MAJOR ARTICLE

Influenza Infections after Hematopoietic Stem Cell Transplantation: Risk Factors, Mortality, and the Effect of Antiviral Therapy

W. Garrett Nichols, Katherine A. Guthrie, Lawrence Corey, and Michael Boeckh

Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington

Background. Community-acquired respiratory viruses, such as influenza virus, are thought to be major causes of morbidity and mortality in patients who had undergone hematopoietic stem cell transplantation (HSCT). Risk factors for acquisition, progression to pneumonia, and the effect of antiviral therapy are unknown.

Methods. We reviewed records from patients with documented influenza over 12 consecutive respiratory-virus infection seasons at a single transplantation center.

Results. From 1 September 1989 through 31 March 2002, influenza virus was isolated from 62 of 4797 persons undergoing HSCT (1.3%); 44 patients had upper respiratory tract infections (URIs) alone, and 18 developed pneumonia. Among patients with influenza virus infection, pneumonia developed more commonly among those infected earlier after transplantation (median, 36 vs. 61 days, $P = .04$) and those with concurrent lymphopenia. Of the 51 cases that were initially diagnosed as URIs, 17 were treated with antivirals, and 34 were not treated. Six untreated patients (18%) developed pneumonia, whereas 1 (13%) of 8 patients treated with rimantadine and 0 of 9 treated with oseltamivir developed pneumonia. The duration of influenza virus shedding was longer in patients treated with steroid doses of >1 mg/kg than among those treated with doses of <1 mg/kg (mean, 15 vs. 9 days); there was a trend towards decreased shedding with oseltamivir therapy (but not rimantadine therapy) after controlling for steroid use ($P < .08$). The 30-day mortality rate was highest among patients who had progression to pneumonia (5 [28%] of 18 patients); pulmonary copathogens (such as *Aspergillus fumigatus*) were commonly isolated.

Conclusions. Influenza virus infection is an important cause of mortality early after HSCT. Our nonrandomized data suggest that early antiviral therapy with neuraminidase inhibitors may prevent progression to pneumonia and decrease viral shedding, which may prevent both influenza-related death in index patients and nosocomial transmission to others.

Community-acquired respiratory viruses, such as respiratory syncytial virus (RSV), parainfluenza viruses, and the influenza viruses are relatively common causes of upper and lower respiratory tract infection in persons undergoing hematopoietic stem cell transplantation (HSCT). The epidemiology of respiratory viral infections in persons who have undergone HSCT closely parallels the occurrence of these infections in the community, such that RSV and influenza infections most commonly occur during the well-defined winter and early spring "flu season." Mortality due to these viruses is host and virus dependent, with most studies showing the highest attributable mortality associated with RSV infections (followed by parainfluenza and influenza virus infections) [1]. All 3 viruses may cause life-threatening pneumonia themselves or may predispose patients to mortal infection with other pathogens, such as *Aspergillus fumigatus* [2, 3].

In contradistinction to the situation with RSV and parainfluenza virus, effective vaccines and easily administered antiviral therapy are available for the treatment and prevention of infections due to influenza virus. These medications include the newly licensed neuraminidase inhibitors (oseltamivir and zanamivir) and the long-available M2 inhibitors (amantadine and rimantadine). Herein, we describe the natural history and epidemiology of influenza virus infections among

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Reprints or correspondence: Dr. W. Garrett Nichols, Program in Infectious Diseases, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N, Seattle, WA 98109-4417 (wgnick2000@yahoo.com).

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persons undergoing HSCT, and we analyze data on the effect of antiviral therapy in this highly immunosuppressed patient population.

METHODS

Setting and patient population. The Fred Hutchinson Cancer Research Center (FHCRC) is a large referral HSCT center in Seattle, Washington. We analyzed data on all patients who underwent their first allogeneic, syngeneic, or autologous HSCT at the FHCRC from September 1989 through March 2002 (12 consecutive respiratory-virus infection seasons), during which we used a standardized protocol for the detection of viral respiratory pathogens for all patients undergoing HSCT (as described in "Virological and microbiological procedures," below). Conditioning for persons undergoing HSCT [4–6] and prophylaxis [7, 8] and treatment [7] of graft-versus-host disease (GVHD) were performed as described elsewhere. Clinical and virological data were extracted from a prospectively compiled, integrated database, and medical records were reviewed. Because capture of influenza infections and accurate ascertainment of all risk factors were less complete after discharge from the health care center, only infections that occurred during the first 120 days after transplantation were considered. The study protocol was reviewed and approved by the FHCRC Institutional Review Board, and all participants provided written informed consent.

Virological and microbiological procedures. Obtainment of a nasopharyngeal-throat (NPT) wash or swab for viral direct fluorescent antibody (DFA) staining and viral culture was standard practice for all patients with upper respiratory tract infection (URI) symptoms throughout the study period. Viral DFA (Bartels VRK; Intracel) and culture were also performed for all bronchoalveolar lavage (BAL), lung biopsy, and autopsy specimens. BAL was performed as standard of care for all patients with new or changing pulmonary infiltrates. Cultures for viruses, bacteria, and fungi were performed for all BAL, biopsy, and autopsy specimens as described elsewhere [3].

Definitions. Influenza URI was defined as the isolation of influenza virus from an NPT specimen by culture or as evidence of influenza antigen detected by DFA in conjunction with consistent symptomatology, without the presence of a new infiltrate visible on a chest radiograph. Influenza lower respiratory tract infection (LRI) was defined as the isolation of influenza virus by culture or DFA from BAL or lung biopsy specimens, in association with symptoms and a new infiltrate visible on a radiograph, or by the presence of new or changing radiograph infiltrates before or after 14 days of influenza isolation.

The presence of a copathogen was defined as the isolation of influenza virus in addition to pathogenic bacterial species, fungal species (such as *A. fumigatus*), or opportunistic viruses from BAL or lung biopsy specimens obtained before or after 14 days of influenza isolation. Day of engraftment after transplantation was defined as the third consecutive day of achievement of an absolute neutrophil count of >500 neutrophils/mm^3. Disease stage was assessed as described elsewhere [3].

Management. Inactivated influenza vaccination was offered free of charge each fall to all health care workers and to family caregivers to decrease health care–associated influenza transmission; staff compliance rates were in the range of 30%–60%. Once NPT or BAL specimens tested positive for influenza virus, patients were placed in respiratory isolation (i.e., wearing of gowns, gloves, and masks with eye protection was required for patient contact) to prevent transmission to staff and other patients. For each patient, an additional NPT wash or swab sample was obtained on the day after identification of influenza virus infection and then at least weekly to document clearance of the virus from nasopharyngeal secretions. Patients were maintained in respiratory isolation until they were free of symptoms and nasopharyngeal secretions yielded negative results of DFA stains and culture.

Antiviral treatment with an M2 inhibitor (rimantadine) or a neuraminidase inhibitor (oseltamivir, which has been avail-

Table 1. Characteristics of 4797 recipients of hematopoietic stem cell transplants, 1989–2002.

Characteristic	Value
Age, median years (range)	39 (0.3–74)
Male sex	2582 (54)
Underlying disease	
Acute leukemia	1492 (31)
Chronic leukemia	1274 (27)
HD, NHL, or MM	858 (18)
Myelodysplasia	466 (9.7)
Aplastic anemia	117 (2.4)
Other	590 (12)
Disease risk	
Nonadvanced	2825 (59)
Advanced	1964 (41)
Donor match	
Autologous	1170 (24)
Matched related allogeneic	1672 (35)
Mismatched related allogeneic	451 (9.4)
Unrelated allogeneic	1442 (30)
Data missing	62 (1.3)
Cell source	
Bone marrow	3239 (68)
PBSCs	1465 (31)
Bone marrow and PBSCs	66 (1.4)
Cord blood	27 (0.6)
CMV seropositivity	2539 (53)

NOTE. Data are no. (%) of patients, unless otherwise indicated. CMV, cytomegalovirus; HD, Hodgkin disease; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; PBSC, peripheral blood stem cell.

Table 2. Risks for influenza acquisition, progression to pneumonia, and 1-year mortality in multivariable models.

Parameter	OR or HR (95% CI)[a]	*P*
Risk for acquisition of influenza		
Female sex	1.72 (1.03–2.88)	.038
Advanced disease	2.04 (1.23–3.38)	.006
Risk for influenza pneumonia		
Lymphocyte count of <100 lymphocytes/μL	4.17 (1.21–14.4)	.024
Steroid use at time of diagnosis	0.22 (0.063–0.79)	.020
Risk for 1-year mortality[b]		
No influenza	1.0	
Influenza URI	0.77 (0.43–1.40)	.39
Influenza LRI	2.60 (1.40–4.86)	.003

NOTE. HR, hazard ratio; LRI, lower respiratory tract infection; URI, upper respiratory tract infection.

[a] ORs are shown for risk for influenza pneumonia, and HRs are shown elsewhere.

[b] Overall mortality, adjusted for age, underlying disease, disease risk, donor type, cell source, cytomegalovirus serostatus, and year of transplantation.

able since 1999) was performed at the discretion of the treating physician. If antivirals were given, they were used until resolution of presenting signs and symptoms and clearance of virus from respiratory secretions. Patients were treated with concomitant antibiotics, antifungals, or antivirals directed at isolated copathogens as indicated.

Statistical analysis. For the determination of risk factors for acquisition of influenza infection, a Cox proportional hazards model was fit with influenza infection as outcome and day 0 as the date of transplantation; patients were censored at day 120 after transplantation, time of the second transplantation, or loss to follow-up (whichever occurred earlier). In addition, all models were adjusted for time at risk during influenza season, defined as 1 November through 30 April; the variable was entered as a dichotomous time-dependent covariate, set to 1 if the day of patient follow-up was within the influenza season limits, and set to 0 otherwise. To investigate factors related to the risk of progression from URI to LRI, we considered only cases that were initially diagnosed as URIs. ORs were calculated using univariable logistic regression models, with *P* values derived using the Wald test. To assess the impact of influenza infection on mortality, URIs and LRIs were regarded as time-dependent covariates in multivariable Cox regression models for 1-year mortality, with adjustment for factors known to be associated with survival. Time 0 for mortality analyses was taken as the date of transplantation. *P* values from regression models were obtained using the Wald test, and no adjustments were made for multiple comparisons.

RESULTS

Epidemiology and clinical manifestations. From September 1989 through March 2002, a total of 4797 patients underwent their first allogeneic, syngeneic, or autologous HSCT at the FHCRC. Table 1 lists the characteristics of the patients in this cohort. Among these patients at risk, 62 (1.3%) had influenza virus infection diagnosed within 120 days after transplantation. Influenza A was isolated from 41 patients (66% of influenza cases); isolates from the remaining 21 patients were typed as influenza B. The seasonality of influenza infections in the HSCT cohort closely paralleled community-wide prevalence, as demonstrated by virologically confirmed cases of influenza with respiratory tract samples sent from the general Seattle community to the University of Washington Virology Laboratory (Seattle) (figure 1).

Fifty-one of these patients initially presented with URI alone, whereas 6 patients presented with LRI alone (i.e., new infiltrates with positive BAL fluid results in the absence of URI symptoms and negative results for NPT samples). Five patients presented with URI and LRI concurrently. Of those who presented with URI alone, 7 (13.7%) had progression to pneumonia a median of 11 days (range, 4–14 days) after onset of upper respiratory tract disease. Thus, influenza pneumonia developed in a total of 18 patients, or 29% of those infected with influenza virus.

Risk factors for acquisition of influenza infection. We first considered patient characteristics to determine whether specific factors were associated with the acquisition of influenza infection. As expected, transplantation during influenza season was highly associated with the risk for influenza infection (figure 1). After adjusting for time at risk during influenza season, multivariable models identified female sex and advanced disease as risk factors associated with an increased hazard of influenza infection (table 2). Age at the time of transplantation, donor type, cell source, cytomegalovirus serostatus, and the occur-

Table 3. Characteristics of patients who underwent hematopoietic stem cell transplantation, by site of influenza virus infection.

Characteristic	URT only (n = 44)	LRT (n = 18)
Male sex	16 (36)	9 (50)
Age, median years (range)	35 (3–66)	39 (3–55)
Donor match		
Autologous or syngeneic	8 (18)	7 (39)
Related-matched	17 (39)	7 (39)
Related-mismatched	6 (14)	1 (6)
Unrelated	13 (30)	3 (17)
CMV seropositivity	20 (45)	10 (56)
Cell source of bone marrow	29 (66)	11 (61)
Acute GVHD grade		
0 or I	10 (23)	6 (33)
II	17 (39)	4 (22)
III or IV	9 (20)	1 (6)
Autologous/syngeneic	8 (18)	7 (39)
Lymphocyte count, lymphocytes/μL		
<100	10 (23)	10 (56)
<300	26 (59)	14 (78)
Steroid therapy, mg/kg per day		
None	16 (36)	13 (72)
<1	19 (43)	2 (11)
1–2	6 (14)	2 (11)
>2	3 (7)	1 (6)
Time to onset influenza, median days (range)	61 (1–101)	36 (1–110)

NOTE. Data are no. (%) of patients, unless otherwise indicated. CMV, cytomegalovirus; GVHD, graft-versus-host disease; LRT, lower respiratory tract; URT, upper respiratory tract.

rence of GVHD were not associated with the risk for influenza virus infection.

Risk factors for the progression of influenza URI to LRI. We next analyzed factors associated with the risk for progression from URI to LRI. Table 3 shows the characteristics of patients who had only URI (n = 44) and for those who ultimately developed pneumonia (n = 18). Influenza virus type (A vs. B) was not associated with risk for progression to pneumonia. The presence of lymphopenia (lymphocyte count, <100 lymphocytes/μL) at the time of the initial diagnosis of influenza was associated with an increased risk for pneumonia (P = .01). Because lymphopenia was primarily present in patients who had not yet achieved lymphocyte engraftment, patients with pneumonia had an earlier onset of infection (median, 36 days after transplantation) than did those who had URI alone (median 61 days, P = .04). Of interest, patients with influenza pneumonia were less likely to be receiving corticosteroids at initial diagnosis of influenza than were those who presented with URI alone (P = .01), and persons undergoing autologous HSCT appeared somewhat more likely to have progression to pneumonia (7 [47%] of 15 patients), compared with the counterparts who received allogeneic HSCT (11 [31%] of 36 patients; P = .08). In multivariable models that assessed the odds of progression to pneumonia among those who presented with URI, lymphopenia at the time of incident influenza was predictive of progression to LRI, whereas the use of corticosteroids appeared to be protective (table 2).

Impact of influenza on mortality. Death within 30 days after influenza infection occurred in 6 (10%) of 62 patients, including 1 (3%) of 36 patients who developed URI and 5 (28%) of 18 patients who developed LRI. Copathogens were detected in 3 of the 5 patients who died within 30 days after onset of influenza LRI (*A. fumigatus*, *Corynebacterium jeikeium,* and respiratory syncytial virus), and all died of respiratory failure. Four additional patients with influenza LRI had concomitant invasive pulmonary aspergillosis diagnosed by examination of BAL fluid; all ultimately died of these infections.

Finally, we analyzed the impact of influenza virus infection during the first 120 days after transplantation on overall 1-year mortality. A total of 1866 deaths occurred ⩽1 year after transplantation; an additional 65 deaths occurred within the first year but were preceded by a second transplantation. The occurrence of influenza (treated as a time-dependent covariate) was not predictive of 1-year mortality. When LRI and URI were entered as separate risk factors, however, influenza LRI was associated with 1-year mortality after adjusting for underlying disease, disease risk, donor type, cell source, cytomegalovirus serostatus, age at transplantation, and year of transplantation (table 2).

Effect of antiviral therapy. Of the 18 patients who developed influenza LRI, 8 were treated with antiviral therapy; the remaining patients were not treated because of late identification of infection (by culture), prominence of copathogens, or infection with influenza B virus (for which no effective therapy was available before the licensure of the neuraminidase inhibitors). The 30-day mortality rate was 30% among the 10 patients who were not treated, 40% among the 5 patients who

Table 4. Interaction between lymphocytopenia, steroid use, and antiviral therapy on progression to pneumonia among 51 patients who presented with influenza upper respiratory tract infection

Antiviral therapy received	Progression to pneumonia, n/N (%)			
	Lymphocyte count of <100 lymphocytes/μL		Steroid use	
	Yes	No	Yes	No
Yes	1/3 (33)	0/14 (0)	1/13 (8)	0/4 (0)
No	4/12 (33)	2/22 (9)	1/17 (6)	5/17 (29)

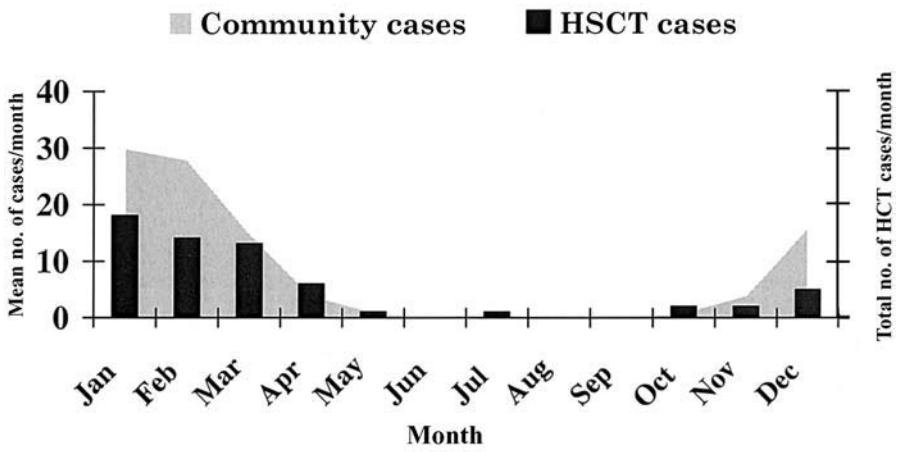

Figure 1. Mean number of influenza cases per month (1989–2002) among persons undergoing hematopoietic stem cell transplantation (HSCT cases) and persons from the local Seattle community who did not undergo transplantation (community cases).

were treated with rimantadine, and 0% among the 3 who were treated with oseltamivir.

Of the 51 patients who initially had URI diagnosed, 34 received no therapy (17 had influenza B virus infection); 6 (18%) ultimately had progression to pneumonia. One (13%) of 8 patients treated with M2 inhibitors had progression to pneumonia, whereas none of the 9 patients treated with neuraminidase inhibitors had progression. Because both lymphocyte count and steroid use were inversely correlated with the risk for progression to pneumonia, we also analyzed whether there were interactions between these variables, antiviral therapy, and risk for progression to LRI (table 4). Although the subgroups were too small to allow definitive conclusions, patients with lymphocytopenia appeared to be equally likely to develop pneumonia regardless of whether they were treated with antivirals (the single breakthrough case in a person receiving treatment, however, occurred with rimantadine therapy). Of interest, patients who received corticosteroids, antivirals, or both were less likely to develop LRI than were the 17 patients who received neither (OR, 0.15; 95% CI, 0.026–0.88; $P = .036$).

Because NPT washes were performed for patients with influenza virus infection at least weekly to document viral clearance, we were also able to assess the impact of antivirals and other factors on the duration of viral shedding. Influenza virus was shed in nasopharyngeal secretions for a median of 7 days (range, 2–37 days). Allogeneic transplant recipients (mean duration of viral shedding, 11.1 days, compared with 6.7 days for recipients of autologous transplants; $P = .05$) and recipients of corticosteroids at dosages of $\geq$1 mg/kg per day (mean, 14.9 days, compared with 8.9 days for recipients of <1 mg/kg per day; $P = .009$) demonstrated prolonged viral shedding (figure 2). Patients who did not receive antiviral therapy shed for longer periods (mean duration, 11.3 days) than did those who were treated with M2 inhibitors (mean duration, 9.7 days) or neuraminidase inhibitors (mean duration, 7.5 days). Therapy with oseltamivir (but not rimantadine) appeared to be associated with shorter duration of shedding after controlling for steroid dose ($P < .08$).

DISCUSSION

Our study provides several new insights regarding the impact of influenza infection on outcomes after stem cell transplantation. Interestingly, the attack rate (1.3%) for influenza was relatively low, compared with other respiratory viruses commonly isolated from our patients (4.5% for RSV [1] and 7.1% for parainfluenza [3]), and the rate at which pneumonia developed (29%) was lower than that described for RSV (~40%) [1]. These observations may be explained by our strong infection-control measures (i.e., screening and isolation of symptomatic patients and free availability of vaccines for staff and family members, both of which likely decrease the incidence of influenza) and the availability of easily administered antiviral

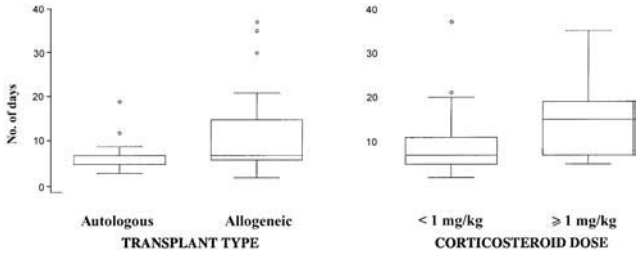

Figure 2. Box plot of influenza shedding (duration in days [median and interquartile range]) from nasopharynx, according to transplant type and dose of corticosteroids.

therapy (which may have both therapeutic and preventative effects, the latter via decreasing viral shedding).

Influenza is widely recognized as a potent cause of morbidity and mortality among very old and very young persons, causing up to 70,000 deaths annually in the United States alone [9]. Influenza-related deaths are thought to be most common in patients with comorbidities, such as recent stem cell transplantation [10]. Although the reported frequency and severity of illness associated with influenza virus infections have varied considerably across transplantation centers [11–15], it is clear from this study that influenza-related mortality is closely linked to the development of pneumonia, with or without the presence of frequently isolated copathogens. Thus, preventing pneumonia among infected persons is paramount, given that our analysis did not identify biologically plausible risk factors for acquisition of infection.

Several factors appear to increase the risk for pneumonia after HSCT. The presence of lymphopenia at the time of infection emerged as the most potent factor in multivariable analysis, as it has in other case series published to date [14]. Of interest, the use of corticosteroids appeared to prevent progression from upper to lower respiratory tract disease, which is a surprising result, given the known correlation between glucocorticoid use and relative lymphopenia [16]. This finding was not explained by greater application of antivirals for patients receiving steroid therapy. It is tempting to hypothesize that steroids produce salutary immunomodulation in such circumstances, but the longer duration of viral shedding in their presence is reason for concern. Steroids are also generally given to patients for GVHD only after lymphoid engraftment (i.e., later in the course of transplantation)—a confounding effect that may explain this relationship.

Although the number of treated patients in our study was small, our data suggest that oseltamivir may be more effective than rimantadine for the treatment of both influenza pneumonia (mortality rate, 0% vs. 40%) and influenza URI (rate of progression to pneumonia, 0% vs. 13%). This clinically observed activity was correlated virologically with a trend towards decreased viral shedding, although the duration of shedding in these immunocompromised hosts was still prolonged, compared with experimental influenza infections in healthy hosts (median shedding times of 107 h in untreated subjects and 56 h in subjects treated with oseltamivir have been documented [17]). Similar efficacy has been demonstrated recently for both oseltamivir (which shortened the duration of influenza virus shedding to <7 days in 21 of 23 persons who underwent HSCT [18]) and for the inhaled neuraminidase inhibitor zanamavir (which led to resolution of both influenza URI and pneumonia in 7 persons who underwent HSCT [19]) in this patient population. Although our retrospective study did not specifically assess resistance, improvements in antiviral activity also may translate into lower rates of antiviral resistance than has been previously demonstrated among immunosuppressed patients treated with the M2 inhibitors [20]. Combination therapy may be required in the most immunosuppressed patients, however, to avoid the emergence of resistance to this class of agents as well [21, 22].

Our findings also highlight the importance of several hospital practices for preventing the spread of this virus. The low attack rate in our patient population may be partially attributable to the fact that influenza (as opposed to infections due to other community-acquired respiratory viruses) is vaccine preventable; our results may be a testament to the effectiveness of an aggressive program for vaccinating both family caregivers and health care workers (given that the patients themselves were not vaccinated during the study period). The aggressive use of antiviral therapy for patients with both upper and lower respiratory tract disease may also decrease the risk for further transmission. Our data suggest that neuraminidase inhibitors, such as oseltamivir, may be preferred for this indication, given their effects on viral shedding; the optimal duration of therapy, however, has not been identified.

Although influenza thus remains a cause of infectious mortality after HSCT, its overall impact may be minimized using targeted surveillance, vaccination of contacts, and preemptive antiviral therapy. Thus, despite the availability of effective prophylactic antivirals [23] and recommendations from the Centers for Disease Control and Prevention to the contrary [24], the widespread use of antiviral prophylaxis in this population is probably unwarranted if there is no outbreak.

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