Adult patients with respiratory syncytial virus infection: impact of solid organ and hematopoietic stem cell transplantation on outcomes

P. Pilie, W.A. Werbel, J. Riddell IV, X. Shu, D. Schaubel, K.S. Gregg. Adult patients with respiratory syncytial virus infection: impact of solid organ and hematopoietic stem cell transplantation on outcomes.
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Abstract: *Background.* Respiratory syncytial virus (RSV) is a common community-acquired pathogen responsible for a substantial disease burden in adults. We investigated the outcomes after RSV infection in hospitalized adults over a 3-year period.
Methods. This single-center, retrospective study identified 174 patients hospitalized with RSV upper or lower respiratory tract infection (LRTI) between January 1, 2009 and June 30, 2012. Clinical data were extracted from medical records. The primary outcome analyzed was all-cause mortality, defined as death during the index hospital admission. Subjects were divided into 3 groups for comparison: hematopoietic stem cell transplant (HSCT) patients, solid organ transplant (SOT) patients, and non-transplant patients.
Results. In our study, 41/174 (23.6%) were HSCT recipients and 28/174 (16.1%) were SOT recipients. Twelve of 174 (6.9%) died. Death occurred in 2/41 (4.9%) HSCT and 3/28 (10.7%) SOT recipients, compared to 7/106 (6.6%) non-transplant patients. When compared to the non-transplant cohort, HSCT and SOT were not found to be significant risk factors for mortality ($P = 0.685$ and 0.645, respectively). In multivariate logistic regression, age >60 was associated with mortality ($P = 0.019$), while lymphopenia on admission trended toward an association with death ($P = 0.054$). HSCT patients were less likely to be admitted to an intensive care unit (odds ratio [OR] 0.26, $P = 0.04$), but were significantly more likely to receive ribavirin therapy (OR 11.62, $P < 0.0001$).
Conclusion. Adults hospitalized with RSV LRTI are at significant risk of mortality, and this risk may be increased in patients age >60 or with lymphopenia on admission. This study did not identify any significant increased mortality or morbidity associated with RSV infection in immune suppressed transplant recipients vs. patients who had not received a transplant.

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Respiratory syncytial virus (RSV) is a single-stranded, enveloped RNA virus of the paramyxoviridae family that causes respiratory infection in 3–20% of adults annually, rivaling the incidence of influenza A infection (1–6).

Multiple studies have identified risk factors for severe RSV infection in adults including advanced age, poor functional status, underlying cardiopulmonary disease, and significant immunocompromised state (7, 8). Hematopoietic stem cell transplant (HSCT) recipients represent a particularly high-risk group, with recent studies showing significant but highly variable mortality rates of 5–80% in patients with lower respiratory tract infection (LRTI) (9–16). In comparison,

studies involving solid organ transplant (SOT) recipients have only demonstrated significant mortality in lung transplant recipients with LRTI (0–20%), although published data for other organs are limited (14, 17, 18). However, measured outcomes of transplant recipients infected with RSV in prior studies are heterogeneous, as are treatment approaches. Unlabeled use of ribavirin, a guanosine analog, has been used as a primary therapy for RSV; however, owing to a lack of large randomized control trials, currently there is no standardized treatment strategy in these at-risk populations. Therefore, in this study, we present a retrospective analysis of 174 RSV assay-confirmed cases, including both transplanted and non-transplanted adults, between 2009 and 2012 at the University of Michigan Hospital, designed to better characterize risk factors leading to severe infection and death, as well as outcomes of RSV LRTI in a diverse hospitalized population.

Patients and methods

This study was conducted at the University of Michigan Hospital, a 980-bed tertiary care medical center, where approximately 350 SOTs and 250 HSCTs are performed each year. After institutional review board approval, subjects were identified using retrospective data of positive RSV viral culture, antigen assay (Diagnostic Hybrids, Athens, Ohio, USA), or polymerase chain reaction (PCR) assay (Prodesse ProFlu+; Hologic, Bedford, Massachusetts, USA) (19) obtained between January 1, 2009 and June 30, 2012, encompassing 4 sequential RSV seasons. In total, 218 adult patients were identified; 44 of these patients were diagnosed and managed as outpatients, and were therefore excluded from analysis, leaving 174 hospitalized subjects for inclusion.

Data related to the hospitalization and outcomes of each patient were abstracted from the electronic medical record system. Demographic data included age, gender, history of malignancy or chronic lung disease (such as chronic obstructive pulmonary disease, interstitial lung disease, pulmonary fibrosis, or bronchiectasis), ongoing chemotherapy, receipt of autologous or allogeneic HSCT, and receipt of SOT. Clinical data abstracted from the medical record included interval time from HSCT or SOT to diagnosis of RSV infection, presenting symptoms, and oxygen saturation at time of admission, chest radiographic findings (x-ray and computed tomography), admission to intensive care unit during hospitalization, mechanical ventilation, pulmonary co-infection(s), receipt and duration of oral and/or inhaled ribavirin, and duration of

hospitalization. Subjects were determined to have had upper respiratory tract infection (URTI) or LRTI based on these data. LRTI was present if either of the following criteria were met: (i) pulse oximetry <90% or requirement of supplemental oxygen therapy on admission with respiratory symptom(s) of infection and radiographic evidence of LRTI and positive nasopharyngeal or throat RSV assay, or (ii) bronchoalveolar lavage specimen positive for RSV. Any subject not meeting LRTI criteria but with an upper respiratory sample positive for RSV and concurrent respiratory tract infection symptoms was defined as having URTI. All testing for RSV at our hospital during the study period was performed at the discretion of the treating physician(s).

Data were obtained from the date of hospital admission until the date of discharge. The primary outcome analyzed was all-cause mortality, defined as death during the index hospital admission. To study the predictors of death (covariate-adjusted), a logistic regression model was used. Covariates included in the model were age, gender, absolute lymphocyte count (ALC) on admission, transplant status, diagnosis of chronic lung disease, fever, computed tomography findings, and URTI symptoms. Age at diagnosis was split into 2 categories: >60 years and ≤60 years.

Secondary analysis was performed with subjects split into SOT, HSCT, and non-transplanted cohorts. Multivariate logistic regression models for death were fitted separately in these 3 groups. Because of the small sample size, some covariates did not have enough variation and, thus, were excluded from the model. The standard significance level (0.05) was applied to delineate statistically significant from non-significant effects.

In addition, in order to describe observed patterns in the number of RSV diagnoses over calendar time, curves displaying RSV incidence (counts of diagnoses vs. time) were plotted by transplant type. All statistical analyses were carried out using SAS v9.2 (SAS Institute, Cary, North Carolina, USA).

Results

During the study period, 174 cases of RSV infection occurred in hospitalized adult patients. Of these, 152 cases (87.3%) were identified by positive nasopharyngeal swab (150 PCR assay, 2 viral culture); 13 cases (7.5%) identified by bronchoalveolar lavage fluid (10 PCR assay, 3 viral culture); and 9 cases (5.2%) identified by sputum culture/tracheal aspirate (4 PCR assay, 3 RSV antigen, 2 viral culture). Epidemiologic curves by transplant type are shown in Figure 1 and include both
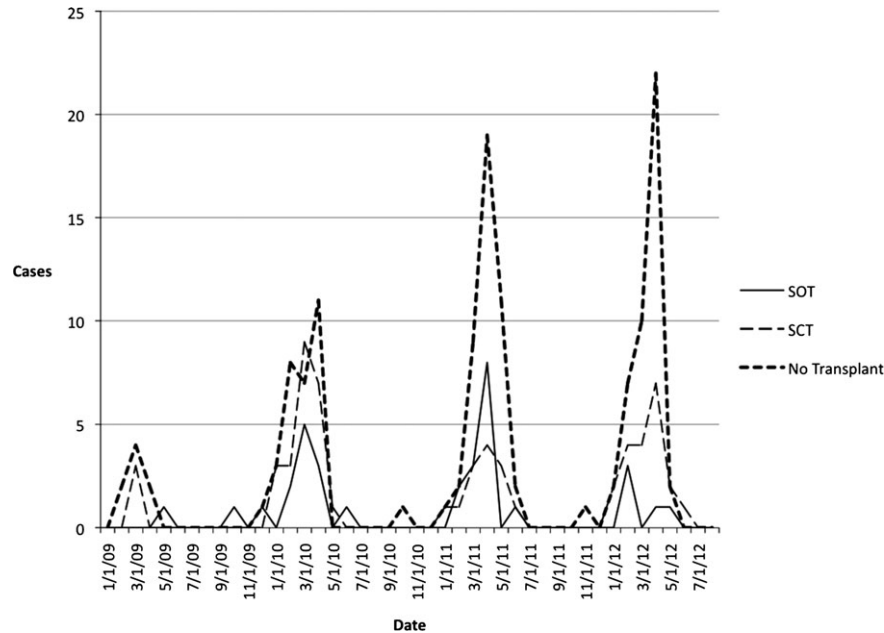
Fig. 1. Epidemiologic curve of confirmed cases of respiratory syncytial virus infection by transplant type: 2009–2012. SOT, solid organ transplant; SCT, stem cell transplant.

outpatient and inpatient subjects. Fifteen RSV cases were detected in the 2009 season, 64 cases in 2009–2010, 72 cases in 2010–2011, and 67 cases in 2011–2012. Of note, the University of Michigan microbiology laboratory transitioned to PCR-based testing for RSV in September 2009 and, thereafter, a consistently higher number of cases were identified each season. The periodic pattern of the curves and the time of onset of infection among SOT, HSCT, and non-transplant cohorts were similar in each season, with cases primarily identified between January and May.

Patient characteristics of the 174 subjects are listed in Table 1. Of these, 41 subjects (23%) were HSCT recipients, 28 subjects (16%) were SOT recipients, and 106 subjects (61%) were not transplant recipients. The SOT cohort included 16 lung, 8 kidney, 3 heart, 1 liver, and 1 kidney/pancreas transplant recipient. One patient received both a HSCT and SOT. LRTI was present in 121 subjects (69.5%). The average length of stay at the hospital was 9.3 ± 11.3 days; 37 subjects (21.2%) required intensive care unit admission, and 17 (9.8%) received mechanical ventilation. The non-transplant cohort was significantly older than the HSCT cohort (62.1 years vs. 53.8 years, $P = 0.001$). Subjects with SOT and non-transplanted subjects were both significantly more likely to have underlying chronic lung disease than were HSCT subjects ($P = 0.003$). The mean durations from date of HSCT or SOT until

RSV infection were 2.60 years and 6.05 years, respectively.

Twelve subjects (6.9%) died during hospitalization. 2 subjects were HSCT recipients, 3 were SOT recipients, and 7 were not transplant recipients. All deaths occurred in patients with LRTI, resulting in a mortality rate of 10% (12/121) in this subset of patients. Results for the logistic regression model of death are listed in Table 2. Death risk was significantly greater for subjects >60 years of age, with a covariate-adjusted odds ratio (OR) of 8.41 ($P = 0.019$) compared with subjects <60 years of age. Each 1 unit (100 cells/μL) increase in ALC on admission was estimated to decrease the odds of in-hospital death by approximately 75% (OR = 0.24), with the effect approaching statistical significance ($P = 0.051$). No other covariate effects approached significance for risk of death.

Results based on logistic regression models of death in HSCT recipients ($n = 41$) and SOT recipients ($n = 28$) did not identify any covariates associated with mortality. For non-transplant subjects, higher ALC was significantly associated with lower odds of death (OR = 0.09; $P = 0.046$). Specifically, each 100 cell/μL increase in ALC resulted in a >90% decrease in the risk of death. Age >60 showed borderline significance, with a trend toward greater risk of mortality (OR = 11.4; $P = 0.065$); i.e., the odds of death in patients age >60 was more than 11 times greater than

Baseline characteristics of study patients

Characteristics	Inpatients with SCT (n = 41)[1]	Inpatients with SOT (n = 28)[1]	Inpatients without transplant (n = 106)
Gender, n (%)			
Female	16 (39.02)	10 (35.71)	75 (70.75)
Male	25 (60.98)	18 (64.29)	31 (29.25)
Age, mean years ± SD	53.78 ± 11.82	55.00 ± 15.12	62.08 ± 19.83
Chronic lung disease, n (%)	4 (9.76)	11 (39.29)	36 (33.96)
Length of stay, mean days ± SD	11.44 ± 13.51	9.29 ± 11.51	8.49 ± 10.30
ICU admission, n (%)	6 (14.63)	5 (17.86)	26 (24.53)
Mechanical ventilation, n (%)	3 (7.32)	4 (14.29)	10 (9.43)
Death, n (%)	2 (4.88)	3 (10.71)	7 (6.60)
Fever, n (%)	22 (53.66)	13 (46.43)	45 (42.45)
Respiratory infection, n (%)			
Upper	11 (26.83)	10 (35.71)	32 (30.19)
Lower	30 (73.17)	18 (64.29)	74 (69.81)
Lymphocyte count[2], mean ± SD	1234 ± 831	860 ± 528	1208 ± 1059
Abnormal CT findings, n (%)			
Yes	19 (46.34)	8 (28.57)	23 (21.70)
No	7 (17.07)	5 (17.86)	7 (6.60)
CT scan not performed	15 (36.59)	15 (53.57)	76 (71.70)
Treated with ribavirin, n (%)	23 (56.10)	6 (21.43)	10 (9.43)
Duration from transplant to infection, mean years ± SD	2.60 ± 2.47	6.05 ± 6.69	NA

[1]One subject had both SCT and SOT, and thus was counted in both groups.
[2]Lymphocyte count data not available for 5 subjects.
SCT, stem cell transplant; SOT, solid organ transplant; SD, standard deviation; ICU, intensive care unit; CT, computed tomography; NA, not applicable.

Table 1

that of patients age ≤60, adjusting for all other covariates.

Ribavirin therapy (either inhaled or systemic) was administered in 39 (22.4%) patients. Overall, 23/40 (56.1%) of HSCT recipients received some form of ribavirin therapy, compared with 6/27 (22.2%) of SOT recipients, and 10/107 (9.3%) of non-transplant recipients. In those who received ribavirin therapy, LRTI was identified in 16/22 (72.7%) HSCT recipients, in 5/6 (83.3%) SOT recipients, and in 8/10 (80%) non-transplant recipients. The average duration of ribavirin therapy was 7.8 days (range 1–15 days, median 7 days). In ribavirin-treated patients, 5/39 (12.8%) received both inhaled and oral ribavirin, all 5 of whom were HSCT recipients, with 1 in-hospital death. Thirty-four of 39 patients (87.2%) received only oral ribavirin (18 HSCT recipients, 6 SOT recipients, and 10 non-transplanted subjects), with 3 in-hospital deaths (1 HSCT recipient, 1 SOT recipient, 1 non-transplant).

Discussion

RSV has been shown to be an important cause of respiratory infection in transplant recipients with significant associated morbidity and mortality. In this single-center study, we retrospectively analyzed the impact of RSV infection in a diverse hospitalized adult population that included HSCT, SOT, and non-transplant patients from 2009 to 2012. The timing of RSV infection in each season did not differ between transplant and non-transplant patients. A dramatic and sustained increase was seen in the number of cases identified between the 2009 RSV season and the

Logistic regression model for death in all inpatients (n = 174)

Parameter	Odds ratio (95% confidence interval)	P-value
Gender = male (vs. female)	3.317 (0.605, 18.195)	0.1674
Age >60[*] (vs. age ≤60)	8.413 (1.429, 49.524)	0.0185
Lymphocyte count (per 100 unit increase)	0.866 (0.749, 1.001)	0.0512
Stem cell transplant (vs. no transplant)	0.595 (0.086, 4.115)	0.5988
Solid organ transplant (vs. no transplant)	0.414 (0.049, 3.496)	0.4178
Chronic lung disease (vs. absent)	1.146 (0.207, 6.346)	0.8760
Fever (vs. absent)	1.298 (0.292, 5.773)	0.7317
No abnormal CT findings (vs. ≥1 finding)	0.282 (0.052, 1.526)	0.1417
Lower respiratory infection (vs. upper)	2.160 (0.192, 24.314)	0.5331

*Significant P < 0.05.
CT, computed tomography.

Table 2

following seasons, which may be attributable to multiple factors. The improved sensitivity of the new testing platform, over that of viral culture and antigen-based assays, may have had an impact, as has been well described (20, 21). More significantly, however, our transition to a PCR platform allowed bundled testing for influenza and RSV, whereas previously, RSV testing required a separate specific order in a patient with an influenza-like illness, likely leading to increased screening for RSV in adults overall. Within the transplant cohorts, patients were typically infected several years after their transplant, reflecting the risk for acquisition of RSV as a community-acquired rather than nosocomial infection.

We did not identify independent risk factors for mortality from RSV infection among the transplant populations. Among the entire study population, only age >60 years was significantly associated with a risk of death from RSV infection. Among the individually analyzed cohorts of HSCT, SOT, and non-transplant patients, age >60 years increased the odds of mortality, but only approached significance in non-transplant recipients (OR = 11.4; P = 0.065). Analysis of other potential risk factors associated with mortality found decreased odds of death of 13.4% (OR = 0.866) per 100 cell increase in ALC among the entire study population, with this effect also approaching statistical significance (P = 0.051). When stratified by HSCT, SOT, and non-

transplant cohorts, ALC was found to be a significant risk factor of death only in non-transplant patients (OR = 0.092; P = 0.045). A recent study of RSV in 181 HSCT recipients showed 24% of patients progressing to LRTI and identified risk factors for progression including smoking, high-dose total body irradiation, and ALC ≤100 mm^3 at the onset of URTI symptoms (22). Many previous studies have commented on the increased risk of progressive infection and mortality in patients with lymphopenia (ALC ≤100 mm^3) and older age (11, 22–25).

In this cohort, mortality was 6.9% (12/174 patients). All 12 patients who died had evidence of LRTI at the time of admission. HSCT and SOT recipients did not have a statistically significant difference in mortality, when compared to non-transplant patients. In fact, HSCT recipients had a lower mortality (4.9%) than either SOT recipients (10.9%) or non-transplant patients (6.6%). Although previous studies have not shown a significant attributable mortality to RSV infection in SOT recipients, recent studies of HSCT recipients with RSV LRTI have demonstrated mortality rates of 30–50% (9–13), and in elderly populations RSV infection may lead to 10,000 deaths annually (25). Several factors may have led to a relatively low mortality among the HSCT recipients in our study. HSCT patients were less likely to have LRTI at the time of admission than were other patients admitted with RSV infection, perhaps owing to clinical awareness of increased mortality risk from respiratory infections in this population, thereby leading to a lower threshold for admission for respiratory infection by healthcare providers, and to more frequent screening in the outpatient setting. The SOT and non-transplant cohorts may also have been at higher risk for mortality for reasons unrelated to transplantation status, such as age and chronic lung disease.

Mortality from RSV in the general population has been demonstrated to disproportionately affect the elderly population, with nearly 80% of deaths occurring in patients >65 years of age (25). Within the elderly population with RSV infection, chronic lung disease has been demonstrated as a risk factor for hospitalization (4). In this study, the non-transplant cohort had a mean age of 62 years, significantly older than the HSCT cohort. Likewise, both the SOT cohort and non-transplant cohort both had significantly higher prevalence of chronic lung disease, potentially contributing to the higher observed mortality rates.

Our study was unable to determine if aerosolized or oral ribavirin had an impact on the overall mortality of RSV in LRTI, or in the HSCT cohort alone. In the study, over half the HSCT patients received ribavirin therapy, compared with only 21% of SOT recipients and 9% of

non-transplant patients. This difference is mostly a reflection of institutional policy, which restricts inhaled ribavirin to patients with a recent HSCT or with chronic graft-versus-host disease requiring immunosuppressive therapy. The efficacy of ribavirin for RSV infection remains controversial, although off-label use in HSCT and in heart and lung transplant recipients is common. The only randomized-controlled trial of ribavirin in HSCT recipients with RSV URTI was not able to definitively demonstrate efficacy, owing to low patient accrual (23). However, observational studies in HSCT recipients have shown oral and aerosolized ribavirin to be well tolerated, to prevent progression of URTI to LRTI, and to decrease mortality in LRTI (9, 13, 26).

Several drugs are currently in the early stages of development for the treatment of RSV, but have not yet received U.S. Food and Drug Administration approval. Compounds are being developed that prevent RSV from fusing with host cell surfaces by targeting the RSV F protein. Other compounds inhibit the RSV polymerase or bind to the N-terminal region of nucleocapsid protein (27). Monoclonal antibodies have not been shown to have significant clinical activity when studied in children (28).

Our study has several limitations. As with most retrospective studies, incomplete or missing data may affect study statistics and outcome measures. Also, as testing for RSV is not mandatory for all adult patients with influenza-like illness at our institution, it is possible that some RSV infections in hospitalized patients were not detected, and therefore not included in the study. Similarly, as many patients transplanted at our institution receive acute care closer to their homes, some RSV infections in these populations may have been missed. Another important point is that no significant conclusions can be made about the treatment effects of oral or inhaled ribavirin for this hospitalized population, because these therapies were not administered in a consistent manner to any of the patient cohorts. Lack of a historical control group also limits assessment of efficacy of this treatment in the patients who received therapy during this study. Finally, the sample size of this study, while larger than many other descriptive studies of RSV infection in immunocompromised hosts, may have lacked the power necessary to identify certain risk factors for mortality.

In conclusion, this study did not identify any significant degree of increased mortality or morbidity associated with RSV infection in hospitalized adult HSCT or SOT recipients vs. non-transplant adult patients. We did demonstrate, however, that increased age and low ALCs are important risk factors for mortality in non-transplant patients, consistent with other prior studies. Although we cannot exclude the possibility of a beneficial treatment effect of ribavirin in the HSCT cohort, our results did not demonstrate decreased mortality in any specific patient cohort treated with ribavirin. Newer antiviral therapies for RSV are also in development and currently undergoing clinical trials in immunocompromised populations (29). Our results suggest that inclusion of certain non-transplant patients in future trials may be of benefit, with particular attention to patients with age >60, who are at high risk of complications from RSV infection.

Acknowledgments:

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