Prophylactic Antifungal Agents Used After Lung Transplantation

Elizabeth Marino and Jason C Gallagher

OBJECTIVE: To review the data supporting available antifungal agents and compare regimens utilized to prevent fungal infection in lung transplant recipients.

DATA SOURCES: Literature retrieval was accessed through MEDLINE (1950 through October 2009) and United Network for Organ Sharing online database (available data through October 2009), using the terms lung transplantation, prophylaxis, and fungal infection. In addition, reference citations from publications identified were reviewed.

STUDY SELECTION AND DATA EXTRACTION: All articles or related abstracts in English identified from the data sources above were evaluated. Literature including adult lung transplant recipients who received systemic antifungal prophylaxis to prevent invasive fungal infections (IFIs) was included in the review.

DATA SYNTHESIS: IFIs after lung transplantation remain a common postoperative problem and are associated with high mortality. The lung is the most vulnerable solid organ to be transplanted, as it is the main organ responsible for gas exchange and therefore the high risk for pulmonary-related IFIs. It is most susceptible to developing an IFI, as it serves as a medium for organisms traveling from air to human tissue, potentially causing life-threatening infections. Such infections typically involve *Candida* and *Aspergillus* spp. and tend to occur within the first 12 months after transplant. Although there has been an increase in lung transplants performed over the past decade, no standard antifungal prophylactic regimen exists. Literature describing antifungals used to prevent IFI after transplant is scarce, which may be due to a lack of consistency in regimens used between transplant centers. Several regimens have been described utilizing different antifungal agents as both monotherapy and combination therapy. The majority of the literature reviewed here describes aerosolized amphotericin B formulations and azole antifungals demonstrating an overall decreased risk of fungal infection after lung transplantation. It has become the standard of practice to initiate some form of antifungal prophylaxis in these patients.

CONCLUSIONS: The risk of fungal infection after lung transplant is multifactorial and optimal prophylactic regimens should include agents with adequate activity against the most pathogenic fungi.

KEY WORDS: fungal infection, lung transplantation, prophylaxis.

Ann Pharmacother 2010;44:546-56.

Published Online, 23 Feb 2010, *theannals.com*, DOI 10.1345/aph.1M377

Since the first series of lung transplantations in the late 1980s there has been an increasing number of successful transplants.[1] Transplant recipients are highly susceptible for a multitude of infections that vary depending on type of transplant, potency of immunosuppression, and time lapsed since transplant. Lung transplant recipients are particularly at high risk for infection since the lung is the main organ responsible for gas exchange throughout the body. As a result, it serves as a medium for organisms traveling from air to human tissue, potentially causing life-threatening systemic fungal and bacterial infections. This mechanism, combined with potent immunosuppression initiated after transplantation, compromises the body's natural ability to resist bacterial, viral, and fungal infection.[2] Patients undergoing lung transplantation have up to a 30% chance of infectious complications due to fungi.[3,4] Fungal infections are the second most common cause of infectious complications in these patients secondary to bacterial infections and are associated with up to 60% mortality.[3,4] There has been an increase in the number of lung transplants performed, yet no standard antifungal prophylactic regimen exists. Little con-

Author information provided at end of text.

sistency exists in regimens used between transplant centers.[5] However, prophylaxis with several classes of antifungals and routes of administration over the past 2 decades has been successful. This paper reviews the data supporting available agents and discusses regimens utilized to prevent invasive fungal infections (IFIs) in lung transplant recipients.

Literature Search

Literature retrieval was accessed through MEDLINE (1950–October 2009) and United Network for Organ Sharing online database (available data through October 2009), using the terms lung transplantation, prophylaxis, mycosis, and fungal infection. In addition, reference citations from publications identified were reviewed. All articles or related abstracts in English identified from the data sources above were evaluated. Literature including adult lung transplant recipients who received systemic or aerosolized antifungal prophylaxis to prevent IFIs was included in the review.

BACKGROUND

Lung transplant recipients are most at risk for infection within the first year of transplant, with IFIs frequently occurring during the first 6 months.[2] These infections arise secondary to numerous mechanisms.[3,4,6] The immunosuppressive regimens used in lung transplant recipients are potent and often given in high doses for long periods of time, leading to suppressed humoral and cell-mediated immunity.[4,7] As immunosuppressant exposure increases, the likelihood that a patient will develop an opportunistic infection with a fungal pathogen increases.[4,7] Also, functional complications occur during the transplant procedure when the lungs are continuously exposed to the external environment. This allows ubiquitous environmental pathogens to enter the airway during surgery.[4,8] The procedure also results in abnormal interstitial structural changes, impaired mucociliary clearance, ischemic airway injury, and altered alveolar macrophage phagocytic function.[4,8,9] These manifestations weaken natural defenses that prevent infection, which do not recover for 6–12 months following transplant.[4,8,9] Finally, immunosuppression and weakened host cell defenses, coupled with suboptimal conditions of the donor lung, may result in new-onset primary infection, reactivated infection, or re-infection.[10]

Additional risk factors may also contribute to new infection in lung transplant recipients. These include pre- and postoperative chronic lung diseases that may have been treated with antifungals or prolonged courses of broad-spectrum antibiotics for multidrug-resistant organisms, early rejection episodes, graft dysfunction, concurrent viral and bacterial infections, and evidence of bronchiolitis obliterans syndrome.[2] In addition, disease caused by cytomegalovirus (CMV) is a known risk factor for development of invasive aspergillosis (IA), and concomitant prophylaxis with anti-CMV agents may reduce the risk of IA.[2,11-13] Another risk is exposure to disruptive environmental triggers, such as faulty ventilation systems or contaminated water supplies, predisposing patients to colonization with *Aspergillus* spp.[14-16] Prevention strategies used to decrease IFIs after lung transplant should include a combination of modalities to control for these risk factors.[8,17]

Prophylactic antifungal agents are frequently given to recipients as soon as possible after transplant. According to surveys conducted between 1999 and 2001 of centers that accounted for 66% of US and 63% of worldwide lung transplants, 69–76% of centers initiated some type of antifungal prophylaxis between days 0 and 1 after transplant and continued for at least 3 months.[5,18] Extended durations of prophylaxis were given to patients with a higher risk of fungal infections, such as those receiving prolonged courses of antibiotics or having positive fungal cultures before transplant.[4,19] Among the centers surveyed, the most common regimens included at least 1 of the following: aerosolized amphotericin B deoxycholate (AABD) (46–61%), itraconazole (37–46%), fluconazole (16–21%), and intravenous amphotericin B (2–25%).[5,18]

Complications Caused by Invasive Fungal Infection

The most common fungi that cause infection after lung transplant are *Candida* spp., *Cryptococcus neoformans*, *Pneumocystis jiroveci*, and the filamentous fungi, most notably *Aspergillus* spp. Dimorphic fungi also cause infection but are restricted by geographic areas.[10] Within the first month after transplant, patients are at highest risk of becoming infected or colonized with yeasts, chiefly, species of *Candida*. *Candida* spp. are normal flora of the gastrointestinal and female genitourinary tract; however, in the immunocompromised host, their potential for pathogenicity is increased.[20] It is sometimes difficult to determine whether an organism represents a colonizer versus a pathogen. *Candida* can colonize in the pulmonary cavity secondary to the invasive surgical techniques used during the transplant procedure and have the potential to progress to local infection of the pulmonary mucosal membranes or widespread dissemination.[2,8,21] Typical pathogenic complications from *Candida* can include fungemia, empyema, and necrotizing anastomotic infections.[8,21,22] Even in the lung transplant population, true *Candida* pneumonia is exceedingly rare.[23,24]

Mold infections, which are predominantly but not solely caused by species of *Aspergillus*, usually occur within the first 3–6 months after transplant.[2,8] Macrophages are the first line of defense against inhaled conidia that reach the

alveoli.[25] In the immunosuppressed state, macrophage dysfunction allows the conidia to germinate and form hyphae.[25] Molds enter the pulmonary cavity in a similar mechanism as yeasts. These infections can present as localized tracheobronchitis/anastomotic infection or invasive pulmonary infection with possible dissemination.[26] The incidence rate of invasive mold infection varies among solid organ transplants, but the highest rate of IA among transplant patients is in the lung transplant population, where it ranges from 8.4% to 17%, with a mortality rate reported as high as 60–80%.[2,9,27-33]

Aspergillus spp. and *Candida* spp. account for about 80% of fungal infections in transplant patients.[3,4,6,17,31,34] Therefore, it is essential for initial prophylactic regimens to include agents with activity against both of these organisms in addition to other pathogenic fungi.

Review of Agents

POLYENE ANTIFUNGAL AGENTS

Amphotericin B is a member of the polyene antifungal class and exerts its fungicidal activity by inhibiting fungal ergosterol, a major component of the fungal cell wall, thus disrupting fungal cell wall synthesis, resulting in leakage of the cell components with subsequent cell death.[35,36] Amphotericin B has a relatively broad spectrum of activity against various fungi including *Aspergillus* and *Candida* spp.[29,37] Several aerosolized formulations of amphotericin B have been utilized and are administered via nebulized inhalation for the prophylaxis of IFI in a variety of transplant recipients.[38-44]

Aerosolized Amphotericin B Deoxycholate

A study published by Reichenspurner et al. was one of the first to publish positive results of prophylactic therapy with aerosolized amphotericin B deoxycholate (AABD) in transplant patients.[38] The study included a mix of 22 lung, 75 heart, and 27 heart-lung transplant patients who received prophylaxis with AABD 5 mg 3 times daily titrated to 20 mg 3 times daily via nebulizer and compared them to a similar cohort of patients who did not receive prophylaxis. AABD was administered as soon as possible after transplant for an unreported period of time. At 3- and 12-month follow-up, the linearized rate/patient of overall IFI and *Aspergillus*-related infection was significantly lower in AABD-treated patients (Table 1) compared to patients who did not receive prophylaxis. Most patients tolerated the study drug, with less than 2% discontinuing treatment due to adverse events, most notably mild nausea. This study had many limitations, such as a relatively small sample size, lack of randomization, and failure to report useful data such as duration of prophylaxis, concomitant immunosuppressive agents, use of concomitant antibiotics or CMV prophylaxis, and the number of patients who developed IFI. However, it was one of the early reports supporting the role of fungal prophylaxis in lung transplant recipients and the results of this study prompted others to investigate AABD as an option for fungal prophylaxis.

Monforte et al. published a study describing risk factors and rates of acquiring IFIs in their first series of lung transplant patients from 1990 through 1997 who received AABD prophylaxis.[39] Fifty-five patients were included in the analysis, of which 44 received prophylaxis with AABD 6 mg every 8 hours for 120 days, then converted to 6 mg daily and continued indefinitely (Table 1). Patients with evidence of sepsis after transplant received intravenous therapy with cefuroxime 1.5 g 3 times daily or amoxicillin/clavulanate 2 g 3 times daily plus aztreonam 1 g 3 times daily, and all patients received CMV prophylaxis with intravenous ganciclovir. After a median follow-up of 14 months, 33% of patients developed IA. On multivariate analysis, AABD was shown to be significantly protective against the development of IA (OR 0.13 [95% CI 0.02 to 0.69]). One patient discontinued treatment secondary to bronchospasm and common adverse events included 32% cough, 9% mild bronchospasm, and 7% nausea.

Aerosolized Amphotericin B Lipid Complex

While AABD is a potentially effective therapy to prevent IFIs, not all patients are able to tolerate the nebulization. In the hematologic stem cell transplant population, discontinuation rates with AABD have been reported as high as 25–48% due to intolerances such as wheezing, cough, taste disturbances, and bronchospasm.[40,41] Lipid formulations of amphotericin B have extended tissue half-lives in animal models and are associated with lower rates of adverse events.[45,46] Palmer et al. were the first to investigate the use of aerosolized amphotericin B lipid complex (AABLC) in 51 lung/heart-lung transplant patients.[44] The primary endpoint was to assess safety and tolerability of AABLC 50–100 mg inhaled daily for 4 days, followed by once-weekly administration for an average of 2 months. A secondary endpoint was the prevention of IFIs after 2 months of prophylaxis. One hundred eighty-eight treatments were administered to evaluable patients. In terms of safety, few adverse events were reported. Nausea and/or vomiting and taste disturbances were most frequent and occurred in 1.6% of treatments administered. Cough, dyspnea, wheezing, or significant bronchospasm were not documented. Only 1 patient withdrew from the study due to medication intolerance. In terms of efficacy, 4% of patients developed IFIs and 8% of patients developed an extrapulmonary infection due to *Candida* spp. (Table 1).

The results of this study support a favorable tolerability profile with AABLC in the short-term setting; however, with the small sample studied and lack of a comparison

group, it was not designed to show a difference in preventing IFI compared to the standard of AABD at that time.

As a result, Drew and colleagues studied AABLC 50–100 mg daily compared to AABD 25–50 mg daily for 4 days followed by weekly administration for 7 weeks in a prospective, randomized, double-blinded comparison. This study was primarily powered to detect differences in adverse event rates to assess the ability of AABLC to optimize patient adherence to antifungal prophylaxis. Secondary outcomes included rate of primary prophylaxis failure defined as incidence of IFIs and number of patients who required systemic antifungal therapy.[42] In order to detect a 7% difference between the groups, 275 patients were needed in each arm. One hundred patients (51 in the AABLC group vs 49 in the AABD group) were treated (Table 1). At the end of follow-up, the AABLC group had fewer reported treatment-related adverse events (13.7% vs 28.6%) compared to AABD and had lower discontinuation rates (5.9% vs 12.2%), respectively. In addition, 14 of 50 patients in the AABLC (28%; 95% CI 0.16 to 0.42) group experienced an adverse event compared to 21 of 49 patients receiving AABD (42%; 95% CI 0.29 to 0.59) and the authors concluded that patients in the AABD arm were more likely to experience an adverse event (OR 2.16; 95% CI 1.10 to 4.24; p = 0.02). Patients receiving AABLC and AABD had similar rates of failed prophylaxis (11.8% vs 14.3%, respectively), with both groups receiving comparable immunosuppression. Due to the number of actual patients enrolled in this study, power was not met and statistical data were not reported.

Although the study was able to show a more favorable tolerability profile with AABLC, there were some limitations of the relatively short observation period of only 2 months. Patients are at an increased risk of developing fungal infections, up to 6 months posttransplant, yet patients in this study were given prophylaxis for a median of only 7 weeks.[33,47,48] Despite the low incidence of fungal infection in the follow-up period, longer durations of prophylaxis may have been warranted.

Aerosolized Liposomal Amphotericin B

To date, there are limited controlled studies reporting use of aerosolized liposomal amphotericin B (ALAmB) for prophylaxis in lung transplant. Most of the literature reports favorable pharmacokinetic and safety profiles for the ALAmB formulation, but limited efficacy data are available.[49,50] Monforte et al. performed a study that is published in abstract form discussing the results of an open-label study designed to describe the pharmacokinetics and assess the safety and efficacy of ALAmB 25 mg 3 times a week for days 0–60 after transplant, followed by weekly administration for 2–6 months, then twice-monthly administration given to 118 lung transplant recipients; 40 patients received ALAmB immediately after transplant and 78 were switched from AABD shortly after transplant.[43] Results of plasma sampling did not detect drug concentrations, yet bronchial alveolar lavage sampling detected significant concentrations of drug in the lung tissue. The authors reported no cases of IA during the prophylaxis period of 12 months. Three patients did withdraw from the study secondary to nausea, cough, or dyspnea. Although efficacy data in this population are scarce, ALAmB has been used in patients with prolonged neutropenia undergoing chemotherapy to prevent invasive pulmonary aspergillosis (IPA). The findings showed a significant difference in preventing IPA and excellent tolerability compared to placebo.[51] ALAmB is likely to be an acceptable option in lung transplant patients as well, but currently there are limited data to support its use in this patient population.

AZOLE ANTIFUNGALS

The azole antifungals exert their activity by inhibiting the cytochrome P450–dependent enzyme lanosterol 14-alpha-demethylase, which is active in the conversion of lanosterol to ergosterol, an essential component of the fungal cell membrane.[52] Inhibition of this pathway leads to accumulation of 14-alpha-methylsterols on the fungal surface, which results in arrest of fungal replication.[52] The azoles are systemic agents and many are available in both oral and intravenous formulations. Common agents used in post-lung transplant protocols are fluconazole, itraconazole, and voriconazole.[5,18] Fluconazole is available in both intravenous and oral formulations and has activity against common *Candida* spp. and some dimorphic fungi, but lacks activity against molds.[52] Itraconazole has activity against *Candida* spp., dimorphic fungi, *Aspergillus* spp., and some other molds and is often given as an oral solution.[52] Itraconazole is associated with erratic absorption, and therapeutic drug monitoring of itraconazole and its active metabolite is necessary to ensure adequacy.[30,53] Voriconazole expands on the spectrum of activity of itraconazole, has a more favorable pharmacokinetic profile, and has been evaluated in larger studies in lung transplant recipients.[9] Its spectrum of activity includes *Candida* spp., dimorphic fungi, *Aspergillus* spp., and many other molds.[52] Posaconazole has not been studied in lung transplant patients; however, it is approved for prophylaxis in patients undergoing hematopoietic stem cell transplant, graft versus host disease, and patients with hematologic malignancies and neutropenia related to chemotherapy.[52] Posaconazole provides coverage against a broad spectrum of yeasts, molds, and dimorphic fungi, and expands on voriconazole's spectrum to include activity against the Zygomycetes.[52] Due to their ease of administration and favorable safety profile, the azole antifungals have been incorporated into many antifungal prophylaxis protocols for lung transplant patients.[5,18]

Table 1. Summary of Clinical Trials of Antifungal Prophylaxis in Lung Transplant Patients

Reference	Design	Pt. Age (y)	Intervention	Endpoints, n/N (%)	Concomitant Immunosuppression or CMV Prophylaxis	Adverse Events, n/N (%)
Calvo (1999)[19]	SC, consecutive pts. with prophylaxis vs cohort with no prophylaxis	38 (14–58); lung	Lung: 52 pts., prophylaxis: fluconazole 200 mg q12h + AABD 0.2 mg/kg q8h + nystatin oral wash q6h Lung: 13 pts., no prophylaxis	IFI in the early high-risk post-operative phase (0–2 mo), 0/65 (0) Mean (range) days of prophl-axis, 42 (30–92)	Immunosuppression, C + CYA + Az + AT (first 20 pts.) Prophylaxis, ganciclovir, first 21 days	NR
Drew (2004)[42]	R, DB, P, SC	51 ± 13.3; lung or heart-lung (n = 100)	AABD 25 mg/day[a] daily × 4 days then weekly for 7 wk (n = 49) AABLC 50 mg/day[a] for 4 days and weekly for 7 wk (n = 51)	Incidence of IFI AABD 7/49 (14.3), IA 1/49 (2), *Candida*-related 6/49 (12.2) AABLC 6/51 (11.8), IA 1 (1.9), *Candida*-related 5 (9.8) No reported difference between groups	Immunosuppression, TAC or CYA + Az + C Prophylaxis, ganciclovir + CMV, IgG when indicated	AABLC: ≥1 AE; 14/50 (28) wheezing, cough, 4/48 (8.3) SOB Discontinued treatment, 3/51 (5.9) AABD: ≥1 AE; 21/49 (42.9) wheezing, cough, 17/47 (36.2) SOB Discontinued treatment, 6/49 (12.2)
Husain (2006)[9]	Nonrandomized, SC, retrospective, sequential, con-secutive pts.	51–54.5; lung (n = 95)	Voriconazole 6 mg/kg iv × 2 doses, then 200 mg orally bid for minimum of 4 mo (n = 65) Other: fluconazole 200 mg/day (n = 15/30) or itraconazole 200 mg bid ± AABD for 4–6 mo if *Aspergillus* spp. present on lung aspirate pretransplant (n = 15/30)	Primary endpoint, IFI 1 y after transplant, n: voriconazole IA 1/65 (1.5) vs 7/30 (23) in other group (p = 0.001) Secondary endpoint: non-*Aspergillus* infections (n), fungal colonization and safety Non-IA 2/65 (3) in voriconazole vs 7/30 (23) in other group (p = 0.004)	Induction immunosuppression, daclizumab, AT (rabbit), or alemtuzumab Maintenance immunosuppression, TAC ± C Prophylaxis, valganciclovir	Elevated LFT results ≥ 3× ULN, voriconazole 47/65 (73) vs other 11 (41) Discontinuation rates due to AE, voriconazole 9/65 (14) vs other 2/27 (7.4)
Minari (2002)[28]	Retrospective review of prophylaxis vs cohort with no prophylaxis	47; lung[b] (n = 183)	Prophylaxis: AABD 5–10 mg bid converted to itraconazole 200 mg/day (n = 81) No prophylaxis (n = 88)	Attack rate of IA, lung transplant, 24/188 (12.8) Prophylaxis, 4/81 (4.9) No prophylaxis, 16/88 (18.2) (p < 0.05)	Immunosupression, CYA + C + Az Prophylaxis, NR	NR
Monforte (2001)[39]	Retrospective review of prophylaxis vs cohort with no prophylaxis; assessed risk factors for IA	43.1 (15–67); lung (n = 55)	AABD 6 mg q8h × 120 days; then 6 mg/day indefinitely (n = 44) No prophylaxis (n = 11)	Risk factors for IA Developed IA on AABD; 10/18 (55.6) vs 34/37 (91.9) (p < 0.01)	Immunosuppression, CYA+ Az with occasional substitution for MMF and MTX Prophylaxis, ganciclovir for 45–90 days after transplant based on CMV status	Cough, 14/44 lung(32); mild bronchospasm, 4/44 (9); nausea 3/44 (7) Discontinued therapy due to bronchospasm, 1/44 (2.2)
Palmer (2001)[44]	P, OL, noncomparative, SC	44.8 ± 14.4; lung or heart-lung (n = 51)	AABLC 50 mg[a] Each group treated daily for 4 days, then once weekly for 2 mo; longer prophylaxis permitted outside the study at the investigator's discretion (n = 51) Total treatments, 381 (98 ventilated and 283 extubated pts.), 7.6 ± 1.7 treatments/pt. (mean ± SD)	Primary endpoint, safety, tolerability, extubated pts., 188 treatments given, excellent tolerance documented Secondary endpoint, incidence of IFI, *Candida* anastomosis, 2/51 (4); extrapulmonary fungal infections, 4/51 (8)	Immunosuppression, CYA + Az + C Prophylaxis, ganciclovir ± CMV IgG	Nausea ± vomiting, 2/51 (3.9); taste alteration, 2/51 (3.9); cough/dyspnea, 0/51 (0) Discontinued treatment due to nausea or vomiting, 1/51 (2)

Reichenspurner (1997)[38]	Retrospective review of prophylaxis vs matched cohort with no prophylaxis	AABD, 39.8 y; lung, heart-lung, or heart (n = 124) Cohort, 40 y; lung (n = 22)	AABD 5 mg tid titrated to 20 mg tid within 5 days (n = 124) Cohort (n = 101)	Incidence of IFI at 3- and 12-mo follow-up (treated group vs control group) 3 mo: overall IFI rate/pt.: 0.08 vs 0.20 ($p < 0.05$) IA rate/pt.: 0 vs 0.11 ($p < 0.005$) *Candida*-related rate/pt.: 0.03 vs 0.04 12 mo: overall IFI rate/pt.: 0.04 vs 0.07 ($p < 0.05$) IA rate/pt.: 0.02 vs 0.12 ($p < 0.005$) *Candida*-related rate/pt.: 0.03 vs 0.06	Immunosuppression, triple drug regimen, NR Prophylaxis, NR	Mild nausea and vomiting, 10/126 (7.9) Discontinued treatment, 2/124 (1.6)

AABD = aerosolized amphotericin B deoxycholate; AABLC = aerosolized amphotericin B lipid complex; AE = adverse event; AT = antithymocyte; Az = azathioprine; C = corticosteroids; CMV = cytomegalovirus; CYA = cyclosporine; DB = double-blind; IA = invasive aspergillosis; IFI = invasive fungal infection; IgG = immunoglobulin G; LFT = liver function test; MMF = mycophenolate mofetil; MTX = methotrexate; NR = not reported; OL = open-label; P = prospective; R = randomized; SC = single-center; SOB = shortness of breath; TAC = tacrolimus; ULN = upper limit of normal.

[a]Doses doubled for ventilated pts.

[b]Includes heart-lung pts. who were not included in the analysis.

Itraconazole

The Cleveland Clinic Foundation investigated prophylaxis with itraconazole in 2046 solid organ transplant patients consisting of 183 lung, 439 liver, 686 heart, 5 heart-lung, 38 kidney-pancreas, and 695 renal transplant recipients (Table 1).[28] The primary objective was to assess the incidence and rate of IA in solid organ transplant and determine the implications of routine prophylaxis in lung transplant patients. Patients were given AABD 5–10 mg twice daily immediately post-transplant, then treatment was converted to 200 mg of itraconazole daily. Routine monitoring of itraconazole was performed to maintain concentrations >50 ng/mL, since itraconazole absorption can be unpredictable due to its dependence on gastric acidity. Lung transplant patients had the highest attack rates of IA (12.8%), with an incidence of 40.5/1000 patient-years and with the greatest incidence occurring within the first year (79%). Those who received itraconazole prophylaxis (4/81, 4.9%) were less likely to develop IA compared to those who were not receiving any prophylaxis (16/88, 18.2%) ($p < 0.05$).

Several interesting implications arose from this study, the first being that the highest incidence of fungal infections was most likely to occur in lung transplant recipients compared to other solid organ transplants. The second is the decrease in fungal infections observed in patients receiving prophylaxis with itraconazole. According to the survey conducted by Dummer et al. that was published in close temporal proximity to this study, 76% of centers surveyed routinely initiated antifungal prophylaxis, but only in specific subgroups, most commonly, patients with cystic fibrosis or chronic obstructive pulmonary disease.[18] Thus, the results from this study[28] highlighted the increased risk of severe fungal infections in the lung transplant population and indicated the need to initiate prophylaxis in all lung transplant patients for at least 1 year. Finally, it was noted that a high percentage of IA occurred within the first year of therapy, 46% within the first 9 months, thus demonstrating the need to potentially continue prophylaxis in lung transplant patients for greater than 30–90 days post-transplant, which was previously reported in aerosolized amphotericin B trials.

Voriconazole

Investigators at the University of Pittsburgh transplant center conducted a retrospective study to assess IA prophylaxis in 95 lung transplant patients comparing 2 doses of voriconazole 6 mg/kg intravenously twice daily followed by 200 mg orally twice daily continued for a minimum of 4 months versus other antifungal regimens consisting of either fluconazole 200 mg daily or itraconazole 200 mg twice daily with or without AABD (dose not reported) immediately after transplant and followed for 1

year (Table 1).[9] At that time, voriconazole had established evidence to support its use in the bone marrow transplant population, yet limited data were published suggesting benefit after lung transplantation.[54-56] The primary endpoint was the incidence of IFI, non-*Aspergillus* infections, fungal colonization, and safety. In addition to antifungal prophylaxis, patients also received CMV and *Pneumocystis* pneumonia prophylaxis. A significantly lower rate of IA 1 year after transplant was noted in the voriconazole group. One year after prophylactic therapy was discontinued, 40% of patients in both groups had evidence of fungal colonization. Interestingly, patients who received voriconazole had a greater incidence of non-*Aspergillus* colonization, primarily with *Candida* spp. Overall mortality was lower in the voriconazole group, although the incidence of adverse events was significantly higher. Specifically, there was a 3-fold higher incidence of elevated results of liver function tests. Ten percent (7/65) and 3% (2/9) of patients discontinued therapy due to increases in the values shown on those tests and intractable nausea/vomiting, respectively. Although the incidence of fungal colonization at the end of the study period was not significantly changed, the time until colonization occurred was prolonged in the voriconazole group (248 vs 71 days). The extended duration for which voriconazole prolongs development of colonization may be advantageous. As time progresses, patients tend to require less immunosuppression, natural host defense mechanisms altered during the transplant procedure begin to regain activity, and the infrastructure of lung anastomoses is relatively healed, thus decreasing the ability of colonized organisms to progress to pathogenic disease.[57] A potential limitation is the nonlinear pharmacokinetic and significant interpatient variability of voriconazole absorption that warrants therapeutic drug monitoring, a process that is yet to be standardized for this drug.[58-60]

Combination Therapy

Extrapulmonary fungal infection rates were reported in only 2 of the above studies, with an incidence ranging from 3% to 8%.[42,44] Without systemic concentrations of aerosolized antifungals, it is not surprising that extrapulmonary fungal infections occur (particularly candidiasis), and combination therapy with aerosolized amphotericin B products plus systemic azole antifungals may be beneficial.[44] Calvo et al. performed an analysis of 52 lung transplant patients who received antifungal prophylaxis with fluconazole 200 mg twice daily, plus AABD 0.2 mg/kg 3 times daily, plus nystatin oral wash 500,000 units 4 times daily, compared to a control group of 13 patients who received no prophylaxis. Patients were followed for a mean of 19 months.[19] Prophylaxis was initiated for the first 30 days after transplant and was continued for longer durations in patients who developed bacterial infection requiring broad-spectrum antibiotics or in patients who were colonized with *Aspergillus* spp. pretransplant. Prophylaxis was given for a mean of 42 days and, at the end of analysis, there were no reported cases of IFIs in the treated group versus the control group (3/13) during the early postoperative phase. There were also no invasive complications at incision sites or adverse events related to the study medications reported. After discontinuing prophylaxis, the investigators did not observe a higher prevalence or severity of fungal infection between the 2 groups. Although there are limited data published using combination antifungal prophylaxis, many transplant centers report using agents with different mechanisms of action in their lung transplant protocols.[5,18]

Echinocandins

The echinocandin class of antifungals (caspofungin, micafungin, anidulafungin) exert their effects by inhibiting the synthesis of β(1,3)-D-glucan, an essential component of the cell wall of susceptible fungi.[8] The echinocandins have documented efficacy against *Aspergillus* and *Candida* spp. infections and their excellent tolerability profile, coupled with a low propensity for drug interactions, makes them an intriguing choice for prophylaxis in lung transplant patients.[8] Micafungin has been shown to be more efficacious in preventing IFIs in hematopoietic stem cell transplantation patients when compared to fluconazole; however, there are no published studies in lung transplant patients utilizing echinocandins for prophylaxis.[61] The echinocandins have a narrower spectrum of antifungal activity against filamentous fungi than amphotericin B and newer azoles, and their current limitation to intravenous formulations is disadvantageous. Studies designed to demonstrate prophylactic efficacy in lung transplant patients are needed before routine use of these agents is considered viable for prophylaxis, and it is unclear if such studies are warranted.

Discussion

There is a clear benefit in using antifungal agents after lung transplant in order to decrease the risk of IFI associated with high mortality. To date, older antifungal regimens including aerosolized amphotericin B have the most cumulative data and are attractive options compared to systemic therapy for several reasons. Administering aerosolized forms of amphotericin B allows for local administration of the drug into pulmonary tissue to attain effective concentrations needed to prevent pulmonary fungal infections and perhaps limits the need for systemic amphotericin B associated with nephrotoxicity, electrolyte wasting, and infusion-related reactions.[49,50] Two pharmacokinetic studies have been published measuring systemic exposure of various aerosolized amphotericin B products. Both studies did

not report systemic concentrations of amphotericin B.[49,50] Various transplant centers have adapted the AABLC protocol of Drew and colleagues. The use of AABLC, which tends not to foam during nebulization, is generally more expensive compared with AABD but is administered less frequently than AABD and yields high adherence rates, with minimal adverse events.[45,46,62,63] Aerosolized drug delivery is also less worrisome in terms of drug-drug interactions with various immunosuppressive medications compared to azole antifungals that require frequent monitoring. In comparison with the systemic azole antifungals, AABD products are similar in costs to fluconazole and itraconazole, and AABLC products are similar in costs to oral voriconazole.

Limitations to studies of aerosolized amphotericin B formulations are the lack of large sample sizes studied to assess efficacy and lack of generalizability. Most studies included relatively small groups of patients, reported results from cohort analyses, or were retrospective comparative analyses that lack adequate power and statistical analysis. However, it may be difficult to conduct larger clinical studies as it has been estimated that 5700 patients would be needed to show a difference in the observed rates of invasive disease between formulations.[42] Although aerosolized amphotericin B attains concentrations in the lung high enough to prevent local infection, use of inhaled products will most likely not protect against extrapulmonary fungal infection.[8,43,49] According to 1 study, candidemia can account for up to 18% of bloodstream infections in newly transplanted patients.[21] Patients who have received transplants are at risk of developing extrapulmonary infections, and clinicians should consider including systemic antifungal prophylaxis in their post-transplant regimen. In addition, there have been reports of contamination with nebulization systems used for administration of amphotericin B, which may be an additional source of infection.[64] Despite these limitations, aerosolized forms of amphotericin B remain viable options to prevent fungal infections after lung transplant.

The extended-spectrum azole antifungals offer attractive benefits to lung transplant patients, as they are easily administered, have extended antifungal activity against many pathogenic fungi, and are probably more effective in preventing extrapulmonary infection. There is increasing research with these agents, as smaller studies have demonstrated adequate protection for lung transplant recipients. However, the azole antifungals are not without limitations. The most significant limitation is the association of drug interactions with immunosuppressants. These agents are both substrates and inhibitors of the cytochrome P450 system and often require dose adjustments and frequent monitoring when given with interacting drugs. In addition, itraconazole and voriconazole have pharmacokinetic limitations that require therapeutic drug monitoring. Finally, intravenous voriconazole is solubilized in a cyclodextrin vehicle associated with possible toxicity when administered to patients with renal insufficiency.[65,66] Fluconazole is the azole antifungal with the lowest potential for drug interactions, and it has the most predictable pharmacokinetics but has an antifungal spectrum that limits its utility.[67] Fluconazole also remains the least expensive systemic antifungal; however, using broader-spectrum, more expensive agents such as voriconazole may be more efficacious in preventing an infection and, in turn, decreasing overall treatment costs.

Summary

The aerosolized amphotericin B products range from relatively inexpensive to moderately expensive and prevent both *Candida* and *Aspergillus* pulmonary complications. Reported discontinuation rates are low and are lowered further with use of the lipid formulations. As lung transplant patients require prolonged antifungal prophylaxis, the ease of once-weekly administration makes the lipid products attractive options. However, these agents have been studied for only short durations and may be more beneficial in the early post-transplant period. In comparison, discontinuation rates for systemic azole antifungal agents are also low and, although they are more expensive and require additional monitoring, the newer azoles may be optimal agents for use in the later phase of post-transplant prophylaxis. They have extended coverage against *Candida* and *Aspergillus* spp., are given orally, and have been studied for longer durations than the amphotericin B products. As with any antifungal agent, prolonged use may increase the risk of selecting resistant fungal strains, making future treatment more difficult. Therefore, it may be beneficial to initiate one agent in the initial post-transplant period and switch to another agent with a different mechanism of action in the delayed post-transplant period.

The risk of fungal infection in lung transplant recipients is multifactorial and optimal regimens should include agents with activity against the most pathogenic fungi. With aerosolized amphotericin B formulations and azole antifungals both demonstrating a decreased risk of fungal infection after lung transplantation, it has become the standard of practice to initiate at least 1 of these agents. Insufficient data exist to recommend a prophylactic treatment of choice and additional well-designed randomized trials comparing different agents in this population would be useful in helping transplant centers standardize prophylactic care. Until more data are generated, clinicians should be cognizant of overall costs and patient adherence in choosing a prophylactic regimen in lung transplant recipients who will require months of adequate prophylaxis to decrease mortality.

Elizabeth Marino PharmD BCPS, Clinical Pharmacy Specialist, Infectious Diseases, Christiana Care Health System, Newark, DE

Jason C Gallagher PharmD BCPS, Clinical Assistant Professor, Clinical Specialist, Infectious Diseases, Department of Pharmacy Practice, School of Pharmacy, Temple University, Philadelphia, PA

Reprints: Dr. Gallagher, Department of Pharmacy Practice, Temple University School of Pharmacy, 3307 N. Broad St., Philadelphia, PA 19140, fax 215/707-8326, jason.gallagher@temple.edu

Financial disclosure: Dr. Gallagher is on the Speaker's Bureau of Astellas Pharmaceuticals, has served on an Advisory Board for Pfizer, and has received a research grant from Merck.

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Repasar el uso de los Agentes Antifúngicos Profilácticos Después de Trasplante Pulmonar

E Marino y JC Gallagher

Ann Pharmacother 2010;44:546-56.

EXTRACTO

OBJETIVO: Repasar los datos disponibles que apoyan el uso de agentes antifúngicos y comparar los regímenes utilizados en la prevención de infecciones en recipientes de trasplante de pulmón.

FUENTES DE INFORMACIÓN: Se identificó literatura por medio de búsquedas en los bancos de datos de MEDLINE (1950 hasta Octubre 2009) y el United Network of Organ Sharing (UNOS) usando los términos lung transplantation, prophylaxis, y fungal infection. Además, se revisaron las referencias citadas en los artículos identificados.

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE DATOS: Todos los artículos o extractos en idioma inglés identificados de las fuentes de información fueron evaluados. Se incluyó en el repaso literatura de pacientes adultos que fueron recipientes de trasplante de pulmón y que recibieron profilaxis antifúngica sistémica para prevenir infecciones fúngicas invasivas (IFIs).

SÍNTESIS DE DATOS: IFIs después de trasplante de pulmón permanecen ser un problema posoperatoria común y está asociado con una alta mortalidad. El pulmón es el órgano sólido más vulnerable a ser trasplantado, ya que es el principal órgano responsable para el intercambio gaseoso y está, por lo tanto, a alto riesgo de desarrollar IFIs pulmonar. El pulmón esta más susceptible al desarrollar IFIs, ya que sirve como un medio para que organismos transmitidos por el aire causen infecciones potencialmente serias. Estas infecciones suelen incluir especies de *Candida* y *Aspergillus* y tienden a ocurrir dentro de los primeros 12 meses después del trasplante. Aunque ha habido un aumento en los trasplantes de pulmón durante la última década, no existen pautas estándar para el uso de regímenes antifúngicos profilácticos. Existe una escases de literatura que describa el uso de agentes antifúngicos en la prevención de IFIs después de trasplante y esto puede ser debido a la falta de consistencia en los regímenes utilizados en los centros de trasplantes. Varios regímenes has descrito la utilización de diferentes agentes antifúngicos, tanto como monoterapia y terapia de combinación. La mayoría de la literatura describe formulaciones de anfotericina B en aerosol y agentes antimicóticos del tipo de los azoles demuestran una disminución en el riesgo general de infecciones fúngicas después de trasplante pulmonar. La práctica actual se ha convertido en el iniciar algún tipo de profilaxis antifúngica en estos pacientes.

CONCLUSIONES: El riesgo de infección por hongos después de trasplante de pulmón es multifactorial y los regímenes profilácticos óptimos deben de contener agentes que tienen actividad adecuada contra la mayoría de patógenos fúngicos.

Traducido por Carlos da Camara

Revue des Agents Antifongiques Utilisés en Prophylaxie Suivant une Transplantation Pulmonaire

E Marino et JC Gallagher

Ann Pharmacother 2010;44:546-56.

RÉSUMÉ

OBJECTIFS: Revoir les données sur les antifongiques disponibles et comparer les régimes thérapeutiques visant à prévenir les infections fongiques chez les patients transplantés du poumon.

SOURCE DES DONNÉES: Une recherche de littérature a été effectuée dans MEDLINE (1950 – octobre 2009) et dans le United Network for Organ Sharing (UNOS–jusqu'à octobre 2009) en utilisant les mots-clés lung transplantation, prophylaxis, fungal infection. De plus, les références croisées ont été revues.

SÉLECTION DES ÉTUDES ET EXTRACTION DES DONNÉES: Tous les articles et résumés reliés en langue anglais identifiés ont été évalués. La littérature portant sur les patients adultes ayant reçu une prophylaxie systémique visant à prévenir les infections fongiques invasives (IFI) a été incluse dans l'analyse.

SYNTHÈSE DES DONNÉES: Les IFI suivant une transplantation pulmonaire demeurent un problème commun en post-opération et est associé à une mortalité élevée. Le poumon est l'organe solide le plus vulnérable à la transplantation parce qu'il est responsable de l'échange des gaz et donc plus à risque aux IFI pulmonaires. Le poumon est plus susceptible aux infections car il peut servir de medium pour les microorganismes voyageant de l'air aux tissus humains et pouvant être la cause d'infections mortelles. Ces infections incluent celles reliées aux *Candida* et *Aspergillus* spp et ont tendance à se présenter dans les 12 mois suivant la transplantation. Bien qu'il y ait eu une augmentation du nombre de transplantations pulmonaires au cours de la dernière décennie, il n'y a aucun régime prophylactique standard. La littérature décrivant l'usage des antifongiques est minime et peut être la conséquence du manque d'harmonisation entre les différents centres de transplantation. Plusieurs régimes ont été suggérés utilisant à la fois des agents en monothérapie ainsi qu'en association. La majorité de la littérature décrit l'utilisation de l'amphotéricine B et des antifongiques de la famille des azoles démontrant une réduction globale du risque d'infections fongiques suivant la transplantation. L'initiation d'une thérapie antifongique après une transplantation pulmonaire est maintenant un standard de soins.

CONCLUSIONS: Le risque d'infection fongique après une transplantation pulmonaire est multifactoriel et les régimes utilisés en prophylaxie devraient inclure les agents ayant une activité adéquate contre les pathogènes les plus souvent virulents.

Traduit par Nicolas Paquette-Lamontagne