OUTCOME OF CHILDREN WITH RHINOVIRUS DETECTION PRIOR TO ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT

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Abstract
Rhinoviruses are commonly detected in symptomatic and asymptomatic children prior to HCT. Unlike pre-HCT detection of other respiratory viruses, it is not known whether RV detection, with or without clinical symptoms, is associated with worse outcomes in children post-HCT. In a retrospective study of children undergoing allogeneic HCT from January 2009 to February 2015, 91 children underwent allogeneic HCT, and 62 children had RPP testing within 30 days pre-HCT. Fifty-six (90%) children had either no pathogen (n = 34, 55%) or single RV detection (n = 22, 35%), which was the most common pathogen identified. Compared with virus negative children, children with pre-HCT RV detection were not more likely to require ventilated support and did not have longer length of stay, higher mortality, or less days alive and out of the hospital within the first 100 days post-HCT. In a secondary analysis of all 56 patients with RPP testing and no pathogen or RV alone detected, the seven children with LRTI had less days alive and out of the hospital within the first 100 days post-HCT compared with the 49 children who were either asymptomatic or had URTI (10 vs 60 days, P = 0.002). In a bootstrapped regression model, presence of LRTI, not RV detection, was significantly associated with decreased days alive and out of the hospital within the first 100 days post-HCT. Thus, pre-HCT detection of RV, without associated LRTI, does not always warrant HCT delay.

Keywords
allogeneic, hematopoietic cell transplant, lower respiratory tract infection, rhinovirus

1 | INTRODUCTION

Respiratory viruses are common pediatric pathogens, and pediatric allogeneic HCT recipients are at risk for severe viral RTI. Therefore, pre-HCT testing for respiratory viruses, regardless of symptomatology, is commonly performed prior to HCT conditioning. Increased utilization of molecular diagnostics, particularly multiplex PCR, has led to the rapid, sensitive detection of respiratory viruses, including RVs.

Rhinoviruses are a leading cause of RTI in the pediatric population as well as in patients undergoing HCT. The use of multiplex PCR, over traditional viral culture, and the identification of RV-C, the newest RV type, have led to frequent detection in ARI-related hospitalizations. Detection can occur in both asymptomatic and symptomatic children, and both viral load and RV type may influence disease severity. RV LRTI can be severe in HCT recipients. Although management recommendations exist for HCT patients infected with viruses with a high likelihood of complications (e.g., influenza and respiratory syncytial virus), management recommendations for HCT patients with RV RTI...
are lacking, despite the frequency of RV detection. Existing data, predominantly based on adult studies, are conflicting as to whether RV detection in the pre-HCT period results in worse outcomes. Pathogen detection often leads to HCT delay due to risk of URTI progressing to LRTI, respiratory failure, and death. The optimal length of HCT delay is unknown, and continued detection of RV by PCR may represent prolonged viral shedding. Thus, pre-HCT RV detection may lead to unnecessary delay of HCT, which can result in worse outcomes or oncologic relapse.

A RPP, a multiplex PCR assay, became available at Children's Mercy Kansas City in December 2008, and the test was offered as part of the pre-HCT evaluation. We aim to determine the prevalence of RV identified pre-allogeneic HCT in children and compare outcomes of children with RV detection to children without viral detection and determine the association of clinical symptoms, or lack thereof, with patient outcomes.

2 | PATIENTS AND METHODS

2.1 | Patient population

We conducted a retrospective study of subjects undergoing allogeneic HCT from January 1, 2009 to February 15, 2015 at Children's Mercy Kansas City who had RPP testing within 30 days prior to HCT.

2.2 | Specimens and virologic testing

Mid-turbinate or nasal aspirate specimens were obtained at the discretion of the HCT physician, for either diagnostic evaluation in symptomatic patients or for pre-HCT surveillance in asymptomatic patients, and tested for clinical purposes. Specimens obtained from January 1, 2009 to August 19, 2012, were tested via Luminex xTAG Respiratory Viral Panel (Austin, TX), which includes targets for respiratory syncytial virus, influenza A, influenza B, parainfluenza 1, 2, and 3, human metapneumovirus, adenovirus, and rhinovirus/enterovirus. Subsequent specimens were tested via BioFire Respiratory Panel (Salt Lake City, Utah), which includes results for the above viruses in addition to coronavirus HKU1, NL63, 229E, and OC43, parainfluenza virus 4, Bordetella pertussis, Chlamydia pneumoniae, and Mycoplasma pneumoniae. Viral culture was also offered by the laboratory during this time; however, these specimens were excluded from the study due to poor sensitivity for rhinovirus. Pre-HCT, repeat testing prior to HCT was obtained at the discretion of the treating physician to determine whether viral detection was ongoing. Post-HCT, repeat testing was obtained at the discretion of the treating physician due to the presence of clinical symptoms. No formal policy, other than hospital-wide isolation precautions, exists regarding the management of patients with a positive test result.

2.3 | Clinical data

Demographics, clinical symptoms, virologic testing, laboratory values, imaging, and outcomes were manually abstracted from the electronic medical record and entered into a REDCap database. Subjects were defined as asymptomatic (ie, no provider documentation of signs or symptoms of respiratory illness in the history or physical examination) or symptomatic (ie, provider documentation of historical symptoms or physical examination signs consistent with respiratory illness). Symptomatic subjects included those with URTI (ie, provider documentation or parental report of respiratory symptoms with no or negative pulmonary imaging, including chest radiograph or chest computed tomography) or LRTI (ie, provider documentation or parental report of respiratory symptoms with abnormal pulmonary imaging). All patients had a scheduled HCT date at the time the specimen was obtained, and HCT delay was determined by whether this date was changed and whether this was due to specimen results.

2.4 | Outcomes

Outcome measures included need for ventilatory support (high flow oxygen >5 L/min), continuous positive airway pressure, bilevel positive airway pressure, or intubation and mechanical ventilation) and length of stay during the initial hospitalization. Outcomes within the first 100 days post-HCT included: number of days alive and out of the hospital, readmission, acute GVHD, relapse, and mortality. Presence of post-HCT infections, including non-respiratory viral reactivation (ie, cytomegalovirus, Epstein-Barr virus, adenovirus, and human herpes virus 6) was assessed.

2.5 | Statistical analysis

Categorical variables were described by number and percentage and analyzed by χ2 or Fisher’s exact test where appropriate. Continuous variables were reported with median and IQR and analyzed by Mann-Whitney U test. A P-value <0.05 was considered significant. Multivariable linear regression was used to determine the adjusted relationship between days alive and out of the hospital with LRTI and RPP result (ie virus negative vs RV-positive). Standard errors and associated percentile-based confidence intervals were calculated using bootstrapped estimations (5000 replications). Statistics were performed in SPSS (version 23; IBM Corp, Armonk, NY) and R (version 3.3.2). Children’s Mercy Kansas City’s Institutional Review Board approved this study.

3 | RESULTS

3.1 | Demographics and baseline HCT data

From January 1, 2009 to February 15, 2015, 91 children underwent allogeneic HCT. Twenty-nine children were excluded, including 19 children with a viral culture only, seven children without any viral testing, and three children with RPP testing performed >30 days pre-HCT. Thus, 62 children were eligible for inclusion in the study. Of the final cohort, 34 (55%) children had no virus detected. The remaining 28 (45%) children had at least one virus
detected. RV was the sole pathogen in 22 (35%) children, accounting for 79% of all virus positive specimens. The remaining virus positive specimens included coronavirus (1), influenza (1), parainfluenza virus (1), respiratory syncytial virus (1), and two RV co-infections (one each with adenovirus and parainfluenza virus). Only patients with sole RV detection and virus negative specimens (n = 56) were included in the analysis since the aim was to evaluate outcomes of children with RV. RV-positive and virus negative children were not significantly different in terms of age, gender, or insurance status, but RV-positive children were significantly less likely to be white (Table 1). The majority of children with an immunodeficiency had RV detection, but the difference in underlying disease was not significant overall. Other HCT-related variables, specimen type, and testing platform were not different between the groups. Specimens were obtained a median of 22.0 days (virus negative) and 19.5 days (RV-positive) prior to HCT. Antimicrobial and GVHD prophylactic regimens were not significantly different between the two groups and were not altered based on detection of RV.

### 3.2 Clinical symptoms and imaging

Of the 56 specimens included in the final analysis, 41 (73%) specimens were obtained from asymptomatic children (Table 2). The majority of both virus negative (n = 28, 82.4%) and RV-positive (n = 13, 59.1%) patients were asymptomatic. Of the 15 symptomatic patients, 12 (80.0%) had pulmonary imaging, which was used for differentiation between upper and LRTI. One (3%) virus negative and seven (32%) RV-positive patients had URTI, and five (15%) virus negative and two (9%) RV-positive patients had LRTI. No significant difference in type of symptoms was noted between virus negative and RV-positive patients (Figure 1A).

### 3.3 Outcomes of RV positive patients compared with virus negative patients

Only one patient, a child with RV LRTI, underwent HCT delay, for 7 days. The virus negative and RV-positive groups had similar rates of ventilated support and length of stay during the initial hospitalization. Within the first 100 days post-HCT, no difference was noted in days alive and out of the hospital, readmission rates, GVHD, relapse rates, or mortality (Table 3). Two RV-positive patients died within the first 100 days post-HCT. Both had negative repeat viral testing pre-HCT, and neither death was attributable to RV. Infection rates of other pathogens were not significantly different between the groups.

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**TABLE 1** Baseline data of children with negative or single RV positive detection pre-HCT

|                      | Virus negative (N = 34) | RV positive (N = 22) | P value |
|----------------------|-------------------------|----------------------|---------|
| Age, y, median (IQR) | 7.8 (4.0-13.9)          | 7.3 (3.0-10.6)       | 0.37    |
| Gender, male         | 18 (52.9%)              | 17 (77.3%)           | 0.09    |
| Race, white          | 28 (82.4%)              | 10 (45.5%)           | 0.004   |
| Insurance, public    | 16 (47.1%)              | 12 (54.5%)           | 0.79    |
| Reason for HCT       |                         |                      | 0.45    |
| Oncologic            | 26 (76.5%)              | 15 (68.2%)           |         |
| Hematologic          | 4 (11.8%)               | 1 (4.5%)             |         |
| Immune deficiency     | 3 (8.8%)                | 5 (22.7%)            |         |
| Metabolic            | 1 (2.9%)                | 1 (4.5%)             |         |
| Cell source          |                         |                      | 0.54    |
| Bone marrow          | 11 (32.4%)              | 8 (36.4%)            |         |
| Peripheral blood     | 11 (32.4%)              | 4 (18.2%)            |         |
| Cord                 | 12 (35.3%)              | 10 (45.5%)           |         |
| Degree of match      |                         |                      | 0.28    |
| Match related        | 7 (17.6%)               | 6 (27.3%)            |         |
| Mismatch related     | 3 (8.8%)                | 0 (0.0%)             |         |
| Unrelated            | 25 (73.5%)              | 16 (72.7%)           |         |
| Non-myeloablative conditioning | 12 (35.3%) | 4 (18.2%) | 0.17    |
| CMV status, recipient positive | 14 (41.2%) | 12 (54.5%) | 0.33    |
| Specimen type, nasal aspirate | 27 (79.4%) | 14 (63.6%) | 0.19    |
| Test type, BioFire   | 16 (47.1%)              | 11 (50.0%)           | 0.83    |
| Absolute lymphocyte count (×10³/μL), median (IQR) | 1.0 (0.7-1.9) | 1.1 (0.4-2.2) | 0.80    |
| Days between specimen and transplant, median (IQR) | 22.0 (16.0-24.0) | 19.5 (14.8-23) | 0.93    |
| GVHD prophylaxis     |                         |                      | 0.48    |
| None                 | 2 (5.9%)                | 0 (0.0%)             |         |
| Tacrolimus and methotrexate | 15 (44.1%) | 8 (36.4%) |         |
| Tacrolimus and mycophenolate | (29.4%) | 10 (45.5%) |         |
| Other                | 7 (20.6%)               | 4 (18.2%)            |         |

**TABLE 2** Clinical symptoms data of children with negative or single RV positive detection pre-HCT

| Symptoms                  | Virus negative (N = 34) | RV positive (N = 22) | P value |
|---------------------------|-------------------------|----------------------|---------|
| Asymptomatic              | 28 (82.4%)              | 13 (59.1%)           | 0.01    |
| URTI only                 | 1 (2.9%)                | 7 (31.8%)            |         |
| LRTI                      | 5 (14.7%)               | 2 (9.1%)             |         |
**FIGURE 1** A. Comparison of symptoms by viral test result. B. Days alive and out of the hospital within the first 100 days post-HCT by presence of LRTI and viral detection

**TABLE 3** Outcomes at 100 days of children with negative or single RV positive detection pre-HCT
Outcomes of patients by clinical symptomatology

Overall, the 15 symptomatic children had less days alive and out of the hospital compared with the 41 asymptomatic children (33.0 vs 63.0 days, \( P = 0.01 \)) without significant differences in other outcomes. However, the symptomatic RV-positive and asymptomatic virus negative patients were not significantly different in terms of need for ventilation, readmission, presence of GVHD, or mortality at 100 days post-HCT. Symptomatic RV-positive children had a median length of stay of 50.0 days (IQR 28.0‐67.5), which was not significantly different than virus negative patients (27.5 days [IQR 19.8‐62.5]), \( P = 0.39 \). Similarly, no significant difference in days alive and out of the hospital was noted between RV-positive (34.0 [IQR 31.0‐65.5] days) and virus negative (13.0 [IQR 9.8‐51.5] days) symptomatic patients, \( P = 0.22 \). Asymptomatic RV-positive and asymptomatic virus negative children also did not have different outcomes (Table 4).

Since HCT patients with LRTI are known to have worse outcomes, we subdivided the symptomatic group into URTI and LRTI and evaluated outcomes by the three classes of symptoms (no symptoms, URTI, and LRTI) in both RV-positive and virus negative patients (Table 4). Since children with no symptoms and URTI had similar days alive and out of the hospital, we evaluated these groups together with LRTI patients representing a unique group. The seven children with LRTI had significantly less days alive and out of the hospital (10.0 vs 60.0 days, \( P = 0.002 \)) than the 49 children without LRTI. Children with LRTI had a similar number of days alive and out of the hospital within the first 100 days post-HCT regardless of whether they were virus negative or RV-positive (10.0 vs 15.5 days, \( P = 0.86 \)). Similarly, non-LRTI patients had a similar number of days alive and out of the hospital unrelated to viral status (virus negative: 58.0 vs RV positive: 60.5 days, \( P = 0.93 \)).

Follow-up testing in RV positive patients

Of the 22 RV-positive patients, 7 (32%) had repeat RPP pre-HCT, and 3 (43%) remained RV-positive. During the first 100 days post-HCT, 19 (86%) had subsequent RPP testing, and eight (42%) were RV-positive. In these eight patients, first RV detection post-HCT occurred a median of 23.0 (IQR 13.5‐60.3) days post-HCT. Four patients had >1 RV positive specimens during the first 100 days post-HCT. To evaluate potential duration of shedding, we evaluated the date of the last RV positive specimen. RV detection occurred a median of 48.0 (IQR 25.3‐67.5) days post-HCT.

Discussion

Respiratory viruses cause significant morbidity and mortality in HCT patients, and the advent of routine molecular testing has led to rapid, sensitive detection of respiratory viruses. Despite the fact that RV is one of the most common respiratory viruses, little data exist for the management of RV detection pre-HCT, unlike

### Table 4: Outcomes of children undergoing allogeneic HCT by clinical illness at the time of RPP test

|                      | Asymptomatic | URTI | LRTI |
|----------------------|--------------|------|------|
|                      | Virus negative N = 28 | RV positive N = 13 | Virus negative N = 1 | RV positive N = 7 | Virus negative N = 5 | RV positive N = 2 |
| Ventilated support   | 7 (25.0%)  | 4 (30.8%) | 0 (0.0%) | 1 (14.3%) | 1 (20.0%) | 2 (100.0%) |
| Length of stay, median (IQR) | 31.0 (24.3-42.3) | 29.0 (23.5-40.0) | 21.0 | 50.0 (25.0-66.0) | 28.0 (21.5-72.0) | 103.0b |
| Days alive and out of the hospital during the first 100 d, median (IQR) | 61.5 (48.3-72.5) | 63.0 (46.5-73.0) | 45.0 | 46.0 (33.0-71.0) | 10.0 (9.5-43.5) | 15.5c |
| Readmission          | 16 (57.1%) | 4 (30.8%) | 1 (100.0%) | 4 (57.1%) | 3 (60.0%) | 0 (0.0%) |
| Acute GVHD           | 5 (17.9%) | 4 (30.8%) | 1 (100.0%) | 1 (14.3%) | 3 (60.0%) | 1 (50.0%) |
| 100-d relapse        | 2 (7.1%) | 0 (0.0%) | 0 (0.0%) | 1 (14.3%) | 0 (0.0%) | 0 (0.0%) |
| 100-d mortality      | 3 (10.7%) | 1 (7.7%) | 0 (0.0%) | 0 (0.0%) | 1 (20.0%) | 1 (50.0%) |

\( ^a \)IQR not displayed because of small sample size.

\( ^b \)Range: 31.0-175.0 days.

\( ^c \)Range: 0.0-31.0 days.
viruses known to have more severe outcomes. Our study highlights the pre-HCT role of clinical symptoms in outcomes of HCT patients.

This study provides unique insight into future studies in this area. Unlike previous studies, specimens were categorized by actual presence of symptoms rather than purpose of the specimen, which may provide additional accuracy as to the association of pathogen detection with symptoms. We evaluated children by both presence of any symptom (ie asymptomatic vs symptomatic) and also subsequently differentiated between type of symptom (ie URTI or LRTI) since additional decision tools, such as imaging, may help determine which cases would most benefit from HCT delay. Our data suggest that outcomes of children with RV detected pre-allogeneic HCT are related to the presence of LRTI. HCT delay can increase the risk of oncologic relapse and/or mortality, so risks and benefits of HCT delay must be evaluated. This study provides data to suggest that for patients with RV detection without LRTI symptoms, clinicians can consider proceeding with HCT in certain circumstances.

The decision of whether and how long to delay HCT in patients with RV detection is complicated by prolonged viral shedding. Almost half of patients with RV detection pre-HCT continued to have RV detection in follow-up testing pre- and post-HCT. Thus, HCT delay until the virus is no longer detected may not be feasible or warranted for patients with high-risk underlying conditions.

Our study has limitations, including a small number of patients. However, no studies have focused on RV detection pre-HCT in pediatrics, a unique population due to high rates of viral detection. Data were collected retrospectively, so clinical symptoms are limited by review of medical record documentation. Viral testing was performed at the discretion of the HCT physician. During the included years, practice patterns and decision-making regarding interpretation and results of viral cultures and PCR changed over the course of the included years with guidelines published during this period. A minority of children undergoing HCT had viral cultures, and they were excluded due to poor sensitivity for RV. This is a single site study, so findings may not be generalizable to children at other hospitals with different underlying conditions and chemotherapy protocols. Viruses were not sequenced, so subsequent detection could represent acquisition of a new strain rather than continued shedding. However, the high rates of RV detection in subsequent specimens highlight that waiting until RV is no longer detected may not be a feasible option for children who urgently need HCT. Additionally, RV are indistinguishable from enteroviruses on these commercial assays; however, previous data suggest that >95% are RV.

We present data related to the outcome of children with RV detected pre-HCT. RV detection occurs in a significant number of children pre-HCT, and the identification of RV does not empirically warrant HCT delay. Clinicians should consider other factors, including the presence of LRTI symptoms, as well as the risk of delaying HCT rather than making a decision based on viral detection alone. Further larger studies are needed to determine the optimal management of these patients.

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CONFLICT OF INTEREST

The authors deny any conflict of interest.

AUTHORS’ CONTRIBUTIONS

CM, RS, and JES developed the concept and designed the study. CM, RG, and JES were responsible for data collection. BRL and JES performed the data analysis/interpretation and statistics. CM and JES drafted the manuscript. All authors participated in critical revision and approval of the manuscript.

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REFERENCES

1. Lujan-Zilbermann J, Benaim E, Tong X, Srivastava DK, Patrick CC, DeVincenzo JP. Respiratory virus infections in pediatric hematopoietic stem cell transplantation. Clin Infect Dis. 2001;33: 962-968.
2. Hassan IA, Chopra R, Swindell R, Mutton KJ. Respiratory viral infections after bone marrow/peripheral stem-cell transplantation: the Christie hospital experience. Bone Marrow Transplant. 2003;32:73-77.
3. Campbell AP, Guthrie KA, Englund JA, et al. Clinical outcomes associated with respiratory virus detection before allogeneic hematopoietic stem cell transplant. Clin Infect Dis. 2015;61:192-202.
4. Iwane MK, Prill MM, Lu X, et al. Human rhinovirus species associated with hospitalizations for acute respiratory illness in young US children. J Infect Dis. 2011;204:1702-1710.
5. Xiao Q, Zheng S, Zhou L, et al. Impact of human rhinovirus types and viral load on the severity of illness in hospitalized children with lower respiratory tract infections. Pediatr Infect Dis J. 2015;34:1187-1192.
6. Ng KT, Oong XY, Lim SH, et al. Viral load and sequence analysis reveal the symptom severity, diversity and transmission clusters of rhinovirus infections. Clin Infect Dis. 2018;67(2):261-268.
7. Seo S, Waghmare A, Scott EM, et al. Human rhinovirus detection in the lower respiratory tract of hematopoietic cell transplant recipients: association with mortality. Haematologica. 2017;102:1120-1130.
8. Chemaly RF, Shah DP, Boeckh MJ. Management of respiratory viral infections in hematopoietic cell transplant recipients and patients with hematologic malignancies. Clin Infect Dis. 2014;59(suppl 5):S344-S351.
9. Abandeh FI, Lustberg M, Devine S, Elder P, Andritsos L, Martin SI. Outcomes of hematopoietic SCT recipients with rhinovirus infection: a matched, case-control study. Bone Marrow Transplant. 2013;48:1554-1557.
10. Zaia J, Baden L, Boeckh MJ, et al. Viral disease prevention after hematopoietic cell transplantation. Bone Marrow Transplant. 2009;44:471-482.
11. Renaud C, Xie H, Seo S, et al. Mortality rates of human metapneumovirus and respiratory syncytial virus lower respiratory tract
infections in hematopoietic cell transplantation recipients. *Biol Blood Marrow Transplant*. 2013;19:1220-1226.

12. Ljungman P, Ward KN, Crooks BN, et al. Respiratory virus infections after stem cell transplantation: a prospective study from the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant*. 2001;28:479-484.

13. Pathak AK, Adams RH, Shah NC, Gustin KE. Persistent human rhinovirus type C infection of the lower respiratory tract in a pediatric cord blood transplant recipient. *Bone Marrow Transplant*. 2013;48:747-748.

14. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) – a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42:377-381.

15. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant*. 2009;15:1143-1238.

16. Martin EK, Kuypers J, Chu HY, et al. Molecular epidemiology of human rhinovirus infections in the pediatric emergency department. *J Clin Virol*. 2015;62:25-31.

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