

# Oral Versus Aerosolized Ribavirin for the Treatment of Respiratory Syncytial Virus Infections in Hematopoietic Cell Transplant Recipients

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**Background.** The use of oral ribavirin (RBV) for respiratory syncytial virus (RSV) infections is not well studied. With the drastic increase in the cost of aerosolized RBV, we aimed to compare outcomes of hematopoietic cell transplant (HCT) recipients treated with oral or aerosolized RBV for RSV infections.

**Methods.** We reviewed the records of 124 HCT recipients with RSV infections treated with oral or aerosolized RBV from September 2014 through April 2017. An immunodeficiency scoring index (ISI) was used to classify patients as low, moderate, or high risk for progression to lower respiratory infection (LRI) or death.

**Results.** Seventy patients (56%) received aerosolized RBV and 54 (44%) oral RBV. Both groups had a 27% rate of progression to LRI ( $P = 1.00$ ). Mortality rates did not significantly differ between groups (30-day: aerosolized 10%, oral 9%,  $P = 1.00$ ; 90-day: aerosolized 23%, oral 11%,  $P = .10$ ). Classification and regression tree analysis identified  $ISI \geq 7$  as an independent predictor of 30-day mortality. For patients with  $ISI \geq 7$ , 30-day mortality was significantly increased overall, yet remained similar between the aerosolized and oral therapy groups (33% for both). After propensity score adjustment, Cox proportional hazards models showed similar mortality rates between oral and aerosolized therapy groups (30-day: hazard ratio [HR], 1.12 [95% confidence interval {CI}, .345–3.65,  $P = .845$ ]).

**Conclusions.** HCT recipients with RSV infections had similar outcomes when treated with aerosolized or oral RBV. Oral ribavirin may be an effective alternative to aerosolized RBV, with potential significant cost savings.

**Keywords.** oral ribavirin; aerosolized ribavirin; respiratory syncytial virus; hematopoietic cell transplant; outcome.

Respiratory syncytial virus (RSV) is a single-stranded RNA virus of the Paramyxoviridae family and a common cause of seasonal respiratory viral infection [1]. Although RSV infection is frequently a self-limiting cause of upper respiratory infection (URI), it may progress to a more severe lower respiratory infection (LRI) in immunocompromised patients, including hematopoietic cell transplant (HCT) recipients. RSV infection in HCT recipients is associated with substantial morbidity and mortality [2–5], and often complicated by respiratory failure [6]. Several risk factors for progression to LRI and/or mortality include myelosuppression, preengraftment or early posttransplantation (ie, within 30 days), age, and mismatched or unrelated donor [6–8].

Ribavirin (RBV), a guanosine analogue active against RNA and DNA viruses, is often used to treat RSV infections. Aerosolized RBV is approved for RSV LRI in pediatric patients,

although it is frequently used off-label in other populations [2, 9]. Data on RBV to treat RSV infections in HCT recipients come from small, retrospective studies with heterogeneous treatment combinations. Nevertheless, treatment with RBV was shown to prevent poor outcomes [2]. In the largest evaluation of RBV therapy for RSV in HCT recipients, Shah et al showed that aerosolized RBV at the URI stage reduced progression to LRI (83%) and RSV-associated mortality (87%) compared with no treatment [6]. Most studies on RSV treatment have evaluated aerosolized RBV [2, 6, 10]; information on other formulations is limited [2, 3, 9, 11, 12].

Aerosolized RBV to treat RSV has remained controversial due to lack of randomized controlled trials, occupational exposure concerns, and the high drug cost. Thus, an immunodeficiency scoring index (ISI) was developed to identify patients who would most benefit from RBV based on risk for progression to LRI and RSV-associated mortality [13]. Patients with high ISI ( $\geq 7$ ) were shown to have the highest rates of progression (48%) and death (29%), as well as the greatest benefit when aerosolized RBV was administered at the URI stage (6- and 8-fold reduction in progression and mortality, respectively) [13].

A dramatic increase in the cost of aerosolized RBV in 2015 [14] limited its use at many institutions and necessitated the

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quest for alternative therapies, mainly via oral RBV. In addition to being inexpensive, oral RBV allows for outpatient therapy. Data on use of oral RBV to treat RSV in HCT recipients are scarce [15]. The purpose of this study was to compare progression to LRI and mortality in HCT recipients with RSV infections treated with either oral or aerosolized RBV.

## METHODS

We reviewed the records of all HCT recipients who received RBV for RSV infections from 1 September 2014, through 30 April 2017, at The University of Texas MD Anderson Cancer Center. The BioFire FilmArray Respiratory Panel (BioFire Diagnostics, Salt Lake City, Utah) was used to diagnose RSV. Patients aged  $\geq 18$  years with a history of HCT were included if they received  $\geq 1$  dose of RBV for RSV infection, as an inpatient or outpatient. Patients were excluded if they were enrolled in a clinical trial for RSV, or received RBV for non-RSV indications. No formal restrictions/review of either formulation of RBV was in place at any time during this study.

Patients were identified by accessing pharmacy records for RBV orders/prescriptions. Only the first episode of RSV infection was considered for each patient. Patients were classified into the aerosolized or oral RBV group if they received that formulation for  $>48$  hours at initiation of therapy. If the formulation was switched before 48 hours, they were classified as the formulation to which they were changed.

URI was defined as signs/symptoms of an RSV infection (rhinorrhea, nasal/sinus congestion, pharyngitis, cough) without chest radiographic imaging suggestive of pneumonia. LRI was defined as respiratory symptoms along with chest radiographic imaging suggestive of LRI (ie, ground glass opacities, interstitial infiltrates) with or without isolation of RSV from a lower respiratory sample. RSV was considered community-acquired if symptoms developed before hospitalization or within 5 days after admission and nosocomial if symptoms developed  $>5$  days after admission.

The primary outcome was 30-day all-cause mortality. Secondary outcomes included progression to LRI for patients with URI upon treatment initiation, 90-day all-cause mortality, and need for intensive care unit (ICU) admission or mechanical ventilation. Risk for progression to LRI and RSV-associated death was stratified by ISI [13] (Table 1).

The following information was collected for all patients: demographics, including age, sex, and race/ethnicity; malignancy; HCT and engraftment date; conditioning regimen; graft-vs-host disease (GVHD) status; immunosuppressive medications within 30 days prior to RSV diagnosis; formulation and duration of RBV therapy; creatinine clearance and hemoglobin; respiratory copathogens; radiographic imaging results; ICU admission and/or mechanical intubation, and date and cause of death. This study was approved by the MD Anderson Institutional Review Board and an informed consent waiver was granted.

## Statistical Analysis

### Comparison of Aerosolized and Oral RBV

Categorical and continuous variables were compared using Fisher exact test and the Wilcoxon-rank sum test, respectively. The primary outcome, 30-day mortality, was assessed visually using Kaplan-Meier curves and multivariate Cox proportional hazards. The final multivariate Cox proportional hazards model incorporated characteristics with a  $P$  value  $<.2$  on bivariate analysis with administration of oral RBV forced into the model. The proportional hazards assumption was visually assessed using a plot of the scaled Schoenfeld residuals against time. A propensity score-based analysis was performed to also control for confounding. To create the propensity score, a nonparsimonious logistic regression model incorporating all measured baseline characteristics (sex, race, transplant type, ISI score, site of infection, time from transplantation, GVHD, steroid use, nosocomial infection status) was created to model the probability of oral RBV treatment. This propensity score was used to generate inverse probability of treatment weight (IPTW) and a subsequent IPTW Cox proportional hazards model [16]. Progression from URI to LRI was assessed among patients treated at the URI stage using a Fine-Gray competing risk model, treating death as a competing risk for progression to LRI [17]. A traditional multivariate model and IPTW competing risk model were constructed.

### Identification of the Optimal ISI Score for Risk Stratification

Progression to LRI and 30- and 90-day mortality were assessed with previously published ISI risk categories [13]. To identify a single group at highest risk, classification and regression tree (CART) analysis was used to identify the ISI score most predictive of 30-day mortality [18]. Progression to LRI and mortality were compared in CART-identified low- and high-risk patients.

Data were collected using REDCap electronic data capture tools [19]. Statistical analyses were performed using Stata

**Table 1. Immunodeficiency Scoring Index Criteria**

Criterion	ISI
ANC $<500$ cells/ $\mu$ L	3
ALC $<200$ cells/ $\mu$ L	3
Age $\geq 40$ y	2
Myeloablative conditioning regimen used	1
GVHD, acute or chronic	1
Corticosteroids within the past 30 d	1
Recent engraftment (within 30 d) or preengraftment	1
Risk of progression from URI to LRI and RSV-associated mortality	
Low	0–2
Moderate	3–6
High	7–12

The overall ISI is the sum of the weighted scores for the immunodeficiency criteria present at the time of RSV diagnosis. Patients with ISI 0–2 were classified as low risk, 3–6 as moderate risk, and 7–12 as high risk for progression to LRI and/or RSV-associated mortality. Abbreviations: ALC, absolute lymphocyte count; ANC, absolute neutrophil count; GVHD, graft-vs-host disease; ISI, immunodeficiency virus scoring index; LRI, lower respiratory infection; RSV, respiratory syncytial virus; URI, upper respiratory infection.

**Table 2. Baseline Demographic and Clinical Characteristics of Hematopoietic Cell Transplant Recipients Who Received Aerosolized or Oral Ribavirin Therapy for Respiratory Syncytial Virus Infection (n = 124)**

Variable	No. (%)			P Value
	Aerosolized (n = 70)	Oral (n = 54)	Total	
Median age at diagnosis, y (range)	60 (21–80)	58 (23–79)	59 (21–80)	.590
Male sex	46 (66)	34 (63)	80 (65)	.850
Race/ethnicity				.832
White	51 (73)	40 (74)	91 (73)	
Hispanic	9 (13)	9 (17)	18 (15)	
Black	6 (9)	4 (7)	10 (8)	
Asian	2 (3)	1 (2)	3 (2)	
Other	2 (3)	0 (0)	2 (2)	
Type of malignancy				.276
AML	19 (27)	14 (26)	33 (27)	
ALL	4 (6)	4 (7)	8 (6)	
CML	1 (1)	4 (7)	5 (4)	
CLL	0 (0)	1 (2)	1 (1)	
MDS	7 (10)	2 (4)	9 (7)	
Hodgkin lymphoma	0 (0)	3 (6)	3 (2)	
Non-Hodgkin lymphoma	6 (9)	3 (6)	9 (7)	
Multiple myeloma	24 (34)	17 (31)	41 (33)	
Other	9 (13)	6 (11)	15 (12)	
Relapsed	17 (24)	16 (30)	33 (27)	.543
Donor relationship				.888
Matched related	15 (21)	14 (26)	29 (23)	
Matched unrelated	18 (26)	12 (22)	30 (24)	
Haploidentical	6 (9)	6 (11)	12 (10)	
Mismatched	2 (3)	0 (0)	2 (2)	
Cord	2 (3)	2 (4)	4 (3)	
Autologous	27 (39)	20 (37)	47 (38)	
Myeloablative conditioning regimen	65 (93)	50 (93)	115 (93)	1.000
Median time from HCT to infection, d (range; IQR)	359 (–1 to 4571; IQR, 118–903)	502 (11–7090; IQR, 236–1092)	466 (–1 to 7090; IQR, 163–1028)	.130
≤30 d from HCT to RSV infection	9 (13)	2 (4)	11 (9)	.111
≤90 d from HCT to RSV infection	15 (21)	6 (11)	21 (17)	.153
Acute GVHD	9 (13)	6 (11)	15 (12)	1.000
Chronic GVHD	14 (20)	13 (24)	27 (22)	.660
Corticosteroid use	37 (53)	29 (54)	66 (53)	1.000
Neutropenia <sup>a</sup>	5 (7)	6 (11)	11 (9)	.531
Lymphopenia <sup>b</sup>	19 (27)	5 (9)	24 (19)	.021
Hb, g/dL, at baseline, median (IQR)	9.6 (8.9–11.0) <sup>c</sup>	9.7 (8.6–11.7)	9.6 (8.7–11.3)	.307
Nosocomial infection	11 (16)	4 (7)	15 (12)	.179
Stage at RSV diagnosis				.857
URI	31 (44)	25 (46)	56 (45)	
LRI	39 (56)	29 (54)	68 (55)	
Stage at RBV initiation				.856
URI	30 (43)	22 (41)	52 (42)	
LRI	40 (57)	32 (59)	72 (58)	
CrCl at RBV initiation, mL/min, median (IQR)	95.12 (68–135) <sup>c</sup>	95.06 (60–136)	95.12 (62–135)	.186
ISI				
Low risk	6 (9)	7 (13)	13 (10)	.557
Moderate risk	52 (74)	41 (76)	93 (75)	1.000
High risk	12 (17)	6 (11)	18 (15)	.444
Duration of therapy, d, median (IQR)	5 (4–5)	5 (5–8)		

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CrCl, creatinine clearance; GVHD, graft-vs-host disease; Hb, hemoglobin; HCT, hematopoietic cell transplant; IQR, interquartile range; ISI, immunodeficiency scoring index; LRI, lower respiratory infection; MDS, myelodysplastic syndrome; RBV, ribavirin; RSV, respiratory syncytial virus; URI, upper respiratory infection.

<sup>a</sup>Absolute neutrophil count <500 cells/μL.

<sup>b</sup>Absolute lymphocyte count <200 cells/μL.

<sup>c</sup>n = 68.

version 14.1 (StataCorp, College Station, Texas) or SAS JMP Pro version 13 (SAS Institute, Cary, North Carolina).

## RESULTS

Over 3 consecutive RSV seasons, 127 adult HCT recipients with microbiologically documented RSV infections received RBV therapy. Three patients were excluded because their transplantation was done at outside institutions, and transplantation date and/or the conditioning regimen was unknown. Of the remaining 124 patients, 70 (56%) received aerosolized and 54 (44%) received oral RBV (Table 2). Only 3 patients (2 oral, 1 aerosolized RBV) received the alternate formulation for <48 hours and were classified as the regimen to which they were switched. Both groups had similar baseline demographics. The median age at RSV diagnosis was 59 years (range, 21–80 years), and multiple myeloma (33%) and AML (27%) were the most common underlying malignancies. Median time from HCT to RSV infection was 466 days (range, –1 to 7090 days). Malignancy relapse at time of RSV infection was similar between groups (aerosolized: 24%, oral: 30%,  $P = .543$ ). Lymphopenia at RSV diagnosis was more common in the aerosolized (27%) than oral RBV group (9%) ( $P = .021$ ), which was the only significant difference between groups. The number/types of respiratory copathogens were similar between both groups (Supplementary Table 1). Fifty-six patients had URI at RSV presentation (45%), and 68 (55%) presented with LRI.

### Identification of High-risk Patients Based on ISI Score

CART analysis identified ISI  $\geq 7$  as the most significant predictor of 30-day mortality (sensitivity 50%, specificity 89%, area under the receiver operating curve 0.70). We found that among patients treated with aerosolized and oral RBV, patients with ISI <7 had similar rates of progression to LRI (24% vs 29%), 30-day mortality (5% vs 6%), and 90-day mortality (16% vs 8%) (Table 3 and Supplementary Tables 2 and 3). Patients with ISI  $\geq 7$  had higher 30-day and 90-day mortality rates than those with ISI <7, but rates remained similar between groups (30-day mortality: aerosolized 33%, oral 33%; 90-day mortality: aerosolized 58%, oral 33%).

**Table 3. Outcomes of Hematopoietic Cell Transplant Recipients Treated With Ribavirin for Respiratory Syncytial Virus Infection Stratified by Immunodeficiency Scoring Index**

Outcome	No. (%)		P Value
	ISI <7	ISI $\geq 7$	
Progression from URI to LRI <sup>a</sup>	13/50 (26)	1/2 (50)	.470
Death at 30 d	6/106 (6)	6/18 (33)	.002
Death at 90 d	13/106 (12)	9/18 (50)	.001

Abbreviations: ISI, immunodeficiency scoring index; LRI, lower respiratory infection; URI, upper respiratory infection.

<sup>a</sup>Evaluated in 52 patients treated at the URI stage (30 in the aerosolized group and 22 in the oral group).

### Mortality Comparison Between Oral and Aerosolized RBV

Patient demographic and clinical characteristics stratified by 30-day mortality are presented in Table 4 and outcomes are shown in Tables 5 and 6. Patients who died within 30 days were more likely to receive corticosteroids than survivors (83% vs 50%;  $P = .034$ ) and to have lymphopenia (50% vs 16%;  $P = .012$ ), nosocomial infection (50% vs 8%;  $P = .001$ ), and a high-risk ISI score (50% vs 11%;  $P = .002$ ). No differences were noted in percentage of patients receiving oral RBV as their initial treatment between survivors (44%) and nonsurvivors (42%) ( $P = 1.000$ ). Significant predictors of 30-day mortality in the multivariate Cox proportional hazards model were nosocomial infection (adjusted hazard ratio [aHR], 4.75 [95% confidence interval {CI}, 1.13–20.01;  $P = .034$ ], LRI at diagnosis (aHR, 8.69 [95% CI, 1.24–60.97];  $P = .030$ ), and haploidentical transplant (aHR, 10.30 [95% CI, 1.04–102.06];  $P = .046$ ). Oral administration did not predict 30-day mortality (aHR, 0.93 [95% CI, .22–4.20];  $P = .960$ ) (Figure 1 and Supplementary Figures 1 and 2). Complete results of univariate and multivariate Cox proportional hazards models are depicted in Table 7. In the IPTW Cox proportional hazards model, treatment with oral RBV was not a significant predictor of 30-day mortality (HR, 1.12 [95% CI, .35–3.65];  $P = .845$ ).

Ninety-day mortality was significantly lower in oral RBV recipients compared with aerosolized RBV via multivariate Cox proportional hazards model (aHR, 0.27 [95% CI, .08–.95];  $P = .04$ ); however, no significant difference was observed in the IPTW model (HR, 0.52 [95% CI, .19–1.41];  $P = .20$ ). Other significant predictors of 90-day mortality generally reflected underlying comorbidities, including relapsed disease and high-risk transplant types (Supplementary Figures 3–5). Full demographic and clinical characteristics of patients and multivariate Cox proportional hazards model for 90-day mortality are presented in Supplementary Tables 4 and 5.

For patients with LRI on presentation, there was no difference in 30- and 90-day mortality between oral and aerosolized therapy (30-day mortality: oral, 4/29 [13.8%] vs aerosolized, 6/39 [15.4%],  $P = 1.0$ ; 90-day mortality: oral, 5/29 [17.2%] vs aerosolized, 12/39 [30.8%],  $P = .263$ ).

### Progression From URI to LRI

Fifty-two patients were treated with RBV at the URI stage and 17 (33%) progressed. Oral RBV was not a significant predictor of progression to LRI in the traditional multivariate Fine-Gray competing risk model (adjusted subhazard ratio [SHR], 0.67 [95% CI, .25–1.83];  $P = .44$ ) (Figure 2) or in the IPTW Fine-Gray competing risk model (SHR, 0.72 [95% CI, .24–2.14];  $P = .55$ ). The full Fine-Gray competing risk model is presented in Supplementary Table 6.

### ICU Transfer and Need for Mechanical Ventilation

The ICU transfer rate and need for mechanical ventilation in oral vs aerosolized RBV patients was similar (ICU transfer: 7% vs 10%,  $P = .76$ ; mechanical ventilation: 6% vs 10%,  $P = .511$ ).

**Table 4. Baseline Demographic and Clinical Characteristics of Hematopoietic Cell Transplant Recipients Stratified by 30-Day Mortality Status (n = 124)**

Variable	No. (%)			P Value
	Alive (n = 112)	Died (n = 12)	Total	
Median age, y (range)	59 (21–79)	62 (28–80)	59 (21–80)	.384
Male sex	72 (64)	8 (67)	80 (65)	1.000
Race/ethnicity				.790
White	80 (71)	11 (92)	91 (73)	
Hispanic	17 (15)	1 (8)	18 (15)	
Black	10 (9)	0 (0)	10 (8)	
Asian	3 (3)	0 (0)	3 (2)	
Other	2 (2)	0 (0)	2 (2)	
Type of malignancy				.740
AML	30 (27)	3 (25)	33 (27)	
ALL	8 (7)	0 (0)	8 (6)	
CML	4 (4)	1 (8)	5 (4)	
CLL	1 (1)	0 (0)	1 (1)	
MDS	9 (8)	0 (0)	9 (7)	
Hodgkin lymphoma	3 (3)	0 (0)	3 (2)	
Non-Hodgkin lymphoma	7 (6)	2 (17)	9 (7)	
Multiple myeloma	36 (32)	5 (42)	41 (33)	
Other	14 (13)	1 (8)	15 (12)	
Relapsed	28 (25)	5 (42)	33 (27)	.300
Donor relationship				.650
Matched related	28 (25)	1 (8)	29 (23)	
Matched unrelated	27 (24)	3 (25)	30 (24)	
Haploidentical	10 (9)	2 (17)	12 (10)	
Mismatched	2 (2)	0 (0)	2 (2)	
Cord	4 (4)	2 (4)	4 (3)	
Autologous	41 (37)	6 (50)	47 (38)	
Myeloablative conditioning regimen	103 (92)	12 (100)	115 (93)	.598
Median time from HCT to infection, d (range)	480 (–1 to 7090)	391 (–1 to 2461)	466 (–1 to 7090)	.710
Acute GVHD	12 (11)	3 (25)	15 (12)	.161
Chronic GVHD	27 (24)	0 (0)	27 (22)	.067
Corticosteroid use	56 (50)	10 (83)	66 (53)	.034
Neutropenia <sup>a</sup>	8 (7)	3 (25)	11 (9)	.074
Lymphopenia <sup>b</sup>	18 (16)	6 (50)	24 (19)	.012
Nosocomial infection	9 (8)	6 (50)	15 (12)	.001
Stage at RSV diagnosis				.064
URI	54 (48)	2 (17)	56 (45)	
LRI	58 (52)	10 (83)	68 (55)	
Stage at RBV initiation				.072
URI	50 (45)	2 (17)	52 (42)	
LRI	62 (55)	10 (83)	72 (58)	
First mode of RBV administration				1.000
Aerosolized	63 (56)	7 (58)	70 (56)	
Oral	49 (44)	5 (42)	54 (44)	
ISI				
Low risk	12 (11)	1 (8)	13 (10)	1.000
Moderate risk	88 (79)	5 (42)	93 (75)	.010
High risk	12 (11)	6 (50)	18 (15)	.002

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; GVHD, graft-vs-host disease; HCT, hematopoietic cell transplant; ISI, immunodeficiency scoring index; LRI, lower respiratory infection; MDS, myelodysplastic syndrome; RBV, ribavirin; RSV, respiratory syncytial virus; URI, upper respiratory infection.

<sup>a</sup>Absolute neutrophil count <500 cells/ $\mu$ L.

<sup>b</sup>Absolute lymphocyte count <200 cells/ $\mu$ L.



**Table 5. Outcomes of Hematopoietic Cell Transplant Recipients Stratified by Treatment With Aerosolized or Oral Ribavirin for Respiratory Syncytial Virus Infection (n = 124)**

Outcome	No. (%)			P Value
	Aerosolized (n = 70)	Oral (n = 54)	Total	
Progression from URI to LRI <sup>a</sup>	8 (27)	6 (27)	14 (27)	1.000
Death at 30 d	7 (10)	5 (9)	12 (10)	1.000
Death at 90 d	16 (23)	6 (11)	22 (18)	.102
Median length of stay, d (IQR)	7 (5–20)	7 (4–16)	NA	.150
Transfer to ICU <sup>b</sup>	7 (10)	4 (7)	11 (9)	.755
Mechanical ventilation <sup>b</sup>	7 (10)	3 (6)	10 (8)	.511

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ICU, intensive care unit; IQR, interquartile range; LRI, lower respiratory infection; NA, not available; URI, upper respiratory infection.

<sup>a</sup>Evaluated in 52 patients treated at the URI stage (30 in the aerosolized group and 22 in the oral group)

<sup>b</sup>After treatment initiation, as assessed by transfer to ICU or initiation of mechanical ventilation 1 calendar day or later after treatment initiation.

### Development of Grade 3 or Greater Anemia

Hemoglobin levels were similar between aerosolized and oral groups at baseline, day 7, and day 14, as was new-onset grade 3 anemia classified by the Common Terminology Criteria for Adverse Events (Supplementary Table 7).

## DISCUSSION

In this study, HCT recipients with RSV infections had similar mortality and progression to LRI when treated with aerosolized or oral RBV. Despite the use of multiple statistical methods including propensity score-based modeling, no signals of increased efficacy of aerosolized RBV were observed. Moreover, oral RBV was not associated with increased rates of grade 3 or greater anemia. These findings suggest that oral RBV may be a safe and effective alternative to aerosolized RBV for the

treatment of RSV in HCT recipients and have important implications for HCT programs given the significant aerosolized RBV costs.

Treatment options for RSV infection in HCT recipients are limited. RBV is the only commonly used pharmaceutical agent and is marketed in 3 formulations: aerosolized, oral, and intravenous. The intravenous formulation is not approved by the US Food and Drug Administration (FDA) and is not routinely available for clinical use [20]. Although aerosolized RBV is only FDA-approved for the treatment of RSV in children, several retrospective studies suggest that treatment with aerosolized RBV is associated with reduced mortality in HCT recipients and is thus broadly used for this indication [13, 21–23]. Due to teratogenicity, aerosolized RBV must be administered while inpatient via a scavenging tent, and the 6- to 18-hour daily administration time is challenging for patients and providers [9].

In 2015, the cost of aerosolized RBV increased by 400% to roughly \$30 000 per day, placing the cost of a 5-day treatment course at a staggering \$150 000 [14]. As a result, aerosolized RBV is no longer viable for many institutions, leaving oral RBV (~\$25/day) as the only available treatment [14, 15]. At our institution, aerosolized RBV remained unrestricted, but given the widespread publicity over the increased cost of therapy and ease of oral administration, a shift in use toward oral RBV occurred naturally over the last 3 RSV seasons. However, the paucity of data on oral RBV for RSV in HCT recipients has limited its widespread acceptability as an equivalent alternative to aerosolized RBV.

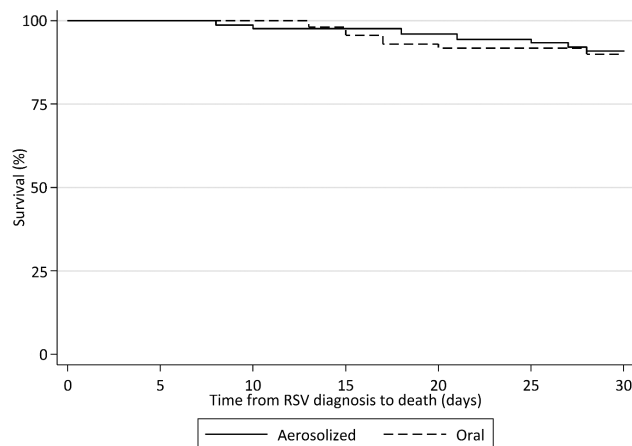
Prior studies of oral RBV in HCT patients provide limited, mixed results [3, 9, 11, 12, 24, 25]. To our knowledge, ours is the largest study to date that compared outcomes of oral and aerosolized RBV for RSV in HCT recipients. Thirty-day mortality rates were similar between groups, while 90-day mortality was significantly lower in recipients of oral RBV in the

**Table 6. Outcomes of Hematopoietic Cell Transplant Recipients Treated With Aerosolized or Oral Ribavirin for Respiratory Syncytial Virus and Stratified by Immunodeficiency Scoring Index**

Outcome	No. (%)		P Value
	ISI <7	ISI ≥7	
Progression from URI to LRI <sup>a</sup>			
Aerosolized	7/29 (24)	1/1 (100)	.270
Oral	6/21 (29)	0/1 (0)	1.000
Death at 30 d			
Aerosolized	3/58 (5)	4/12 (33)	.010
Oral	3/48 (6)	2/6 (33)	.090
Death at 90 d			
Aerosolized	9/58 (16)	7/12 (58)	.004
Oral	4/48 (8)	2/6 (33)	.130

Abbreviations: ISI, immunodeficiency scoring index; LRI, lower respiratory infection; URI, upper respiratory infection.

<sup>a</sup>Evaluated in 52 patients treated at the URI stage (30 in the aerosolized group and 22 in the oral group).



**Figure 1.** Kaplan-Meier 30-day survival curve for hematopoietic cell transplant recipients treated with aerosolized or oral ribavirin for respiratory syncytial virus infection (n = 124). Abbreviation: RSV, respiratory syncytial virus.

**Table 7. Cox Proportional Hazards Regression Model for 30-Day Mortality**

Factor	Bivariate Model			Multivariate Model		
	HR	(95% CI)	PValue	HR	(95% CI)	PValue
Oral RBV	0.93	(.29–2.92)	.90	0.96	(.22–4.20)	.96
Neutropenia <sup>a</sup>	3.88	(1.05–14.35)	.04	0.60	(.09–4.10)	.61
Lymphopenia <sup>b</sup>	4.88	(1.57–15.14)	<.01	0.90	(.07–11.08)	.94
Acute or chronic GVHD	0.63	(.17–2.33)	.49	...	...	...
Age >65 y	0.75	(.20–2.79)	.67	...	...	...
Recent corticosteroid use	4.73	(1.04–21.58)	.05	3.32	(.55–20.24)	.19
Recent HCT	0.97	(.13–7.51)	.98	...	...	...
High ISI risk	7.39	(2.38–22.97)	<.01	2.60	(.16–41.47)	.50
Male sex	0.93	(.28–3.08)	.90	...	...	...
White race	4.20	(.54–32.54)	.17	10.08	(.78–130.60)	.08
AML diagnosis	0.91	(.25–3.35)	.89	...	...	...
Relapsed disease	2.04	(.65–6.43)	.22	...	...	...
Nosocomial infection	8.74	(2.81–27.13)	<.01	4.75	(1.13–20.01)	.03
LRI at diagnosis	4.49	(.98–20.47)	.05	8.69	(1.24–60.97)	.03
<b>HCT type</b>						
MRD	Ref	...	...	...	...	...
MUD	3.00	(.31–28.94)	.34	...	...	...
Mismatched	NE	...	...	...	...	...
Haploidentical	4.94	(.45–54.63)	.19	10.30	(1.04–102.06)	.05
Cord	NE	...	...	...	...	...
Autologous	3.94	(.47–32.69)	.21	...	...	...

Abbreviations: AML, acute myeloid leukemia; CI, confidence interval; GVHD, graft-vs-host disease; HCT, hematopoietic cell transplant; HR, hazard ratio; ISI, immunodeficiency scoring index; LRI, lower respiratory infection; MRD, matched related donor; MUD, matched unrelated donor; NE, not estimated; RBV, ribavirin.

<sup>a</sup>Absolute neutrophil count <500 cells/ $\mu$ L.

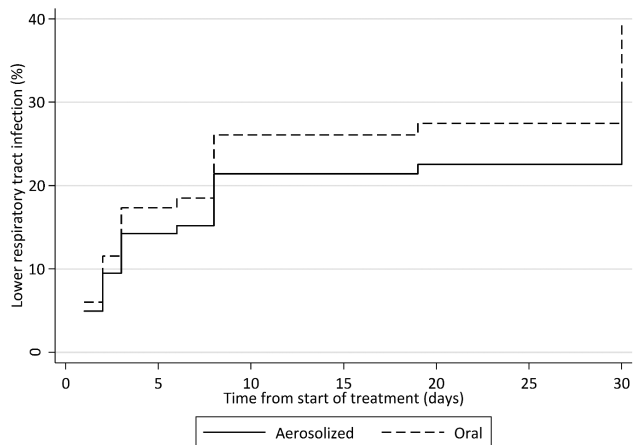
<sup>b</sup>Absolute lymphocyte count <200 cells/ $\mu$ L.

multivariate Cox proportional hazards model. As several other significant predictors of 90-day mortality reflect underlying high-risk transplants and relapse of the underlying malignancy, it is more likely that this reflects a degree of residual selection bias rather than a true efficacy signal. Although the number of patients at high risk (ISI  $\geq$ 7) was relatively low, no indicators of increased mortality were observed in patients treated with

oral RBV. Additionally, 30- and 90-day mortality was the same with oral or aerosolized RBV for patients with LRI, suggesting that the oral formulation is as effective as aerosolized therapy for lower respiratory disease.

Patients with URI had a similar progression rates to LRI regardless of treatment with oral or aerosolized RBV (both 27%). This finding was robust in both a standard Fine-Gray competing risk model and a propensity score-based analysis. As with mortality, patients at high risk for progression did not appear to be at any additional risk if treated with oral RBV. These findings contrast with those of Casey et al, who evaluated 13 patients treated with oral RBV for RSV infection after allogeneic HCT (7 URI) [11]. In that cohort, URI progression was documented in every case and 3 patients (23%) died from respiratory failure. However, those patients were treated a median of 14 days following transplantation, so were high risk for progression regardless of treatment, whereas our cohort included the entire posttransplantation spectrum.

Our study did not include a comparator group that did not receive RBV and there are limited data comparing oral RBV to no therapy. Fifty-six patients at the University of Heidelberg were treated with oral RBV during an RSV outbreak, 32 of whom were HCT recipients and received oral RBV [25]. Multivariable analysis identified that treatment with RBV was a protective factor against fatal outcomes ( $P = .02$ ). Marcelin



**Figure 2.** Cumulative incidence function for progression to lower respiratory infection in hematopoietic cell transplant recipients treated with aerosolized or oral ribavirin for upper respiratory syncytial virus infection (n = 52).

et al assessed oral RBV administered to immunocompromised patients with RSV infection, including 25 recipients of HCT, with no patient deaths attributable to RSV [12]. More recently, Gorcea et al examined the effectiveness of oral RBV treatment of RSV in 23 allogeneic HCT recipients. No patients had a high-risk ISI score, and 4 patients were escalated to aerosolized therapy. After a median 17 months of follow-up, 17 of 23 patients (74%) were alive and only 1 death was RSV related [9].

At our institution, aerosolized RBV is most commonly dosed intermittently at 2 g over 3 hours 3 times per day. Two common dosing strategies for oral RBV are used: (1) a fixed dose of 600 mg every 8 hours or (2) a loading dose of 10 mg/kg followed by 20 mg/kg/day divided into 3 doses, both with adjustments for renal dysfunction [26–28]. Both of the doses used are based on those reported in the literature; however, the optimal dosing of RBV for RSV has not been established [7, 15]. Similarly, the optimal duration of therapy is unknown and substantial heterogeneity in practice is reported [3, 7, 9, 11, 12, 14, 24, 25]. Assessment of the optimal dose and duration of oral RBV is an area of ongoing research for our group.

Strengths of our study include comparisons of outcomes by both RBV formulation and disease severity after controlling for many cofounders. Additionally, the size of our institution and inclusion of 3 consecutive RSV seasons allowed for the inclusion of a large number of patients with different HCT types and risk strata, including relapsed disease. However, our study has some limitations. This was a single-center study that evaluated only HCT recipients; therefore, generalizability to non-transplant recipients and other institutions may be limited. Our study included low-risk HCT patients (ISI = 0–2) that may not require treatment with RBV; however, this group comprised a small portion (10%) of our cohort. Similarly, the number of patients in the high-risk group (ISI = 7–12) was low (15% of the cohort); thus, the impact of oral RBV in these high-risk patients needs further study. Last, our study was retrospective in nature and there were significantly more patients with lymphopenia in the aerosolized group, although this was not found to be independently associated with mortality on the multivariate analysis (Table 7).

In summary, our study provides evidence supporting the use of oral RBV in place of aerosolized RBV for the treatment of RSV infection in HCT recipients, including patients at high risk for progression and mortality. These findings still require validation, preferably via prospective trial. As many institutions have already adopted this practice, our findings may address some of the remaining concerns over the use of oral instead of aerosolized RBV in HCT patients.

### Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

### Notes

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