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Lung Function, Pulmonary Complications, and Mortality after Allogeneic Blood and Marrow Transplantation in Children

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Pulmonary complications (PC) remain a significant barrier to the success of allogeneic blood and marrow transplantation (BMT). Pretransplant pulmonary function tests (PFTs) have been correlated with risk of early respiratory failure and mortality in adult BMT recipients. There is limited data on their relationship to posttransplant outcomes in pediatric patients. We sought, in pediatric allo-BMT recipients (1) to analyze the spectrum of infectious and noninfectious PCs, (2) to evaluate the prevalence and course of PFT abnormalities before and after transplant, and (3) to correlate pretransplant PFT findings with patient outcomes, specifically risk of PC, respiratory failure, and death. We conducted a retrospective review of PC in all patients who underwent allo-BMT at Children's Hospital of Pittsburgh during 1996 to 2006. PFTs were performed in children 6 years and older pretransplant, 3, 6, 12, and 24 months after transplant. PCs occurring within 100 days of BMT were considered early. One hundred ten consecutive children who underwent allo-BMT were included (median age = 9.7 years; 67 males, 43 females). Seventy-five of 110 patients had 370 PFT studies performed; 62 of 73 patients >6 years of age (85%) underwent PFT studies pre-BMT. There was a significantly higher risk of early respiratory failure in patients with reduced pretransplant forced expiratory volume in 1 second (FEV_1) ($P = .0001$, odds ratio [OR] 5.1) or forced vital capacity (FVC) ($P = .0001$, OR 8.5). Forty-three of 110 (39%) patients required mechanical ventilation, and in 30 episodes (70%), patients remained ventilator-dependent until time of death. Posttransplant, we observed statistically significant reductions in FEV_1, FVC, total lung capacity (TLC), and diffusing capacity of the lungs (DLco) at 3 months post-BMT and similar reductions at 6 months post-BMT except for DLco (not significant). Between 12 and 24 months, FEV_1, FVC, TLC, and DLco improved significantly from earlier declines post-BMT; however FEV_1 and FVC remained significantly below pretransplant values. At a median follow-up of 5.5 (1.6-11.6) years, 58 of 110 (53%) patients were surviving. The majority of the patients who died from transplant-related complications suffered from 1 or more PCs (31/32, 97%). Early PC was associated with over 4-fold reduction in probability of survival at 10 years (8/44, 18% with early PC versus 50/66, 76% without early PC). On multivariate analysis, risk of death was significantly associated with high-risk disease status ($P = .015$; hazard ratio [HR] = 2.5), unrelated donor ($P = .03$; HR = 2.1), early PC ($P = .0001$; HR = 7.7) and pathogen identification ($P = .02$; HR = 2.7). These results suggest that, in children undergoing allo-BMT (1) compromised pretransplant lung function is significantly correlated with risk of early respiratory failure but not of overall survival (OS), (2) reductions in lung volumes and diffusion capacity are common 3- to 6-month posttransplant with partial recovery by 12 to 24 months, (3) there is high mortality following mechanical ventilation, and (4) early PCs are associated with significantly worse OS.

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INTRODUCTION

Allogeneic blood and marrow transplantation (allo-BMT) has been successfully used to treat malignant and nonmalignant diseases in both adults and children. Despite application of stringent HLA matching criteria and advances in supportive care, success of transplantation is frequently compromised by infectious and noninfectious pulmonary complications (PCs) [1-3]. PCs have been reported in 40% to 60% of adult BMT recipients, and may contribute to death in over one-third of these cases; similar data in children are limited, and natural history of PCs remains incompletely understood [4-7].

Pulmonary function tests (PFTs) are widely performed before BMT to screen for underlying respiratory abnormalities and to provide baseline lung function measurements. Previous studies have examined the predictive value of baseline PFTs for posttransplant complications [8-10]. However, the majority of published data is on adults, includes auto- as well as allo-BMT patients, and findings are not consistent. Recently, Parimon and colleagues [11] published data from a retrospective analysis of a large cohort of adult allogeneic BMT recipients. Their results showed that compromised pretransplant lung function significantly contributes to risk of early respiratory failure and mortality. There are limited data on their relationship in pediatric patients.

In this study, we undertook a retrospective review of PCs in all patients who underwent allo-BMT at Children's Hospital of Pittsburgh over a 10-year period. We analyzed the spectrum of infectious and noninfectious PCs and evaluated serial PFTs before and after transplant. We hypothesized that pretransplant PFTs would correlate with development of pulmonary complications and survival. We also sought to examine the impact of early respiratory failure on posttransplant outcomes, and relationship between PCs and death.

PATIENTS AND METHODS

The study was approved by the institutional review board of the University of Pittsburgh. Clinical, laboratory, pathology, and imaging data were retrieved for all consecutive patients who underwent allo-BMT at Children's Hospital of Pittsburgh between October 10, 1996, and September 1, 2006.

Definition of PCs

PC in a BMT recipient was defined as development of 1 or more of the following: new or persistent pulmonary infiltrates on chest radiograph or chest computed tomography (CT) scan; signs of lower respiratory tract disease including wheezing, increased work of breathing, crackles on auscultation of chest; hemoptysis; hypoxemia (arterial oxygen saturations <90% on room air) in the absence of primary cardiogenic etiology [1,2].

Classification of PCs

1. Early versus late: PCs that occur within 100 days of BMT were considered "early" and those after 100 days were considered "late."
   a. Patients were defined as having developed early respiratory failure if they required mechanical ventilation for a nonelective reason within 100 days after transplant.
2. Infectious versus noninfectious:
   a. Infectious or presumably infectious: if a pathogenic microbial agent was detected from bronchoalveolar lavage (BAL), lung biopsy, nasal wash, tracheal aspirate, autopsy, or no pathogen agent was detected, but clinical findings were highly suggestive of infection (high fever, localized pneumonia by radiographic studies, concomitant positive blood cultures for common agents for pneumonia), the PC was defined as infectious or presumably infectious. Invasive fungal infections were recorded based on published criteria from European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group [12]. The presence of a pulmonary copathogen was defined as the isolation of more than 1 pathogenic bacterial species, fungal species (such as *Aspergillus fumigatus*), or viruses from the same BAL or lung biopsy specimen [13].
   b. Noninfectious: clinical descriptions from Michelson et al. [1] and Gower et al. [14] were used for classification of noninfectious and late complications. Briefly,
      i. Idiopathic pneumonia syndrome (IPS)—dyspnea, nonproductive cough, hypoxemia, nonlobar radiographic infiltrates in absence of lower respiratory tract infection or heart failure [15,16].
      ii. Pulmonary edema—dyspnea, nonproductive cough, hypoxemia, nonlobar radiographic infiltrates because of heart failure.
      iii. Pulmonary hemorrhage—bleeding from endotracheal tube with infiltrate on chest X-ray, bleeding seen at bronchoscopy, X-ray infiltrate with drop in Hgb, or occult hemorrhage that was shown by hemosiderin containing alveolar macrophages in BAL or biopsy.
      iv. Bronchiolitis obliterans—chronic lower airway obstruction, cough, dyspnea, small fixed airway obstruction on PFTs, mosaic

perfusion on high resolution chest CT, and when biopsies were performed histopathologic findings of organizing exudates with plugs of granulation and connective tissue in the distal airway.

v. Bronchiolitis obliterans organizing pneumonia (BOOP)—diagnosed by histology. Characteristic findings include polypoid endobronchial myxoid fibroblastic tissue masses filling the lumens of terminal and respiratory bronchioles and extending into alveolar ducts and alveoli, representing an organizing pneumonia.

Evaluation of Risk Factors

This included age at BMT; disease status prior to conditioning (standard risk—acute leukemia or lymphoma in complete remission (CR)1 or CR2, CMV in first chronic phase; high-risk—acute leukemia or lymphoma in relapse or ≥CR3, CML beyond first chronic phase, myelodysplastic syndrome (MDS), or secondary acute myelogenous leukemia (AML) as previously defined [17]); history of pretransplant pulmonary disease; HLA match; donor-recipient CMV status; conditioning regimen; graft-versus-host disease (GVHD) prophylaxis; and acute GVHD (aGVHD). Posttransplant outcomes including timing, type, severity, and course of PCs, and GVHD and chronic GVHD (cGVHD) were abstracted. All chest X- ray and CT scan reports; microbiology and pathology results of BAL samples, nasal wash, tracheal aspirate, lung biopsies, and autopsies were reviewed.

Pulmonary Function Studies

PFTs were performed in children 6 years and older pretransplant, 3, 6, 12, and 24 months after transplant and at other time points when clinically indicated. Spirometry, body plethysmography, and diffusing capacity were performed in the Pulmonary Function Laboratory of Children's Hospital of Pittsburgh by a certified technician following the American Thoracic Society/European Respiratory Society Guidelines [18]. Equipment utilized included the Sensormedics 2100 and the Sensormedics V-Max 22 with Autobox 6200 (Sensormedics Co., Yorba Linda, CA).

PFT study consisted of spirometry before and after bronchodilator, lung volumes, and diffusion capacity. Total lung capacity (TLC), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), FEV_1/FVC ratio, and carbon monoxide diffusing capacity of the lungs (DLco) were included for this analysis [19-22]. Actual values were normalized for sex and height according to age-sex-race specific reference equations. Lung volumes in African Americans were adjusted with a fixed (0.85) correction. The DLco was corrected for hemoglobin content ($DLco_c$) if a measurement was available within the prior 30 days.

PFT measurements were converted to a percentage of the predicted value, and a standard deviation score. Using this normalization, FVC, FEV_1, TLC, FEV_1/FVC, and DLco were categorized as normal (>80%) or reduced (≤80%) [23-25].

Statistical Methods

Statistical analyses were performed using SPSS 11, 5 (SPSS Inc., Chicago, IL), and P values of <.05 were considered statistically significant. Changes in PFTs from pretransplant values were performed using the Wilcoxon test. Mann Whitney-U test was used to compare the changes in PFTs between PC versus no PC groups. Categoric data were compared by chi-squared and Fisher exacts tests to study the relationship between covariates and PFT abnormalities. Survival rates were estimated by the Kaplan-Meier method. For multivariate analysis, clinical risk factors with a value of $P \leq .1$ on univariate analysis were included. Cox proportional hazards regression model was used in multivariate analysis to identify risk factors associated with mortality. Results are presented as hazard ratio (HR) with 95% confidence intervals (CIs) and significance.

RESULTS

From October 10, 1996, to September 1, 2006, 110 patients underwent 114 allo-BMT at Children's Hospital of Pittsburgh. One hundred two of 110 (93%) patients underwent ablative conditioning patients received reduced-intensity conditioning (RIC) in 11 of 114 transplants. Median length of follow-up is 5.5 years (1.6–11.6 years). Median age at BMT was 9.7 years (0.3-23.3 years). There were 67 (61%) males and 43 (39%) females. Ninety-one percent of transplants were for malignant diseases; 72% patients were high risk; 57% donors were unrelated; stem cell sources included BN 73%, cord blood 23%, and peripheral blood (PBSC) 4%; 22% grafts were T cell depleted in vitro; 58% patients developed aGVHD and 27% of surviving patients developed cGVHD.

Salient patient characteristics are summarized in Table 1. HLA mismatched transplants (18/31; 58%) were associated with greater risk of early PCs compared with HLA matched transplants (26/79; 33%)($P = .027$). No significant relationship was found among other clinical characteristics and occurrence of early PCs.

Pretransplant Pulmonary Disease

Forty-two of 110 (38%) patients had history of lower respiratory tract infection (LRTI) pretransplant. Sixteen of 104 (15%) patients had known history of asthma. Ten patients underwent mechanical ventilation pre-BMT; 9 of 10 had mechanical ventilation

Table 1. Characteristics of the Allotransplant Recipients with and without Early Pulmonary Complications (PC)

	With Early PCs* (n = 44)	Without Early PCs* (n = 66)	Total (n = 110)
Age at BMT (years) median (range)	10.3 (0.3-23.3)	9.5 (0.5-20.1)	9.7 (0.3-23.3)
Sex (female/male)	16/28	27/39	43/67
Disease status			
Standard risk	11 (25.0%)	26 (39.4%)	37 (33.6%)
High risk	33 (75.0%)	40 (60.6%)	73 (66.4%)
Prior pulmonary disease			
Yes	21 (47.7%)	36 (54.5%)	57 (51.8%)
No	23 (52.3%)	30 (45.5%)	53 (48.2%)
Donor type			
HLA matched	26 (59.1%)*	53 (80.3%)*	79 (71.8%)
HLA mismatch	18 (40.9%)*	13 (19.7%)*	31 (28.2%)
CMV status (%)			
Host/donor/both seropositive	23 (52.3%)	24 (36.4%)	47 (42.7%)
Both seronegative	21 (47.7%)	42 (63.6%)	63 (57.3%)
Conditioning regimen (%)			
TBI-based	30 (68.2%)	37 (56.1%)	67 (60.9%)
Chemotherapy-based	14 (31.8%)	29 (43.9%)	43 (39.1%)
GVHD prophylaxis (%)			
Methotrexate-containing	23 (52.3%)	40 (60.6%)	63 (57.3%)
No methotrexate	21 (47.7%)	26 (39.4%)	47 (42.7%)
Acute GVHD			
Yes	28 (63.6%)	36 (54.5%)	64 (58.2%)
No	16 (36.4%)	30 (45.5%)	46 (41.8%)

GVHD indicates graft-versus-host disease; BMT, blood and marrow transplantation; CMV, cytomegalovirus; TBI, total body irradiation.
*Differences between the 2 groups were not statistically significant except for HLA match versus mismatch donor ($P = .027$).

within 1 to 6 months prior to transplant. No patient had prior lung radiation; 9 patients had received prior craniospinal radiation therapy. Three of 3 patients with sickle cell disease had prior history of recurrent acute chest syndrome. Three patients had history of sleep apnea. One patient suffered from longstanding bronchiectasis and chronic respiratory failure.

PC

Eighty-one of 110 (74%) patients developed 1 or more PCs. These included 53 patients with LRTI and 31 with noninfectious PC episodes; 3 patients developed both infectious and noninfectious PCs at different timepoints posttransplant. Forty-four of 110 (40%) patients developed early PCs (within 100 days posttransplant). Median time to onset of early PCs was 29 days (3-98 days) and of late PCs 350 days (102-2591 days) post-BMT.

Infectious PCs

Fifty-three of 110 (48%) patients had 56 episodes of LRTIs. Thirty of 56 (54%) episodes in 29 patients were found to have microbiologic/histopathologic evidence of infection. Pathogens (41) were demonstrated from tracheal aspirate or BAL (32), lung biopsy or autopsy (5), nasopharyngeal secretions (1; parainfluenza), skin biopsy (1; aspergillus), liver biopsy (1; aspergillus) and blood culture (1; *Mycobacterium avium-intracellulare* [MAI]) (Table 2A). In 9 of 29 (31%) cases there were 2 to 3 pulmonary copathogens identified from the same BAL or lung biopsy sample; 5 of 9 cases had 1 or more fungal copathogens (*Aspergillus* + *E. coli* + CMV; *Aspergillus* + *Fusarium* + *Rhizopus*; *Aspergillus* + *Citrobacter*; *Candida* + HSV + Coagulase-negative *Staphylococcus*; *Enterococcus* + Coagulase-negative *Staphylococcus* + Parainfluenza; *Candida* + *Klebsiella*; *Klebsiella* + HHV-6; MAI + *Enterococcus*, and *Enterobacter* + *Staphylococcus aureus*). Sinusitis

Table 2A. Microbiological Yield

Category	Pathogen	Number	Total	Comment
Bacterial			15	
	Staph aureus	3		MRSA (1)
	Coagulase Negative *Staphylococcus*	2		
	Enterobacter	2		
	Enterococcus	2		
	Klebsiella	2		
	Streptococcus	2		
	E. coli	1		
	Citrobacter	1		
Fungal			14	
	Aspergillus	9		
	Candida	2		
	Fusarium	1		
	Rhizopus	1		
	Pneumocystis jiroveci	1		
Viral			9	
	Parainfluenza	2		1 addl. case -URTI only
	CMV	2		
	HHV-6	1		
	HSV	1		
	RSV	1		1 addl. case - URTI only
	Adenovirus	1		
	Influenza	1		
Mycobacterial			3	
	MAI	3		
Total			41	

MRSA indicates methicillin-resistant *Staphylcoccus aureus*; URTI, upper respiratory tract infection; CMV, cytomegalovirus; RSV, respiratory syncytial virus; HSV, herpes simplex virus; HHV-6, human herpes virus 6; MAI, Mycobacterium avium intracellulare.

was diagnosed in 25 cases based on clinical criteria alone (9) and with radiologic findings (16); in 8 of 25 cases, there was no associated LRTI.

BAL

Thirty-eight (35%) patients underwent 41 BAL procedures post-BMT. Twenty of 44 (45%) patients with early PC and 18 of 37 (49%) patients with late PCs underwent BAL procedure. Thirteen of these procedures (32%) yielded 23 pathogens. One patient was diagnosed with relapsed AML from BAL sample. Ten of 38 (26%) patients who underwent BAL were surviving compared to 48 of 72 (67%) of those who did not undergo the procedure. Eight of 29 (28%) patients with pathogen identification were surviving versus 50 of 81 (62%) who did not (multivariate $P = .02$; HR = 2.7, 95% CI = 1.5-4.8) (Table 3).

Noninfectious PCs

Thirty-one of 110 (28%) patients developed 1 or more noninfectious PCs (Table 2B). These included: IPS (26 episodes in 25 patients)—associated diagnoses were veno-occlusive (VOD) (9), multiorgan failure (7), and antithymocyte globulin (ATG) reaction (1); cardiogenic pulmonary edema (2); pleural effusion (23); pulmonary hemorrhage (15); air leak (9); reactive airway disease (10); bronchiectasis (4), bronchiolitis obliterans (6), BOOP (4); and others (7). IPS was a contributing cause of death in 14 of 25 cases (56%).

Table 2B. Noninfectious PCs

Idiopathic pneumonia syndrome	26	Associated diagnoses—VOD (9), multiorgan failure (7), and ATG reaction (1)
Pleural effusion	23	1 malignant
Pulmonary hemorrhage	15	
Reactive airway disease	10	
Air leak	9	
Bronchiolitis obliterans	6	Diagnosis made by HRCT and PFT (3), biopsy (1), and at autopsy (2)
BOOP	4	Diagnosed at autopsy (4) with parainfluenza (1), HSV 1 (1), enterococcus (1), and MRSA (1) on cultures
Bronchiectasis	4	
Cardiogenic pulmonary edema	2	
Interstitial fibrosis	2	
Chest wall weakness	1	
Chronic interstitial lung Disease	1	
Hemothorax	1	
Hypersensitivity pneumonitis	1	
Pleural fibrosis	1	

VOD indicates veno-occulsive disease; BOOP, Bronchiolitis obliterans organizing pneumonia; HSV, herpes simplex virus; MRSA, methicillin-resistant *Staphylcoccus aureus*; HRCT, high-resolution chest computed tomography; PFT, pulmonary function test; PC, pulmonary complication.

Mechanical Ventilation

Forty-three of 110 (39%) patients required mechanical ventilation, 1 twice. Indications for mechanical ventilation included: LRTI (16), sepsis and multiorgan failure (MOF) (16), pulmonary hemorrhage (15), IPS (8), VOD and MOF (6), late noninfectious PCs and respiratory failure (3), heart failure (2), and other (4; intravenous immunoglobulin (IVIG) anaphylaxis 1, AML of lungs 1, seizure 1, and hypertensive encephalopathy 1). Patients were successfully extubated in 13/44 episodes (30%) with median 2 (10.3 ± 17.7) days of mechanical ventilation, whereas in 30 episodes (70%), patients remained ventilator-dependent with median 10 (17.5 ± 27.1) days of mechanical ventilation till time of death; this difference in days of mechanical ventilation was not statistically significant ($P = .62$).

Survival

At a median follow-up of 5.5 years (1.6-11.6), 58 of 110 (53%) patients were surviving. Ten-year probability of overall survival (OS) is 76% (95% CI = 66.5-85.1) for those without early PC versus 18% (95% CI = 9.9-27.3) for those with early PC ($P = .0001$) (Figure 1).

There were 52 deaths among 110 children (47%); 32 of the 52 (62%) deaths were because of transplant-related complications and 20 of 52 (38%) because of disease relapse. Majority of patients who died from transplant-related complications suffered from 1 or more PC (31/32, 97%).

On univariate analysis, OS was significantly associated with high-risk disease status, unrelated donor, total body irradiation (TBI)-containing regimen, and presence of early PC, but not with HLA match, any PC, aGVHD, or cGVHD. On multivariate analysis, risk of death was significantly associated with high-risk disease status ($P = .015$; HR = 2.5), unrelated donor ($P = .03$; HR = 2.1), early PC ($P = .0001$; HR = 7.7), and pathogen identification ($P = .02$; HR = 2.7) (Table 3).

Pulmonary Function Tests

In all, 75 of 110 patients had 370 PFT studies performed.

Pretransplant PFTs

Sixty-two of 73 patients ≥6 years of age (85%) underwent PFT studies pre-BMT. Twelve of 62 (19%) of the patients had reduced FVC, 12/62 (20%) reduced FEV_1, 8 of 62 (13%) reduced FEV_1/FVC ratio, 4 of 55 (9%) reduced TLC, and 29 of 50 (58%) reduced DLco pretransplant (Table 4). Isolated reduction in DLco was the most common PFT abnormality, observed in 18 of 50 patients (36%).

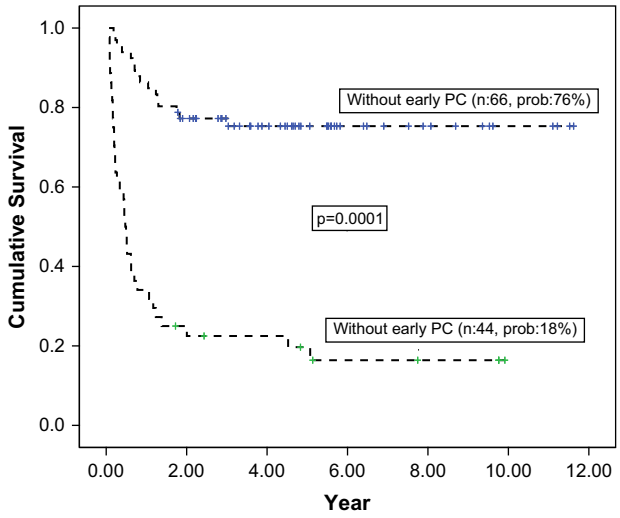

Figure 1. Ten-year probabilities of OS after allo-BMT by occurrence of early PC.

Pretransplant PFTs and Clinical Correlates

Patients with reduced pretransplant FEV_1 or FVC were significantly more likely to develop early respiratory failure (FEV_1 $P = .0001$, OR = 5.1, 95% CI = 1.3-19.8; FVC $P = .0001$, OR = 8.5, 95% CI = 2.1-36.4) leading to mechanical ventilation with high mortality rates in ventilated patients, as described under the Mechanical Ventilation section. However, pretransplant PFTs were not significantly correlated to risk of PC or OS.

Posttransplant PFTs

PFT studies posttransplant showed 36%, 46%, 30%, and 77% of patients with FVC, FEV_1, TLC, and DLco abnormalities at 3 months, respectively, and 42%, 49%, 27%, 75%, of patients with FVC, FEV_1, TLC, and DLco abnormalities at 6 post-BMT, respectively (Table 4 and Figure 2). Between 12 and 24 months, PFT abnormalities tended to improve. A longitudinal analysis was performed on 20 patients for whom complete PFT data was available

Table 3. Association of Clinical Risk Factors and Survival

Variable	Total n	Nonsurvivors n (%)	Univariate *P* Value	Multivariate *P* Value	Hazards Ratio (95% CI)
Disease status at BMT					
Standard risk	37	9 (24%)	.001	.015	2.5 (1.2-5.4)
High risk	73	43 (59%)			
HLA					
Matched	79	33 (42%)	.10		
Mismatched	31	19 (61%)			
Donor					
Related	46	14 (30%)	.005	.03	2.1 (1.1-4.3)
Unrelated	64	38 (59%)			
Conditioning regimen					
TBI containing	67	40 (60%)	.002	.32	
Non-TBI containing	43	12 (28%)			
PC					
Yes	81	43 (53%)	.06		
No	29	9 (31%)			
Early PC					
Yes	44	36 (82%)	.0001	.0001	7.7 (3.7-16.1)
No	66	16 (24%)			
Acute GVHD					
Yes	64	35 (55%)	.10		
No	46	17 (37%)			
Chronic GVHD					
Yes	30	14 (47%)	.93		
No	80	38 (48%)			
Pathogen identification					
Yes	29	21(72%)	.001	.02	2.7 (1.5-4.8)
No	81	31(38%)			

CI indicates confidence interval; GVHD, graft-versus-host disease; PC, pulmonary complication; TBI, total body irradiation; BMT, blood and marrow transplantation.

Table 4. PFT Findings

	Pre-BMT	3 Months	6 Months	12 Months	24 Months	36 Months	48 Months	>60 Months
FVC	n = 62	n = 46	n = 43	n = 37	n = 26	n = 15	n = 10	n = 8
Normal	50 (81%)	30 (64%)	25 (58%)	27 (73%)	21 (81%)	13 (86%)	8 (80%)	7 (87%)
Reduced	12 (19%)	15 (36%)	18 (42%)	10 (27%)	5 (19%)	2 (14%)	2 (20%)	1 (13%)
FEV_1	n = 62	n = 46	n = 43	n = 37	n = 26	n = 15	n = 10	n = 8
Normal	50 (80%)	25 (54%)	22 (51%)	24 (65%)	17 (65%)	10 (67%)	7 (70%)	6 (75%)
Reduced	12 (20%)	21 (46%)	21 (49%)	13 (35%)	9 (35%)	5 (33%)	3 (30%)	2 (25%)
FEV_1/FVC	n = 62	n = 46	n = 43	n = 36	n = 25	n = 14	n = 8	n = 7
Normal	54 (87%)	35 (76%)	32 (74%)	29 (80%)	22 (88%)	12 (86%)	7 (88%)	5 (72%)
Reduced	8 (13%)	11 (24%)	11 (26%)	7 (20%)	3 (12%)	2 (14%)	1 (12%)	2 (28%)
TLC	n:55	n:40	n:37	n:28	n:20	n:9	n:5	n:7
Normal	50 (91%)	28 (70%)	27 (73%)	22 (80%)	19 (95%)	8 (89%)	5 (100%)	6 (86%)
Reduced	4 (9%)	12 (30%)	10 (27%)	6 (20%)	1 (5%)	1 (11%)	—	1 (14%)
DLco	n = 50	n = 35	n = 32	n = 26	n = 20	n = 17	n = 7	n = 4
Normal	21 (42%)	8 (23%)	8 (25%)	9 (35%)	10 (50%)	10 (59%)	4 (57%)	3 (75%)
Reduced	29 (58%)	27 (77%)	24 (75%)	17 (65%)	10 (50%)	7 (41%)	3 (43%)	1 (25%)

PFT indicates pulmonary function test; BMT, blood and marrow transplantation; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; DLco, diffusing capacity of the lungs.

pretransplant, and at 3, 6, 12, and 24 months posttransplant (Table 5). It confirmed the findings observed in the entire cohort with statistically significant reductions in FEV_1, FVC, TLC, and DLco at 3 months post-BMT, and similar reductions at 6 months post-BMT except for DLco (not significant). Between 12 and 24 months, FEV_1, FVC, TLC, and DLco improved significantly from earlier declines post-BMT; however FEV_1 and FVC reductions remained significantly below pretransplant values.

Posttransplant PFTs and Clinical Correlates

PFT findings at 3 months post-BMT were correlated with clinical outcomes posttransplant (Table 6). Mean FEV_1 and FVC predicted were significantly lower in patients who developed pulmonary complication, and those with early respiratory failure. TLC and DLco were also significantly lower in patients who developed early respiratory failure. FEV_1 was significantly lower in patients who received non-TBI (busulfan [Bu]-based) versus those who received TBI conditioning. FEV_1 and FVC were significantly higher in those with aGVHD versus those without aGVHD. There was no correlation between posttransplant PFTs and risk of cGVHD or OS.

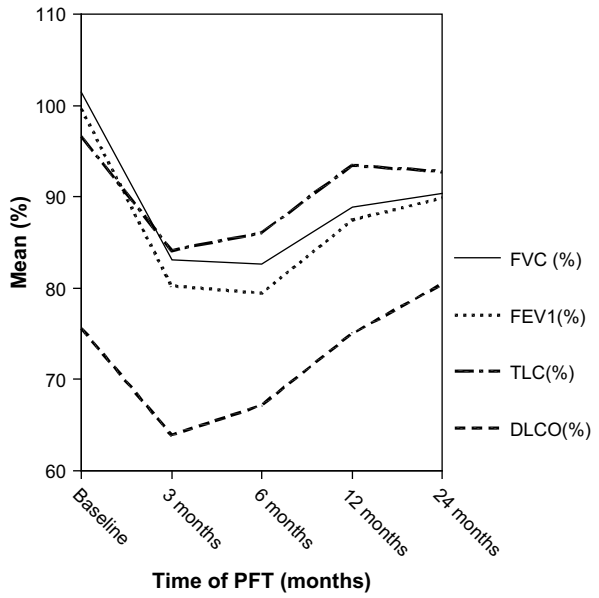

Figure 2. Changes in PFTs over time in 20 patients with PFT data at pretransplant, 3, 6, 12, and 24 months.

DISCUSSION

The data presented in this study show that development of PCs after allo-BMT is associated with poor outcome in children. This appears to be particularly true for those with early PC (occurring within 100 days of allo-BMT) with about 1.7 times higher risk of mortality, which translated into over 3-fold reduction in 10-year probability of OS. A majority of patients who died from transplant-related complications suffered from 1 or more PC (97%). Case fatality rate was high in patients with IPS (56%). Clinical outcomes among patients with IPS after conventional BMT have been uniformly poor, with estimated 60% to 80% mortality rates regardless of therapy and over 95% for those requiring mechanical ventilation (reviewed in Cooke et al. [16]).

Thirty-nine percent of patients required mechanical ventilation, and 70% of them remained ventilator-dependent until time of death. Although median days of mechanical ventilation was longer in nonsurviving patients (10 versus 2 days), this difference was not statistically significant; this may be because of the small number of extubated patients in our study. It would be of interest to see if future studies may indicate a time at which further mechanical ventilation may be deemed futile. Warwick and colleagues [26] in an earlier study analyzed 196 BMT recipients <19 years of age who underwent mechanical ventilation with

Table 5. Changes in Pulmonary Function Tests over time (n = 20)

		P Values			
FEV_1		Pre-BMT	3 Months	6 Months	12 Months
Pre-BMT	97 ± 20				
3 months	77 ± 24	.0001			
6 months	79 ± 22	.0001	.50		
12 months	89 ± 22	.004	.003	.02	
24 months	91 ± 20	.007	.001	.004	.34

		P Values			
FVC		Pre-BMT	3 Months	6 Months	12 Months
Pre-BMT	99 ± 17				
3 months	80 ± 24	.0001			
6 months	82 ± 22	.0001	.45		
12 months	92±21	.001	.01	.03	
24 months	92 ±22	.006	.006	.008	.55

		P Values			
TLC		Pre-BMT	3 Months	6 Months	12 Months
Pre-BMT	96 ± 15				
3 months	82 ± 17	.001			
6 months	86 ± 15	.003	.12		
12 months	93 ± 15	.078	.007	.01	
24 months	92 ± 15	.32	.003	.01	.91

		P Values			
DLco		Pre-BMT	3 Months	6 Months	12 Months
Pre-BMT	75 ± 28				
3 months	63 ± 27	.006			
6 months	67 ± 19	.14	.35		
12 mo	75 ± 21	.93	.05	.04	
24 monnths	80 ± 16	.63	.01	.01	.32

BMT indicates bone marrow? transplantation; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; TLC, total lung capacity; DLco, diffusing capacity of the lungs.

Table 6. Posttransplant PFTs Predicted and Clinical Outcomes

	Total n	FEV_1 *P*	FVC *P*	TLC *P*	DLco *P*
PC					
No	14	.025	.016	.12	.85
Yes	32				
Early respiratory failure					
No	10	.015	.014	.008	.009
Yes	36				
Conditioning					
TBI	26	.035	.08	.55	.11
Non-TBI	20				
aGVHD					
No	17	.007	.018	.41	.24
Yes	29				
cGVHD					
No	28	.28	.31	.42	.21
Yes	18				
Survival					
Alive	33	.40	.54	.53	.23
Dead	13				

cGVHD indicates chronic graft-versus-host disease; aGVHD, acute graft-versus-host disease; TBI, total body irradiation; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; TLC, total lung capacity; DLco, diffusing capacity of the lungs; PC, pulmonary complication; FPT, pulmonary function test.

a 60% mortality rate. In a recent report, Tamburro and colleagues [27] reported a 60% mortality among 161 pediatric allogeneic transplant recipients requiring invasive mechanical ventilation. Parimon et al. [11] found a high mortality rate in adult patients developing early respiratory failure and received mechanical ventilation (359/396; 91%). Van Gestel and colleagues [28] recently reported 42% case fatality rate (16/35) in mechanical ventilation pediatric allogeneic BMT recipients. Although these results need to be interpreted cautiously given the retrospective nature of our study and relatively small number of mechanical ventilation patients, OS rate after mechanical ventilation has not improved substantially over the last 2 decades.

We found microbiologic/histopathologic evidence of infection in 54% episodes of LRTI; potential pulmonary copathogens were demonstrated in 31% of cases. About one-third of the BAL procedures revealed potential pulmonary pathogens. It is possible that some of the bacterial pathogens from tracheal secretions in intubated patients were not contributing to invasive infection, but represented colonization. Until recently, it was not common practice to obtain quantitative cultures of BAL, which would aid in making that distinction. Our findings are concordant with a recent report of large adult-pediatric series of BMT recipients from Yanik and colleagues [29]. They reported data on 347 BAL procedures in 300 patients; BAL rate for allogeneic patients was 30.4%. Potential pathogens were identified in 117 procedures (26.4%); multiple pathogens were found in 30 of 117 (25.6%) BAL studies. Nichols and colleagues [13] also found copathogens in 29 of 55 (53%) BMT cases of parainfluenza-3 pneumonia. Copathogen isolation was associated with higher case fatality rate. Our report contrasts with von Eiff et al. [30], wherein diagnostic bronchoscopy conferred improved outcome in adults with hematologic malignancies. More recently, Eikenberry and colleagues [6] reported 46% diagnostic yield of BAL in pediatric BMT recipients and no difference in survival in those who underwent BAL or those with pathogen identification. In our series, there was a higher mortality rate in those undergoing BAL and those with identification of microbial pathogen, suggesting that diagnostic BAL was probably undertaken in sicker patients and that our series represents high-risk allogeneic patients.

Studies that have examined the predictive value of pretransplant PFTs for posttransplant complications suggest that poor lung function before transplant increases the risk of posttransplant respiratory failure, PC, and mortality (summarized in Chien et al [25]). Parimon and colleagues [11], in a large retrospective analysis of 2852 adults, found that reductions in pre-BMT was significantly associated with risk of early

respiratory failure (396 patients; 14%) and death (359/396; 91%). Efrati and colleagues [31] recently reported abnormal baseline FEF_{25-75} combined with a high residual volume (RV)/TLC ratio may be risk factors for development of bronchiolitis obliterans. Our analysis demonstrates for the first time that pediatric allo-BMT recipients with reduced pretransplant FEV_1, or FVC compared with those with normal values were significantly more likely to develop early respiratory failure. Mortality rate among patients who develop early respiratory failure requiring mechanical ventilation was very high (70%). This is in agreement with previous findings in adults with risk of early mortality [9-11]. In contrast to Parimon et al. [11], we did not find a relationship between pretransplant DLco and risk of early respiratory failure following transplant.

Previous pediatric studies of pulmonary function have shown variable decline in PFTs at differing time points and data on late follow-up is conflicting [5,23,32-34]. This may be related to a small cohort size with differences in patient and transplant characteristics, inclusion of auto- and allo-BMT recipients, and significant changes in supportive care over the last decade. Leneveu and colleagues [23] described PFT findings in 39 patients and found that after BMT, FVC, TLC, and FEV_1 were significantly lower at 100 days compared with pre-BMT data. The observed respiratory abnormalities were not clinically relevant, and no subsequent PFTs were available. Cerveri and colleagues [32], in a study of 50 children, found significant reduction in mean FVC and DLco at 3 to 6 months after BMT; these values tended to recover progressively, although at 12 months and 24 months after BMT, they still remained more negative than the pretransplant values [32]. At the time of BMT, the most common alteration in pulmonary function was an isolated impairment of DLco, whereas at both 3 to 6 months and 1 year after transplantation, a restrictive pattern was the most frequent abnormality. Our study represents a fair-sized cohort of pediatric allo-BMT patients with pretransplant baseline and adequate post-transplant PFT data obtained at regular scheduled intervals and clinical outcomes for correlative analyses. The results of the current study are in general agreement with and extend the findings reported by Cerveri and colleagues. PFT abnormalities were common before BMT and isolated reduction in DLco noted in 36% patients. Posttransplant PFTs showed significant reductions in FVC, FEV_1, TLC, and DLco at 3 and 6 months; at 12 to 24 months, these abnormalities in FEV_1, FVC, TLC, and DLco improved significantly from earlier declines post-BMT; however FEV_1 and FVC reductions remained significantly below pretransplant values. Unlike Cerveri et al. [32], we observed abnormalities in all lung function parameters and did not see a predominant restrictive pattern at these time points.

In conclusion, an important finding emerging from this study is that pretransplant PFT abnormalities correlate with risk of early respiratory failure, but not directly with OS. The observed relationship between pretransplant FEV_1 and FVC and development of respiratory failure would need validation in larger prospective studies, and these data may be useful in identifying children for whom the risk of respiratory failure and mortality with standard (myeloablative) BMT is so high that alternative treatment options such as RIC should be considered.

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