LETTER TO THE EDITOR

Nebulized liposomal amphotericin prophylaxis in lung transplantation: shall we take it or leave it?

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Dear Editors,

We read with interest the paper by Peghin *et al.* [1] presenting the largest observational study on nebulized liposomal amphotericin B (n-LAB) as prophylaxis of aspergillosis in lung transplantation (LT). These authors adopted a lifelong approach with n-LAB administered at fixed dosage and frequency during the first 6 months and tapered thereafter.

With a mean postoperative follow-up of 2.56 years, they reported *Aspergillus* spp. infections and invasive aspergillosis (IA) at a rate of 12.8% and 5.3%, respectively.

As *Aspergillus* spp. is ubiquitous and it is transmitted by air, the degree of environmental exposure is critical and it contributes to the wide rate variability of *Aspergillus* spp. isolation in respiratory samples of lung transplanted patients as well as to the rate of IA, the latter ranging from 3% to 15% [2,3]. Local epidemiology must then be known when measuring the efficacy of antifungal prophylaxis.

Although tolerability and safety of prophylaxis with n-LAB have been consistently proven in preclinical and clinical studies, its universal adoption has never come because of unanswered questions as correct type of nebulizer for proper flow rates, optimal dosing, frequency and duration of treatment [4,5].

As about 25% of Italian LT is performed at our Institution, we also have tested the efficacy of prophylactic nebulized amphotericin B lipid complex (nABLC). This treatment is incorporated in the following protocol: starting the day after LT, all patients receive IV ABLC 5 mg/kg OD for the first 5 days post-transplant and then they are continued on nABLC 50 mg (100 mg if the patient is mechanically ventilated) daily for 4 days and then once weekly till discharge. We chose to administer IV ABLC in the immediate post-transplant period as nebulization into the transplanted lung may be erratic due to transient ventilation mismatch [6]. No further prophylaxis is then administered and patients are followed up regularly up to 6 months. Surveillance bronchoscopies are also performed at 1, 3 and 6 months and at any time by clinical criteria, including worsening of respiratory function or suspected pulmonary or bronchial disease.

From 2008 to 2012, 84 patients have received nABLC for an average of 4 weeks (range 2-8) (Table 1). Prophylaxis was stopped in one patient because of secondary effects (1.9%). Nine patients (9.5%) developed probable or proven IA, in seven cases (8.3%) by 8 weeks from transplantation and in two subjects (2.4%) from 8 to 24 weeks. Therefore, in the immediate

Table 1. Patient characteristics.

Characteristics	Patients *n* (%)
Patients	84
Age, mean (range)	46 (11–68)
Sex	
Male	47 (55.9)
Female	37 (44.1)
Lung disease	
IPF	35 (41.6)
CF	25 (29.7)
COPD	6 (7.1)
Others	18 (21.4)
Risk factors for aspergillosis	
CMV reactivation	29 (34.5)
Severe bacterial infections	41 (48.8)
Steroids	36 (42.8)
Diabetes	39 (46.4)
Immunosuppressive therapy	
CNI/azathioprine/steroids	55 (65.5)
CNI/MMF/steroids	21 (25)
Including mTOR inhibitors	8 (9.5)

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post-transplant period, we found no reduction in the rate of IA aspergillosis compared with our local historical data in this subset of patients (about 6%). It is also worth commenting on the low rate of IA over the 4 months from prophylaxis discontinuation. This likely depends on factors like type and degree of immunosuppression, environmental exposure, technical aspects of the transplant and antimicrobial use in the pre- and postoperative period. Also, since 2008, most of our patients are started on CMV prophylaxis for 6 months after transplantation and our low rate of CMV reactivation probably contributes to limit IA [7]. Of importance, this low rate of IA in lung transplant patients would make difficult to foresee a significant impact of prophylaxis with n-LAB and it further strengthens the importance of local epidemiology in the identification of subjects who may benefit from prophylaxis.

Although we do only report data on early-onset (<6 months) IA, our observation is relevant in the light of the fact that about 70% of *Aspergillus* infections occur within 6 months from transplantation [2,8].

Besides reported success and failure of n-LAB, and even considering that this approach has minimal side effects, relatively low cost and convenient schedule of administration, it should be noticed that it is still an off-label use of the parenteral drug. In fact, no randomized clinical studies have been conducted to address efficacy and methodology in the lung transplantation setting. A randomized interventional trial aiming to determine the safety and clinical efficacy of prophylactic nABL in lung transplant recipient has been recently suspended due to unavailability of funding (https://clinicaltrials.gov/ct2/show/NCT01254708). Fields like oncohaematology where data are available from prospective randomized multicenter trials did not observe significant benefit from inhalation therapy [9].

As a final consideration, the future scenario of antifungal prophylaxis may soon change as voriconazole will soon come off patent. This may offer an alternative and equally cheap prophylaxis of proved efficacy in lung transplantation.

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