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Community respiratory viruses are generally well-tolerated in hematopoietic stem cell transplant recipients: a brief report from the TRANSPIRE study

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Letter to the Editor:

Hematopoietic stem cell transplant (HSCT) is a treatment for malignant and non-malignant conditions. There are multiple studies detailing pulmonary complications in adult HSCT patients but fewer describing complications in pediatric patients[1-5].

The introduction of rapid respiratory viral panel testing via polymerase chain reaction (PCR) has led to a significant increase in the identification of common respiratory viral pathogens. This testing is commonly performed on post-HSCT patients who present with fever or respiratory symptoms. However, it has not yet been reported how pediatric HSCT patients are tolerating these seasonal respiratory viral infections and whether viral identification should change clinical management. Two different adult studies in HSCT patients have shown a high morbidity and mortality in HSCT patients with viral pneumonias with 15-30% causing respiratory failure requiring mechanical ventilation or death[6,7]. Few pediatric studies reporting on incidence of infectious pulmonary complications post-HSCT demonstrated that infectious pulmonary complications after HSCT in pediatric patients are common in both allogenic and autologous HSCT recipients and occur in approximately 20-30% of patient, but did not discuss patient outcomes after infection[1,8]. Respiratory viral testing and identification are now more readily available through molecular testing using polymerase chain reaction (PCR) and multiplex assays. This leads to more frequent evaluation for respiratory viral pathogens which can lead to increased patient and provider anxiety and potentially unnecessary hospital admissions. The primary endpoint was to characterize the morbidity and mortality related to community acquired respiratory infections in a cohort of pediatric and young adult HSCT recipients. Morbidity was defined as need for admission to the pediatric intensive care unit (PICU) and mechanical ventilatory support. Mortality was defined as death secondary to a respiratory viral infection.

The TRANSPIRE study is a multi-institutional prospective cohort study of pediatric and young adult HSCT recipients from eight different institutions. Data for this study was taken from patients seen at Cincinnati Children's Hospital Medical Center that were enrolled in the TRANSPIRE study between September 2021 and September 2024. All patients received standard pulmonary evaluations, biological sample collection, and clinical data collection at set timepoints throughout their transplant course and in response to any significant

clinical events. Evaluations were done pre-transplant and post-transplant at day 60, day 100, 6 months, and annually starting at 12 months post-transplant. All reported infections for this study were identified on nasopharyngeal swabs or broncho-alveolar lavage (BAL) samples that were obtained for clinical purposes. Patients with newly diagnosed viral infections were included only if they had simultaneous symptoms (ie fever, cough, congestion, rhinorrhea) and/or required continuous oxygen supplementation. All patients who required higher levels of respiratory support (ie mechanical ventilation) had bronchoscopy with BAL as part of their diagnostic evaluation. To assess morbidity secondary to respiratory viral infections we analyzed the level of oxygen supplementation required by the patient, including mechanical ventilation and admissions to the PICU for respiratory distress/failure. Patients with respiratory viral infections were managed according to our institutional protocol. Oseltamivir was administered to patients who tested positive for influenza, while remdesivir was used for those who tested positive for SARS-CoV-2. Immunosuppressive therapy was not routinely reduced unless viremia was present. In cases where fever was accompanied by a positive respiratory viral swab identifying a source of infection, antibacterial therapy was de-escalated. This study was conducted in accordance with the principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Board.

Patient demographics and transplant characteristics are included in Table 1. We had 146 patients included in the entire cohort. The group was subdivided into patients diagnosed with respiratory viral infections (n=78) and no infections (n=68). The most common indication for HSCT was malignancy (32.3%). The most common stem cell source was bone marrow (60.9%) and received myeloablative conditioning (50.6%). The majority of patients had fully matched donors (63%) from unrelated donors (65.1%). Patients with a pulmonary infectious event were younger at the time of HSCT compared to patients without infectious events (6.8 years vs 11.4 years, respectively).

The majority of patients (83.6%) received calcineurin-based graft-vs-host-disease (GVHD) prophylaxis with 16.4% undergoing *ex vivo* T-cell depletion. There was no difference in infectious events between the two prophylaxis regimens. Interestingly, patients with respiratory viral infections had higher rates of acute GVHD compared to patients without infectious events (p= 0.002).

Multivariate analysis was performing examining pre-transplant variables and association with the development of community acquired viral infections (Table 2). Multivariate analysis showed that only younger age was associated with increased risk of respiratory viral infections (OR 0.91 95% CI 0.85-0.97, p=0.005). Sex, race, primary diagnosis, conditioning regimen intensity, stem cell source degree of match, donor status and GVHD prophylaxis had no impact on risk of developing viral infections in our cohort.

We observed 130 respiratory viral infections in our entire cohort. While not the focus of our manuscript, we also identified five fungal infections and two bacterial infections (Figure 1A). Thirty-three (22.6%) patients were diagnosed with more than one viral infection. Rhinovirus was the most common infection, accounting for 38.5% (n=50) of viral infections. Adenovirus (n=16, 12.3%) and SARS-CoV-2 (n=15, 11.5%) were also frequently identified. Interestingly, only 7 (43.8%) of patients with positive respiratory viral swabs for adenovirus had concurrent viremia. There was a wide range of other common respiratory viruses that each made up less than 10% of viral infections: coronavirus (n=11, 8.5%), RSV (n=10, 7.7%), parainfluenza (n=8, 6.2%), metapneumovirus (n=5, 3.8%), and influenza (n=3, 2.3%). While not considered to be respiratory community viruses, other viruses that were identified on BAL samples included CMV (n=6, 4.6%). HHV6 (n=3, 2.3%), EBV (n=2, 1.5%), and HSV (n=1, <1%). Identification of HHV6 and EBV were likely due to low-level viremia leading to BAL identification and not true pulmonary infections. Given GVHD was seen more frequently and was more severe in patients with infectious events than in those without indicating that development of GVHD may be a risk factor for infectious pulmonary events we evaluated the temporality between timing of GVHD and infection. The vast majority of patients with infectious events (n=59, 75.6%) had respiratory infections prior to the development of GVHD. We also evaluated the frequency of viral infections temporally diagnosed specifically in patients with GVHD. There was a total of 56 infections in patients with GVHD. Rhinovirus remained the most common infection (n=21, 80.8%) followed by adenovirus (n=9, 16%).

The majority of viral infections occurred early in the transplant course, with most occurring prior to day 100 post-HSCT (Figure 1B). There was a wide range in median time from HSCT to onset of viral infection for specific viruses, ranging from 40 days (influenza and EBV) to 366 days (HSV).

The most encouraging conclusion from this study is that there was no increase in morbidity or mortality in pediatric patients after infection with common seasonal respiratory viruses compared to patients with no viral infections. We observed n=13 (16.7%) of patients who required admissions to the PICU for a primary indication of respiratory distress or failure in the setting of newly diagnosed respiratory viral infection. Median duration of PICU admission was 17.5 days (range 3-78 days). Only 4.1% (n=6) of patients required mechanical ventilation in the PICU after diagnosis of viral respiratory infection. The remaining patients required nasal cannula (n=3) and oxymask (n=4). The four patients requiring mechanical ventilation were infected with CMV, one with adenovirus and one with aspergillus. All of these infections were identified by bronchoscopy with BAL. Importantly, only one patient required escalation of care including mechanical ventilation due to a common community respiratory viral infection (adenovirus). In contrast to published adult data, our data show that pediatric patients are tolerating common seasonal respiratory viral infections exceptionally well after HSCT. These patients do however continue to be at significant risk for poor outcomes from reactivated viruses that cause viremias such as CMV, EBV, and adenovirus. Furthermore, the predominance of viral infections observed in this study likely reflects differences in sampling methods, with nasal swabs—more easily obtained—being the primary diagnostic tool for viral infections. This is in contrast to the use of BAL sampling, which are used predominantly to evaluate for other bacterial and fungal infections and were more likely collected from sicker patients. This distinction should be acknowledged as it may have influenced the infection profile reported.

We observed more infectious events more frequently in patients with GVHD and observed that the majority of these infections occurred prior to the diagnosis of GVHD. The observation that respiratory infections often precede GVHD raises important questions regarding their role in modulating the immune environment. It is plausible that respiratory infections may induce a heightened inflammatory state or dysregulate immune homeostasis, priming patients for more severe GVHD. Management of severe respiratory infections in HSCT recipients frequently necessitates the use of modulation or reduction of immunosuppressive therapies. While these treatments are essential to control infection and prevent further organ injury, they can significantly alter immune regulation. This alteration may predispose patients to GVHD or exacerbate pre-existing GVHD by

disrupting the balance of T-cell activation and suppressing regulatory T-cell function. Additionally, prolonged immune suppression can lead to delayed recovery of the host immune system, potentially enhancing the alloimmune response that drives GVHD in the setting of these respiratory infections. Alternatively, these infections may reflect an underlying immune vulnerability in certain patients that predisposes them to both infections and GVHD. From a clinical perspective, these findings underscore the importance of proactive infection prevention and management strategies in the post-transplant period, particularly in patients at high risk for GVHD.

There were 16 deaths in the study population from 2021 to 2024, however only four of these deaths (40%) were related to respiratory viral infections. Two (12.4%) patients died from pulmonary CMV infection and two (12.4%) patients died of disseminated adenovirus with respiratory involvement. Other causes of death in this patient population were disease relapse (n=6), diffuse alveolar hemorrhage (DAH, n=3), and idiopathic pneumonia syndrome (IPS, n=1). The three patients who died from DAH had preceding RSV (n=1) and CMV (n=2) identified on prior bronchoscopies. The patient who died from IPS had no preceding respiratory infections identified.

Taken together, our data show that viral infections are frequent after HSCT, but serious morbidity is largely limited to well-known pathogens like CMV and adenovirus. This is important to consider when counseling patients and families on the risks of viral infections post-HSCT and planning in-patient or out-patient care for patients. This data should be taken into consideration when weighing the cost-benefit analysis of ordering expensive PCR-based respiratory viral panel testing.

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Table 1. Cohort demographics and transplant characteristics

	Total Cohort n=146	**Infectious Event** n=78	**No Infectious Event** n=68	***p-value***
Sex, **n (%)**				
Male	78 (53.3)	46 (59)	32 (47.1)	0.47
Female	68 (46.6)	32 (41)	36 (52.9)	
Race, **n (%)**				
White	101 (69.2)	56 (71.8)	46 (67.6)	0.18
African American	9 (6.1)	7 (9)	3 (4.4)	
Asian	4 (2.7)	1 (1.3)	3 (4.4)	
Mixed	3 (2)	2 (2.6)	1 (1.5)	
Unknown/Not reported	25 (17)	12 (15.3)	15 (22.1)	
Primary diagnosis, **n (%)**				
Malignancy	47 (32.2)	25 (32)	22 (32.4)	0.89
Marrow failure	34 (23.3)	18 (23.1)	16 (23.5)	
Benign Hematology	21 (14.4)	14 (18)	7 (10.3)	
Immune Deficiency	37 (25.3)	16 (20.5)	21 (30.9)	
Genetic/Metabolic	7 (4.8)	5 (6.4)	2 (2.9)	
Age in years at HSCT, median (range)	9.1 (8.6-24.1)	6.8 (0.3-23)	11.4 (0.2-24.1)	**0.02**
Stem cell source, n (%)				
Bone marrow	89 (60.9)	47 (60.3)	42 (61.8)	0.77
Peripheral blood stem cell	39 (26.7)	20 (25.6)	19 (27.9)	
Cord	18 (12.4)	11 (14.1)	7 (10.3)	
Conditioning regimen, **n (%)**				
Myeloablative	74 (50.6)	47 (60.3)	27 (39.7)	0.09
Reduced-intensity	72 (49.4)	31 (39.7)	41 (60.3)	
TBI*	17 (11.6)	9 (11.5)	7 (10.3)	
Degree of match, **n (%)**				
Fully matched	92 (63)	47 (60.3)	45 (66.2)	0.11
Mismatched	54 (37)	31 (39.7)	23 (33.8)	
Donor source, n (%)				
Related	51 (34.9)	30 (38.5)	21 (30.9)	0.72
Unrelated	95 (65.1)	48 (61.5)	47 (69.1)	
GVHD[#] prophylaxis, **n (%)**				
Calcineurin-based	122 (83.6)	67 (85.9)	55 (80.9)	0.6
Ex vivo T-cell depletion	24 (16.4)	11 (14.1)	13 (19.1)	
Serotherapy, n (%)				
Alemtuzumab	16 (11)	8 (10.3)	8 (11.8)	0.1
Anti-thymocyte globulin	49 (89)	21 (89.7)	28 (88.2)	
GVHD Day 100 Grade, **n (%)**	*n=121*	*n=69*	*n=52*	
None	94 (77.7)	46 (66.7)	48 (92.3)	**0.002**
Grade I	12 (9.9)	12 (17.4)	0	
Grade II	10 (8.3)	8 (11.6)	2 (3.8)	
Grade III	5 (4.1)	3 (4.4)	2 (3.8)	

*TBI: Total body irradiation; [#]GVHD: graft-vs-host-disease

Table 2. Multivariate analysis of factors contributing to respiratory viral infections

Variable	OR (95% CI)	*p*-value
Sex		
Male	1.82 (0.91-3.71)	0.09
Race		
Caucasian	0.91 (0.3-2.72)	0.86
Other	1	
Primary diagnosis		
Malignancy	0.88 (0.28-2.78)	0.83
Other	1	
Age at HSCT*	0.91 (0.85-0.97)	0.005
Conditioning regimen		
Reduced intensity	0.57 (0.22-1.41)	0.23
Myeloablative	1	
Stem cell source		
Cord	0.47 (0.12-1.75)	0.26
PBSC[#]	1.88 (0.58-6.46)	0.97
BM[$]	1	
GVHD prophylaxis		
T cell depletion	0.48 (0.12-1.85)	0.29
Donor status		
Unrelated	0.99 (0.44-2.19)	0.97
Related	1	
Degree of match		
Mismatched	1.52 (0.69-3.42)	0.30
Fully matched		

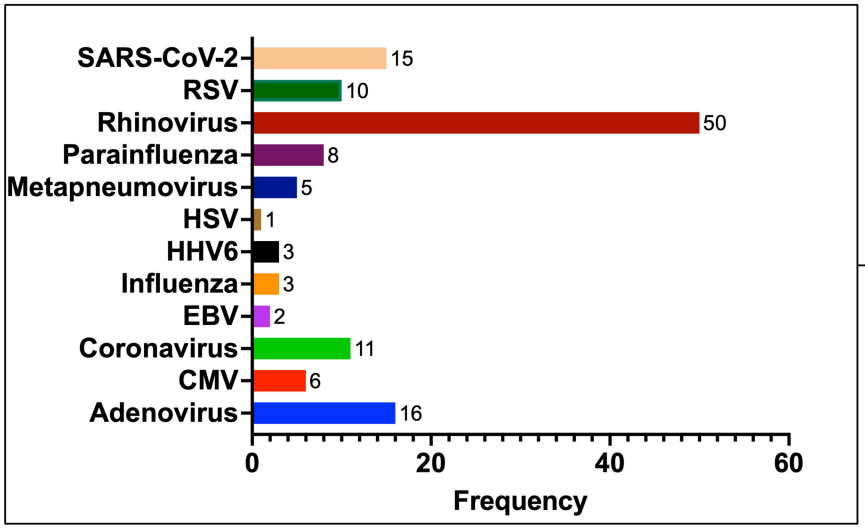
*HSCT: hematopoietic stem cell transplant; [#]PBSC: peripheral blood stem cell; [$]BM: bone marrow

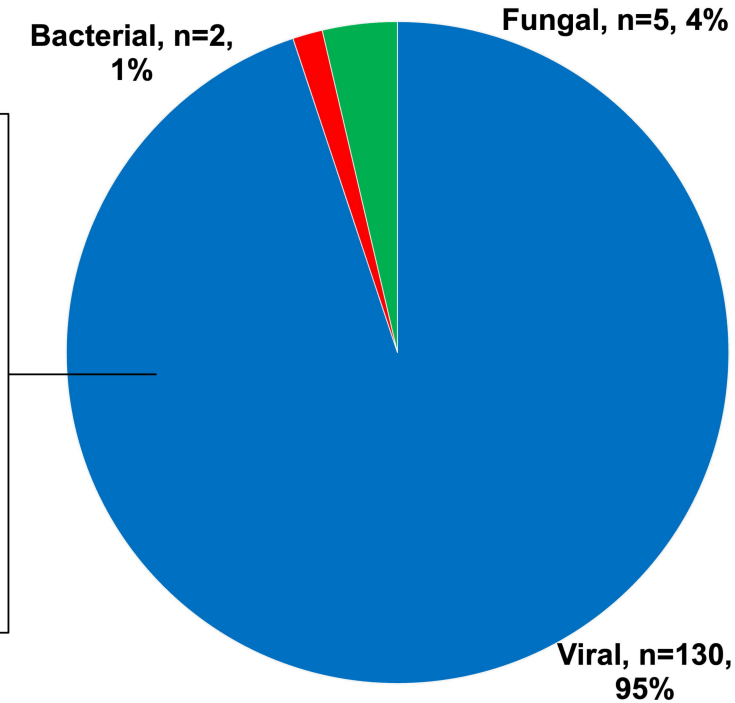
Figure Legends

Figure 1. Frequency and timing of infections after hematopoietic stem cell transplant. (A) The pie chart shows the distribution of viral (blue), fungal (green) and bacterial (red) infections that were identified after HSCT. Viral infections were the most frequent infections identified (n=130, 95%) followed by fungal (n=5, 4%) and bacterial (n=2, 1%). The specific organisms identified for each subtype of infection are summarized in the boxes. Rhinovirus (n=50, 38.5%) was the most common viral infection identified after HSCT. (B) A violin plot summarizing the timing of viral infection diagnosis after HSCT. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.
CMV: Cytomegalovirus; EBV: Epstein Barr Virus, HHV6: Human herpes virus 6; HSV: Herpes simplex virus; RSV: respiratory syncytial virus; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Figure 1. Frequency and timing of respiratory viral infections

A.





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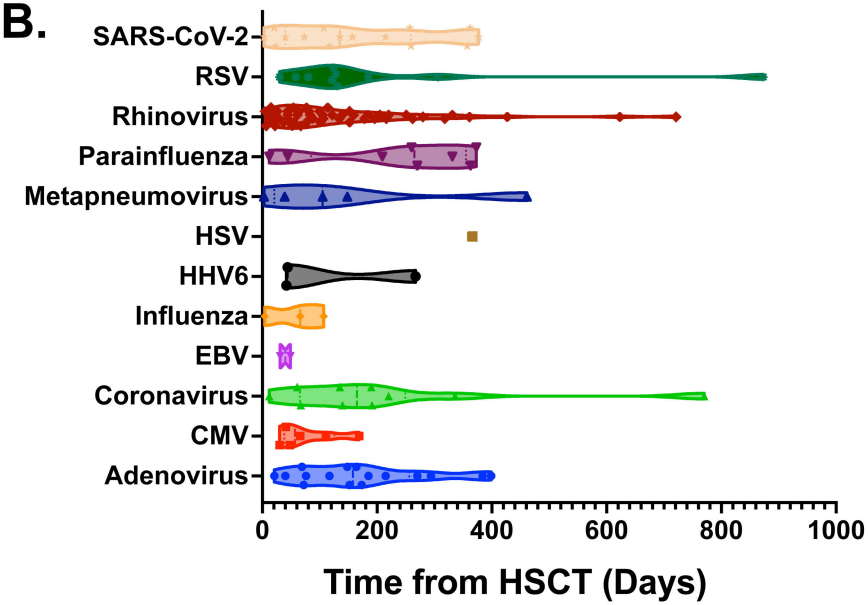

Organism	Time from HSCT (days)
Viral infections, median days from HSCT (IQR)	
Adenovirus	158 (73-256.3)
CMV	57 (38.3-125.5)
Coronavirus	165 (65.5-249)
EBV	40 (31-49)
Influenza	40 (4-107)
HHV6	44 (42-267)
HSV	366
Metapneumovirus	105 (21-304.5)
Parainfluenza	265 (85.3-355)
Rhinovirus	100.5 (46-193)
RSV	126 (74.5-215.3)
SARS-CoV-19	135 (40-259)