

Airflow Decline after Myeloablative Allogeneic Hematopoietic Cell Transplantation: The Role of Community Respiratory Viruses

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We conducted a 12-year retrospective study to determine the effects that the community respiratory-virus species and the localization of respiratory-tract virus infection have on severe airflow decline, a serious and fatal complication occurring after hematopoietic cell transplantation (HCT). Of 132 HCT recipients with respiratory-tract virus infection during the initial 100 days after HCT, 50 (38%) developed airflow decline ≤ 1 year after HCT. Lower-respiratory-tract infection with parainfluenza (odds ratio [OR], 17.9 [95% confidence interval {CI}, 2.0–160]; $P = .01$) and respiratory syncytial virus (OR, 3.6 [95% CI, 1.0–13]; $P = .05$) independently increased the risk of development of airflow decline ≤ 1 year after HCT. The airflow decline was immediately detectable after infection and was strongest for lower-respiratory-tract infection with parainfluenza virus; it stabilized during the months after the respiratory-tract virus infection, but, at ≤ 1 year after HCT, the initial lung function was not restored. Thus, community respiratory virus-associated airflow decline seems to be specific to viral species and infection localization.

Airflow decline is a frequent pulmonary complication occurring in long-term survivors of hematopoietic cell transplantation (HCT). Using a recently validated definition of significant airflow decline, an analysis of >1000 allogeneic HCT recipients revealed that, among patients who survived to 1 year after HCT, 1 in 4 ex-

perienced significant airflow decline and a significantly increased mortality risk that were attributable to this syndrome [1]. This analysis also identified community respiratory-virus infections during the initial 100 days after HCT as being a significant risk factor for development of severe airflow decline but did not differentiate between specific viral infections or between infection localization in the upper respiratory tract (URT) or lower respiratory tract (LRT) [1]. Given the known association between infections with specific community respiratory viruses and other forms of airways disease [2, 3], we investigated the contributions that the virus species and infection localization made to the development of this syndrome.

PATIENTS AND METHODS

Study population. A well-characterized cohort of patients who received their first allogeneic transplantation at the Fred Hutchinson Cancer Research Center (FHCRC) between 1 January 1990 and 31 December 2000 were evaluated by pulmonary function tests (PFTs)

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prior to HCT and ≤ 1 year after HCT. The analysis was restricted to patients who survived to 6 months after HCT and for whom PFT results were available both before (baseline PFT) and after that period. Clinical variables were collected prospectively as part of the usual clinical care and were stored in a centralized database. Disease risk for all malignancies at the time of HCT was classified as low, intermediate, or high, on the basis of previously published criteria [4]. Donor type was determined according to donor-recipients ABO compatibility and HLA-A, HLA-B, and HLA-DR status. Acute graft-versus-host disease (GVHD) was graded using standard criteria [5] and was categorized as yes-acute GVHD (grades 3-4) or no-acute GVHD (grades 0-2). The diagnosis and staging of chronic GVHD were established using previously published criteria [6]. Acute and chronic classes of GVHD were then integrated and categorized as no-acute GVHD or chronic GVHD, acute GVHD alone, de novo chronic GVHD (not preceded by acute GVHD), and chronic GVHD (preceded by acute GVHD that was or was not followed by a period of quiescence).

The impact that community respiratory-virus URT infection and LRT infection had on severe airflow decline was examined. In addition, cytomegalovirus (CMV) pneumonia and pulmonary aspergillosis (definite and probable) also were evaluated as infections not typically associated with airflow decline. The FHCRC Institutional Review Board approved the study.

Respiratory specimen and virology procedures. Throughout the study period, all HCT recipients with URT infection symptoms, such as rhinorrhea, pharyngitis, or coryza, during the first 100 days after HCT underwent nasopharyngeal-throat wash and swab testing. All patients with radiographic signs of LRT infection underwent a bronchoalveolar lavage (BAL). Nasopharyngeal-throat wash and swab samples, BAL specimens, and/or tissue-biopsy or autopsy material were tested for community respiratory viruses (respiratory syncytial virus [RSV], parainfluenza virus types 1-3, influenza virus A and B, adenovirus, and rhinovirus), by direct immunofluorescence (DFA) testing, shell vial centrifugation culture, and conventional culture. Cultures were inoculated into tissue cultures containing rhesus monkey kidney, human foreskin fibroblasts, and A549 cells. Type-specific respiratory DFA smears were performed using commercially available, type-specific antiserum (Bartels VRK; Intracel) [7]. BAL samples were also tested for CMV, by viral culture, shell vial centrifugation culture, and DFA. Probable or proven aspergillus pulmonary infection was confirmed by a positive culture or by histopathological results of BAL or lung biopsies [8]. Community respiratory-virus URT infection was defined as the detection of any community respiratory virus from a nasopharyngeal-throat specimen, by culture, shell vial culture, or DFA, in conjunction with consistent symptoms in the absence of a new infiltrate detected by chest radiography. Community respiratory-virus LRT infection was defined as the

isolation of any respiratory virus, by culture or DFA from BAL or lung biopsy or autopsy specimens, in conjunction with symptoms and a radiographically new or changing infiltrate [7, 9]. On the basis of the viruses detected in the clinical specimen,

Table 1. Clinical characteristics of the study population.

Characteristic	Distribution
Age	
<20 years	166 (15)
20-60 years	951 (84)
>60 years	14 (1)
Recipient sex, M:F	1.4:1
White race	961 (85)
Disease at HCT ^a	
Low	491 (43)
Intermediate	199 (18)
High	441 (39)
Donor match	
Related	
HLA matched	599 (53)
HLA mismatched	111 (10)
Unrelated	421 (37)
Stem cell source	
Bone marrow	1010 (89)
Peripheral blood	115 (10)
Cord blood	3 (<1)
Cord blood and peripheral blood	3 (<1)
GVHD category ^b	
No GVHD	360 (32)
Acute GVHD only (grade 3-4)	58 (5)
De novo chronic GVHD	126 (11)
Chronic GVHD	587 (52)
Pretransplantation FEV ₁ :FVC ratio	
80%-100%	483 (43)
70%-80%	539 (48)
60%-70%	93 (8)
<60%	16 (1)
Community respiratory-virus infection	132 (12)

NOTE. Data indicate no. (%) of 1131 subjects, unless otherwise indicated [1]. FEV₁, first-1-s forced expiratory volume; FVC, forced volume capacity; GVHD, graft-versus-host disease; HCT, hematopoietic stem cell transplantation.

^a Disease at HCT: low-risk diseases included chronic myeloid leukemia in chronic phase, refractory anemia, and aplastic anemia; intermediate-risk diseases included chronic myeloid leukemia in accelerated phase or in chronic phase after blast phase, acute leukemia or lymphoma in remission, refractory anemia with excess blasts, chronic lymphocytic leukemia, and paroxysmal nocturnal hemoglobinuria; and high-risk diseases included chronic myeloid leukemia in blast phase, juvenile chronic myeloid leukemia, acute leukemia or lymphoma in relapse, refractory anemia with excess blasts in transformation, and myeloma.

^b De novo chronic GVHD indicates the absence of prior acute GVHD, and chronic GVHD indicates a history of acute GVHD that either did or did not resolve before the onset of chronic GVHD.

Table 2. Distribution of severe airflow decline by 1 year after hematopoietic stem cell transplantation, for different categories of respiratory-tract virus infection.

Respiratory-tract infection	Airflow decline	No airflow decline	Total
No respiratory-tract infection	249 (25)	750 (75)	999
Parainfluenza			
Upper-respiratory-tract infection	23 (40)	35 (60)	58
Lower-respiratory-tract infection	6 (86)	1 (14)	7
Respiratory syncytial virus infection			
Upper-respiratory-tract infection	7 (26)	20 (74)	27
Lower-respiratory-tract infection	6 (55)	5 (45)	11
Others ^a , Upper-respiratory-tract infection	8 (28)	21 (72)	29

NOTE. Data indicate no. (%) of 1131 subjects. Of the 8 patients who had coinfections, 2 had respiratory syncytial virus (RSV) and parainfluenza, 3 had parainfluenza and influenza A, 2 had RSV and influenza A, and 1 had parainfluenza and adenovirus.

^a Includes infection with adenovirus ($n = 9$), rhinovirus ($n = 2$), or influenza virus A and B ($n = 18$).

3 categories of community respiratory-virus infection were defined: parainfluenza infection, RSV infection, and “other” infection, which included rhinovirus, adenovirus, and influenza virus A or B. Any patient with a parainfluenza infection, regardless of coinfections, was considered as having parainfluenza infection and was analyzed in the parainfluenza category only. The same criterion was applied to patients with RSV infections, unless parainfluenza virus was also detected, in which case patients were analyzed in the parainfluenza category.

PFT, airflow decline definition, and data analysis. PFTs were performed as described elsewhere [1]. The first-1-s forced expiratory volume (FEV₁) and forced vital capacity (FVC) were expressed as a percentage of predicted normal values, calculated using published equations for children and adults [10, 11]. Baseline (before HCT), day 100 (100 days after HCT), and year 1 (1 year after HCT) PFT results were obtained routinely, regardless of the presence or absence of symptoms.

Significant airflow decline was defined as a >5%/year decline in percentage of predicted FEV₁ during year 1, with the year 1 FEV₁:FVC ratio <0.8 [1]. The annualized rate of airflow decline (decline in percentage of predicted FEV₁) by year 1 was calculated using a least squares regression method [1].

The annualized rate of decline in percentage of predicted FEV₁ in patients who had developed respiratory infection with community respiratory viruses was also calculated from baseline to day 100 ($[(\text{day 100 FEV}_1 - \text{baseline FEV}_1) / (\text{day 100 PFT date} - \text{baseline PFT date})] \times 365$) and from day 100 to year 1 ($[(\text{year 1 FEV}_1 - \text{day 100 FEV}_1) / (\text{year 1 PFT date} - \text{day 100 PFT date})] \times 365$).

Statistical analysis. Statistical analyses were performed using Stata (version 8.0; StataCorp) and the R statistical program [12] (available at: <http://www.R-project.org>). Two-sided P values <.05 were considered to be statistically significant. Univariate analyses were conducted using the χ^2 test. The presence of significant airflow decline by year 1 was analyzed in a mul-

tivariable logistic regression model. The outcome, significant airflow decline, was defined as a binary variable. The independent variable included the localization of the infection and the species of community respiratory virus. An additional analysis was performed to determine the risk of severe airflow decline associated with LRT CMV infection and pulmonary aspergillosis. The model was adjusted for age at HCT, baseline FEV₁:FVC ratio, and GVHD category. These were covariates that had been found to be significant risk factors for airflow decline in the previous analysis [1]. The Kruskal-Wallis test was used to compare the median rate of decline in percentage of predicted FEV₁ of each viral-infection category, from baseline to day 100 and from day 100 to year 1.

The mortality cohort consisted of patients for whom year 1 follow-up PFT results were available. The probability of overall survival (Kaplan-Meier method) and the multivariable Cox proportional-hazard analysis, comparing patients with severe airflow decline to patients without severe airflow decline, had been described in the initial study [1].

RESULTS

Patients’ characteristics. Of the 3002 first-myceloablative allogeneic-HCT recipients between 1 January 1990 and 31 December 2000, 1131 (38%) were eligible for the study, and 299 (26%) cases of severe airflow decline were identified when the recently validated definition of severe airflow decline was applied [1]. The clinical characteristics of the study population are shown in table 1.

During the initial 100 days after HCT, 132 patients (12%) had a documented viral infection with community respiratory viruses. Of these 132 patients, 114 (86%) had a URT viral infection, and 38 (33%) of these 114 developed significant airflow decline by year 1. Two additional common, LRT infections were evaluated regarding their ability to cause severe airflow decline.

Table 3. Risk of severe airflow decline by 1 year after hematopoietic stem cell transplantation, according to virus species and localization of respiratory infection.

Risk factor	Adjusted OR (95% CI)	P
Age		
<20 years	1.0	
20–60 years	2.1 (1.2–3.8)	.009
>60 years	5.9 (1.7–21)	.006
Baseline FEV₁:FVC		
80%–100%	1.0	
70%–80%	2.6 (1.9–3.7)	<.001
<70%	4.5 (2.8–7.3)	<.001
GVHD category		
None	1.0	
Acute GVHD only	1.4 (0.7–3.0)	.38
De novo chronic GVHD	1.6 (1.0–2.6)	.07
Chronic GVHD	2.1 (1.5–2.9)	<.001
History of respiratory-tract virus infection		
No	1.0	
Yes	1.4 (1.04–1.8)	.03
Respiratory-tract virus infection		
No infection	1.0	
URT parainfluenza-virus infection	1.8 (1.0–3.3)	.04
LRT parainfluenza-virus infection	17.9 (2.0–160)	.01
URT RSV infection	1.3 (0.5–3.1)	.63
LRT RSV infection	3.6 (1.0–13)	.05
Other URT infection	1.2 (0.5–2.9)	.73

NOTE. A logistic regression model was used, with development of airflow decline defined as a binary variable. CI, confidence interval; FEV₁, first-1-s forced expiratory volume; FVC, forced volume capacity; GVHD, graft-versus-host disease; LRT, lower respiratory tract; OR, odds ratio; RSV, respiratory syncytial virus; URT, upper respiratory tract.

Of long-term survivors, 9 patients (1%) were identified as having CMV pneumonia during the first 100 days (and 1 of these 9 was coinfecting with rhinovirus), and 16 (1%) were identified as having pulmonary aspergillosis.

Severe airflow decline by year 1. Of the 132 patients who had a documented viral infection, 18 (14%) had an LRT viral infection, and, of these 18 patients, 12 (67%) developed significant airflow decline by year 1. Table 2 displays the distribution of the different categories of respiratory-tract virus infection, according to the presence or absence of significant airflow decline by year 1. The majority of patients with LRT parainfluenza-virus infection (86%) and LRT RSV infection (55%) during the first 100 days developed significant airflow decline by year 1. None of these patients were coinfecting or developed a superinfection with a bacterial pathogen. Multivariable analysis, including covariates previously determined to be significant risk factors for significant airflow decline [1], demonstrated that the presence of community respiratory-virus

LRT infection was associated with an increased risk of having a significant airflow decline by year 1 (odds ratio [OR], 4.1 [95% confidence interval {CI}, 1.2–14]; $P = .02$). This risk was highest for LRT parainfluenza-virus infection during the first 100 days after HCT (OR, 17.9 [95% CI, 2.0–160]; $P = .01$) (table 3) but was also significant for URT parainfluenza-virus infection (OR, 1.8 [95% CI, 1.0–3.3]; $P = .04$) and LRT RSV infection (OR, 3.6 [95% CI, 1.0–13]; $P = .05$). Neither LRT CMV infection nor LRT aspergillus infection was found to predict severe airflow decline (data not shown).

FEV₁ changes during study periods. In addition to the annualized rate of airflow decline, we estimated the impact that the infection status had on lung function, by using the change in percentage of predicted FEV₁ from baseline to day 100 and from day 100 (when the viral infection was diagnosed) to year 1. By day 100, the median rates of decline in percentage of predicted FEV₁ for patients who had LRT infection with either parainfluenza virus or RSV were 13% and 11%, respectively. All patients with URT viral infection only experienced a rate of decline in percentage of predicted FEV₁ that was <5% (figure 1). The median (range) percentage of predicted FEV₁ for patients with versus patients without community respiratory-virus infection was 0.97 (range, 0.58–1.33) versus 0.96 (range, 0.53–1.34) at baseline, 0.88 (range, 0.48–1.28) versus 0.90 (range, 0.36–2.42) at day 100, and 0.90 (range, 0.49–1.32) versus 0.92 (range, 0.27–1.31) at year 1. Comparison of the median rate of decline in percentage of predicted FEV₁ in the different groups of community respiratory-virus infections demonstrated that patients with LRT parainfluenza-virus infection experienced the most pronounced decline of airflow (figure 1). The difference was statistically significant when LRT parainfluenza-virus infection was compared with each of the community respiratory-tract virus infections ($P < .03$), except in the case of LRT RSV infection ($P = .09$). The rate of decline in percentage of predicted FEV₁ for patients with LRT RSV infection did not reach statistical significance (when compared with that in the other groups). During the months after infection (day 100 to year 1), there was a slight improvement in the function, with the median rate of percentage of predicted FEV₁ increasing from 1.6% to 5%, depending on the type of infection with which patients presented during the initial 100 days (figure 1). The median rate of improvement in percentage of predicted FEV₁ was not statistically different between the different categories of infection ($P = .74$).

DISCUSSION

Because of their ability to cause fatal pneumonia, community respiratory viruses are widely recognized as a significant cause of morbidity and mortality after HCT [13–15]. The present study suggests that community respiratory-virus infections might contribute to increased overall mortality [7, 16], not only

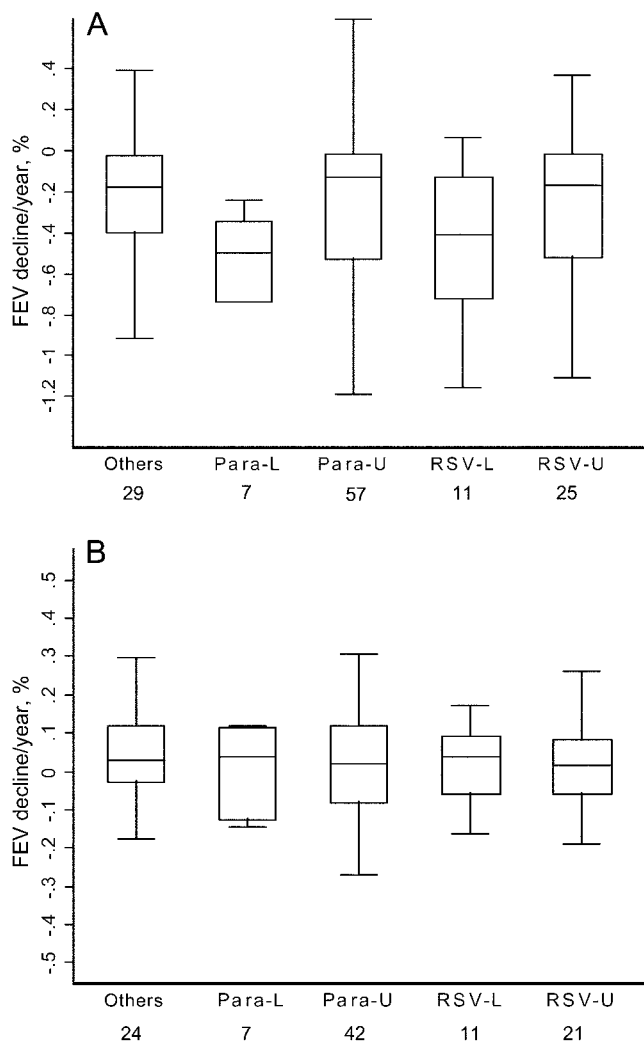


Figure 1. Annualized rates of decline in percentage of predicted first-second forced expiratory volume (FEV₁), for each category of respiratory-tract infection, from baseline to day 100 (A) and from day 100 to year 1 (B). Nos. below the graph denote the no. of patients evaluated by pulmonary function tests at day 100 (A) and at year 1 (B). Other categories are infection with adenovirus ($n = 9$), rhinovirus ($n = 2$), or influenza virus A and B ($n = 18$). Para-L, lower respiratory tract (LRT) parainfluenza-virus infection; Para-U, upper respiratory tract (URT) parainfluenza-virus infection; RSV-L, LRT respiratory syncytial virus infection; RSV-U, URT respiratory syncytial virus infection.

by causing fatal pneumonia but also via a long-term decline in lung function. Indeed, the initial study has revealed that severe airflow decline has a significant adverse effect on mortality after adjustment for other common causes of death among long-term survivors of HCT [1].

We found that the association between community respiratory viruses and HCT-related airflow decline may be influenced by the specific type and location of respiratory-virus infection. In multivariable analysis, LRT viral infection was found to significantly increase the risk of development of air-

flow decline ≤ 1 year after HCT, and this risk was particularly high for patients who developed an LRT parainfluenza-virus infection (table 3). LRT RSV infection probably also increases this risk; however, the number of cases was too small to reach statistical significance. Interestingly, even URT parainfluenza-virus infection was notably associated with airflow decline, suggesting a potential mechanism for the previously reported poor outcomes associated with URT parainfluenza-virus infection [7]. The presence of copathogens has been reported as being a significant risk factor for death in patients with parainfluenza pneumonia [17]. In the present study, none of the patients with LRT viral infection were infected with a copathogen, precluding us from assessing the impact that copathogens might have on airflow decline associated with respiratory-tract virus infection. The absence of copathogens in this study is probably due to the fact that only long-term survivors of respiratory-tract virus infections were included. We did, however, examine the impact that 2 common pulmonary pathogens had on airflow decline. As expected, neither LRT CMV infection nor LRT aspergillus infection increased the risk of severe airflow decline in patients who survived the infection.

We also examined the timing of the development of airflow decline relative to the community respiratory-virus infection. The most significant decline of the percentage of predicted FEV₁ was observed between the day of HCT and day 100, during which time the respiratory-tract virus infection occurred. The significant decline observed for LRT infections compared with URT infections has to be considered with caution, because of the limitation inherent in performing multiple testing. Although the percentage of predicted FEV₁ of patients who experienced a significant FEV₁ decline during the first 100 days after HCT improved between day 100 and year 1, none of those patients' levels of FEV₁ returned to their baseline, suggesting that, despite some recovery, LRT infection with community respiratory viruses can result in permanent loss of lung function. There are several possible explanations for this phenomenon. Prolonged shedding of parainfluenza is known to occur in immunosuppressed patients [18], and subclinical shedding of respiratory viruses has been documented in HCT recipients [19]. Thus, subclinical persistence of the virus in the respiratory tract after the initial infection might maintain sustained airway inflammation, which may ultimately lead to permanent loss of lung function, even after apparent clinical clearance of the infection. Community respiratory viruses might also activate an inflammatory process in the LRT that, in the patients who survive the acute phase of an LRT virus infection, might lead to irreversible damage to the tissue of the small airways that is independent of viral replication [20].

The present study has strengths and limitations. Its strengths include the large sample size, a standardized diagnostic approach for URT and LRT infections, and standardized PFTs

throughout the study period. One limitation is that the predictor of interest (community respiratory-virus infections) was assessed only during the first 100 days after HCT. It is likely that respiratory-tract virus infections can also occur later, after patients have been discharged from the transplantation center and return to a less protected environment. In addition, other potential contributors, such as bacterial coinfection, were not examined. Another possible limitation is that the conventional detection methods used in this study, because of their lack of sensitivity, may have underestimated the true rate of respiratory infections [21]. These assays were also unable to detect uncultivated pathogens, such as human metapneumovirus and coronaviruses [22–24]. However, both undetected pathogens and asymptomatic shedders [25, 26] would be included in the noninfected group and would therefore make the significance of our findings even stronger. A further possible limitation is that the number of cases was not large to provide adequate power to assess the individual role that viruses such as adenovirus, rhinovirus, and influenza virus play in the occurrence of significant airflow decline. Finally, only patients who survived the infection were included in the estimation of the rate of airflow decline, resulting in a potential “healthy survivor effect.” However, this limitation might actually have resulted in an underestimation of the impact that respiratory infection had on the rate of lung decline.

In conclusion, the present study revealed that parainfluenza virus and RSV are associated with late severe airflow decline, which may suggest an additional mechanism by which some respiratory viruses may cause morbidity and perhaps even mortality after HCT. These data deserve further investigation, which is focused on understanding the mechanisms by which viral infections may lead to the development of severe airflow decline after HCT. Such studies may ultimately lead to insight into the role that viral infections play in other, more common airway diseases, such as asthma.

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