Published in final edited form as:

J Heart Lung Transplant. 2008 June ; 27(6): 655–661.

INCREASED MORTALITY AFTER PULMONARY FUNGAL INFECTION WITHIN THE FIRST YEAR AFTER PEDIATRIC LUNG TRANSPLANTATION

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Abstract

BACKGROUND—Risk factors, morbidity and mortality from pulmonary fungal infections (PFI) within the first year after pediatric lung transplant have not previously been characterized.

METHODS—A retrospective multi-center study from 1988–2005 was conducted with institutional approval at 12 centers in North America and Europe. Data were recorded for the first posttransplant year. Log-rank test assessed for association between PFI and survival. Associations between time to PFI and risk factors were assessed by Cox proportional hazards models.

RESULTS—Of 555 subjects transplanted, 58(10.5%) had 62 proven (*Candida*, *Aspergillus* or other) or probable (*Aspergillus* or other) PFI within the first year posttransplant. The mean age for subjects

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Presented: American Society of Transplantation Annual Meeting, May 2007, San Francisco, CA

with PFI was 14.0 years versus 11.4 years without PFI ($P<0.01$). *Candida* and *Aspergillus* species were recovered equally for proven disease. Comparing subjects with PFI ($n=58$) to those without fungal infection ($n=404$), pre-transplant colonization was associated with PFI (HR = 2.0; 95% CI 0.95, 4.3, $p=0.067$). CMV-mismatch, tacrolimus-based regimen, and age over 15 years were associated with PFI ($P<0.05$). PFI was associated with any prior rejection greater than A2 (HR 2.1; 95% CI 1.2, 3.6). Cystic fibrosis, induction therapy, transplant era and type of transplant were not associated with PFI. PFI was independently associated with decreased 12-month survival (HR 3.9, 95% CI 2.2, 6.8).

CONCLUSIONS—Risk factors for PFI include A2 rejection, repeated acute rejection, CMV-positive donor, tacrolimus-based regimen and pre-transplant colonization.

Keywords

Lung transplantation; Fungal; Pediatrics; *Aspergillus*

Introduction

Pediatric lung transplantation is an established therapy for end-stage lung disease in children. Infectious complications occur frequently following lung transplantation with up to 60–90% of recipients experiencing at least one episode of infection^{1–3}. In particular, fungal infection remains a serious complication after lung transplantation. Invasive *Aspergillus* infection has been reported in 3–16% of adult lung transplant recipients with a mortality of 41–50% for invasive pneumonia^{4–9}. Additional studies in adults demonstrate transmission of fungal infection from colonized donors¹⁰, increased colonization after transplant with pretransplant colonization^{11, 12}, increased infection in subjects with cystic fibrosis¹¹, and decreased rates of infection with antifungal prophylaxis^{7, 13}.

The impact of fungal infections in the pediatric lung transplant population is undetermined. A report from France indicated only 2 of 49 developed post-transplant mycotic lung infection, while another group reported invasive fungal infections diagnosed postmortem in conjunction with bronchiolitis obliterans^{14, 15}. Cases of *Paecilomyces variotii* and zygomycetes in pediatric lung recipients have been reported^{16, 17}.

A comprehensive evaluation of pulmonary fungal infections (PFI) including associated risks after pediatric lung transplantation has not been previously reported. This multi-center retrospective cohort reports the incidence of and risk factors for PFI within the first year after primary pediatric lung transplantation. We hypothesize that PFI in the first year after transplantation is associated with increased mortality in primary pediatric lung transplant recipients.

Materials and Methods

Study Design

Members of the International Pediatric Lung Transplant Collaborative (IPTLC) were invited to participate in this multi-center retrospective cohort with 12 of 15 centers contributing data for this study. Participating centers obtained Institutional Review Board (United States centers) or Ethics Committee (European centers) approval. The principal investigator performed a chart review on the medical records of all primary lung transplants performed between January 1988 and the time of data collection (August 2004 to September 2006). Patient data were de-identified at data extraction from the medical record. Information was collected from the time of transplant for one year or until either death or retransplantation if they occurred before the end of the one-year observational period.

Therapy Regimens

Patients underwent standard pre-transplantation evaluation at their participating center. Induction immunosuppressive therapy varied during the study period and across participating centers, ranging from no therapy to receipt of lympholytic agents or IL-2 receptor antagonists. After transplantation, most recipients received triple-drug immunosuppression with a calcineurin inhibitor (CNI), prednisone and either azathioprine or mycophenolate mofetil. Immunosuppression was gradually decreased as time from transplantation increased if substantial graft rejection did not occur. Target CNI trough serum concentrations varied by center. Additionally, prophylaxis for cytomegalovirus (CMV) and routine transbronchial biopsies to assess for rejection were not standardized across centers and changed over time within centers. Fungal prophylaxis was not standardized across participating centers, was individualized and changed over time. Data on individual patient prophylaxis was not available. Fungal cultures were obtained based on the protocol at each participating center. Some centers obtained routine fungal cultures with each surveillance bronchoscopy or with suspicion of infection, and other centers obtained fungal cultures only with suspicion of infection.

Definitions

Pretransplant colonization or infection—Evidence of a positive culture for fungus from sputum, trachea, bronchoalveolar lavage or explanted lung prior to or at the time of transplantation.

Posttransplant infection definitions are adapted from those proposed by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group¹⁸ and previously reported studies of fungal infection after transplantation¹⁹.

Proven Fungal Infection—Defined as one of the following: (1) positive histopathology for fungal organisms with tissue damage from affected site or (2) culture from sterile site with radiographic or clinical evidence of infection at the cultured site including new radiographic infiltrate, pleural effusion or cough with fever without evidence of concurrent respiratory viral infection or acute rejection (excludes cultures of mucous membranes and urine).

Probable Fungal Infection—Defined as a positive culture of yeast (other than *Candida* species) or mould from bronchoalveolar lavage fluid with clinical evidence of infection as noted above.

Acute rejection—Based on pathology specimens obtained from transbronchial biopsy according to the working formulation for pulmonary allograft rejection classification in 1990 and 1996^{20, 21}. Additionally, clinical suspicion of acute rejection resulting in augmentation of immunosuppression was recorded.

Bronchiolitis Obliterans Syndrome/Bronchiolitis Obliterans—Diagnosis was based on pulmonary function testing with standardization of FEV₁ at 3 months after transplantation and measurement of deterioration from this level or by pathology specimen as outlined by the International Society for Heart and Lung Transplantation²².

Statistical analysis

Data were entered into an ORACLE database, analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC), and graphics were produced using R version 2.0.1 software (The R Foundation for Statistical Computing, Vienna, Austria). Associations between PFI and continuous and categorical risk factors were assessed using Wilcoxon rank-sum tests and Chi-square and Fisher's exact tests, respectively. Associations between PFI and survival time, and

between time to PFI and risk factors were assessed by univariable and multivariable Cox proportional hazards models; subjects were also considered censored at death for the time to PFI model. For each proportional hazards model, the proportional hazards assumption was assessed by entering risk-factor-by-time interactions into the model; this assumption was also assessed graphically using log-log-survival plots. Events that occurred during post-transplant follow-up, such as PFI, CMV infection, and rejection were modeled as time-dependent covariates. The functional form for age at transplant was chosen by modeling deciles of age as risk factors for time to PFI and assessing the resulting parameter estimates. The multivariable model for time to PFI was chosen by performing backwards selection, with a significance criteria of 0.05, on an initial model containing all risk factors. Interactions suggested by the data or by clinical importance were included in the model selection process. Subjects with fungal infections localized to the urinary tract, central nervous system, and bloodstream as well as superficial skin infections were excluded from all analyses. One subject with a PFI diagnosed on the day of transplant was also excluded. All tests were two-tailed.

Results

PFI occur frequently within the first year after pediatric lung transplantation

From this retrospective cohort, 555 subjects met eligibility criteria for inclusion in the study. Subjects were transplanted between 1988 and 2005 at 12 centers in the United States and Europe. Of these 555 subjects, 58 (10.5%) developed 62 pulmonary fungal infections categorized as either proven or probable based on the diagnostic criteria. *Candida* species and *Aspergillus* species were equally represented for proven infections; other fungal organisms were less common (Table 1 & Table 2). PFI were noted to occur early in the first post-transplant year (median 100 days posttransplant), Figure 1. The majority (55%) of PFI occurred by 3 months post-transplant, and 70% occurred within 6 months after transplantation. PFI were common within the first posttransplant year after pediatric lung transplantation.

PFI associated with death

Subjects with PFI (n=58) within the first post-transplant year were compared to pediatric lung transplant recipients without any fungal infections (n=404). Mortality related directly to PFI was 24% (9 of 38) for *Aspergillus* species, 38% (3 of 8) for *Candida* species, and 0% for other organisms. Mortality for proven and probable PFI was 38% and 11% respectively. PFI within the first post-transplant year was significantly associated with increased risk of all-cause mortality at one year posttransplant (HR 4.0, 95% CI 2.3–6.9, $P < 0.001$), Figure 2. The association was also observed in a multivariable model adjusting for demographics, immunosuppressive regimen, complications (acute rejection, posttransplant lymphoproliferative disease, CMV, and bronchiolitis obliterans) and year of transplantation (PFI HR 3.8, 95% CI 2.2–6.8, $P < 0.001$).

Demographic and event risks for PFI by univariable analyses

The impact of demographic characteristics, immunosuppressive regimen, and posttransplant complications (acute rejection, CMV infection/disease) occurring prior to PFI was assessed using Cox proportional hazards models. Several risk factors for PFI were identified: age over 15 years at transplant, CMV D+/R– status, and tacrolimus-based regimen ($p < 0.05$). Gender, ethnicity, cystic fibrosis, type of transplant received, era of transplant and induction therapy were not associated with the development of PFI ($P > 0.1$). The following patterns of acute rejection were associated with an increased risk of PFI: two or more episodes of acute rejection including A1 and clinical diagnoses (Hazard ratio 1.82.0, 95% CI 1.03–3.8, $P = 0.04$) or a single episode of A2 or higher rejection (HR 2.2, 1.2–3.8, $P = 0.006$). Prior episode of CMV infection/disease was not associated with the development of PFI (HR 1.3, 0.7–2.6, $P = 0.4$), Table 3 & Table 4.

Pretransplant colonization increased risk of PFI

Pretransplant colonization with yeast or mould increased the risk of PFI. Culture results from 272 subjects prior to transplantation were available (30 with PFI, 242 without fungal infection). The sensitivity and specificity of pretransplant cultures with respect to the development of posttransplant PFI in this subgroup were 67% and 52%, respectively. Evidence of pretransplant colonization was associated with almost twice the risk of PFI, 7% to 15%, and pretransplant colonization was significantly associated with the posttransplant PFI although not necessarily from the same organism recovered from the pretransplant culture (OR 2.2, 0.99–4.92, logistic regression $P=0.052$).

Multivariable models show independence of risks

Multivariable Cox proportional hazards models were constructed to model the risks for PFI within the first year after pediatric lung transplant. The risk factors discovered in univariable analysis including age 15 years or older at transplant, CMV D+/R–, tacrolimus-based regimen, and an episode of A2 rejection or greater prior to PFI remained significantly predictive. An additional model was evaluated using two or more episodes of any acute rejection, and results were similar to the first model (Table 5). No additional risk factors were significantly predictive in either model. Pretransplant colonization was not included in the model due to the limited number of subjects with pretransplant culture data, creating a sampling bias. In a subgroup multivariable analysis including only the subjects with pretransplant fungal culture data available, addition or exclusion of positive fungal culture did not alter the model (data not shown).

Discussion

Pulmonary fungal infection has been reported after lung transplantation in up to 15% of adult recipients. Risks for pulmonary fungal infection in adult lung transplant recipients include pretransplant colonization with *Aspergillus* species, acute rejection, chronic obstructive pulmonary disease, and single lung transplantation^{8, 23, 24}. Cytomegalovirus and steroid therapy have been reported as risk factors for fungal infection in some but not all studies^{5, 11, 24, 25}. Pulmonary *Aspergillus* infections have been associated with decreased survival^{8, 23, 24} in adult transplant recipients, especially for older recipients and those with late infection. In addition, late infections with *Aspergillus* species have been reported²⁶. This study is the first to investigate the risk factors for PFI in pediatric lung transplant recipients within the first year after transplantation.

PFI occurred at rates similar to adults, 10.5% compared to a range of 3–16%. Compared to published adult studies, mortality is slightly lower in the pediatric population for *Aspergillus* infections (24%), although the 38% mortality for proven PFI approach that reported in the adult literature^{4–9}. The risks for PFI including pretransplant colonization and acute rejection mirror risks in adults. However, additional risk factors are identified in pediatric recipients. Adolescence, associated with a lower rate of survival in other solid organ transplant recipients^{27–31}, is an independent risk factor for PFI in this study. The effect of adherence in this retrospective study is not assessed, but ascertaining that age over 15 years increases the risk of PFI allows for potential intervention, especially as 60% of pediatric lung recipients in the United States occur in children 11–17 years old. Devising metrics to measure adherence to immunosuppressive and antifungal medications will be crucial to evaluation of any intervention in this population.

Another risk factor identified in this study was the tacrolimus-based immunosuppressive regimen. While tacrolimus was not associated with invasive pulmonary aspergillosis in adult lung transplant recipients²⁴, tacrolimus increased the risk of PFI within the first posttransplant

year in pediatric recipients. Although rarely used in patients less than 2 years of age in this cohort, tacrolimus use was evenly distributed across all other ages in this study, and a tacrolimus-based regimen remained predictive of PFI in multivariable models. Further, the immunosuppressive regimen was categorized at initial hospital discharge, and therefore a tacrolimus-based regimen does not represent higher immunosuppression secondary to repeated or severe rejection which could be a potential confounder. Tacrolimus used in conjunction with sirolimus is associated with increased risk of fungal infection in adult thoracic transplant recipients^{32, 33}, but tacrolimus alone has not previously been associated with fungal infections.

The contribution of dose and blood levels of tacrolimus to the association with PFI was not explored in this study since immunosuppressive protocols and target trough levels were not standardized across participating centers. While tacrolimus-based immunosuppression is associated with decreased calcineurin-related renal dysfunction, hypercholesterolemia and hypertension compared with cyclosporine-based regimens, an association between tacrolimus and PFI must be considered. Although tacrolimus has some in vitro anti-aspergillus properties, the in vivo immunosuppressive effects appear to outweigh the antifungal capabilities²⁶. It is plausible to consider that higher functional immunosuppression is being achieved with tacrolimus as compared to cyclosporine increasing the risk of PFI in recipients on tacrolimus-based immunosuppression. As the IPLTC moves toward a more unified protocol with tacrolimus-based immunosuppression, the identification of tacrolimus-based immunosuppression as a risk factor of PFI highlights the importance of immunosuppressive regimen in designing clinical trials to decrease infection-related morbidity and mortality.

CMV infection has been reported as a significant risk factor for invasive fungal infections in adult lung transplant recipients^{5, 34, 35}. In this study, only CMV-mismatch, not CMV infection, was associated with an increased risk of PFI. Diagnostic methods for CMV infection varied over the study period and may have contributed to this finding. Subclinical CMV infection and its potential immunomodulatory effects cannot be excluded as factors. Similar to age, CMV status represents a non-modifiable risk factor for PFI in pediatric lung transplant recipients. For this reason, these parameters should be considered in patient care and future clinical trial design.

As with any retrospective study, there are limitations inherent in this study design. Pretransplant cultures were not routinely obtained at all participating sites or from all subjects. However, a subgroup analysis of subjects with pretransplant fungal culture available produced the same model with and without inclusion of the culture variable. No additional factors were identified or excluded in this subgroup analysis. Secondly, the use of data from multiple centers without unified protocols also presents a limitation. However, the data collection was performed by the principal investigator at all participating sites using predetermined definitions in an effort to decrease differences in data collection methods compared to each site collecting data independently. Antifungal prophylaxis was not standardized within or across participating centers and was not obtained during the data collection. While many centers in the IPLTC use targeted antifungal prophylaxis for subjects colonized before transplant, antifungal prophylaxis was not consistently used during the time in which subjects were enrolled in this cohort, and changed within individual centers over time. Further, pretransplant colonization remained a risk factor in the multivariable subgroup analysis. Agreement about the optimal antifungal prophylaxis regimen in the lung transplant community is lacking^{36, 37}, and a prospective trial offers both a standardized approach and a clearer comparison.

Another limitation is that only PFI that were identified on fungal culture or tissue histology were categorized. This may underestimate the number of PFI by excluding clinically diagnosed cases and likely bias our results toward the null hypothesis. Limiting the diagnosis to the

established definitions provided does, however, allow for comparison of these pediatric-specific results with other previously published adult studies.

In conclusion, PFI occurs frequently in the first year after pediatric lung transplantation and is associated with increased 1-year mortality. Non-modifiable risk factors including CMV-mismatch, age over 15 years, pretransplant fungal colonization, and episodes of acute rejection were found in this retrospective study. The immunosuppressive regimen may be modified, but the diminished metabolic, cardiovascular and renal side effects, aside from an increased risk of PFI presented here, favor a tacrolimus-based immunosuppression regimen. Antifungal prophylaxis after adult lung transplantation remains variable; several antifungal regimens suggest prophylaxis decreases incidence of PFI ^{7, 38–40}. However, antifungal prophylaxis after adult lung transplantation remains variable given the lack of evidence on the optimal prevention regimen ^{36, 37}. Future prevention of PFI in pediatric lung transplant recipients will require an innovative prospective study design to address issues related to limited sample size and adherence in this population.

ACKNOWLEDGEMENTS

This manuscript represents a collaborative effort among pediatric lung transplant programs. In addition to the authors listed, we wish to acknowledge the contributions of the following individuals: Craig Cole, Jaime Fox, Pauline Whitmore, Christian Benden, Kathy Iurlano, Carsten Mueller, and Allison Drabble.

Funding: Supported by Thrasher Research Fund National Institutes of Health/K23 RR022956 (LDI)

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FIGURE 1.
Time to first PFI after Pediatric Lung Transplantation

FIGURE 2.
12-month survival in pediatric lung transplant recipients with and without PFI

TABLE 1Identified organisms from *Proven and Probable Pulmonary Fungal Infections*

SITE	All organisms	Candida species	Aspergillus species	Other
<i>Pulmonary (Total)</i>	<i>62</i>	<i>10</i>	<i>39</i>	<i>13</i>
Proven	20	8	11	1
Probable	42	2 [*]	28	12

* Candida species recovered in same culture as Aspergillus probable episode.

TABLE 2

Organisms recovered in PFI

Organism		Number (%)	Mortality due PFI
Aspergillus		38 patients	9/38 (24%)
	<i>Aspergillus</i>	23	
	<i>Aspergillus fumigatus</i>	16	
	<i>Aspergillus niger</i>	1	
Candida		10 patients	3/8(38%)
	<i>Candida</i> species	4	
	<i>Candida albicans</i>	6	
	<i>Candida krusei</i>	1	
Other		13 patients	0/13 (0%)
	Fungus	2	
	Mold	1	
	<i>Mucormycosis</i>	1	
	<i>Ochroconis humicola</i>	1	
	<i>Paecilomyces</i>	2	
	<i>Penicillium</i>	2	
	<i>Saccharomyces</i>	1	
	<i>Scedosporium</i>	2	

TABLE 3

Demographics of subjects with PFI compared to those without any fungal infections

		With PFI (n = 58)	Without any FI (n = 404)	P-value*
Age	Mean	13.7 years	11.4 years	0.002
Underlying diagnosis	Cystic Fibrosis	59%	53%	0.50
	PHTN from heart	9%	14%	
	Idiopathic PHTN	10%	7%	
	Bronchiolitis obliterans	4%	5%	
Transplant type	Double deceased donor	76%	70%	0.35**
	Heart/lung	17%	24%	
	Bilateral living donor	2%	5%	
	Single (either)	5%	3%	
CMV serostatus	Donor + / Recipient +	19%	19%	0.36
	Donor + / Recipient –	40%	28%	
	Donor – / Recipient +	10%	13%	
	Donor – / Recipient –	31%	40%	
CMV donor status	Donor +	59%	48%	0.12
Induction therapy	Yes	44%	41%	0.70
Calcineurin therapy	Cyclosporine	57%	77%	<0.001
	Tacrolimus	43%	22%	

PHTN: Pulmonary hypertension

*

Chi-square test

**

Fisher's exact test

TABLE 4

Univariable hazard ratios for time to PFI

Risk factor	Level	Hazard ratio (95% CI)	P-value
Donor and recipient CMV status	CMV D-/R-	REF	0.25
	CMV D-/R+	0.96 (0.38, 2.4)	.
	CMV D+/R+	1.2 (0.58, 2.6)	.
	CMV D+/R-	1.8 (0.96, 3.3)	.
Year of transplantation (quintiles)	1985–1992	REF	0.74
	1993–1995	0.76 (0.30, 1.9)	
	1996–1998	0.72 (0.26, 2.0)	
	1999–2001	1.1 (0.52, 2.5)	
	2002–2005	1.1 (0.50, 2.6)	
Cystic Fibrosis Etiology		1.3 (0.75, 2.1)	0.38
Age at transplant ≥ 15 years		2.2 (1.3, 3.7)	0.003
Pre-transplant culture positive		2.0 (0.95, 4.3)	0.067
CMV prior to PFI		1.3 (0.67, 2.6)	0.43
Any rejection prior to PFI		2.0 (1.03, 3.8)	0.041
Two rejections prior to PFI		2.0 (1.08, 3.6)	0.028
A2 rejection prior to PFI		2.2 (1.2, 3.8)	0.006
Two treated rejections prior to PFI		1.8 (0.99, 3.4)	0.054

TABLE 5

Multivariable models for time to Pulmonary Fungal Infection

Variable	Hazard Ratio (95% Confidence Interval)	
	Model 1	Model 2
Age $\geq$ 15 years	2.0 (1.2, 3.4) p=0.01	2.0 (1.2, 3.5) p=0.008
CMV Donor +/Recipient –	1.9 (1.1, 3.3) p=0.014	2.0 (1.2, 3.3) p=0.013
Tacrolimus regimen	2.4 (1.4, 4.1) p=0.001	2.4 (1.4, 4.1) p=0.001
Prior A2 or greater rejection	2.1 (1.2, 3.6) p=0.013	
Two or more prior episodes of any rejection		2.1 (1.1, 3.9) p=0.017