

Parainfluenza virus infections after hematopoietic stem cell transplantation: risk factors, response to antiviral therapy, and effect on transplant outcome

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Parainfluenza virus (PIV) infections may be significant causes of morbidity and mortality in patients undergoing stem cell transplantation, but data regarding their impact on transplant-related mortality is limited. This study sought to determine the risk factors of PIV acquisition and progression to lower respiratory tract infection, their impact on transplant-related mortality, and the effectiveness of antiviral therapy. A total of 3577 recipients of hematopoietic stem cell transplantation (HSCT) between 1990 and 1999 were studied. PIV infections occurred in 253 patients (7.1%); 78% of these infections were community acquired. Multivariable

analysis identified the receipt of an unrelated transplant as the only risk factor for PIV acquisition; the dose of corticosteroids at the time of PIV infection acquisition was the primary factor associated with the development of PIV-3 pneumonia, both among allogeneic and autologous HSCT recipients. Both PIV-3 upper respiratory infection and pneumonia were associated with overall mortality. Pulmonary copathogens were isolated from 29 patients (53%) with pneumonia. Mortality was highly influenced by the presence of copathogens and the need for mechanical ventilation. Aerosolized ribavirin with or without intravenous immunoglobulin

did not appear to alter mortality from PIV-3 pneumonia, nor did such therapy decrease the duration of viral shedding from the nasopharynx among patients with pneumonia. Corticosteroid administration thus drives the development of PIV pneumonia in a dose-dependent fashion, even among autologous HSCT recipients. Both upper and lower tract PIV infections are predictors of mortality after HSCT. Currently available antiviral therapy appears to be inadequate in reducing viral shedding or mortality once pneumonia is established. (*Blood*. 2001;98:573-578)

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Introduction

Parainfluenza virus (PIV) is a common cause of respiratory disease in young children and has been implicated in up to 3% of cases of community-acquired pneumonia among adults.¹ PIV infections have also been documented in 2% to 5% of patients undergoing hematopoietic stem cell transplantation (HSCT) in large transplant centers.^{2,3} The spectrum of PIV disease in transplant recipients ranges from apparently uncomplicated upper respiratory infections (URI), characterized by symptoms of rhinorrhea, pharyngitis, and coryza, to more severe lower respiratory tract infections (LRI), which may lead to pneumonia and respiratory failure. Risk factors for acquisition of PIV infections, the factors that are associated with progression to pneumonia, and the clinical response to antiviral therapy, however, remain to be defined.

Since 1990, the Fred Hutchinson Cancer Research Center (FHCRC) has screened patients with signs and symptoms of upper or lower respiratory tract disease for the presence of community-acquired respiratory viruses. We performed a retrospective cohort study to describe the epidemiology, risk factors, and outcomes of parainfluenza infection among over 3000 HSCT recipients at our center over the past 9 years.

records and identified all HSCT recipients with the isolation of PIV-1, -2, -3, or -4 from respiratory secretions or the demonstration of parainfluenza antigen by direct fluorescent antibody (DFA); infections occurring before the start of conditioning were excluded. Clinical data were extracted from a prospectively entered database, and medical records were reviewed.

Virology and microbiology procedures

A nasopharyngeal-throat (NPT) wash or swab for viral DFA staining and viral culture was standard practice for all patients with URI symptoms throughout the study period. Viral DFA and cultures were also performed on all bronchoalveolar lavage (BAL), lung biopsy, and autopsy specimens. Cultures for respiratory viruses were inoculated into tissue cultures containing rhesus monkey kidney, human foreskin fibroblasts, and A-549 cells. Upper respiratory cultures were kept for 10 days before reporting as negative; lower respiratory tract cultures were kept for at least 21 days. Hemadsorption was done on days 2 or 3, day 5, and day 10; confirmation was based on type-specific fluorescent antibody staining as well as the positive hemadsorption test. Type-specific respiratory DFA smears were also prepared on all NPT and BAL specimens using commercially available, type-specific antiserum (Bartels VRK, Intracel, Issaquah, WA).

All BAL, biopsy, and autopsy specimens were also submitted for routine bacterial, fungal, and acid-fast bacilli cultures, and DFA staining and culture was performed for *Legionella* species. Cytospins were performed for cytomegalovirus (CMV) and herpes simplex virus (HSV), and shell vials for CMV and respiratory syncytial virus (RSV) were also performed.

Patients, materials, and methods

Patient population

From July 1990 through June 1999, 3577 patients underwent allogeneic, syngeneic, or autologous HSCT at the FHCRC. We reviewed virology

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Definitions

Parainfluenza URI was defined as the isolation of PIV from NPT by culture or evidence of parainfluenza antigen by DFA in conjunction with consistent symptomatology without the presence of a new infiltrate on chest radiography. Parainfluenza LRI was defined as the isolation of PIV by culture or evidence of parainfluenza antigen by DFA from BAL or lung biopsy specimens in association with symptoms and a new radiographic infiltrate. Hospital-acquired infections were defined as those occurring 7 days or more after admission to the inpatient wards; the remainder were defined as community-acquired infections. The presence of a copathogen was defined as the isolation of PIV in addition to pathogenic bacterial species, fungal species (such as *Aspergillus fumigatus*), or opportunistic viruses from the same BAL or lung biopsy specimen. Day of engraftment after transplantation was defined as the third consecutive day of achieving an absolute neutrophil count of greater than 500/ μ L.

Underlying disease was classified as advanced for all patients not in remission, patients with acute nonlymphocytic leukemia in second or later remission, and patients with acute lymphocytic leukemia in third remission or later. Patients with chronic myelogenous leukemia were classified as having advanced disease when in blast crisis at time of transplant. Patients with multiple myeloma, refractory anemia with excess blasts, or refractory anemia with excess blasts in transformation were also classified as having advanced disease. All other patients were classified as not having advanced disease.

Assessment and staging of graft-versus-host disease (GVHD) was made according to consensus criteria.⁴ Primary treatment of GVHD was with corticosteroids and was performed as previously described.⁵

Management

Once positive by NPT or BAL for PIV, patients were placed in respiratory isolation to prevent transmission to staff and other patients. Patients underwent repeat NPT on the day following identification of PIV infection and then at least weekly to document clearance of the virus from nasopharyngeal secretions.

Treatment with aerosolized ribavirin for LRI was performed at the discretion of the treating physician. However, the dose and duration of ribavirin therapy was standardized by protocol: 2 g (60 mg/mL) was administered 3 times daily over 2 hours via nebulizer for 7 days. A subset of patients also received 3 to 5 doses of intravenous immune globulin (0.5 g/kg) given every other day as therapy for parainfluenza pneumonia. Patients were treated with antibiotics or antifungals directed at isolated copathogens as indicated.

Statistical analysis

For the determination of risk factors for acquisition of PIV infection, a Cox proportional hazards model was fit with PIV infection as outcome and day zero as the date of transplant. Logistic regression was used to examine the association of various factors with the probability of LRI among patients with URI. To assess the impact of PIV infection on mortality, URI and LRI were regarded as time-dependent covariates in multivariable Cox regression models for mortality with adjustment for factors known to be associated with survival. Time zero for mortality analyses was taken as date of transplant. Among patients who developed LRI, Cox regression was used to assess potential risk factors for mortality, where time zero was taken to be time of development of LRI. Unadjusted estimates of survival were obtained using the method of Kaplan and Meier. *P* values from regression models were obtained from the Wald test, and no adjustments were made for multiple comparisons.

Results

Epidemiology

Parainfluenza viruses were isolated from 253 (7.1%) of the 3577 patients undergoing HSCT at the FHCRC between July 1990 and

June 1999. PIV-3 accounted for the majority of the isolates (228 of 253, or 90%); PIV-3 was also the most common parainfluenza isolate in passive laboratory surveillance in Seattle during the study period (data not shown). Fifteen cases of PIV-1 infection, 9 cases of PIV-2 infection, and 1 case of PIV-4 infection were documented. Sporadic cases of PIV-3 infection occurred year-round and tended to be clustered into small outbreaks within our patient population (Figure 1). Seasonal outbreaks tended to occur in the spring and summer, though the largest increase in incidence was seen during the fall outbreak of 1998. This was in contrast to PIV-1, -2, and -4 infections, which tended to occur during the winter respiratory virus season.

Overall, 55 of 253 (21.7%) of the cases were hospital acquired, whereas 198 of 253 (78.3%) were considered community-acquired infections. Hospital-acquired cases were scattered throughout the observation period; clusters of more than 3 cases per month on the same hospital ward were noted in only 4 time periods, accounting for only 14 cases (25% of hospital-acquired infections). In contrast, community-acquired cases tended to occur in clusters—more than 3 cases per month were noted during 16 separate months of observation. These clusters accounted for 115 cases (58%).

The median interval from transplantation to parainfluenza URI was 62 days (range, 1-973 days); for LRI, the median interval was 63 days (range, 3-973 days).

Clinical presentation

Of the 15 cases of PIV-1 infection, 14 were URI, whereas 1 patient presented with simultaneous URI and LRI. All 9 cases of PIV-2 and the case of PIV-4 infection were URIs.

Of the 228 cases of PIV-3 infection, 198 (87%) presented with URI symptoms without LRI, whereas 13 (6%) presented with simultaneous URI and LRI. Seventeen patients (7%) presented with PIV-3 pneumonitis without concurrent URI symptoms and had negative NPT tests at the time of their diagnosis by BAL. Of the 198 patients who presented with PIV-3 URI alone, an additional 25 patients (13%) developed lower tract involvement diagnosed by BAL a median of 3 days (range, 0-30 days) after developing URI symptoms, for a total of 55 cases of PIV-3 LRI.

Due to the small number of cases of PIV-1, PIV-2, and PIV-4 disease, further analysis was performed for PIV-3 infections alone. In addition, 6 of the cases occurred following a second transplant; statistical analysis was restricted to those infections that occurred following the first transplant. The clinical characteristics of the 222

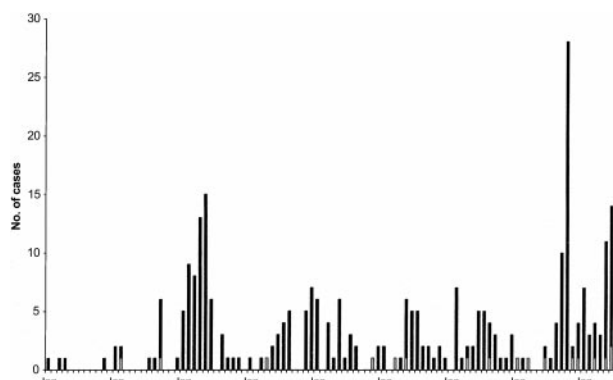


Figure 1. Parainfluenza virus (PIV) infection among 3411 HSCT recipients, 1991–1999. PIV was isolated from 253 patients (7.4%) during the study period (see text). Sporadic PIV-1, -2, and -4 (▨) cases occurred primarily during the winter and spring; PIV-3 (■) cases occurred year-round, as either sporadic disease or within “outbreaks.” The majority of outbreak cases were community acquired.

patients who contracted PIV-3 during the study period and the 3355 patients who did not develop PIV-3 infection are shown in Table 1.

Risk factors for the development of PIV-3 infection

Proportional hazards regression models were fashioned to examine the association of various factors with the acquisition of any PIV-3 infection after first transplant; the 222 case patients were compared with the cohort of 3355 patients who did not develop any parainfluenza infection. Only receipt of HSCT from an unrelated donor was significantly associated with the hazard of PIV-3 infection when compared to autologous transplantation (hazard ratio [HR] 1.6, 95% confidence interval [CI] 1.1-2.3, $P = .01$). Patients who had a mismatched sibling or nonsibling related donor were more likely to develop PIV-3 compared to autologous patients, but the difference was not statistically significant (HR 1.5, 95% CI 0.9-2.4, $P = .10$). Patients who received a transplant from either an unrelated donor, a mismatched sibling donor, or a nonsibling related donor had a higher hazard of PIV-3 when compared to autologous patients or matched-sibling recipients (HR 1.5, 95% CI 1.1-1.9, $P = .003$). Patient age, disease risk, conditioning regimen, CMV serostatus, engraftment status, and the presence of acute GVHD were not significantly associated with PIV-3 infection.

Risk factors for the progression of PIV-3 URI to LRI

Logistic regression analysis was performed to define factors associated with the development of LRI among patients with PIV-3 URI. As shown in Table 2, the receipt of corticosteroids at the time of URI diagnosis was identified as a dose-dependent risk factor associated with the development of PIV-3 LRI in a multivariable regression model. The dose of corticosteroids at the time of URI was highly correlated with the presence of GVHD. After control-

Table 1. Characteristics of 228 stem cell transplant recipients with parainfluenza virus-3 infection

	PIV-3 (N = 222) N (%)	No PIV-3 (N = 3355) N (%)
Median age in y (range)	37.7 (0.6-67)	38.7 (0.3-68.3)
Gender		
Female	93 (42)	1547 (46)
Male	129 (58)	1808 (54)
Underlying disease		
Acute leukemia	78 (35)	1011 (30)
Chronic myelogenous leukemia	64 (29)	918 (27)
Non-Hodgkin lymphoma/Hodgkin disease/multiple myeloma	32 (14)	557 (17)
Myelodysplasia	14 (6)	281 (8)
Solid malignancy	11 (5)	242 (7)
Nonmalignant diseases	23 (10)	346 (10)
Disease risk		
Nonadvanced	148 (67)	1155 (66)
Advanced	74 (33)	2200 (34)
CMV serostatus		
D+/R+	51 (29)	710 (28)
D+/R-	24 (14)	371 (15)
D-/R+	40 (23)	594 (23)
D-/R-	62 (35)	838 (33)
Autologous R+	29 (64)	447 (55)
Donor type		
Matched sibling	71 (32)	1191 (35)
Mismatched/nonsibling related	26 (12)	361 (11)
Unrelated	80 (36)	985 (29)
Autologous	45 (20)	818 (24)

CMV indicates cytomegalovirus; PIV-3, parainfluenza virus-3.

Table 2. Factors associated with progression from parainfluenza virus-3 upper respiratory infections to lower respiratory tract infections among allogeneic hematopoietic stem cell transplant recipients in multivariable analysis

Covariate	Odds ratio	95% CI	P
Donor CMV serostatus			
Negative	1.0	—	—
Positive	2.1	1.0-4.6	.06
Corticosteroid dose			
None	1.0	—	—
Less than 1 mg/kg/d	2.8	0.8-9.9	.10
1 – less than 2 mg/kg/d	8.6	2.6-27.8	.0003
At least 2 mg/kg/d	19.8	5.2-74.6	< .0001

Not significant: patient/donor age, donor type, patient CMV serostatus, disease risk, receipt of total body irradiation, engraftment status, graft-versus-host disease. CMV indicates cytomegalovirus; CI, confidence interval.

ling for steroid dose, acute GVHD did not significantly improve the model without GVHD ($P = .54$). After controlling for GVHD (grades II-IV) at the time of URI; however, further consideration of steroid dose significantly improved the regression model ($P < .0001$). Donor type, patient CMV serostatus, disease risk, and engraftment status were not significant factors in univariate analysis, nor did their inclusion significantly improve the model summarized in Table 2. In addition, age at transplantation, analyzed as a continuous variable, demonstrated no association with odds for LRI.

The association of corticosteroid use with PIV-3 pneumonia also appeared to be present among autologous patients. Thirty-eight patients who had autologous transplants had corticosteroid data available. Among these patients, 32 were not receiving steroids at the time of URI and 5 (16%) progressed to pneumonia. Four of 6 (67%) of patients who were receiving corticosteroids for pseudo-GVHD progressed (Figure 2). These proportions were suggestively different ($P = .02$, Fisher exact test). Unfortunately, the limited number of cases precluded a rigorous multivariable regression model.

Association of PIV-3 infection with mortality

After adjusting for age, CMV serostatus, donor type, and disease risk, PIV-3 URI (considered as a time-dependent covariate) was associated with an increased hazard of mortality after transplant (HR 1.3, 95% CI 1.1-1.6; Table 3). The association of PIV-3 LRI with mortality was even stronger, with an HR of 3.4 (95% CI 2.4-4.7). Overall mortality from PIV-3 LRI was 35% (19 of 55 patients) at 30 days and 75% (41 of 55 patients) at 180 days after diagnosis of pneumonia. The majority of these patients died with

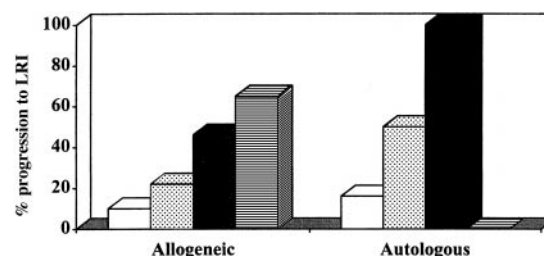


Figure 2. Corticosteroid dose and risk for progression from PIV-3 URI to pneumonia. Higher doses of steroids at the time of PIV-3 URI diagnosis were associated with increased risk for progression to PIV-3 LRI, both among allogeneic and autologous transplant recipients. No autologous transplant recipient received steroids in excess of 2 mg/kg per day. None, □; < 1 mg/kg/d, ▨; 1-2 mg/kg/d, ▩; > 2 mg/kg/d, ■.

Table 3. Parainfluenza virus-3 infection and mortality after hematopoietic stem cell transplantation: multivariable analysis

Covariate	HR*	95% CI	P
<i>Among all patients</i>			
No PIV-3 infection	1.0		
PIV-3 URI	1.3	1.1-1.6	.02
PIV-3 LRI	3.4	2.4-4.7	< .001
<i>Among patients with PIV-3 LRI</i>			
Copathogen present?			
No	1.0		
Yes	2.75	1.4-5.4	.003
Ventilator requirement?			
No	1.0		
Yes	3.29	1.2-9.0	.02

HR, indicates hazard ratio; URI, upper respiratory infections; LRI, lower respiratory tract infections; for other abbreviations, see Tables 1 and 2.

*Adjusted for age, underlying disease, disease risk, CMV serostatus, donor type.

persistent radiographic or clinical evidence of pneumonia (17 of 19 at 30 days, 35 of 41 at 180 days).

Risk factors for mortality in patients with PIV-3 pneumonia

Of the 55 patients with PIV-3 LRI, 29 (53%) had copathogens isolated from the BAL fluid at the time of PIV-3 diagnosis; these copathogens are listed in Table 4. *Aspergillus fumigatus* was the most common copathogen isolated, occurring in 13 of 55 (24%) cases of PIV-3 LRI. The 30-day mortality rate was significantly higher among those with copathogens at the time PIV-3 was diagnosed by BAL (14 of 29, 48%) than among those without copathogens (5 of 26, 19%; $P = .024$); the 180-day mortality rate showed similar trends (96% with copathogens versus 50% without copathogens, $P < .001$). The need for mechanical ventilation was also associated with mortality after PIV-3 pneumonia (Table 3). Donor type, CMV serostatus, disease risk, conditioning regimen, engraftment status, the presence of acute GVHD, oxygen requirement at diagnosis, and concomitant steroid therapy were not associated with increased risk of death after controlling for presence of a copathogen and need for mechanical ventilation.

Impact of ribavirin and intravenous immunoglobulin therapy

Thirty-one of 55 patients with PIV-3 pneumonia were treated with aerosolized ribavirin therapy with or without intravenous immunoglobulin (IVIG) in a nonrandomized fashion. Characteristics of

Table 4. Copathogens isolated by bronchoalveolar lavage in 55 cases of parainfluenza virus-3 lower respiratory tract infections

Copathogen	No. of cases
<i>Fungal pathogens</i>	
<i>Aspergillus fumigatus</i>	14
<i>Candida glabrata</i> *	1
<i>Viral pathogens</i>	
Cytomegalovirus	10
Respiratory syncytial virus	6
Herpes simplex virus*	3
<i>Bacterial pathogens</i>	
<i>Acinetobacter</i> spp.	1
<i>Legionella</i> spp.	9
<i>Streptococcus pneumoniae</i>	2
<i>Corynebacterium JK</i>	2
<i>Pseudomonas aeruginosa</i>	1
<i>Klebsiella pneumoniae</i>	1
<i>Moraxella catarrhalis</i>	1

*Biopsy-proven disease.

Table 5. Characteristics of 55 patients with parainfluenza virus-3 lower respiratory tract infections, according to ribavirin therapy

Characteristic	Treated with ribavirin (n = 31)	No ribavirin (n = 24)
<i>Underlying disease</i>		
Acute leukemia	11 (35%)	10 (42%)
CML	8 (26%)	8 (33%)
HD/MM/NHL	6 (19%)	4 (17%)
MDS	3 (10%)	0 (0%)
Other	3 (10%)	2 (8%)
<i>Donor type</i>		
Matched related	10 (32%)	8 (33%)
Mismatched/unrelated	16 (52%)	11 (46%)
Autologous	5 (16%)	5 (21%)
<i>Acute GVHD*</i>		
Grade 0-II	16 (62%)	10 (56%)
Grade III-IV	10 (38%)	8 (44%)
<i>Engrafted at diagnosis?</i>		
Yes	21 (68%)	19 (79%)
No	10 (32%)	5 (21%)
<i>Ventilated at diagnosis?</i>		
Yes	4 (13%)	1 (4%)
No	27 (87%)	23 (96%)
<i>Oxygen requirement at diagnosis?</i>		
Yes	15 (48%)	9 (38%)
No	16 (52%)	15 (62%)

CML indicates chronic myelogenous leukemia; HD, Hodgkin disease; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; MDS, myelodysplasia; GVHD, graft-versus-host disease.

*Allogeneic recipients only.

treated and untreated patients were similar (Table 5). The 30-day mortality rate did not appear to be affected by the use of ribavirin or IVIG, even after stratification for the presence of copathogens (Figure 3B). Finally, mortality among those who were treated early

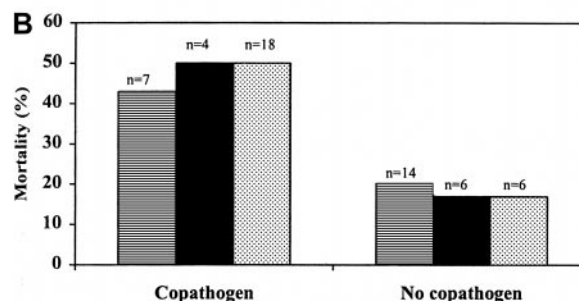
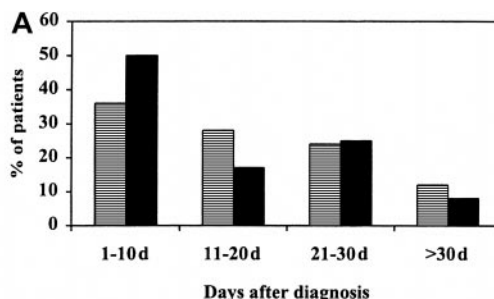


Figure 3. Effect of ribavirin on viral shedding and mortality among 55 patients with PIV-3 LRI. (A) Duration of PIV-3 shedding from the nasopharynx was similar for patients who did not (hatched) and who did (solid black) receive aerosolized ribavirin. **(B)** The 30-day mortality with PIV-3 LRI, stratified by presence of copathogens and no treatment (hatched), treatment with ribavirin (solid black), and treatment with ribavirin and IVIG (dotted). Mortality rates were comparable for all treatment groups and were influenced by copathogen status.

due to parainfluenza virus DFA positivity did not differ from those who were treated based on PIV culture positivity (data not shown).

We performed serial NPT cultures on all patients with PIV-3 LRI and were thus able to assess the impact of aerosolized ribavirin on clearance of PIV-3 from upper respiratory secretions. As shown in Figure 3A, 11 of 31 (35%) patients treated with ribavirin continued to shed PIV-3 from the nasopharynx for 3 weeks or longer; these figures were similar to the 8 of 24 (33%) of untreated patients who shed PIV-3 for this duration. Only 11 of 31 (35%) patients treated with ribavirin shed virus for less than 10 days, whereas 12 of 24 (50%) untreated patients shed for this duration.

Discussion

Our study provides several new insights about the clinical course and complications of PIV infections after stem cell transplantation. PIV infections were relatively common after HSCT and were associated with a high incidence of transplant-related mortality. PIV infections were seen among both autologous and allogeneic transplant recipients; recipients of unrelated transplants were at slightly higher risk. Overall, 24.1% of patients with PIV-3 infection developed virologically proven pneumonia; the development of lower tract disease was driven primarily by the administration of corticosteroids for GVHD and pseudo-GVHD. Copathogens were commonly isolated from patients with PIV pneumonia and were highly associated with mortality from this disease. Although therapy with aerosolized ribavirin was not applied in a randomized fashion, this agent failed to demonstrate any trends toward decreased viral shedding or improved survival in those with established pneumonia.

One of the strengths of this study was the standardized clinical protocol used. All HSCT recipients with symptoms of URI had NPT washes submitted for culture for community-acquired respiratory viruses. More importantly, culture for parainfluenza viruses was uniformly applied for all BAL, biopsy, and autopsy specimens performed throughout the study. Because virtually all patients at our center with signs or symptoms of pneumonitis undergo BAL (and many also undergo open lung biopsy), an accurate measure of the frequency of parainfluenza LRI and the prevalence of pulmonary copathogens was possible.

Progression from upper to lower tract disease occurred in 24% of PIV-3 infections. Among those with preceding URI, the receipt of corticosteroids for GVHD or pseudo-GVHD appeared as the only significant risk factor for progression in multivariable models (Table 2, Figure 2). GVHD (and the steroid therapy that accompanies it) is well known to be associated with both noninfectious and infectious interstitial pneumonia.⁶ When steroid use was added to logistic regression models that contained various combinations of predictor variables (including GVHD), however, the models were always significantly improved. On the other hand, once steroid use was included in a regression model, inclusion of other variables led to models that were improved very little (Table 2). Importantly, steroids were associated with PIV-3 pneumonia among autologous transplant recipients with pseudo-GVHD as well; their use in the autologous setting effectively raises the risk for progression to that of the highly immunosuppressed allogeneic transplant recipient. Thus, the correlation between GVHD and PIV pneumonia appears to be primarily driven by the corticosteroids patients receive for this condition. It is likely that the "steroid effect" is related to an acute decline in T-cell-mediated immunity that occurs after the administration of high-dose corticosteroids. These data suggest that

tapering of corticosteroids at the time of PIV-3 URI diagnosis may be one strategy to prevent progression to pneumonia.

The high prevalence (53%) of pulmonary copathogens (*A fumigatus* in particular) in patients with PIV-3 pneumonia is noteworthy; a high incidence of aspergillosis (29%) among patients with PIV-3 pneumonia was also noted in a recent report.⁷ This association is reminiscent of the well-known association between bacterial pneumonia and influenza virus infection. PIV may predispose patients to such infections by damaging the respiratory epithelium and allowing other organisms to penetrate or may exert a direct immunosuppressive effect. Recent data have suggested that antecedent PIV-1 infection may predispose to bacterial pneumonia in the elderly⁸ and may inhibit T-cell function *in vitro*,^{9,10} raising the possibility that either local or global immunosuppression may be operative. Further studies regarding the interaction of PIV-3 with other posttransplant infections are needed.

Ribavirin has activity *in vitro* against a broad spectrum of DNA and RNA viruses and reduces PIV titers in animal models.¹¹ Small case series have reported clinical success with the use of aerosolized ribavirin in the treatment of parainfluenza pneumonia among recipients of HSCT.² Although ours was not a randomized trial, the use of aerosolized ribavirin with or without concomitant IVIG did not modify the high mortality rates in patients so treated. No differences in survival were demonstrated in an earlier study of aerosolized ribavirin therapy; mortality was 22% regardless of treatment.³ Patients in that study, however, were treated a median of 11 days after symptom onset. In our study, all individuals who received ribavirin did so within 48 hours of diagnosis of parainfluenza 3 infection by BAL; rapid diagnosis was achieved in over half of these individuals via DFA staining, allowing initiation of ribavirin a median of 2 days after LRI was identified. Unfortunately, mortality did not appear significantly lower in those who were identified early, even among those without significant copathogens isolated; early diagnosis and therapy also failed to result in improved mortality in another recent report.⁷ Furthermore, ribavirin failed to shorten the time for viral shedding from the nasopharynx among those treated, arguing against a significant antiviral effect.

It remains possible that earlier diagnosis of PIV-3 pneumonia may allow for more expeditious therapy with ribavirin, thereby potentially improving outcome.¹² Alternatively, ribavirin could be applied to patients with parainfluenza URI to prevent progression to LRI; this approach could have merit in patients with GVHD on high-dose corticosteroids, who appear to be at higher risk for progression (Table 2). Finally, other investigators have reported some anecdotal success with systemic ribavirin therapy administered orally or intravenously, though hemolysis is a notable complication.^{12,13} Given the significant morbidity and mortality associated with PIV-3 pneumonia, there is a pressing need for systematic evaluation of these approaches via randomized, controlled trials. In addition, newer, more active antiviral agents are needed.

Because current therapeutic options are limited, the prevention of PIV infections is paramount. Unfortunately, the epidemiology of PIV-3 infections makes infection control daunting. Strict infection control practices can decrease nosocomial or patient-to-patient transmission; these have been in place at the FHCRC for the past 9 years. Despite these measures, incident infections continued to occur in outpatients, most notably in a prolonged outbreak from September 1998 to June 1999 (Figure 1). This outbreak was coincident with a dramatic rise in community-wide prevalence

(data not shown). In contrast to RSV infection (which is usually symptomatic), PIV-3 can be associated with minimal symptoms in the immunocompetent host, who may shed the virus for up to 1 month¹⁴; the avoidance of “symptomatic” individuals may thus be ineffective. Peaks in community PIV-3 activity occur in parallel with allergy season, further complicating the interpretation of individuals with rhinorrhea. Given the year-round distribution of cases and prolonged shedding among those infected, constant vigilance to staff, family, and patient symptomatology may be needed to prevent transmission outside of the “respiratory virus season.” Vaccine or chemoprophylaxis agents (once available) should prove highly useful in this setting as well.

In conclusion, PIV infections occurred in approximately 7% of patients after HSCT at our center. Almost 25% of patients with PIV-3 URI progress to pneumonia. Corticosteroid therapy was highly associated with pneumonia in a dose-dependent

fashion, and dramatically increased the risk for pneumonia among autologous transplant recipients as well. Mortality from PIV-3 pneumonia was high and driven higher by the presence of copathogens; ribavirin with or without IVIG did not appear to improve survival or decrease viral shedding. New agents are sorely needed for PIV infections in the immunocompromised host. Until then, strict infection control measures based on virologic surveillance of symptomatic patients remain the cornerstone of preventive strategy.

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