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Human Parainfluenza Virus Infection after Hematopoietic Stem Cell Transplantation: Risk Factors, Management, Mortality, and Changes over Time

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Human parainfluenza viruses (HPIVs) are uncommon, yet high-risk pathogens after hematopoietic stem cell transplant (HCT). We evaluated 5178 pediatric and adult patients undergoing HCT between 1974 and 2010 to determine the incidence, risk factors, response to treatment, and outcome of HPIV infection as well as any change in frequency or character of HPIV infection over time. HPIV was identified in 173 patients (3.3%); type 3 was most common (66%). HPIV involved upper respiratory tract infection (URTI; 57%), lower respiratory tract infection (LRTI; 9%), and both areas of the respiratory tract (34%), at a median of 62 days after transplantation. In more recent years, HPIV has occurred later after HCT, whereas the proportion with nosocomial infection and mortality decreased. Over the last decade, HPIV was more common in older patients and in those receiving reduced intensity conditioning (RIC). RIC was a significant risk factor for later (beyond day +30). HPIV infections, and this association was strongest in patients with URTI. HCT using a matched unrelated donor (MURD), mismatched related donor (MMRD), age 10 to 19 years, and graft-versus-host disease (GVHD) were all risk factors for HPIV infections. LRTI, early (<30 days), age 10 to 19 years, MMRD, steroid use, and coinfection with other pathogens were risk factors for mortality. The survival of patients with LRTI, especially very early infections, was poor regardless of ribavirin treatment. HPIV incidence remains low, but may have delayed onset associated with RIC regimens and improving survival. Effective prophylaxis and treatment for HPIV are needed.

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INTRODUCTION

Human parainfluenza viruses (HPIVs), medium-sized enveloped single-stranded RNA viruses, belong to the *Paramyxoviridae* family. HPIVs are divided into 4 different types due to their genetic and antigenic characteristics, although most clinical infections are due to types 1, 2, and 3. HPIV can cause both upper and lower respiratory tract infections (URTIs and LRTIs), and less frequently, central nervous system infections [1-3]. Clinical manifestations range widely, from croup, otitis media, and bronchitis to life-threatening pneumonitis [4-6]. The vast majority of HPIV infections occur in infants and children [2]. A second population vulnerable to HPIV infections is immunocompromised patients including hematopoietic stem cell transplant (HCT) recipients [1,7-14]. The incidence of HPIV has been reported between 2% to 7% after HCT [1,9,13]. Beyond this variation in HPIV incidence after HCT, the preferred treatment and impact on mortality are uncertain [9,13,15,16].

We evaluated HPIV incidence, risk factors, outcome, and response to treatment in pediatric and adult patients undergoing autologous or allogeneic HCT

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(autoHCT or alloHCT) at the University of Minnesota. We evaluated changes in the timing and character of HPIV infection over several decades, comparing the frequency of HPIV infection, type of HPIV, clusters or isolated infections, nosocomial or community-acquired infections, URTIs or lower LRTIs, and seasonal predominance.

PATIENTS AND METHODS

Patient Population

This retrospective cohort study included 5178 consecutive pediatric and adult patients who received HCT at the University of Minnesota (median age, 29; range, 0-74 years) between January 1974 and December 2010. Transplantation types included 1717 autoHCT (33%) and 3461 alloHCT (67%). One hundred seventy-three HPIV cases were identified, including 7 diagnosed in the 2 weeks before HCT. Patients received conditioning for transplantation, prophylaxis of graft-versus-host disease (GVHD) and infections per active institutional protocols, which varied over the period of study [17-19]. The intensity of conditioning regimens was defined according to the Center for International Blood and Marrow Transplant Research (CIBMTR) guidelines [20]. For analysis, ex vivo and in vivo (eg, antithymocyte globulin) T cell depletion were combined as T cell depletion. All transplantation protocols were approved by the University of Minnesota Institutional Review Board. All patients or their legal guardians provided written informed consent for the transplantation procedure including collection of long-term prospective outcome data. The median follow-up time for all survivors and for patients with HPIV was 6.5 and 6.0 years, respectively.

For patients demonstrating acute onset of URTI symptoms, respiratory virus cultures of throat and/or nasopharyngeal swabs or washes were obtained. For any patient with HCT undergoing bronchoalveolar lavage (BAL), lung biopsy, or autopsy, respiratory virus cultures were part of preplanned diagnostic protocols and obtained on all samples.

Hospital in-patients with HPIV infection were placed in droplet precautions, which involved using gown, glove, and mask procedures to prevent spread of infection to other patients or healthcare workers.

To evaluate any changing characteristics of HPIV over time, we examined patients in 3 time periods: 1974 to 1992, 1993 to 2001, and 2002 to 2010. The first period was composed of almost 2 decades because it had fewer patients and it reflected the data from an early transplantation era. Available data on 387 adult patients surviving greater than 80 days were also evaluated for late-onset noninfectious pulmonary complications (LONIPCs) between 2002 and 2007. Diffuse alveolar hemorrhage, idiopathic pneumonia syndrome, bronchiolitis obliterans, and bronchiolitis obliterans with organizing pneumonia were considered as LONIPCs.

Virology Procedures

Standard methods were used for isolation of HPIV from respiratory samples. HPIV was isolated in tube cultures containing a monolayer of primary rhesus-monkey kidney cells and detected by hemadsorption with guinea pig red cells at 3, 7, and 10 days. All negative viral cultures were finalized at 21 days of incubation. All BAL and lung tissue specimens were concurrently submitted for bacterial, mycobacterial, and fungal cultures. Sputum and autopsy samples were submitted for bacterial and fungal cultures.

Isolates recovered in culture were typed by immunofluorescence with commercially available antiserum. HPIV virus identification typically took 7 to 10 days overall: 7 days for types 1 and 3, and 8 to 9 days for type 2.

Since January of 2004, the method of conventional tube culture was supplemented with an R-Mix shell vial culture (Diagnostic Hybrids, Athens, Ohio). Monolayer staining was checked at 2 days using a pooled stain to detect parainfluenza viruses 1, 2, and 3, in addition to other respiratory viruses.

Definitions

"Infection episode" was defined as the cultured presence of HPIV in a sample from the pulmonary tree of a patient concomitantly displaying symptoms compatible with clinical infection. Patients with symptoms/signs of croup, nasopharyngitis, conjunctivitis, and otitis media were defined as URTI. URTI excluded dyspnea and/or newly appearing infiltrates on radiographic imaging methods (chest radiograph or computed tomography scan). Patients were considered to have LRTI if they had symptoms/signs (eg, fever, expiratory wheezing, tachypnea, dyspnea, retractions, rales, or pulmonary infiltrates on chest X-ray or computed tomography) of tracheobronchitis or pneumonia. Respiratory failure is defined as mechanical ventilation occurring within 30 days of HPIV.

"Nosocomial infection" was defined as infection developing 5 or more days after hospital admission. All other infections were classified as community acquired.

"Cluster infection" was defined as 3 or more cases of nosocomial or community-acquired infection apparent within a 30-day period.

"Coinfection" was a second respiratory pathogen occurring within a month of HPIV infection. Fever of unknown origin was not categorized as coinfection.

Treatment of HPIV Infection

Treatment of HPIV infections depended on the patient's condition, URTI or LRTI, and was at the

discretion of treating physician. Those patients who required treatment received aerosolized ribavirin. Aerosolized ribavirin was administered as nebulization through a mask or endotracheal tube. From 1984 to 1995, the drug was generally administered as 6 grams in a continuous aerosol nebulization for 18 to 24 hours per day. From 1995 to 2005, some patients received aerosolized ribavirin using a schedule of 2 grams over 2 hours 3 times daily. The duration of therapy differed between patients. Usually, a 5-day course of treatment was delivered, unless continued symptoms and/or ongoing positive cultures indicated a clinical need for repeated or longer courses. Some patients received i.v. immune globulin (Ig) along with ribavirin.

Data and Statistical Analysis

Analysis of the University of Minnesota Blood and Marrow Transplant database was used for data extraction. The University of Minnesota HCT database contains prospectively collected data on all patients who underwent transplantation at our center. Clinical data in this computerized research database included details of antiviral medications used to treat HPIV infection episodes. Additional clinical information was collected from available medical records. For patients who never developed HPIV, their first transplantation was included for analysis. For patients with HPIV, the most recent transplantation relative to HPIV onset was used.

Patient characteristics were compared by the chi-square test. Cox regression was used to identify risk factors for HPIV, with time 0 set as the transplantation date and time to HPIV as the outcome. A Fine and Gray competing risks model was also fit to identify risk factors for HPIV, accounting for death as a competing risk. These results (not reported) showed good agreement with the Cox model. Cox regression was used to identify risk factors for mortality within 100 days of HPIV and for subgroups with LRTI. Survival time was taken as time from infection. No violations of proportional hazards were detected. Multivariate Cox models used a forward stepwise selection process with a P value cutoff of .15 for inclusion in the final model. Acute and chronic GVHD (aGVHD and cGVHD) were considered as time-dependent covariates. Additionally, the association between HPIV and mortality was tested using a Cox model, with URTI and LRTI as time-dependent covariates and adjusting for other factors (diagnosis category, donor type, transplant year, age, conditioning intensity, and cytomegalovirus [CMV]) potentially associated with survival.

RESULTS

HPIV Patient and Infection Characteristics

Transplantation characteristics for patients with HPIV infection and controls with no infection are shown in Table 1. HPIV infection was diagnosed in 173 patients (3.3%). The majority of HPIV infections were caused by HPIV type 3 (66%; Figure 1). The observed rates of nosocomial (41%) or community-acquired (59%) infection and of cluster (45%) or single case (55%) infection were similar. The median interval from transplantation to HPIV infection was 62 days (range −8 to +259 days). Most infections (83%) occurred during the first year after transplantation, and more than one-half of infections (58%) were diagnosed in the first 100 days; 34% in the first 30 days. HPIV infection affected only the upper respiratory tract in 98 patients (57%), only lower respiratory tract in 15 patients (9%), and both in 60 patients (34%). Among the 75 patients with LRTI, 43 (57%) were culture-positive in BAL; the rest of the patients were diagnosed via radiologic or physical examination findings supported by virologic diagnostic material from noninvasive (nasal or throat) sampling. Ribavirin with or without i.v. Ig was administered to 51 patients (29%), 10 with URTI (10%), and 41 with LRTI (55%).

Seasonal Prevalence of HPIV

HPIV infections occurred throughout the year with similar rates, ranging from 40 to 53 events over the 4 seasons (Figure 1). HPIV 3 was the most common isolate compared to other HPIV types throughout the year and was more common in warmer seasons (spring and summer, 76 events) compared with autumn and winter (31 events; Figure 1).

Changes in HPIV over Time

Over time (1973-1992 versus 1993-2001 versus 2002-2010), the type of HPIV and total HPIV infection rate did not change (3.0% versus 3.2% versus 3.9%; $P = .31$; Figure 2). The proportion of nosocomial HPIV infections (74% versus 30% versus 27%; $P < .01$) and early HPIV infections (diagnosed within 30 days post-HCT; 58% versus 24% versus 35%; $P < .01$) decreased in the more recent eras. The median time to HPIV infection was later as well occurring at a median of 21 days (interquartile range [IQR], 6-79 days) from 1974 to 1992 compared with 135 days (IQR, 45-395 days) from 1993 to 2001 and 75 days (IQR, 18-210 days) from 2002 to 2010. The proportion of cluster HPIV cases increased (29% versus 59% versus 50%; $P < .01$; Figure 2), although this may partly be due to more aggressive surveillance in the latter eras.

A comparison of demographic data between the patients with HPIV and the control group without HPIV infection in different transplantation eras is shown in Table 1. Over the last decade, HPIV occurred more often in older patients and in patients who received reduced-intensity conditioning (RIC;

Table 1. Comparison of Patients with HPIV with Patients with no HPIV over 3 Different Time Eras

	Transplantation Era								
	1974-1992			1993-2001			2002-2010		
	Controls n (%)	HPIV Cases n (%)	*P* Value	Controls n (%)	HPIV Cases n (%)	*P* Value	Controls n (%)	HPIV Cases n (%)	*P* Value
Number	1657	51		1737	57		1611	65	
Median age	18.3	17.5	.85	32.8	33.1	.97	39.0	46.9	.14
Age by range			.80			.10			.03
Age <10	514 (31)	18 (35)		424 (24)	14 (25)		346 (21)	8 (12)	
Age 10-19	359 (22)	10 (20)		224 (13)	2 (4)		210 (13)	4 (6)	
Age ≥20	784 (47)	23 (45)		1089 (63)	41 (72)		1055 (65)	53 (82)	
Male	977 (59)	33 (65)	.41	933 (54)	36 (63)	.16	984 (61)	35 (54)	.24
Donor sex match			.57			.23			.60
Match	554 (51)	16 (46)		565 (52)	29 (60)		488 (43)	20 (39)	
Mismatch	540 (49)	19 (54)		531 (48)	19 (40)		649 (57)	31 (61)	
Diagnosis category			.30			.39			.30
Lymphoid-malignant	227 (14)	4 (8)		306 (18)	12 (21)		401 (25)	18 (28)	
Myeloid-malignant	1174 (71)	36 (71)		1127 (65)	32 (56)		886 (55)	39 (60)	
Non-malignant	256 (15)	11 (22)		304 (18)	13 (23)		324 (20)	8 (12)	
Autologous	563 (34)	16 (32)	.70	641 (37)	9 (16)	<.01	474 (29)	14 (22)	.17
Allogeneic			<.01			.76			.32
UCB	1 (<1)	0 (0)		140 (8)	7 (13)		590 (37)	26 (40)	
Matched sibling	824 (50)	19 (37)		445 (26)	16 (28)		359 (22)	14 (22)	
Other relatives	67 (4)	8 (16)		49 (3)	3 (5)		49 (3)	5 (8)	
Unrelated	202 (12)	8 (16)		462 (27)	22 (39)		139 (9)	6 (9)	
CMV serostatus			.30			.84			.61
R+	893 (54)	33 (65)		813 (47)	28 (49)		859 (53)	31 (48)	
R−/D−	608 (37)	15 (30)		754 (43)	22 (39)		676 (42)	29 (45)	
R−/D+	115 (7)	2 (4)		165 (10)	5 (9)		69 (4)	4 (6)	
Unknown	41 (3)	1 (2)		5 (<1)	2 (4)		7 (<1)	1 (2)	
Conditioning intensity			.20			.11			.01
Myeloablative + TBI	1266 (76)	35 (69)		1225 (71)	42 (74)		631 (39)	23 (35)	
Myeloablative, no TBI	391 (24)	16 (31)		461 (27)	11 (19)		529 (33)	13 (20)	
RIC	0 (0)	0 (0)		49 (3)	4 (7)		447 (28)	29 (45)	
T depletion	433 (26)	20 (39)	.04	288 (18)	19 (33)	<.01	404 (25)	17 (26)	.85

HPIV indicates human parainfluenza virus; UCB, umbilical cord blood; CMV, cytomegalovirus; R, recipient; D, donor; TBI, total body irradiation; RIC, reduced-intensity conditioning.
P values represent chi-square comparisons of characteristics of HPIV infected versus control patients within each time era.

Table 1; Figure 3). In earlier decades, this age and conditioning regimen disparity in HPIV infection rates was not apparent. In contrast, T cell depletion was associated with more HPIV infections in earlier decades; however, this difference was not noted over the last decade. Sibling alloHCT was associated with less HPIV in the earliest transplantation era compared with the more recent decades of study.

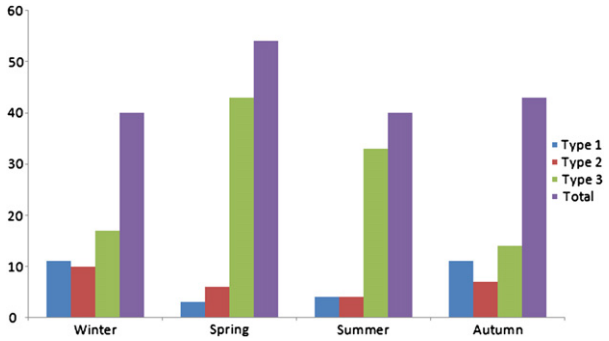

Figure 1. Frequency of human parainfluenza virus (HPIV) infections per season.

Coinfections

Coexisting infection with other pathogens was detected in 68 patients with HPIV (39%). Organisms identified concurrent with HPIV infections included bacteria (55 patients), viruses (37 patients), and fungi (19 patients, including 13 cases of *Aspergillus*). Polymicrobial infection occurred in 35 patients.

Association of HPIV with LONIPCs

Of 387 patients (22 with HPIV and 365 with no HPIV), 65 developed LONIPCs. The rates of LONIPCs were 23% and 17% in patients with HPIV and no HPIV ($P = .39$), respectively.

Risk Factors for all-HPIV and LRT-HPIV Infections

Multivariate analysis showed that mismatched related donor (MMRD) and preceding cGVHD were independent risk factors for both all-HPIV and LRT-HPIV infections. The aGHVD and a matched unrelated donor (MURD) were risk factors for HPIV infection. RIC regimens were risk factors

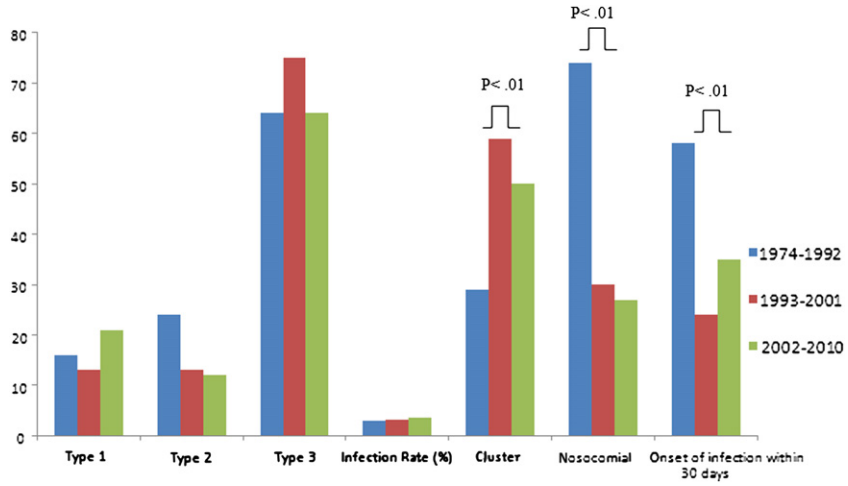

Figure 2. Trends of infection characteristics over time.

for HPIV infections beyond 30 days after HCT (Table 2). This effect was strongest in patients with URTI (hazard ratio [HR], 3.0; 95% confidence interval [CI], 1.4-6.1; $P < .01$). Male recipients had more frequent LRTI. Umbilical cord blood transplants and MURDs showed a trend for increased LRTIs.

Respiratory Failure and Survival

The need for mechanical ventilation within 30 days of HPIV infections and of LRT-HPIV infections was 19% and 43%, respectively. The 100-day survival from the onset of mechanical ventilation was 23% in these patients. By comparison, 100-day survival from the onset of mechanical ventilation was similar in other patients with uninfected HPIV (22%). In multivariate analysis, LRTI (HR, 2.6; 95% CI, 1.3-5.4; $P < .01$) but not URTI was associated with increased mortality (Figure 4A), and the mortality of patients with LRTI at 100 days after infection decreased over time: 71% (15 of 21 patients) from 1974 to 1992, 25% (6 of 24 patients) from 1993 to 2001, and 37% (11 of 30 patients) from 2002 to 2010.

In multivariate analysis, LRTI, age 10 to 19 years (HR, 4.2; 95% CI, 1.8-9.9; $P < .01$), MMRD (HR, 3.8; 95% CI, 1.7-8.5; $P < .01$), early HPIV infection (HR, 2.3; 95% CI, 1.2-4.3; $P < .01$; Figure 4B), the presence of coinfection (HR, 2.1; 95% CI, 1.0-4.2; $P = .04$), and steroid use (HR, 2.0; 95% CI, 1.0-3.9; $P = .05$) were also found to be risk factors for mortality. Transplantation era and nosocomial acquisition of HPIV were not independent risk factors for mortality as they were significant only in univariate analysis.

Anti-Viral Treatment and Outcome

Overall, treated patients with HPIV had higher mortality rates at 100 days after infection compared with those who were not treated (40% versus 15%; $P < .01$; Figure 4C), although clinical factors including the acuity at presentation may, of course, have directly influenced the decision to initiate specific therapy.

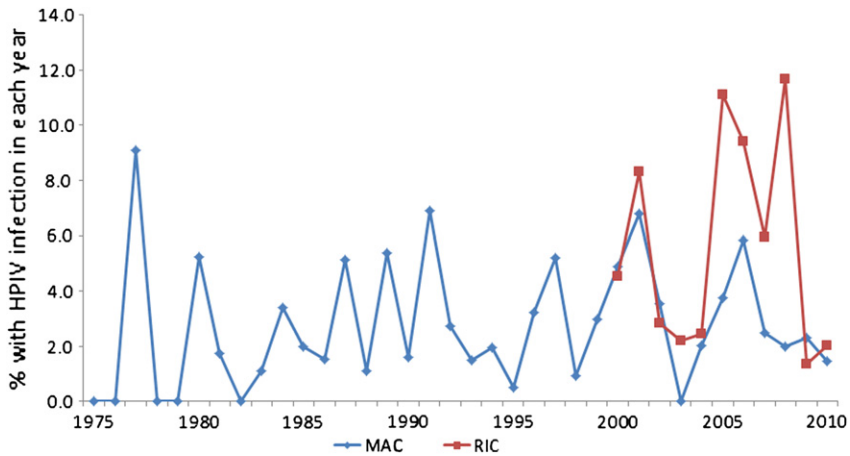

Figure 3. Incidence of human parainfluenza virus (HPIV) by year and conditioning intensity.

Table 2. Multivariate Analysis of Risk Factors for All and LRT-HPIV Infections

	All HPIV		LRTI	
Factor	Risk ratio (95% CI)	*P* Value	Risk ratio (95% CI)	*P* Value
Donor type				
Autologous	Ref		Ref	
UCB	1.4 (0.8-2.5)	.31	2.4 (1.0-6.1)	.06
Matched related	0.9 (0.6-1.6)	.80	1.4 (0.6-3.2)	.41
Matched unrelated	2.0 (1.1-3.7)	.03	2.3 (0.8-6.0)	.11
Mismatched related	3.2 (1.6-6.3)	<.01	7.0 (2.7-18.3)	<.01
Mismatched unrelated	1.3 (0.6-2.7)	.55	0.9 (0.3-3.8)	.98
Gender				
Male	Ref		Ref	
Female	0.9 (0.7-1.3)	.75	0.6 (0.3-1.0)	.04
Diagnosis category				
Lymphoid/malignant	1.2 (0.8-1.8)	.46	1.0 (0.5-1.9)	.89
Myeloid/malignant	Ref		Ref	
Non-malignant	1.1 (0.7-1.8)	.66	0.9 (0.4-2.1)	.89
CMV				
R+	1.0 (0.7-1.5)	.80	1.5 (0.9-2.5)	.15
R−/D−	Ref		Ref	
R−/D+	0.9 (0.4-1.7)	.66	1.2 (0.5-3.2)	.66
Unknown	2.1 (0.6-6.9)	.22	0.0 (0.0-0.0)	.98
Age				
Age <10	0.8 (0.5-1.3)	.42	0.6 (0.3-1.3)	.18
Age 10-19	0.5 (0.3-0.9)	.03	0.5 (0.2-1.1)	.07
Age ≥20	Ref		Ref	
Transplantation era				
1974-1992	0.8 (0.5-1.4)	.56	0.8 (0.4-1.6)	.47
1993-2001	0.7 (0.3-1.8)	.48	0.9 (0.5-1.7)	.71
2002-2010	Ref		Ref	
RIC (risk <30 d)	0.7 (0.3-1.8)	.48	0.5 (0.1-1.9)	.54
RIC (risk ≥30 d)	2.1 (1.2-3.5)	.01	1.4 (0.6-3.1)	.42
aGVHD	1.9 (1.1-3.4)	.03	2.1 (0.8-5.3)	.11
cGVHD	6.2 (3.7-10.4)	<.01	7.1 (3.4-14.8)	<.01

LRT indicates lower respiratory tract; HPIV, human parainfluenza virus; LRTI, lower respiratory tract infection; CI, confidence interval; UCB, umbilical cord blood; CMV, cytomegalovirus; R, recipient; D, donor; RIC, reduced-intensity conditioning; Ref, reference group for each comparison category; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease.

However, even among those patients with LRTI, ribavirin treatment led to similar mortality at 100 days after infection (46%) as compared with no treatment with ribavirin (38%; $P = .60$).

DISCUSSION

This long-term study has shown, we believe for the first time, how RIC has changed HPIV infections over time. Over the 35 years of study, we observed a relatively stable incidence (approximately 3%) of HPIV infection in our large HCT population, similar to that shown by our and other earlier studies [1,9,13]. Notably, the age of patients with HPIV has increased over the decades of study. HPIV 3 was the most common type we observed, which is consistent with data showing that HPIV 3 is the most common type in healthy community-based pediatric populations [1,2,9,13,21]. Most HPIV 3 cases were diagnosed in warmer seasons among our patients with HCT, which was also consistent with data showing that spring is its peak season in the general population [22]. Limitations of this retrospective cohort study include changes in the duration of follow-up of patients over time, as patients in the latter years of the study had only several years of long-term follow-up.

RIC regimens were found to be a risk factor for HPIV infection occurring later than the first 30 days posttransplantation. Most of these patients had URTIs. Although RIC was used mostly in older patients, older patients experienced similar HPIV compared with younger patients, and higher incidents of HPIV among patients with RIC were present in all age groups. Moreover, although both aGVHD and cGVHD increased HPIV infections, RIC remained as a risk factor in the multivariate analysis. Recent patients who underwent transplantation might be followed longer at transplantation centers, live longer, or HPIV might be considered more often within time, which could have explained the increased HPIV with RIC regimens. On the other hand, transplantation era was not a significant factor for HPIV infections in the multivariate analysis. Therefore, RIC regimens seem to increase delayed HPIV infections.

Despite stability in the incidence of HPIV, there has been a change in the day of onset with more recent HPIV infections occurring later post-HCT. This later

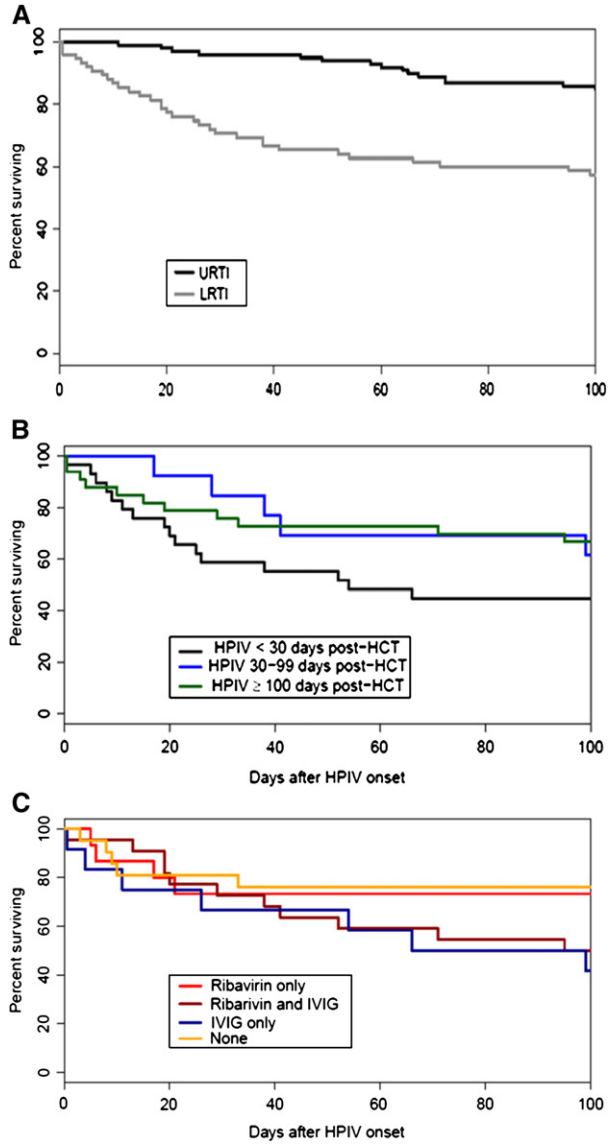

Figure 4. (A) Lower respiratory tract infection (LRTI) with human parainfluenza virus (HPIV) is associated with higher mortality than upper respiratory tract infection (URTI). (B) Higher mortality with early onset (<30 days) of LRT-HPIV. (C) Effect of antiviral treatment for LRT-HPIV on survival. Abbreviations: IVIG = intravenous immune globulin.

onset of infection was also associated with fewer nosocomial infections, more cluster infections, and slightly lower mortality. This delay may be due in part to a change in screening practices, as well as ongoing virologic surveillance at later time points after HCT. Our recognition of late infections has increased, because patients remain under review at transplantation centers longer, and patients survive longer, remaining at risk to develop infection later after HCT. Other as yet undefined changes in our clinical practice of HCT may influence this epidemiology as well.

In recent years, testing for respiratory viruses has come to include PCR testing, together with or in place of culture or shell vial testing. Several studies have shown that RT-PCR and real-time PCR with specific primers and probes for each type of HPIV are more sensitive and specific than both viral culture and immunofluorescence-based detection methods [23-27]. The use of nucleic acid detection is so new that only future studies will be able to determine whether the incidence will change once most centers start exclusively using PCR testing. In the setting of alloHCT, these methods have detected viruses even in asymptomatic patients with negative cultures [8,27]. Taking into account these asymptomatic patients and low sensitivity of cultures, the current incidence of HPIV may be underestimated.

Higher risks for developing HPIV infection were observed with certain donor types (MUD and MMRD), and in patients with aGVHD and cGVHD. RIC was also a risk factor for later infection. RIC regimens are reportedly associated with increased delayed rate of viral infections, including CMV [28,29]. Chakrabarti et al. [21] reported that median time to HPIV infection from RIC alloHCT was 72 days, which is very similar to our finding (75 days) over the last decade. Alemtuzumab-containing RIC regimens were associated with increased HPIV infections, but not with high mortality rates [21].

Risks for mortality after HPIV infection included LRTI and early infections after HCT. Mortality from LRTI has improved over decades. However, respiratory failure requiring mechanical ventilation remained a poor prognostic factor for survival, which was similar to patients with uninfected HPIV in this study. Mechanical ventilation need was a significant risk factor for mortality in a report from Seattle as well [9]. Early HPIV infection associated with higher mortality was reported with 16% (10 of 61 patients) mortality in patients with HPIV overall, which was higher (21%) in patients with early (<100 days) HPIV infection versus only 5% for later infections [13]. We also observed higher mortality after MURD and MMRD HCT, patients age 10 to 19, steroid use, and the presence of coinfections. Concurrent other infections have also been noted to increase risks of mortality in other studies [9,13].

Ribavirin with or without i.v. Ig was administered for some patients with HPIV, but with no demonstrable improvement in survival, similar to some, but not all earlier reports [9,30,31]. However, differences in prognostic factors in those treated or not treated may preclude definitive conclusions. There is clinical bias in choosing who to treat with ribavirin, as they may seem sicker. Moreover, because of the limited number of treated patients with URTI, the efficacy of ribavirin in patients with less-severe infections is unknown. Sparrelid et al. [30] suggested that in patients with viral LRTIs, the level of nebulized ribavirin might be limited by bronchospasm or tissue inflammation blocking delivery of an aerosolized drug to distal parts of the lungs. This early study suggested that

using i.v. ribavirin, but open label use of i.v. ribavirin was associated with hemolysis [32].

Prophylaxis of HPIV infection may be more important given that no effective antiviral therapy is available. HPIV vaccines have been developed, but are not licensed or used for routine clinical practice [33,34]. The nonseasonal nature of HPIV differs from respiratory syncytial virus, which is distinctly seasonal and can be recognized as a threat during community-associated outbreaks in children. Moreover, asymptomatic HPIV infection and shedding may occur in the HCT setting, making it difficult to know who is contagious [8]. The low rate of shedding also makes surveillance using PCR analysis cost-prohibitive and thereby impairs the prevention of HPIV infection by isolation for these contagious, yet asymptomatic patients with HPIV. Aggressive screening for respiratory viral infection during any URTI symptoms (year-round) may be the most valuable method to limit HPIV infections and their associated morbidity and mortality after HCT. Once an HPIV vaccine is commercially available, systematic vaccination of donors, HCT staff, and close patient contacts would be an additional prophylactic measure to prevent HPIV infections.

This study shows that HPIV infection occurring in later phases of alloHCT (RIC is a risk factor) may be less serious than HPIV infections occurring very early posttransplantation, which can increase mortality. Treatment of HPIV in LRTIs has not improved survival. Therefore, extreme caution should be taken to prevent infection from infected individuals to these hospitalized patients. Moreover, any patients with respiratory symptoms with imminent transplantation should be tested for HPIV, and transplantation should be postponed until the results are negative for HPIV.

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