Lung Transplanation

# Comparison of Prophylactic Regimens to Prevent Aspergillus Colonization in Lung Transplant Recipients

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**Abstract**

**Background:** *Aspergillus* infections limit survival in lung transplant recipients. This single center retrospective cohort describes our experience with multiple regimens that were used to prevent colonization with *Aspergillus* spp. after lung transplantation: no antifungal therapy (none), oral voriconazole (voriconazole), and inhaled liposomal amphotericin B (amphotericin).

**Methods:** Fungal cultures from bronchoalveolar lavages and bronchial washings for a predefined surveillance period following transplantation were assessed for all recipients who received a lung allograft between March 26, 2003 through December 16, 2013 (n = 108). Patients who were colonized prior to transplantation or had multiple treatment strategies before first colonization were excluded. Ninety-one patients were analyzed in groups determined by their initial prophylactic

regimen. The event-free survival from colonization up to 730 days after transplant was calculated by the Kaplan-Meier product limit estimator, and survival curves were compared using the log-rank test.

**Results:** There were no differences in time to colonization with *Aspergillus* spp. in lung transplant recipients among the groups in the post-transplant period. The point estimate for the hazard ratio (HR) for colonization in the post-transplant period was lower with voriconazole when compared to either amphotericin (HR = 0.71, p = 0.58) or none (HR = 0.37, p = 0.14).

**Conclusion:** Voriconazole showed a trend towards superiority in preventing colonization with *Aspergillus* spp. in lung transplant recipients. Due to a limitation in sample size and bias by indication, a dedicated randomized controlled trial is needed to determine the optimal prophylactic regimen in this patient group.

*Keywords: lung transplantation; anti-fungal; Aspergillus; prophylaxis; voriconazole; amphotericin*

## 1. Introduction

Lung transplantation is often the last line of therapeutic intervention for a variety of end stage lung diseases. In the last year, over 1600 lung transplantations were done among the 72 centers in the United States (1, 2). Infections account for the highest percentage of morbidity and mortality in lung transplant recipients (3). Similar to other solid organ transplants, post-transplant fungal infections are a common occurrence, with an incidence between 7% and 42% (4). Fungal infections represent a significant proportion of all-cause mortality in lung transplant recipients. They account for 20% of deaths within 30 days after transplantation and 38% of deaths between 31 days to 1-year post- transplantation (5).

Among fungal infections in lung transplant recipients, Aspergillus spp. are the most common organisms (6). There is a wide range of manifestations including airway colonization, tracheobronchitis, or frank invasive disease (7). The incidence of invasive aspergillosis in lung transplant recipients is much higher (40.5 cases/1,000 patient years) when compared to recipients of other solid organs: liver 2.1/1,000 patient years, heart 1.4 per 1,000 patient years, and renal 1.2 per 1,000 patient years (8). This comparison illustrates the prevalence and importance of Aspergillus spp. discovered in the lung transplant recipients.

Colonization of the airways with Aspergillus spp. is a risk factor for invasive infections in lung transplant recipients; it is estimated to occur in 25-30% of patients (9). Surveillance bronchoscopy is a proven method to assess for allograft rejection and infection. It has allowed transplant centers to detect asymptomatic fungal growth through the analysis of bronchial washings and/or bronchoalveolar lavage (BAL) (10). Most centers use some form of antifungal prophylaxis for the majority of their lung transplant recipients, including systemic voriconazole, inhaled amphotericin B, or systemic itraconazole (11). However, the optimal agent for Aspergillus prophylaxis post-transplantation is unknown (12).

The primary objective of this study was to describe the Aspergillus colonization-free time for three anti-fungal prophylactic strategies used by our lung transplant program from 2003 to 2013: systemic voriconazole, inhaled amphotericin B, or no antifungal therapy. These prophylactic strategies were used during distinct time periods, allowing us to compare three continuous historical control groups. We hypothesized that amphotericin was equivalent to voriconazole in preventing colonization with Aspergillus spp..

## 2. Methods

As part of a single center retrospective cohort study, each lung transplant done at our academic

urban medical center from March 26, 2003 through December 16, 2013 was evaluated (n = 108). All data was gathered using the hospital's electronic medical record systems. Baseline demographics and characteristics for each patient were also collected, including sex, age at the time of transplantation, indication for transplantation, and bilateral versus single lung transplantation.

The year of transplantation dictated the prophylactic regimen to be used. Patients transplanted earlier in the ten-year period received no prophylaxis against Aspergillus spp. Our lung transplant program then used systemic voriconazole for several years, and this has since been replaced by our current regimen, inhaled liposomal amphotericin B (LAB). Our institution's voriconazole strategy was 200 mg twice daily for 3 months and the LAB strategy was 6 months in duration (LAB 50 mg thrice weekly for 1 week while on the ventilator, 25 mg thrice weekly for 7 weeks, and 25 mg once weekly for 4 months). All fungal cultures from BAL and bronchial washings samples for the 108 patients through February 11, 2014 were reviewed. Only the cultures that grew Aspergillus spp. were considered a positive culture and included for further analysis. Positive fungal cultures that grew non-Aspergillus spp. were excluded as this was not the focus of the study. Those patients whose BAL and bronchial washing cultures were positive for Aspergillus spp. growth prior to their transplantation were excluded (n = 12). Patients whose prophylactic regimen changed prior to the date of the first positive culture for Aspergillus spp. were also excluded (n = 5). There were 91 patients included in the final analysis. An assumption we made in our study was that all of our patients followed our program's standard bronchoscopy schedule for lung transplant patients: 1, 3, 6, 9, 12, 18, and 24 months from transplantation. However, we knew that there would be some exceptions, such as an emergency or urgent indication for a bronchoscopy.

Each patient was categorized into their initial prophylactic group: no prophylaxis (none), voriconazole, or LAB. The fungal cultures from every patient's BAL and/or bronchial washing from the day of transplantation (day 0) up to the end of the surveillance period was reviewed. The end of the surveillance period was defined as either 730 days post-transplantation or February 11, 2014, whichever came first. The days free from colonization were counted until one of four end points was reached: initial Aspergillus spp. growth, death, crossover of treatment regimen, or the end of the surveillance period. Figure 1 depicts a graphical representation of the study design.

Table 1 Recipient Characteristics

| **Characteristic** | **N (%)** |
|---|---|
| **Gender** | |
| Male | 57 (63) |
| Female | 34 (37) |
| **Laterality of lung transplantation** | |
| Unilateral | 21 (23) |
| Bilateral | 70 (77) |
| **Primary indication for lung transplantation** | |
| Emphysema/Chronic obstructive pulmonary disease | 36 (40) |
| Alpha-1 antitrypsin deficiency | 1 (1) |
| Idiopathic pulmonary fibrosis | 33 (36) |
| Cystic fibrosis | 3 (3) |
| Sarcoidosis | 6 (7) |
| Idiopathic pulmonary arterial hypertension | 2 (2) |
| Bronchiectasis | 7 (7) |
| Bronchiolitis | 2 (2) |
| Other | 1 (1) |

Time to colonization was calculated as a survival curve for each of the various groups. The event-free survival from colonization was calculated by the Kaplan-Meier product limit estimator and survival curves were compared using the log-rank test. All transplants included in this study were compliant with The International Society for Heart and Lung Transplantation's ethics statement. The study was approved by Henry Ford Hospital's Institutional Review Boar (IRB #7891).

## 3. Results

A total of 108 patients underwent lung transplantation between March 26, 2003 and December 16, 2013. Twelve patients were excluded at the onset of the study because they were colonized prior to transplantation; 5 of the remaining patients had multiple prophylactic regimens prior to a positive culture result. Ninety-one patients met the inclusion criteria. The average age was 56.6 years (range 21-69 years) and 57 patients were male (63%) (Table 1). Twenty-eight patients were deceased by the end of the surveillance period. Twenty patients crossed over between treatment regimens at some point. Seventy patients (77%) had bilateral lung transplants; the most common indication was emphysema/chronic obstructive pulmonary disease (36 patients, 40%).

A total of 91 patients were analyzed in groups determined by their initial prophylactic regimen: none (n = 32), voriconazole (n = 19), and LAB (n = 40). The study was underpowered to detect statistically significant differences among the 3 different groups. There were no differences in time to colonization with Aspergillus spp. in lung transplant recipients among the groups in the post-transplant period. Although not statistically significant, the point estimate for the hazard ratio (HR) for colonization in the post-transplant period was lower with voriconazole when compared to either LAB (HR = 0.711, p = 0.5797) or none (HR = 0.374, p = 0.1412). A Kaplan-Meier survival curve comparing the 3 groups is depicted in Figure 2.

## 4. Discussion

Our results suggest a trend towards superiority of voriconazole compared to LAB in preventing airway colonization with Aspergillus in lung transplant recipients. This is an important finding for several reasons. Not only is the optimal prophylactic agent not known, there is also no consensus for a duration of treatment (12). However, evidence exists that some form of prophylactic antifungal agent is better than no agent at all (12). A recent worldwide survey conducted to gauge the use of prophylaxis shows that not all centers employed routine prophylaxis for Aspergillus spp. after lung transplantation. Fifty-eight centers responded to the survey, 34 of which employed universal prophylaxis within the first 6 months post-transplantation, most of whom used voriconazole (either as a monotherapy or combined with inhaled amphotericin or miconazole) (11).

Voriconazole is not without systemic side effects, especially hepatic dysfunction (13). Additionally, a number of drug interactions exist between

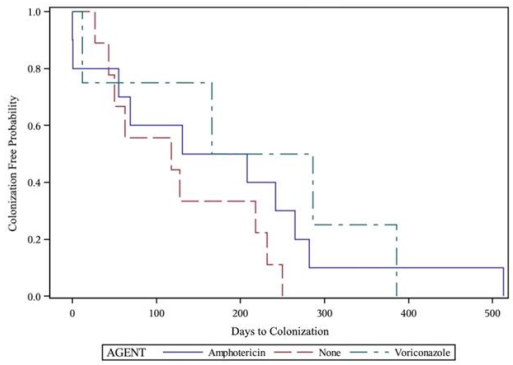


Figure 2. Kaplan-Meier Survival Curse Comparing the Three Prophylactic Regimen Groups

voriconazole and immunosuppressive medications that are used in lung transplant recipients (tacrolimus, cyclosporine, and sirolimus) (14). The dose of these immunosuppressive medications may need to be reduced if concomitantly used with voriconazole (15). Unlike inhaled amphotericin, voriconazole has the benefit of simple oral administration. A previous study designed to evaluate fungal infection rates in lung transplant recipients compared those who were managed with voriconazole (n = 65) or targeted

prophylaxis (n = 30) with itraconazole and/or inhaled amphotericin in patients with pre- or post-transplant Aspergillus colonization (except Aspergillus niger). The rate of invasive aspergillosis at 1 year was lower in lung transplant recipients who received voriconazole prophylaxis as compared to the cohort managed with targeted prophylaxis (1.5% vs. 23%; p = 0.001)(16). This evidence is conflicted by results of a more recent study which suggest that voriconazole prophylaxis does not have a significant effect in reducing Aspergillus infections in lung transplant recipients (17)

Amphotericin comes in a variety of aerosolized forms, and are generally well tolerated: amphotericin B lipid complex (ABLC), LAB, or amphotericin B deoxycholate (AMB-D)(18). ABLC and LAB are both lipid-based formulations of AMB-D. The agent used at our center is inhaled LAB. A study in patients receiving aerosolized ABLC or AMB-D found clinically significant differences in respiratory side effects, taste perversion, nausea, and vomiting favoring ABLC(19). Also, lipid-based formulations improve lung retention requiring less frequent administration. In animal models, the drug retention of LAB and ABLC was higher than AMB-D resulting in higher and prolonged concentrations of the antifungal in the lungs (20, 21). One animal model found LAB to be more long lasting than ABLC (22). A study in 2004 showed that aerosolized administrations of AMB-D and ABLC were effective in reducing invasive pulmonary fungal infection after transplantation (19). A more recent retrospective review showed that ABLC (50 mg every other day for 2 weeks, then once weekly for at least 13 weeks post-transplant) is a highly effective regimen (1/61 patients developed an invasive fungal infection due to A. fumigatus)(23). Although the aerosolized route appears to be promising, there are concerns regarding dose variations depending on the nebulizer system that is being used (24). Obstructive airway diseases impede drug delivery to the peripheral lung (25). This may be clinically significant since Aspergillus infections tend to be first documented in the native lung in patients with invasive aspergillosis(26).

Our selected voriconazole regimen is estimated to cost one and a half times more than our LAB regimen. The average wholesale price of the voriconazole regimen is $8443.02; voriconazole 200 mg administered orally twice daily for 3 months. The average wholesale price of the LAB regimen is $5584.13; LAB B 50 mg administered 3 times a week for 1 week (while on ventilator), then 25 mg 3 times a week for 7 weeks, and then 25 mg once a week for 4 months. This cost also includes a nebulizer with reusable tubing ($75 per month for 6 months), concurrent nebulized albuterol treatment (40 doses in total, each dose costing $0.90), and filters for the inhaled amphotericin (40 filters in total, each costing $16). This cost difference appears to hold true when comparing similar prophylactic regimens in indications other than post lung transplantation (27).

Depending on the site of infection, aspergillosis infections carries a 52%-55% overall mortality among lung transplant recipients (9). Those with tracheobronchitis have a lower mortality rate (23.7%-29%) when compared to those with invasive aspergillosis (67%-82%)(9). Invasive aspergillosis is more common in those patients who received a single lung transplant; subsequently, they have poorer outcomes (9). We were aware that colonization with Aspergillus does not indicate an active infection. However, any growth was labelled as prophylactic failure as all of these patients were immunocompromised and were at a high risk for invasive pulmonary aspergillosis (28).

Although there are no consensus guidelines for prophylaxis against Aspergillus spp. in lung transplant recipients, there is a paucity of randomized controlled trials to test regimens. At this time, it appears most centers either use systemic voriconazole, systemic voriconazole and inhaled amphotericin B, or systemic itraconazole (11).

Our study has several limitations. Being a single center retrospective cohort study, selection bias and information bias (misclassification bias) is a concern. Another weakness of our study is our sample size. With a sample size of 91 patients, we were unable to report any statistically significant findings. One patient's culture from the day of transplantation was positive for Aspergillus spp., that patient was not considered to be pre-colonized since in this study, pre-colonization was defined as growth of Aspergillus spp. in a BAL or bronchial washing sample obtained prior to the date of transplantation.

Although costly, more likely to have adverse effects, and more likely to have drug interactions

with immunosuppressive medications, systemic voriconazole may be more effective than inhaled amphotericin in preventing colonization with Aspergillus spp. in lung transplant patients in the first 2 years following transplantation. One noteworthy advantage of oral voriconazole over inhaled amphotericin is ease of use. Due to a limitation in sample size and potential bias due to the nature of the study design, a dedicated randomized controlled trial is needed to determine the optimal prophylactic regimen in lung transplant recipients.

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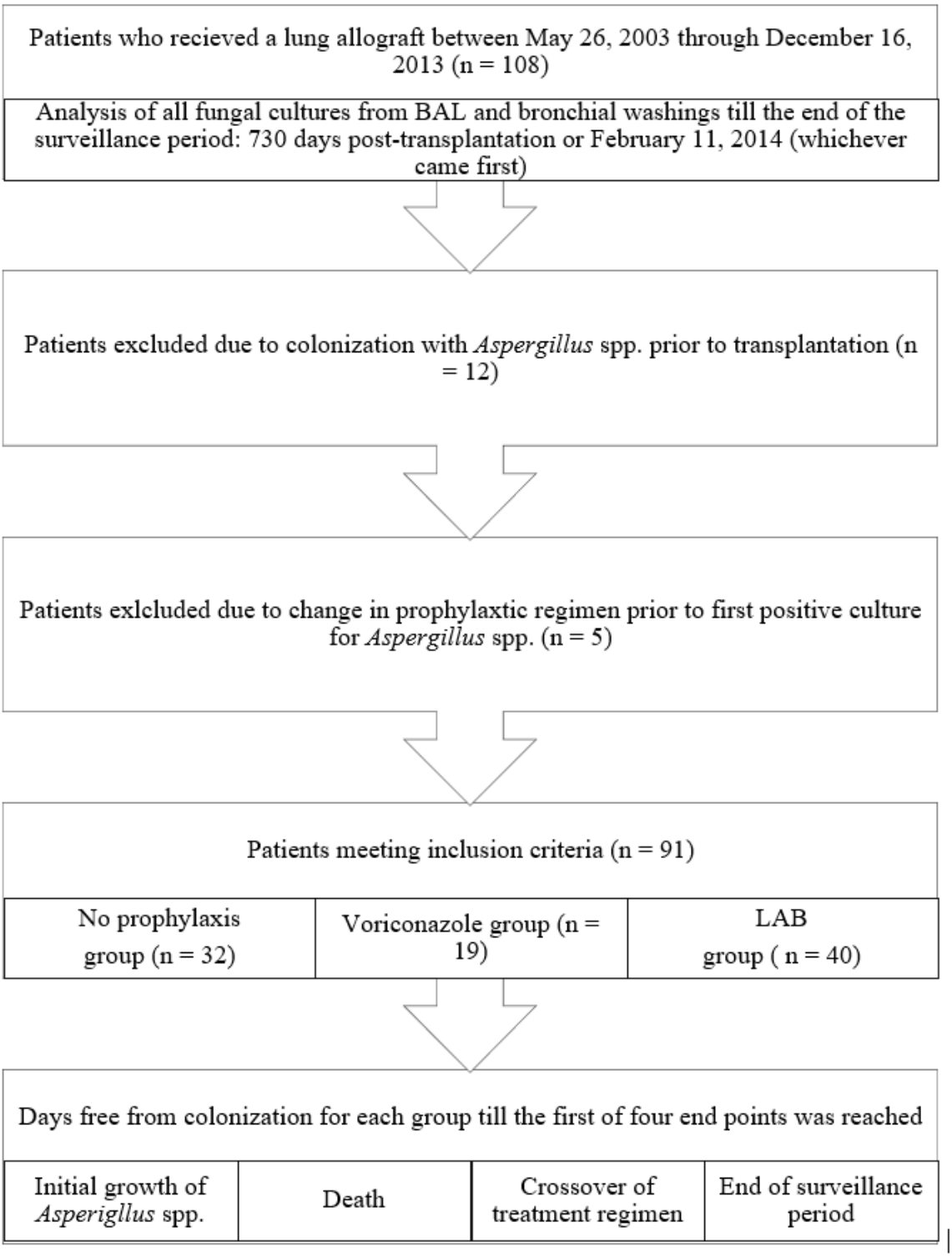


Figure 1. Graphical Representation of Study Design