveillance bronchoscopy examination 4 to 6 weeks after transplantation, according to our protocol. In addition, bronchoscopy was indicated by clinical criteria, including worsening of respiratory function or suspected pulmonary or bronchial disease at any time in the post-operative period. Samples obtained by bronchoscopy included bronchus aspirate and bronchoalveolar lavage for cell examination and gram stain and acid-fast bacilli stain, as well as bacterial, fungal, mycobacterial, and *Legionella* spp culture. Transbronchial biopsy specimens were taken for histopathologic assessment and immunohistochemical staining.

Statistics

The study and control group were compared. Categoric variables were analyzed using the chi-square test. Analysis of variance or the *t*-test was used to compare the means of continuous variables with an approximately normal distribution, and the Mann-Whitney *U* test was used to compare continuous variables with a non-normal distribution. Differences were considered significant at a value of $p < 0.05$. Statistical analyses were performed with SPSS 11.0 software (SPSS Inc, Chicago, IL).

Results

Some differences were observed in the between-group comparisons (Tables 1 and 2). The incidence of CMV pneumonitis was higher in the n-ABD group and close to statistical significance. Rates of acute rejection and BOS were similar. The percentage of patients receiving induction therapy and mycophenolate was significantly higher in the group receiving n-LAB. At the end of the study (12 months after transplant), 83 patients (77.9%) were alive in study group and 34 (69.4 %) in the control group ($p = 0.26$).

Table 2 Characteristics of Immunosuppressive Therapy

Variable	n-LAB prophylaxis, No. (%) (study group)	n-ABD prophylaxis, No. (%) (control group)	*p*-value
Patients	104	49	
Induction therapy	48 (46.2)	9 (18.4)	<0.01
Received cyclosporine			
At 4 months	65/84 (77.4)	25/36 (69.4)	0.36
At 12 months	57/81 (70.4)	23/35 (65.7)	0.62
Received tacrolimus			
At 4 months	19/84 (22.6)	11/36 (30.6)	0.36
At 12 months	24/81 (29.6)	12/35 (34.3)	0.62
Received at some point			
Azathioprine	95 (90.1)	45 (93.1)	0.92
Mycophenolate	38 (39.3)	5 (10.3)	<0.01
Rapamycin/everolimus	2 (1.9)	0	0.49

n-ABD, nebulized amphotericin B deoxycholate; n-LAB, nebulized liposomal amphotericin B.

Aspergillus infection developed in 8 of 104 patients (7.7%) with n-LAB prophylaxis, consisting of 5 with colonization, and 1 each with simple tracheobronchitis, ulcerative tracheobronchitis, and invasive pulmonary infection. Thus, the incidence of invasive disease (ulcerative tracheobronchitis and invasive pulmonary infection) was low, affecting 2 of 104 patients (1.9%). Results were similar among the 49 patients in the n-ABD group, where *Aspergillus* infection occurred in 5 (10.2%; $p = 0.6$) and invasive disease in 2 (4.1%; $p = 0.43$). *Aspergillus* infection in these patients was categorized in 2 patients as simple tracheobronchitis and in 1 patient each as colonization, ulcerative tracheobronchitis, and invasive pulmonary infection with extrapulmonary dissemination. Two patients receiving n-ABD prophylaxis died of *Aspergillus* infection, for a mortality rate of 15.4% (2 of 13 patients). There were no *Aspergillus*-related deaths among the n-LAB patients. Mortality caused by invasive disease was 50% vs 0% in noninvasive forms. Overall, 2 of 153 patients (1.3%) who underwent lung transplantation died of *Aspergillus* infection, which accounted for 2 of the 38 deaths (5.2%) in these patients.

The risk of experiencing *Aspergillus* infection in the first year after lung transplantation was similar in the 2 prophylaxis regimens (Figure 1). Overall, *Aspergillus* infection developed in 9 of 13 patients within 3 months after transplantation, in 1 patient between 3 and 6 months, and in 3 patients between 6 and 12 months. The 6 patients with *Aspergillus* colonization received treatment according to the local protocol: itraconazole in 1 patient, voriconazole in 2, caspofungin in 1, and IV amphotericin B lipid complex in 2. None of the patients showed new positive cultures for *Aspergillus* spp after treatment.

Three patients who experienced tracheobronchitis were treated with IV amphotericin B lipid complex and 2 received IV liposomal amphotericin B. Relapses of *Aspergillus* infection occurred in 1 patient. The characteristics and outcomes of patients with invasive disease (ulcerative tracheobronchitis or invasive pulmonary infection) are reported in Table 3.

Four lung transplant recipients had pre-transplant colonization, and *Aspergillus* infection developed in 2, consisting of 1 with simple tracheobronchitis and 1 with invasive pulmonary disease with cerebral dissemination. *Aspergillus* spp were isolated in donor samples in the other 2 recipients, and 1 died of hemoptysis related to ulcerative tracheobronchitis caused by *Aspergillus* spp.

Aspergillus fumigatus was the etiologic agent in 8 of 13 episodes (61.5%); the remaining infections were caused by *A flavus* in 4 patients and *A niger* in 1. Other fungal infections developed in some patients during prophylaxis with n-LAB or n-ABD. *Candida* infection developed in 6 patients, including esophagitis in 2, candiduria in 2, candidemia in 1, and gastric ulcer in 1, and 1 patient died of gastrointestinal bleeding related to *Candida* infection. *Scedosporium prolificans* caused respiratory infection in 2 patients, and 1 died of invasive pulmonary infection.

The adverse effects occurring with n-LAB prophylaxis were not severe. Cough after n-LAB was observed in 21 of 104 patients (20.2%), mild and transitory difficulty breathing in 8 (7.7%), and nausea in 8 (7.7%). In 3 patients (2.9%), n-LAB was discontinued due to bronchospasm in 2 and nausea in 1. The adverse effects occurring in the 49 n-ABD recipients were similar: cough in 12 (24.5% $p = 0.55$), mild difficulty breathing in 4 (8.2%; $p = 0.92$), and nausea in 3 (6.1%; $p = 0.73$). Prophylaxis had to be stopped in 2 patients (4.1%; $p = 0.69$) because of bronchospasm. Of 81 patients alive at 12 months after transplantation, 5 (6.1%) abandoned n-LAB prophylaxis spontaneously.

Discussion

This study assessed the feasibility, tolerability, and outcomes of n-LAB as prophylaxis for *Aspergillus* spp in lung transplant recipients. Our results show a low incidence of *Aspergillus* infection during the first year after transplanta-

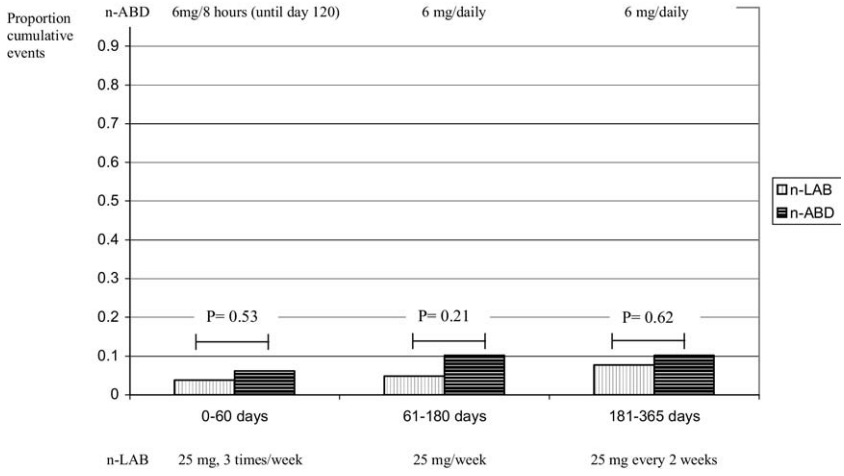

Figure 1 Proportional cumulative events of *Aspergillus* infection are shown over the key time points at which the nebulized liposomal amphotericin B (n-LAB) dosing schedule was changed. No significant differences were observed between the n-LAB group and the historical controls who received nebulized amphotericin B deoxycholate (n-ABD).

Table 3 Clinical Characteristics of Patients With Invasive Disease

Age	Transplant	Time elapsed, days	Prophylaxis	Main risk factor	Type of infection
51	Double	223	n-LAB	Refractory acute rejection	Invasive pulmonary
63	Single	12	n-LAB	None observed	Ulcerative tracheobronchitis
30	Double	0	n-ABD	Pre-Tx colonization	Invasive pulmonary with cerebral dissemination
54	Double	9	n-ABD	Isolated *Aspergillus* spp in donor	Ulcerative tracheobronchitis

IV LAB, intravenous liposomal amphotericin B; n-ABD, nebulized amphotericin B deoxycholate; n-LAB, nebulized liposomal amphotericin B; NR, no response; TX, transplantation.
Continued on page 529.

tion, with good tolerance to the drug and a convenient administration regimen.

In patients who do not receive prophylaxis, rates of invasive disease of about 15% have been described.[1,4,22,23] The 7.7% incidence of infection due to *Aspergillus* spp and 1.9% of invasive disease observed in the present study in a large lung transplant population with lengthy follow-up in 2 different centers indicate that prophylaxis with n-LAB is at least as effective as the other current choices. Although it is difficult to compare the incidence rates of *Aspergillus* infection between different studies, the reported rates of invasive disease with n-ABD prophylaxis of 0% to 7% are similar to ours.[7,8,10,21] Other forms of inhaled amphotericin B, such as amphotericin B lipid complex, have also been proposed as prophylaxis.

In a prospective, randomized, double-blind study, Drew et al[10] compared amphotericin B lipid complex and n-ABD. These authors documented only 2% of primary prophylaxis failure with *Aspergillus* infection and no cases of fungal pneumonia. The planned treatment was 25 mg once daily for 4 days, and the same dose once weekly thereafter. Similar results were reported by Borro et al[24] in a retrospective and noncontrolled study, which showed only 1.6% of invasive disease. The main limitation of these 2 studies was a short follow-up of 2 and 3 months, respectively.

Interestingly, *Aspergillus* infection developed in 4 of 13 patients in our study at more than 3 months after transplantation. Similarly, Singh et al[6] reported 28% of infections after 6 months, and Sole et al[7] reported 11 episodes of *Aspergillus* infection in 19 patients 12 months after transplantation. In a Spanish multicenter study, Gavalda et al[25] observed 43% of invasive disease 13 months after transplantation. Thus, there is considerable evidence supporting the idea of late *Aspergillus* infection after lung transplantation.

Nevertheless, the median duration of prophylaxis with n-ABD was 90 days in a survey of 50 centers across the world.[14] In the light of the published data and our experience, we believe that the duration of prophylaxis should be longer, especially in high-risk patients, including those with suture abnormalities, culture isolation of *Aspergillus* spp after transplantation, CMV disease, increased immunosuppression, and even BOS. Our current practice is to maintain prophylaxis for the life of the patient. In this situation, the fact that n-LAB can be administered every 2 weeks is convenient and increases adherence to treatment.

Azole anti-fungal drugs also are used as prophylaxis in lung transplant patients. Itraconazole is used alone or is combined with n-ABD in 44% of centers.[14] The incidence of invasive disease is reported at up to 6% with itraconazole.[23,26–28] In the largest studies, Minari et al[23] observed a decrease in the attack rate of invasive aspergillosis from 18.2% to 4.9% when itraconazole prophylaxis was implemented with amphotericin B in the immediate post-operative period, and Mattner et al[27] reported a rate of 6% in 101 patients.

Voriconazole has also been proposed as prophylaxis for these patients, with better results than itraconazole.[27] Husain et al[29] reported a 1.5% rate of invasive aspergillosis in 65 patients receiving universal prophylaxis with voriconazole. The theoretic advantage of voriconazole compared with the various types of inhaled amphotericin is that it may be effective prophylaxis against emerging fungi[30] that are usually resistant to amphotericin B and against non-respiratory fungal infections. Currently, the incidence of infections by emerging fungi is rising.[31] In our study, 1 patient died of a gastrointestinal tract infection caused by *Candida* spp and another died of invasive pulmonary disease by *Scedosporium prolificans*. Aguilar-Guisado et al[32] observed 8 cases of fungal pneumonia in 236 lung transplant recipients (3.4%) in 5 Spanish centers. Emerging fungi caused 3 of these pneumonia cases.

Prophylaxis with n-LAB was well tolerated, with only 2.9% of patients requiring treatment withdrawal due to adverse effects. Similar tolerance has been reported in other studies. In a study comparing the adverse effects of n-LAB and n-ABD, Lowry et al[12] reported good tolerance in both groups. The number of complaints vs the number of doses administered was 1.2% and 1.0%, respectively.[12] In a previous study,[16] we found no changes in the mean FEV_1 value before and after n-LAB. A significant FEV_1 decrease (14%) was observed in only 1 of 22 patients, who, nonetheless, remained asymptomatic.

Prophylaxis with inhaled amphotericin B in lipid complex also seems to be well tolerated. Palmer et al[33] reported that pulmonary mechanics worsened in less than 5% of 381 treatments administered in 51 patients. Drew et al[10] described a need to discontinue prophylaxis due to intolerance in 5.9% of 51 patients. In addition, no significant plasma concentrations of amphotericin B were found in lung transplant patients receiving n-LAB prophylaxis.[12,16] This characteristic averts the risk of nephrotoxicity and allows the

Table 3 *Continued from page 528.*

Diagnosis	*Aspergillus* spp	Treatment	Response	Outcome at 1 year
Nodules with "halo sign" at CT and purulent secretions at bronchoscopy	*A fumigatus*	IV LAB	Complete	Alive
Pseudomembrane at bronchoscopy	*A fumigatus*	Caspofungin, voriconazole	Complete	Alive
Necropsy	*A fumigatus*	IV LAB	NR	Dead
Pseudomembrane and ulcers at bronchoscopy	*A fumigatus*	IV LAB	NR	Dead

drug to be administered over lengthy periods. Therefore, n-LAB has an optimal safety profile. The main advantages with respect to the azole anti-fungal drugs are the absence of interactions with immunosuppressive drugs, including glucocorticoids,[34] and the lower incidence of adverse effects. In a study of voriconazole prophylaxis,[29] 14% of patients had discontinued prophylaxis due to side effects, most because of elevated liver enzymes.

Compared with n-ABD, n-LAB presents the advantage of a more convenient administration regimen, which will likely result in better adherence to treatment and a lower possibility of contamination of the nebulization system.[35] The optimal safety and convenience profile of the drug allows dose increases or prolongation of prophylaxis when other potential risk factors are present, such as suture abnormalities,[36,37] culture isolation of *Aspergillus* spp in the donor,[38] colonization before transplantation,[39,40] culture isolation of *Aspergillus* spp after transplantation,[3,4] CMV disease,[1,4,9,39,41] increased immunosuppression,[25,42,43] BOS,[7] and even single-lung transplantation.[2,6]

The cost of prophylaxis with n-LAB is higher than with n-ABD, but lower than with other drugs. The estimated cost of our current protocol (25 mg thrice weekly up to 60 days, 25 mg once weekly up to 180 days) is €2,997 per patient in the first 6 months. This figure is higher than the amphotericin B deoxycholate prophylaxis formerly used in our department, which was €511 for the same period (18 mg/day up to 120 days, and 6 mg/day thereafter). However, it is somewhat lower than itraconazole in solution (€3,591 with a dose of 400 mg/day) and much lower than voriconazole (€14,105 at a dose of 400 mg/day) for the same period. The cost of maintaining n-LAB prophylaxis after 6 months (25 mg every 2 weeks) in Spain is €140 per month.[44]

The main limitations of this study are its observational design and that the comparison group was a historical cohort. Because of the differing time frame of the 2 groups, it is likely that they had some inherent differences, such as dissimilar CMV prophylaxis and the documented differing percentage of patients who received induction therapy or mycophenolate. Moreover, it is difficult to factor in other potential differences, such as the expertise gained over time of professionals managing these patients, the progressive expansion of the criteria for lung donation, and the differences in clinical management that have occurred during this period.

Nonetheless, these limitations do not detract from the results showing that prophylaxis with nebulized liposomal amphotericin B at the dose and frequency described seems effective, safe, and convenient, and has the advantage of allowing prolonged administration if needed. Clinical trials comparing different drugs are required to determine the most suitable prophylaxis in lung transplantation.

Disclosure statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

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