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LONG-TERM IMPACT OF RESPIRATORY VIRAL INFECTION AFTER PEDIATRIC LUNG TRANSPLANTATION

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Abstract

To evaluate the epidemiology and to investigate the impact of respiratory viral infections (RVI) on chronic allograft rejection after pediatric lung transplantation, a retrospective study of pediatric lung transplant recipients from 2002 to 2007 was conducted. Association between RVI and continuous and categorical risk factors was assessed using Wilcoxon rank-sum tests and Fisher's exact tests, respectively. Association between risk factors and outcomes were assessed using Cox proportional hazards models.

Results—Fifty-five subjects were followed for a mean of 674 days (range 14–1790). Twenty-eight (51%) developed 51 RVI at a median of 144 days posttransplant (mean 246; range 1–1276); 41% of infections were diagnosed within 90 days. 25 subjects developed 39 lower respiratory infections, and eight subjects had 11 upper respiratory infections (URI). Organisms recovered included rhinovirus(n=14), adenovirus(n=10), parainfluenza(n=10), influenza(n=5) and RSV(n=4). Three subjects expired secondary to their RVI (2 adenovirus, 1 RSV). Younger age and prior CMV infection were risks for RVI (HR 2.4 95% CI 1.1–5.3 and 17.0; 3.0–96.2, respectively). RVI was not associated with the development of chronic allograft rejection (P=0.25) or death during the study period.

Conclusions—RVI occur in the majority of pediatric lung transplant recipients, but were not associated with mortality or chronic allograft rejection.

Keywords

Lung transplantation; Respiratory virus infection; Pediatrics

INTRODUCTION

End-stage pulmonary disease in children can be treated with lung transplantation; however, despite the therapeutic potential of lung transplantation, the 1-year and 5-year post-LTX survival rates remain poor at only 80% and 50%, respectively (1). Most lung transplant recipients develop an infectious episode and infection accounts for nearly 40% of all posttransplant mortality (1–4). Respiratory viral infections (RVI) have been reported in 9–66% of evaluated lung transplant recipients in the literature include a rate of 14% in a large retrospective cohort of pediatric lung transplant recipients (5–11).

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Aside from the direct effects of infection, RVI has been epidemiologically associated with chronic graft rejection in lung transplant recipients. Several centers have reported that viruses such as influenza, parainfluenza, adenovirus, and respiratory syncytial virus (RSV) are associated with the development of bronchiolitis obliterans (BO) and bronchiolitis obliterans syndrome (BOS)(7–9,12–17). In animal models, introduction of respiratory viruses increased allograft rejection(18,19). Although the underlying mechanisms remain to be elucidated, it is hypothesized that respiratory viral infections injure the graft and activate a cascade of events to culminate in chronic graft rejection. However, in a recent review of RVI within the first year after transplantation, RVI was associated with death but not BOS in a cohort of nearly 600 pediatric lung transplant recipients (11). To further assess the association between RVI and chronic allograft failure, a longitudinal single-center evaluation of pediatric lung transplant recipients evaluated the hypothesis that an RVI was associated with BOS or mortality in primary pediatric lung transplant recipients beyond the first year following transplantation.

MATERIALS & METHODS

A longitudinal retrospective review of respiratory viral infection (RVI) in pediatric lung transplant recipients was performed. After Institutional Review Board approval, a comprehensive evaluation of clinical, microbiologic and pathology records was completed. Subjects transplanted at Texas Children's Hospital from the inception of the program in 2002 until 2007 were eligible for enrollment. Data was collected from the date of transplant until September 2007 unless the subject expired or transferred care.

Immunosuppressive regimen

All subjects received induction therapy with basiliximab, an IL-2 receptor antagonist on day 0 and 4 posttransplant. In addition, triple-drug immunosuppressive therapy including a calcineurin inhibitor, mycophenolate mofetil and prednisone was initiated at transplantation. Subjects received cytomegalovirus prophylaxis for 5.5 months with a combination of intravenous ganciclovir transitioned to valganciclovir when tolerating oral medications.

Definitions

Respiratory Viral Infection (RVI)—Diagnosis was based upon positive viral identification in bronchoalveolar lavage, bronchial wash, tracheal aspirate, sputum, or nasopharyngeal swab specimens in addition to clinical evidence of infection. Clinical evidence of viral infection was indicated by rhinorrhea, cough, and fever and supported by radiographic and/or transbronchial biopsy findings. Distinction between upper respiratory tract infection (URI) and lower respiratory tract infection (LRI) was based on the presence of clinicopathological changes on physical examination, chest imaging and site of viral recovery. Subjects without respiratory distress, hypoxia, new wheezing or crackles on exam, or new abnormal chest imaging were considered to have URI. Viral cultures, rapid detection with enzyme immunoassay (EIA) and polymerase chain reaction (PCR) were the principal diagnostic methods used. The application and specific methodology varied over the duration of the study. Episodes with clinical evidence of viral infection but without identification of specific viral pathogens were not included. **Posttransplant fungal infection (PFI)** definitions are adapted from those proposed by the European Organization for Research and Treatment of Cancer/Mycoses Study Group (20) and previously reported studies of fungal infection after transplantation (21,22).

Posttransplant outcome measures including **acute rejection (AR)** and **bronchiolitis obliterans/bronchiolitis obliterans syndrome (BO/BOS)** were based on definitions

proposed by working groups from the International Society for Heart and Lung Transplantation (ISHLT) (23–25).

Statistical methods

Comparisons of patients with and without RVI on demographic data and outcomes were performed using Wilcoxon rank-sum tests for continuous variables and Chi-square tests or Fisher's exact tests for categorical variables as appropriate. Associations between risk factors and time to RVI and other posttransplant outcomes were assessed using univariable and multivariable Cox proportional hazards models. Events that occurred during post-transplant follow-up, such as CMV infection and rejection, were modeled as time-dependent covariates. The functional forms for age and era of transplant were chosen by modeling the quartiles of these variables as categorical variables and assessing the resulting parameter estimates, and final models were chosen using backwards selection with a significance criterion of 0.05. The proportional hazards assumption for the multivariable models was assessed by entering risk-factor-by-time interactions into the model; this assumption was also assessed graphically using log-log-survival plots. All tests were two-tailed and performed at a significance level of 0.05. SAS version 9.2 (SAS Institute, Cary, NC) was used for all analyses.

RESULTS

Demographics

Of the fifty-five subjects evaluated, the majority (95%) received bilateral cadaveric lung transplantation and was Caucasian (75%). Transplantation was performed secondary to cystic fibrosis (62%), pulmonary hypertension (9%), bronchiolitis obliterans (5%), interstitial pneumonitis (5%) and other etiologies (19%).

Transplant related outcomes

Subjects were followed for an average of 22.2 month (median 21.8 months) after transplantation, with 45% being followed for more than 2 year after transplant. Of the 55 subjects, histopathologic diagnosis of bronchiolitis obliterans (BO) occurred in six (11%) while clinical diagnosis of BOS (of any grade including 0-p) developed in twelve (22%). BO and BOS both occurred at a mean of 20.6 months after transplant (median 16.5 and 21.8 months, respectively). Acute rejection occurred commonly with 65% of subjects having at least one episode of AR at a mean of 3.5 and median of 1.4 months after transplant. A2 or greater AR occurred in 27 subjects (49.1%) at a mean of 5.3 months and a median of 2.8 months posttransplant.

RVI episodes

Twenty-eight subjects (51%) developed 46 RVI during the study period (range 1–6 episodes). RVI occurred at a median of 144 days posttransplant (range 1–1276 days; mean 246 days). Organisms included rhinovirus (14), adenovirus (10), parainfluenza (10), influenza (3) and RSV (4). Of the RVI, thirty-eight (82.6%) met the criteria for lower respiratory tract infection (LRI) while eight (17.4%) were recovered from the upper respiratory tract (URI). All episodes of adenovirus infection were LRI as were the majority of rhinovirus infections (11/14) and parainfluenza infections (9/10), Table 2. Viral detection was predominantly from culture (38) in addition to PCR (2), and enzyme immunoassay (3). Infections occurred during the seasons when the viruses are known to circulate, Figure 1. Rhinovirus showed no seasonal predilection compared to influenza and RSV which occurred during the winter months. Of the 15 subjects who expired during the study period, three died

from RVI (adenovirus = 2, RSV = 1). Of the 28 with RVI, eleven subsequently developed BOS/BO while seven of 18 without RVI developed BOS/BO.

Risk for RVI

Univariable analyses evaluated potential risks for RVI, only history of a treated rejection episode or an episode of CMV infection prior to RVI were statistically significant. We explored age in greater detail as those with RVI were younger, although not statistically significantly as a continuous variable, Table 3.

In the multivariable model, age was evaluated as a discrete variable comparing the risk for subject less than 10 years compared to those over 10 years at transplantation. Increased risk of RVI included patients younger than 10 years of age at transplant (HR 2.4; 95% CI 1.1–5.3, p = 0.028) and those with a history of CMV infection prior to RVI (HR 17.0; 95% CI 3.0–96.2, p=0.001). In the multivariable model, treated acute rejection was not an independent predictor of subsequent RVI.

Risk after RVI

RVI was assessed as a risk factor for outcomes. RVI trended toward a statistically significant two-fold increase in the risk ensuing A2 or greater acute rejection (HR 2.2, 95% CI 0.99–4.9; p=0.053). However, RVI was not a significant risk factor for subsequent pulmonary fungal infection, CMV infection, post-transplant lymphoproliferative disease or BO/BOS (p>0.20). RVI was not associated with increased risk for death/retransplantation. In addition, LRI was not a risk factor for subsequent BOS or death/retransplantation when the subjects with LRI were evaluated (p >0.2).

DISCUSSION

Infection remains a significant complication after lung transplantation and mortality has only minimally improved in the past decade for pediatric lung transplant recipients. Few studies in pediatric lung transplant recipients have evaluated the impact of RVI on outcome. In a small cohort of pediatric subjects, adenovirus infection was associated with graft failure and death, while a larger cohort followed for only one year posttransplant showed RVI was associated with death but not BOS (7,11).

RVI occurred in 51% of the pediatric subjects in this cohort, compared to prior reports ranging from 9–66%(7–9,26). As in prior reports, viral infections occurred in typical seasonal patterns and clinicians should maintain vigilance regarding circulating community viral infections (11). Rhinovirus, adenovirus and parainfluenza were the most common viruses recovered (8,9). Rhinovirus was detected by conventional viral culture in this cohort; however, new molecular methods for viral detection will likely increase the recovery of this and other viruses, including human metapneumovirus, coronaviruses and bocaviruses (9,26,27).

Younger age at transplant was again a risk factor for RVI similar to previous reports (LDI, RVI, Txp ID). CMV infection prior to RVI was associated with a 17-fold increased risk for subsequent RVI although CMV donor/recipient serostatus was not associated with an increased risk. CMV infection may be a marker for over-immunosuppression of the transplant recipient. Alternatively, the immunomodulatory effects of CMV may allow for viral infection after exposure compared to subjects without CMV infection and similar exposure profiles.

RVI was not associated with increased risk of BOS after transplant in this cohort which is similar to the larger pediatric cohort followed for one-year after transplantation but is

distinct from the adult lung transplant literature (7–9,12–17). However, the multi-factorial nature of BOS and the number of events in the cohort, limit the extent to which BOS could be explored. Preceding RVI did trend toward increased statistically significant risk of ensuing A2 acute rejection indicating that the inflammatory cascade or reduction in immunosuppression related to an episode of RVI may not be inconsequential in the pediatric lung transplant population.

As with any retrospective study, there are limitations related to the study design, availability of data, and selection bias. This study was performed at a single center with routine induction and immunosuppressive strategies and routine bronchoscopy for surveillance including viral studies. As the only pediatric lung transplant center in the region, the follow-up and retention of patients was high. Additional limitation include the number of available subjects and the duration of follow-up which may impact the results. However, a significant proportion of subjects were followed for at least two years after transplantation (mean follow-up 22 months).

Another limitation of this study involves RVI diagnosis and diagnostic testing. Most episodes of cold symptoms were routinely evaluated and included in this report decreasing the potential to underestimate the number of episodes of RVI that existed in prior studies (11). Fifty-one percent of subjects experienced an RVI compared to only 13% in the previous pediatric lung transplant cohort. Still, specimens were not banked or evaluated with advanced molecular diagnostics routinely. Therefore, evaluation specifically for recently identified viruses like human metapneumovirus, human coronaviruses and bocaviruses was not performed which could affect the number of RVI recovered.

Unlike previous studies in pediatric patients, differentiation between upper and lower RVI was assessed in this cohort. RVI of the lower tract have been reported to carry more serious risks for subsequent mortality and rejection post-transplant (8); however, LRI in our cohort was not associated with increased risk of BOS or death.

This study provides a longitudinal evaluation of RVI in the pediatric lung transplant population. The data indicates that younger age and CMV infection are independent risk factors for the development of RVI after pediatric lung transplantation. In addition, a single episode of RVI trends toward increased subsequent A2 acute rejection but is not associated with BOS or death. Future studies must prospectively evaluate the incidence of RVI in this population, including potential consequences to RVI related to graft injury.

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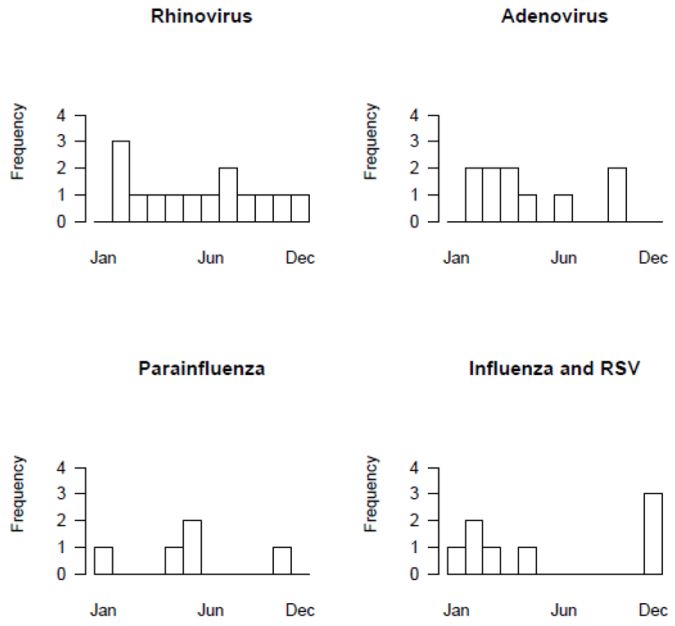

Figure 1. Viral Recovery by Calendar Month

The figure demonstrates the recovery of the five most common viruses divided by month of recovery. Rhinovirus recovery was steady throughout the year. Adenovirus occurred primarily in the spring while influenza and RSV predominated in the winter months.

Table 1

Demographics of Pediatric Lung Transplant Recipients

		n=55 (%)	With RVI n = 28	Without RVI n = 27	P-value
Age at Transplant	Mean (Median) in years		10.6 (11.3)	12.3 (13.9)	0.36*
Female		28(51%)	16 (57%)	12 (44%)	0.35**
Transplant	Bilateral cadaveric	52 (95%)	27 (96%)	25 (93%)	0.74***
	Heart-Lung	2(4%)	1 (4%)	1 (4%)	
	Living Donor	1(2%)		1 (4%)	
Ethnicity	Caucasian	39 (71%)	17 (68%)	22 (82%)	0.67***
	African-American	2(4%)	1 (4%)	1 (4%)	
	Hispanic	9 (16%)	6 (24%)	3 (11%)	
	Others	2 (4%)	1 (4%)	1 (4%)	
Etiology	Cystic Fibrosis	34 (62%)	17 (61%)	17 (63%)	0.91***
	Pulmonary Hypertension (Idiopathic/Secondary)	3 (5%)/2(4%)	1 (4%)/2 (7%)	2 (7%)/0	
	Bronchiolitis obliterans	3 (5%)	1 (4%)	2 (7%)	
	Interstitial pneumonitis	3 (5%)	1 (4%)	2 (7%)	
	Others	10 (18%)	6 (21%)	4 (15%)	
Cyclosporine		49 (91%)	27 (96%)	22 (85%)	0.18***

*Wilcoxon rank-sum test

**Chi-square test

***Fisher's exact test

Table 2

Viral Recovery

Virus		LRI	URI
Adenovirus		10	
Rhinovirus		11	3
Influenza (any)		4	1
	Influenza A	3	1
	Influenza B	1	
Parainfluenza (any)		9	1
	Parainfluenza 1	3	
	Parainfluenza 2	1	
	Parainfluenza 3	4	1
Respiratory syncytial virus		3	1
Enterovirus			1
Herpes simplex virus		1	1
TOTAL		38	8

LRI – lower respiratory tract infection; URI – upper respiratory tract infection

Table 3

Univariable risks for RVI

Univariable hazards for RVI Risk factor		N	Hazard ratio (95% CI)	P-value
D/R CMV status verses D-/R-		43		0.97
	1.Donor +/Recipient +		1.1 (0.36, 3.5)	
	2.Donor +/Recipient −		1.3 (0.44, 3.9)	
	3.Donor −/Recipient +		1.3 (0.26, 6.4)	
CMV prior to RVI		55	15.0 (2.9, 77.4)	0.001
Age at transplant verses 16.5–20.9		55		0.27
	0.2–6.6 yrs		2.9 (0.92, 8.9)	
	6.6–13.6 yrs		1.3 (0.41, 4.1)	
	13.6–16.5 yrs		1.5 (0.50, 4.7)	
Year of transplant verses 2006		55		0.62
	2002–2004		1.8 (0.58, 5.7)	
	2004–2005		1.09 (0.35, 3.4)	
	2005–2006		1.7 (0.61, 4.6)	
Any Rejection prior to RVI		55	1.5 (0.63, 3.4)	0.38
Treated Rejection prior to RVI		55	2.5 (1.08, 5.8)	0.031
Pulmonary fungal infection prior to RVI		55	0.60 (0.08, 4.6)	0.62

Table 4

Multivariable model for RVI after Pediatric Lung Transplantation (55 subjects with 28 events)

Label	Hazard ratio (95% CI)	P-value
Age <= 10 vs > 10	2.4 (1.10, 5.3)	0.028
CMV (time dependent)	17.0 (3.0, 96.2)	0.001