Received: 10 March 2020 | Revised: 11 July 2020 | Accepted: 1 August 2020

DOI: 10.1111/tid.13448

ORIGINAL REPORT

WILEY

Evaluation of targeted versus universal prophylaxis for the prevention of invasive fungal infections following lung transplantation

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Funding information
Veterans Educational and Research Association of Michigan. The Michigan Institute for Clinical and Health Research receives funding from the National Center for Advancing Translational Sciences (NCATS Grant Number: UL1TR002240).

Abstract

Background: Antifungal prophylaxis to prevent invasive fungal infections (IFI) is widely used following lung transplantation, but the optimal strategy remains unclear. We compared universal with targeted antifungal prophylaxis for effectiveness in preventing IFI.

Methods: Adult patients who underwent lung transplantation at the University of Michigan from /1 July 2014-31 December 2017 were studied for 18 months post-transplant. Universal prophylaxis consisted of itraconazole with or without inhaled liposomal amphotericin B. Using specific criteria, targeted prophylaxis was given with voriconazole for patients at risk for invasive pulmonary aspergillosis (IPA) and with fluconazole or micafungin for patients at risk for invasive candidiasis. Risk factors, occurrence of proven/probable IFI, and mortality were analyzed for the two prophylaxis cohorts.

Results: Of 105 lung transplant recipients, 84 (80%) received a double lung transplant, and 38 (36%) of patients underwent transplant for pulmonary fibrosis. Fifty-nine (56%) patients received universal antifungal prophylaxis, and 46 (44%), targeted antifungal prophylaxis. Among 20 proven/probable IFI, there were 14 IPA, 4 invasive candidiasis, 1 cryptococcosis, and 1 deep sternal mold infection. Six (10%) IFI occurred in the universal prophylaxis cohort and 14 (30%) in the targeted prophylaxis cohort. Five of 6 (83%) IFI in the universal prophylaxis cohort, compared with 9/14 (64%) in the targeted prophylaxis cohort, were IPA *Candida* infections occurred only in the targeted prophylaxis cohort. The development of IFI was more likely in the targeted prophylaxis cohort than the universal prophylaxis cohort, HR = 4.32 (1.51-12.38), $P = .0064$.

Conclusions: Universal antifungal prophylaxis appears to be more effective than targeted antifungal prophylaxis for prevention of IFI after lung transplant.

KEYWORDS

antifungal prophylaxis, aspergillosis, Candida infection, invasive fungal infections, lung transplant recipients

1 | INTRODUCTION

Invasive fungal infection (IFI) is an important complication of lung transplantation; development of an IFI can increase the risk of post-transplant death by as much as threefold.[1] Invasive pulmonary aspergillosis (IPA) is the most common IFI following lung transplantation, with a reported incidence that varies from 4% to 23% and mortality rates from 23%-82%.[2-4] Invasive candidiasis is less common than IPA after lung transplantation, but mortality rates have been reported as high as 40%, and receipt of a lung transplant is an independent predictor of mortality from invasive candidiasis.[4,5] Most lung transplant centers elect to give antifungal prophylaxis to prevent IFI, but prophylaxis strategies vary and there is no standardization among centers regarding the optimal agent or duration of antifungal prophylaxis.[6-9] Universal antifungal prophylaxis is performed in 58%-90% of lung transplant centers, but other centers apply a targeted strategy, in which only high-risk patients are treated. [3,6,8,9]

Our center had previously employed a universal antifungal prophylaxis strategy with itraconazole. In July 2016, this prophylactic strategy was changed to a targeted strategy that used voriconazole or fluconazole/micafungin for selected patients at higher risk for mold or *Candida* infections, respectively. Following this, there was a perceived increase in the number of IFIs. We sought to compare outcomes between the universal and targeted antifungal prophylaxis strategies, hypothesizing that an increase in IFI was related to the change to a targeted antifungal prophylaxis strategy.

2 | MATERIALS AND METHODS

2.1 | Patients and setting

This retrospective study was carried out at the University of Michigan Medical Center, a 1000-bed tertiary care referral center in southeastern Michigan with a comprehensive lung transplant program that performs from 25 to 34 lung transplants yearly. This study was approved by the Institutional Review Board.

All adult patients ≥ age 18 who received a single or double lung transplant between 1 July 2014 and 31 December 2017 were reviewed for inclusion in this study. Patients were excluded if they were on a non-protocol-based strategy for antifungal prophylaxis or if there were insufficient data available to follow their post-transplant clinical course. Data were collected for 18 months following transplant.

2.2 | Immunosuppression

The immunosuppression protocol for lung transplant recipients included calcineurin inhibitors (tacrolimus or modified cyclosporine), azathioprine or mycophenolate, and a corticosteroid taper. Induction therapy with basiliximab was indicated in the setting of immediate post-transplant renal insufficiency when the calcineurin inhibitor was held until renal recovery. Induction with anti-thymocyte globulin was considered in certain scenarios in which recipients had antibodies to the donor organ (positive cross-match or high refractory panel reactive antibodies) or had renal insufficiency.

2.3 | Surveillance bronchoscopy

All patients had bronchoscopy with biopsy and cultures routinely performed at 3 weeks, 6 weeks, 3 months, 6 months, and 12 months post-transplant, and as clinically indicated.

2.4 | Antiviral prophylaxis

Viral infection prophylaxis was tailored to donor and recipient cytomegalovirus (CMV) status. Patients at high risk of CMV disease (donor (D) +/recipient (R) -) received ganciclovir/valganciclovir starting on postoperative day 3 for a total of 12 months and 6 doses of CMV intravenous immunoglobulin over 24 weeks post-transplant. Moderate risk patients (D+/R + or D-/R+) received ganciclovir/valganciclovir for 6 months, then prophylaxis with acyclovir for at least an additional 6 months. Low risk patients (D-/R-) received prophylaxis with acyclovir for at least 12 months. CMV prophylaxis with valganciclovir was also recommended for 30 days after acute rejection treatment with anti-thymocyte globulin or high-dose "pulse" corticosteroids.

2.5 | Antifungal prophylaxis

The universal strategy for antifungal prophylaxis, which was in place from 1 July 2014 until 30 April 2015, consisted of oral itraconazole capsules for 6 months, and inhaled liposomal amphotericin B for at least 3 weeks or until a surveillance bronchoscopy was negative for *Aspergillus* (Table 1). Therapeutic drug monitoring was not routinely performed for itraconazole. In June 2015, inhaled liposomal amphotericin B was removed from the protocol because of tolerability concerns and availability issues. The patient characteristics of those who received amphotericin B plus itraconazole and those who received itraconazole alone did not differ, nor were outcomes significantly different (P=.07). These two cohorts were grouped together as the universal cohort for subsequent analyses.

The targeted antifungal prophylaxis strategy replaced the universal strategy on 1 July 2016 (Table 1). Under this strategy, antifungal prophylaxis was given with an azole or micafungin only to those patients at increased risk for either *Aspergillus* or *Candida* infection post-transplant, based on the criteria listed in Table 1.

Pneumocystis jirovecii prophylaxis with trimethoprim/sulfamethoxazole or alternative drugs, such as dapsone, atovaquone, or

TABLE 1 Criteria for use of universal or targeted antifungal prophylaxis following lung transplantation

UNIVERSAL PROPHYLAXIS (from 1 July 2014 - 30 June 2016)		
Criteria		**Recommendation**
All patients prior to June 2015		Itraconazole capsules 200mg PO daily x6 months + inhaled liposomal amphotericin B 12.5 mg three times a week until 3-week surveillance bronchoscopy negative
All patients after June 2015		Itraconazole 200mg PO daily x6 months
TARGETED PROPHYLAXIS (beginning 1 July 2016)		
Pathogen	**Criteria**	**Recommendation**
Aspergillus spp.	Recipient with pre-Tx colonization with *A fumigatus*, *A terreus*, *A flavus*, *A niger* or prior IPA	Voriconazole 4 mg/kg PO bid x3 months
	Post- transplant surveillance BAL culture positive for *Aspergillus* spp., CT negative for IPA, serum GM negative	
	Anti-thymocyte globulin therapy initiated	
Candida spp.[a]	Intraoperative donor tissue culture or post- transplant 3-week surveillance bronchoscopy culture growing non-*glabrata Candida* spp.	Fluconazole 400mg PO daily x14 days
	Intraoperative donor culture or post-transplant 3-week surveillance bronchoscopy culture growing *Candida glabrata*	Micafungin 100mg IV daily; if MIC appropriate, change to fluconazole 800mg PO daily x14 days

Abbreviations: BAL, bronchoalveolar lavage; bid, twice a day; CT, computed tomography scan; GM, galactomannan; IPA, invasive pulmonary aspergillosis; PO, by mouth; Tx, transplant.

[a]All patients receive oral thrush prophylaxis with nystatin for 6 weeks after transplantation

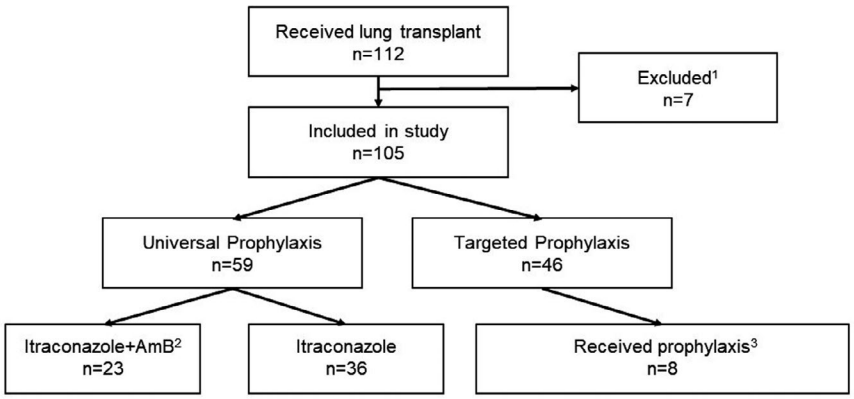

FIGURE 1 Study patient selection for universal and targeted prophylaxis cohorts. AmB = liposomal amphotericin B

[1] excluded: non-protocol prophylaxis n=4, died prior to receiving prophylaxis n=2, intolerant of azoles n=1
[2] inhaled liposomal amphotericin B
[3] voriconazole n=5, fluconazole n=3

inhaled pentamidine, was started on postoperative day 5 and continued lifelong for all patients.

2.6 | Data collection

The electronic medical record and Organ Transplant Information Systems were reviewed to collect demographics, medical history, transplant characteristics, including donor information when available, medication data, bronchoscopy results, occurrence of IFI, and mortality at 18 months after transplant and at 12 weeks after IFI when applicable.[10] IFI were defined per the 2008 EORTC/MSG consensus criteria[11]; only proven or probable IFI were included for analysis; episodes of possible IFI were excluded from further study. Data were entered into the REDCap electronic database at the University of Michigan.

CMV infection at any time within the 18-month study period was defined using criteria proposed by Ljungman et al[12] Patients who had IFI were considered to have concomitant CMV infection if the latter was diagnosed within 30 days prior to IFI onset.

Acute organ rejection was established at any point in the 18-month study period by pathological examination of tissue taken at surveillance bronchoscopy. Patients with IFI were considered to have concomitant rejection if they were started on increased immunosuppression with high dose/pulse steroids or anti-thymoglobulin in the 30 days prior to IFI onset.

2.7 | Statistical methods

Univariable analysis of demographic and transplant data between the targeted and the universal prophylaxis strategies was performed using the Fisher's exact test for categorical variables and two-sample t-test or Wilcoxon rank sum test for continuous variables. For analyses involving death and IFI outcomes, Cox proportional hazards regression models and Fine and Gray sub-distribution proportional hazards models to account for competing risks were used. Predictors with $P < .1$ from univariable analyses were entered into multivariable models using a backwards selection process. Kaplan-Meier survival analyses were conducted for the probability of surviving and for the probability of remaining free of IFI at 18 months. The difference in both survival and survival free of IFI between the prophylaxis strategies were assessed by the log-rank test. *P*-values < 0.05 were considered statistically significant. SAS 9.4 statistical software (Cary, NC) was used for all analyses.

3 | RESULTS

3.1 | Patients

Of 112 adult patients who received a lung transplant from 1 July 2014 to 31 December 2017, 105 met inclusion criteria and were included in the study (Figure 1). Reasons for exclusion included use of off-protocol prophylaxis (n = 4), death prior to post-transplant day 5 (n = 2), and a history of intolerance to azole drugs (n = 1). There were 59 (56%) patients in the universal prophylaxis cohort and 46 (44%) patients in the targeted prophylaxis cohort. The two different prophylaxis cohorts differed only in use of cyclosporine (Table 2).

3.2 | Invasive fungal infections

There were 20 proven/probable IFI in 19 patients including invasive pulmonary aspergillosis (n = 14), invasive *Candida* infections (n = 4), and one each *Cryptococcus neoformans* pneumonia and deep surgical site infection involving sternal hardware due to a hyaline mold that could not be further identified (Table 3). In the cohort receiving universal prophylaxis there were 6 IFIs (10%) compared with 14 IFIs (30%) in 13 patients in the targeted prophylaxis cohort. Time to proven/probable IFI was similar between the two prophylaxis strategies; the median time to occurrence of IFI was 107 (range 23-186) days in the universal cohort and 109 (range 14-510) days in the targeted cohort. Five of 6 (83%) IFIs in the universal prophylaxis cohort, compared with 9 of 14 (64%) in the targeted prophylaxis cohort, were IPA *Candida* infections occurred only among patients in the targeted prophylaxis cohort.

All six cases in the universal cohort were breakthrough infections in patients receiving itraconazole; itraconazole serum concentrations were 1 μg/mL and 0.1 μg/mL in the 2 patients for whom drug levels were measured. Five of these 6 patients had received inhaled liposomal amphotericin B, as well as itraconazole for prophylaxis.

TABLE 2 Demographic information, transplant data, and maintenance immunosuppression regimens of lung transplant recipients who received antifungal prophylaxis by either the universal or targeted strategy

	Universal cohort, n = 59 (n, %)	Targeted cohort, n = 46 (n, %)	*P* value
Male sex	41 (70)	32 (70)	1.00
Age, years median (IQR)	60 (56-64)	61 (46-65)	.21
Race[a]			
Caucasian	52 (88)	42 (91)	1.00
African-American	5 (8.5)	4 (9)	1.00
Weight, kg median (IQR)	82 (64-98)	77 (63-90)	.27
Reason for transplant[b]			
Cystic fibrosis	2 (3)	6 (13)	.13
COPD	22 (37)	10 (22)	.09
Pulmonary fibrosis	19 (32)	19 (41)	.41
ILD	10 (17)	9 (20)	.80
α-1-antitrypsin deficiency	5 (9)	1 (2)	.23
Transplant data			
Double lung transplant	46 (78)	38 (83)	.63
Single lung transplant	13 (22)	8 (17)	.63
Basiliximab induction	13 (22)	10 (22)	1.00
CMV status[c]			
D+/R+	17 (29)	11 (24)	.75
D+/R-	16 (28)	10 (22)	
D-/R+	14 (24)	14 (30)	
D-/R-	11 (19)	11 (24)	
Maintenance immunosuppression			
Calcineurin inhibitor			
Tacrolimus	50 (85)	42 (91)	.38
Cyclosporine	6 (10)	0 (0)	.03
Antiproliferatives			
Azathioprine	24 (41)	19 (41)	1.00
Mycophenolate mofetil	22 (37)	23 (50)	.23
Mycophenolate sodium	9 (15)	2 (4)	.11
Prednisone[d]			
High dose[e]	51 (86)	42 (91)	.54

Abbreviations: CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; D, donor; ILD, interstitial lung disease; IQR, interquartile range; R, recipient.

[a]not known for 2 patients

[b]Additional reasons for transplant include: Universal cohort: sarcoidosis n = 2, secondary pulmonary hypertension n = 2, prior lung transplant failure n = 2, autoimmune disease n = 2, bronchiolitis obliterans n = 1, bronchiectasis = 1; Targeted cohort: sarcoidosis n = 1, eosinophilic granulomatosis n = 1

[c]Information on donor CMV status was not available for 1 patient who received universal prophylaxis

[d]Information on prednisone dose was not available for 1 patient who received universal prophylaxis

[e]High dose prednisone = dose equivalent to ≥ 0.3 mg/kg prednisone daily for ≥ 3 weeks

Of the 46 patients in the targeted prophylaxis cohort, only 8 met criteria for receiving prophylaxis; five patients received voriconazole and 3, fluconazole (Figure 1). None of the patients who received voriconazole targeted prophylaxis developed an IFI. Among the 9 cases of probable IPA, none had received antifungal prophylaxis. There were 4 proven *Candida* infections involving thoracic structures, including empyema in 3 patients and distal sternal osteomyelitis with hardware infection associated with the operative clamshell incision in another patient. Two patients who developed empyema within 3 weeks of transplant had positive donor bronchus cultures and negative recipient bronchus cultures for *Candida*; both had received targeted prophylaxis with fluconazole. The other two patients had infections that occurred more than 3 months after transplant. The patient with sternal osteomyelitis had both donor and recipient bronchus cultures positive for *C albicans* 3 months before, and one patient with *C tropicalis* empyema had negative recipient and donor fungal cultures at the time of transplant. One patient, who had a *C albicans* empyema shortly after transplant subsequently developed probable IPA 2 months later, after having completed 4 weeks of treatment with fluconazole (Table 3).

3.3 | Outcomes

During the 18-month follow-up period, the probability of survival free from IFI was significantly higher in the universal antifungal prophylaxis cohort, $P = .03$ (Figure 2A). Univariable Fine and Gray sub-distribution proportional hazards models showed that only the use of the targeted prophylaxis strategy, hazards ratio (HR)=2.98 (95% CI 1.14-7.84), $P = .03$ and α_1-antitrypsin deficiency, HR = 4.06 (1.18-13.98), $P = .03$ were risk factors for the development of proven or probable IFI within 18 months of transplant (Table 4). The multivariable model showed HR = 4.32 (1.51-12.38), $P = .0064$, for the development of IFI when targeted antifungal prophylaxis was compared with universal antifungal prophylaxis and HR = 8.28 (2.50-27.47), $P=.0005$, for development of an IFI when patients with and without α_1-antitrypsin deficiency were compared.

All-cause mortality was 10% (n = 11), including 8 of 59 (14%) in the universal antifungal prophylaxis cohort and 3 of 46 (7%) in the targeted antifungal prophylaxis cohort. Survival curves by Kaplan-Meier analysis did not differ significantly between the two cohorts, $P = .27$ (Figure 2B). Among patients who developed an IFI, only one

TABLE 3 Twenty episodes of invasive fungal infections after lung transplant in 105 patients receiving either universal or targeted antifungal prophylaxis

Prophylaxis	IFI proven/probable	LTx to IFI (days)	Diagnosis	B-IFI yes/no	Mycological findings	Outcome at 12 weeks after IFI diagnosis
Universal	Probable	125	Deep surgical site infection[a]	Yes	Tissue: hyaline mold, not further identified	Alive
Universal	Probable	118	IPA	Yes	BAL GM 1.7	Alive
Universal	Probable	96	IPA	Yes	BAL: *A fumigatus*	Alive
Universal	Probable	186	IPA	Yes	BAL: *A fumigatus*	Alive
Universal	Probable	23	IPA	Yes	BAL: *A fumigatus*	Alive
Universal	Probable	25	IPA	Yes	BAL GM 6.9	Alive
Targeted	Proven	18	*Candida* empyema	Yes	Pleural fluid: *C glabrata*, *C dubliniensis*	Alive
Targeted	Proven	98	*Candida* deep surgical site infection[a]	No	Tissue: *C albicans*	Alive
Targeted	Proven	322	*Candida* empyema and fungemia	No	Pleural fluid: *C tropicalis*	Dead
Targeted	Proven	18	*Candida* empyema	Yes	Pleural fluid: *C albicans*, *C dubliniensis*	Alive
	Probable	77	IPA	No	BAL: *A niger*, GM 0.55	Alive
Targeted	Probable	82	IPA	No	BAL: *A fumigatus;* GM 7.4	Alive
Targeted	Probable	233	IPA	No	BAL: *A fumigatus;*	Alive
Targeted	Probable	179	IPA	No	BAL: *A fumigatus*	Alive
Targeted	Probable	309	IPA	No	BAL GM 0.57	Alive
Targeted	Probable	109	IPA	No	BAL GM 5.9	Alive
Targeted	Probable	105	IPA and anastomosis infection	No	BAL: *A fumigatus*	Alive
Targeted	Probable	93	IPA and anastomosis infection	No	BAL: *A fumigatus*, GM 1.5	Alive
Targeted	Probable	510	IPA	No	BAL: *A fumigatus*, GM 5.1	Alive
Targeted	Probable	124	Cryptococcosis	No	BAL: *C neoformans*	Alive

Abbreviations: BAL, bronchoalveolar lavage; B-IFI, breakthrough IFI; GM, galactomannan; IFI, invasive fungal infection; IPA, invasive pulmonary aspergillosis; LTx, lung transplantation.

[a]Distal sternum osteomyelitis and hardware infection associated with the clamshell incision from lung transplantation.

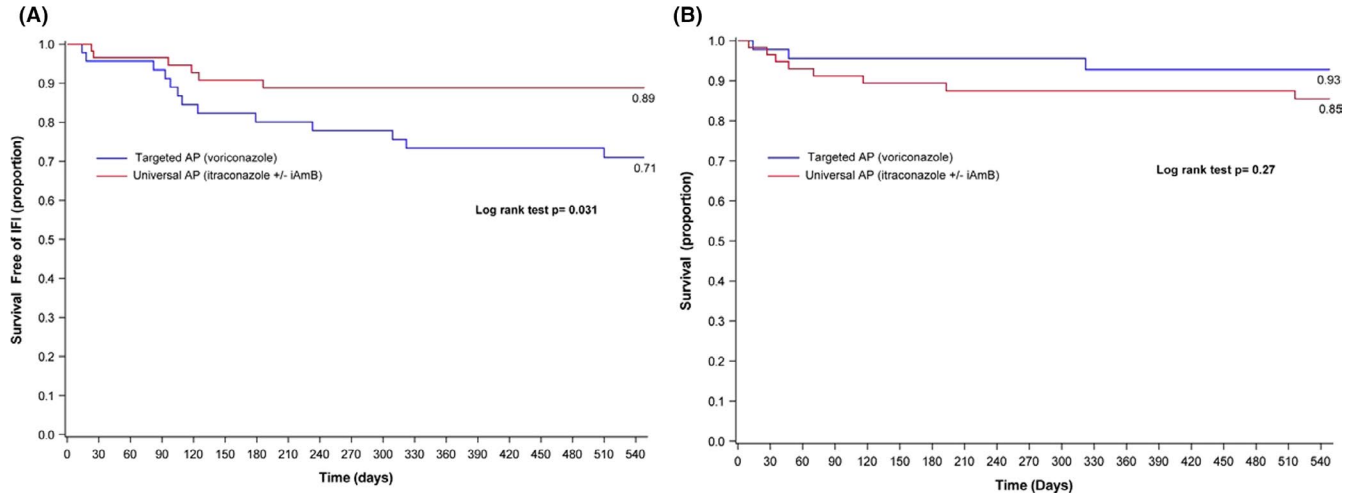

FIGURE 2 A, Kaplan-Meier curve of survival free from IFI comparing targeted prophylaxis cohort with universal prophylaxis cohort. B, Kaplan-Meier curve showing survival at 18 months comparing targeted prophylaxis cohort with universal prophylaxis cohort

patient, who was in the targeted prophylaxis cohort, died within 12 weeks of IFI onset. Two other patients, one in each cohort, died more than 12 weeks after the IFI diagnosis. No deaths were directly attributed to IFI. The only identified independent risk factor for death within 18 months of transplant in a Cox proportional hazards regression model was the use of basiliximab induction, HR = 5.1 (1.55-16.73), $P = .007$.

4 | DISCUSSION

We compared a universal antifungal prophylaxis strategy with a targeted antifungal prophylaxis strategy for prevention of IFI following lung transplant and found that the risk of developing an IFI in the 18 months following transplant was significantly greater in the cohort receiving targeted prophylaxis. The 10% incidence of IFIs in the universal prophylaxis cohort was similar to that reported from other single and multi-center experiences.[2,4,13] However, the 30% incidence of IFIs in the targeted prophylaxis cohort was higher than that noted in most prior studies of IFI in lung transplant recipients.[2,13,14]

IPA, as expected, was the most common IFI seen in this patient population. Older studies suggest mortality as high as 80% in lung transplant recipients who develop IPA,[15,16] but more contemporary studies have found lower mortality rates of 22% to.59%.[2,17] Lung transplant recipients are at particular risk for IFIs because of continuous environmental exposure and impairment of cough reflex and mucociliary clearance.[3] Previously described risk factors for IPA after lung transplant include single lung transplant, anastomotic ischemia, cytomegalovirus (CMV) infection, organ rejection, and respiratory colonization with *Aspergillus* pre- or post-transplant.[3,8,16,18,19] We did not find an association with these previously described risk factors and development of IFI, perhaps because our population had fewer patients with cystic fibrosis and fewer single lung transplants than noted in several other series.[8,19]

Invasive candidiasis, seen in the targeted prophylaxis cohort, was the second most common IFI, similar to the experience at other transplant centers.[4,14] Especially troublesome were pleural space infections and surgical site infections involving sternal hardware used in the transplant procedure; this is consistent with prior studies showing *Candida* as the most common cause of pleural space infection in this population, particularly early after transplant.[20] In 2 patients who developed *Candida* empyema within 3 weeks of transplantation, the donor lung was colonized with *Candida* and infection developed in spite of targeted prophylaxis. If a targeted approach is used, it will be necessary to better define the risk factors post-transplant that lead to these types of intra-thoracic infections and to further evaluate the most appropriate agent and duration of prophylaxis.[14]

Current guidelines support the use of antifungal prophylaxis to prevent IPA after lung transplantation, but do not speak to prevention of intra-thoracic post-transplant invasive candidiasis. There is not general agreement on which approach to prophylaxis is most effective. A recent survey of transplant centers in the United States showed that 90% of respondents used a universal prophylaxis strategy, most commonly with inhaled amphotericin B and either itraconazole or voriconazole.[9] In contrast, worldwide, universal prophylaxis was used in only 59% of centers, and monotherapy with only an azole (usually voriconazole) was most common.[6]

Recommendations from professional societies, including the Infectious Disease Society of America (IDSA), the American Society of Transplantation Infectious Diseases Community of Practice (AST-IDCOP), and the International Society for Heart and Lung Transplantation (ISHLT), differ in regard to their approach to antifungal prophylaxis.[3,21,22] The IDSA guidelines recommend antifungal prophylaxis with either a systemic triazole or inhaled amphotericin B for 3-4 months after lung transplantation or when augmentation of immunosuppression occurs beyond this period. Preference is given to the use of systemic mold-active azoles rather than inhaled amphotericin B for transplant recipients who

TABLE 4 Risk factors for proven/probable IFI in 105 lung transplant recipients

Variable	Patients with IFI (N = 19)	Patients without IFI (n = 86)	*P*-value (univariable analysis)	*P*-value; Hazard ratio (95% CI) (multivariable analysis)[a]
Sex				
Male	13	60	.95	
Female	6	26		
Race[b]				
Caucasian	17	77	.81	
African-American	2	7		
Age, years median (IQR)	58 (47-63)	61 (53-64)	.34	
Weight, kg median (IQR)	80 (73-100)	78 (61-95)	.18	
BMI, median (IQR)	28 (25-31)	27 (22-30)	.11	
Underlying lung diseases				
Cystic fibrosis	2	6	.64	
COPD	5	27	.70	
Pulmonary fibrosis	7	31	.96	
ILD	2	17	.39	
α-1-antitrypsin deficiency	3	3	.03	.0005 8.28 (2.50-27.47)
Transplant type				
Double lung transplant	18	66	.11	
Single lung transplant	1	20		
Induction				
Basiliximab	4	19	.89	
Transplant complications				
CMV infection[c]	2	16	.35	
Organ rejection[d]	3	19	.58	
Colonization status[e]				
Colonized	9	46	.56	
Not colonized	10	40		
Antifungal prophylaxis				
Universal	6	53	.03	.0064 4.32 (1.51-12.38)
Targeted	13	33		

Abbreviations: CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; IFI, invasive fungal infection; ILD, interstitial lung disease; IPF, pulmonary fibrosis; IQR, interquartile range.

[a]Fine & Gray sub-distribution proportional hazards regression model incorporating factors with $P < .1$ into the selection process

[b]Race was not specified in 2 patients

[c]CMV infection at any time within 18 months after lung transplantation for those patients without IFI and within 30 days of IFI for those who developed IFI

[d]Organ rejection requiring high dose immunosuppression at any time within 18 months after transplantation for those without IFI and within 30 days for those who developed IFI

[e]Patients were considered colonized if they had pre-transplant colonization with *Aspergillus*, if they had donor lung colonization with *Candida*, or if they had *Candida* spp. or *Aspergillus* spp. present on a 3-week surveillance bronchoscopy after lung transplantation

have a prior history of mold infection or have pre- or post-transplant mold colonization documented.[21] The AST-IDCOP discusses several different approaches, including universal, preemptive, and targeted strategies, for the prevention of IPA, based on previously described risk factors.[3] No specific recommendation for a preferred agent is given, but mold active azoles, such as voriconazole or posaconazole, are suggested, and inhaled amphotericin B is offered as an option.[3] The ISHLT recommends that universal prophylaxis with an anti-*Candida* agent be considered in the first 2-4 weeks after transplant and that subsequently a mold-active agent such as voriconazole should be used as either universal prophylaxis for 6 months or preemptive treatment for 3-4 months. No preference is recommended between universal prophylaxis and preemptive treatment, but the duration proposed for anti-*Candida*

prophylaxis is longer than the 2 weeks used in our institution during this study period.[22]

Prior to the introduction of the newer triazoles, itraconazole was used most often for prophylaxis following lung transplantation.[7,9] Currently, this agent is less preferred given its poor absorption, especially in patients who require gastric acid blocking agents, and its adverse effects profile, especially those related to cardiac dysfunction. The dose of itraconazole recommended by the IDSA for the prevention of IA is 200mg of itraconazole solution twice a day; in our study cohort, daily dosing of the capsule formulation was administered instead, due to a combination of provider preference and poor tolerability of twice-daily dosing.[21] Therapeutic drug monitoring for itraconazole is recommended,[23] but in our study itraconazole serum concentrations were checked infrequently and doses were not always adjusted when the concentration was found to be low. Low serum levels of itraconazole likely contributed to the occurrence of several cases of IPA in the universal prophylaxis cohort. Other studies have noted high rates of breakthrough IFI, even when seemingly appropriate itraconazole serum concentrations were attained, suggesting that an effective target concentration for prophylaxis in lung transplant recipients has not been defined.[8,24]

Voriconazole is an attractive alternative to itraconazole for several reasons, including reliable absorption and the availability of both oral and intravenous formulations. However, because of its complex interactions with multiple cytochrome P450 enzymes, voriconazole has many drug-drug interactions. Therapeutic drug monitoring is strongly recommended, not only to ensure adequate serum concentrations given both inter- and intra-patient variability in pharmacokinetics, but also to avoid adverse events associated with higher serum concentrations, such as hallucinations and hepatotoxicity.[21,24,25] Posaconazole and isavuconazole could also be considered for prophylaxis, but experience to date is limited to two studies, both of which showed efficacy of these agents.[26,27]

Several prior studies have demonstrated the lack of efficacy for inhaled amphotericin B as a single agent for prophylaxis in the lung transplant population, but it is still recommended as an option by several groups.[3,21,28] We did not see a difference in IFI occurrence when inhaled liposomal amphotericin B was no longer used for patients in the universal prophylaxis cohort, suggesting that it was not effective for the prevention of IFI.

Our findings suggest that the criteria used for initiating prophylaxis for those in the targeted cohort fell short of identifying patients at increased risk for IFI. All but two patients who developed an IFI in this cohort did not meet criteria to receive antifungal prophylaxis. Although pre- and post- transplant colonization with *Aspergillus* are important factors for the development of IFI, there are clearly other risk factors for infection that should be considered when deciding to initiate targeted prophylaxis. It is also possible that the duration of prophylaxis was too short for those patients who had donor bronchus cultures positive for *Candida* species.

In our study, patients with α_1-antitrypsin deficiency were at increased risk for developing an IFI. α_1-antitrypsin inactivates pro-inflammatory proteases, such as neutrophil elastase in the lung; these proteases have been noted to play a role in bacterial pneumonias, and likely are important in some fungal pneumonias, as well.[29-31] Even after lung transplantation, it is likely that patients with α_1-antitrypsin deficiency are less able to counteract a detrimental pro-inflammatory state.[32]

Monoclonal antibody inhibitors of lymphocyte activation, proliferation or migration, such as basiliximab, are commonly used for early immunosuppression after lung transplantation.[33,34] Our study, as well as several others, did not find an increased risk for IFI in patients receiving basiliximab.[35,36] However, we did find that basiliximab was the only independent risk factor for death in our patients. The fact that basiliximab was reserved for use in patients who developed post-operative acute kidney injury may explain this association as post-transplant acute kidney injury has been associated with poor survival in this patient population.[37]

Limitations of this study include the retrospective design, which might have resulted in our not collecting all pertinent factors leading to IFIs. The results reflect a single center's experience; findings may not be generalizable to other transplant programs that serve different patient populations or that encounter different epidemiological patterns of IFIs.

In summary, we compared two different strategies for antifungal prophylaxis after lung transplantation and found that universal prophylaxis was associated with fewer IFI than targeted prophylaxis. Not only *Aspergillus* species, but also *Candida* species caused post-transplant infections in patients receiving targeted prophylaxis.

CONFLICTS OF INTEREST

All authors declare that they have no conflicts of interest related to this study.

AUTHORS CONTRIBUTION

Kathleen A. Linder contributed to study design, data management, and manuscript draft writing. Carol A. Kauffman contributed to conceptualization, manuscript writing review, and supervision. Twisha S. Patel contributed to conceptualization and study design. Linda J. Fitzgerald contributed to study design and data management. Blair J. Richards contributed to statistical analysis. Marisa H. Miceli contributed to conceptualization, study design, data analysis, manuscript review, and supervision.

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How to cite this article: Linder KA, Kauffman CA, Patel TS, Fitzgerald LJ, Richards BJ, Miceli MH. Evaluation of targeted versus universal prophylaxis for the prevention of invasive fungal infections following lung transplantation. *Transpl Infect Dis*. 2021;23:e13448. https://doi.org/10.1111/tid.13448