



Respiratory syncytial virus in hematopoietic cell transplant recipients and patients with hematologic malignancies

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ABSTRACT

In the USA and other western nations, respiratory syncytial virus is one of the most commonly encountered respiratory viruses among patients who have been diagnosed with a hematologic malignancy or who have undergone a stem cell transplant. Multiple studies have been performed to evaluate the complications associated with respiratory syncytial virus infections. Other studies have evaluated therapeutic agents and strategies in which these agents can be used. There have also been numerous reports of outbreaks in bone marrow transplant units and oncology wards, where infection control measures have been invaluable in controlling the spread of disease. However, despite these novel approaches, respiratory syncytial virus continues to be potentially fatal in immunocompromised populations. In this review, we discuss the incidence of respiratory syncytial viral infections, risk factors associated with progression from upper respiratory tract infection to lower respiratory tract infection, other complications and outcomes (including mortality), management strategies, and prevention strategies in patients with a hematologic malignancy and in hematopoietic cell transplant recipients.

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Introduction

Community respiratory viruses are a common cause of respiratory infections.¹⁻³ These viruses are perhaps best known for their seasonal variation. The outcomes of these infections vary on the basis of the patient population, with adverse outcomes having been described in hematopoietic cell transplant (HCT) recipients and patients with a hematologic malignancy (HM).⁴⁻⁹ One of the most common community respiratory viruses that may lead to the death of HCT recipients and HM patients is respiratory syncytial virus (RSV),⁴⁻¹⁰ whose incidence is second only to that of influenza according to prior reports;^{4,5,8,11,12} other viruses include parainfluenza virus, metapneumovirus, adenovirus, rhinovirus, and bocavirus.

Different strategies have been used for the management of RSV infections in immunocompromised patients, and HCT recipients in particular, including ribavirin in its different formulations, intravenous immunoglobulins (IVIG), RSV immunoglobulins, and RSV monoclonal antibodies.⁶ In addition, effective measures have been used to curtail outbreaks of RSV infection in numerous bone marrow transplantation units and oncology wards, with some success;¹³⁻¹⁹ however, despite some advances over the past two decades in early detection and management of RSV infections in immunocompromised patients, the outcomes related to these infections remain poor.

In this review, we summarize the published data on RSV infections in adult HCT recipients and HM patients, focusing on recent findings. We highlight the incidence of RSV infections, risk factors associated with progression from upper respiratory tract infection (URTI) to lower respiratory tract infection (LRTI), other complications and outcomes (including mortality), management strategies including new agents under investigation, and prevention strategies.

Incidence of respiratory syncytial virus Infection

RSV has been considered a major cause of respiratory viral infection in HM and HCT patients since the 1980s. In the USA alone, RSV accounts for approximately

30% to 37% of respiratory viral infections in this population, with approximately 19% to 36% of these infections resulting in LRTI.^{4,20} Determination of the true incidence of RSV infection among HCT recipients has been challenging, with a reported wide range of 5% to 49%,^{5,8,18,21-28} as many studies included symptomatic patients diagnosed with different laboratory assays such as RSV antigen detection, identification of RSV by direct fluorescent antibody, viral cultures, and molecular assays in recent years (Table 1). In addition, the wide range of reported incidences of RSV infections could be due to the increased awareness of this virus over the years and its impact on immunocompromised patients. On the other hand, lower incidences of RSV infections were reported in studies in which molecular assays such as multiplex polymerase chain reaction were used to detect RSV, with the reported range in these cases being 8-30%.^{8,9,29} This lower incidence could be explained by the increased rate of diagnosing other respiratory viruses, such as coronavirus, rhinovirus, and parainfluenza, with the use of molecular assays.

The proportion of RSV infections causing LRTI in HCT recipients ranges from 30% to 60% with higher rates reported in earlier years (in the early 1990s),^{5,21,22} whereas in more recent studies, since year 2000, lower rates of LRTI (24-44%) have been observed.^{4,11,23-25,29,30} This could possibly be explained by the increased use of ribavirin at earlier stages of RSV infection to prevent the infection from progressing to the lower respiratory tract, as well as the use

of molecular assays for the detection not only of RSV but also other respiratory viruses. Recent studies from the Fred Hutchinson Cancer Research Center on respiratory viral infections in HCT patients applied specific definitions to better delineate the types of LRTI associated with respiratory viral infections.³¹ Patients with proven or probable LRTI were defined as patients with microbiological detection of respiratory viruses in the lower respiratory tract with or without radiological evidence of disease in the lungs, respectively. Patients with possible LRTI were defined as patients with microbiological detection of respiratory viruses in the upper respiratory tract only and with radiological evidence of disease in the lungs.³¹ In one of the studies, the proportions of patients with proven/probable or possible RSV LRTI were 48% and 52%, respectively.³¹ Interestingly, the authors showed that patients with proven or probable LRTI had a higher need for supplemental oxygen use and for mechanical ventilation compared to those with possible LRTI. These definitions were also applied in studies on coronavirus,³² parainfluenza virus³³ and rhinovirus.³⁴

Data on RSV infections in HM patients are scarce. Some studies have reported the rate of RSV infections in these patients.^{4,28,29,35-37} In an early study, the incidence of RSV was 31% among all symptomatic HM patients, including HCT recipients. A large proportion of these infections were diagnosed as LRTI (36%).²⁹ Similar studies reported a range of 3% to 37%, but the sample sizes were relative-

Table 1. Incidence rates of respiratory syncytial virus infections and lower respiratory tract infections among symptomatic hematopoietic cell transplant recipients.

Date of publication	Country	Study type	Detection methods	Percentage of allogeneic HCT	Total number of RSV cases (%)	Percentage of LRTI	Authors
1991	USA	Retrospective observational	RSV antigen and viral culture	73%	3 (5%)	33%	Garcia <i>et al.</i> ¹⁸
1996	USA	Retrospective observational	RSV antigen, viral culture and pathology	52%	33 (49%)	61%	Whimbey <i>et al.</i> ²¹
2001	Multiple European nations	Prospective observational	RSV antigen and viral culture	90%	20 (10%)	60%	Ljungman <i>et al.</i> ⁵
2002	England	Retrospective observational	RSV antigen and viral culture	100%	13 (37%)	46%	Chakrabarti <i>et al.</i> ²³
2002	USA	Retrospective observational	RSV DFA, RSV antigen and viral culture	89%	48 (9%)	52%	Small <i>et al.</i> ²²
2003	Brazil	Prospective observational	RSV antigen	72%	27 (40%)	56%	Machado <i>et al.</i> ²⁷
2003	USA	Prospective observational	Viral culture and RSV PCR	45%	11 (30%)	36%	Rogmann <i>et al.</i> ²⁹
2003	England	Retrospective observational	RSV antigen and viral culture	83%	6 (21%)	33%	Hassan <i>et al.</i> ²⁵
2005	Spain	Prospective observational	RSV antigen and viral culture	54%	19 (11%)	37%	Martino <i>et al.</i> ²⁸
2009	Sweden	Retrospective observational	RSV antigen and viral culture	100%	32 (12%)	44%	Avetisyan <i>et al.</i> ²⁴
2013	Brazil	Retrospective observational	RSV PCR	29%	14 (14%)	NA	Moreira <i>et al.</i> ⁸
2014	Italy	Prospective observational	RSV PCR	95%	21 (8%)	11%	Mikulska <i>et al.</i> ⁷

HCT: hematopoietic cell transplant; RSV: respiratory syncytial virus; LRTI: lower respiratory tract infection; DFA: direct fluorescent antibody detection; PCR: polymerase chain reaction, NA: not available.

ly small.^{28,35,36} In a recent study, 181 HM patients with RSV infections were identified over 13 years.³⁷ Of these, 65% and 35% presented with URTI and LRTI, respectively. Among the HM patients with URTI, 13% progressed to develop a LRTI (73% were patients with leukemia, 27% with multiple myeloma, and none with lymphoma).³⁷ In a recent study from our institution focusing on RSV LRTI in HM patients who had or had not undergone HCT, we found that most HM patients who had not undergone HCT were defined as having possible RSV LRTI as bronchoscopy had not been performed in most of these patients at the time of diagnosis.³⁸

Few data are available with regards to RSV infections in pediatric HCT recipients. The estimated incidence of RSV infections among this population is 3% to 7%,^{39,40} with 22%-37%^{39,41} developing LRTI.

Risk factors for the progression of upper to lower respiratory tract infection

The most significant complication of RSV infection in HM patients and HCT recipients is progression to LRTI, which is associated with a higher mortality rate.^{5,20,22,24,25,42,51} Many risk factors for progression have been identified in the hopes that target populations that could benefit from early therapy could be identified. These risk factors primarily consist of host factors, as previous studies on RSV serotypes A and B found no differences in outcomes.^{35,52}

To assist with the identification of HCT recipients who are at risk of progression to LRTI and a fatal outcome, an Immunodeficiency Scoring Index (ISI) for RSV was developed based on a combination of multiple host risk factors,⁵³ which means it is applicable to other respiratory viruses. Six factors were included in the scoring index: neutropenia of less than 500 neutrophils/mL, lymphopenia of less than 200 lymphocytes/mL, age greater than 40 years, graft-versus-host disease, steroid use, myeloablative chemotherapy, and time from HCT.⁵³ On the basis of the total score, the ISI stratifies HCT recipients with RSV URTI into low-risk (score of 0-2), medium-risk (score of 3-6), and high-risk (score of 7-12) categories.⁵³ Other risk factors that were identified in other studies and were not included in the ISI were smoking status,⁵⁴ hypoxia,²⁸ nosocomial infection,^{28,37} matched unrelated donor/mismatched donor status,^{25,42,55} prior autologous HCT, and stem cell source^{25,28} (Table 2). The ISI for RSV has been validated by other authors^{12,56} (Table 3). Wang *et al.* found that allogenic HCT recipients with high ISI scores experienced progression to pneumonia after being diagnosed with RSV, influenza, coronavirus, or adenovirus.¹²

There is currently no predictive scoring index for the progression of respiratory viruses in patients with leukemia, lymphoma, or multiple myeloma. On the other

hand, there are well-described risk factors that are associated with progression to LRTI in HM patients; these include lymphopenia and neutropenia,^{4,28,37,54,55,57} which are generally defined as ≤ 200 lymphocytes/mL^{37,54,57} and ≤ 500 neutrophils/mL, respectively. In multiple retrospective analyses of HCT recipients, lymphocytopenia^{4,37,54,57} and neutropenia^{4,37,54,57} at the time of the diagnosis of RSV were independent predictors of progression to LRTI.

In a cohort of 237 allogeneic HCT recipients with RSV infection, the hazard ratio (HR) of experiencing progression from RSV URTI to LRTI was 4.1 for an absolute neutrophil count of < 500 cells/mL and 2.6 for an absolute lymphocyte count of < 200 cells/mL,⁵³ making them the most predictive factors for progression.⁵³ Among leukemia patients, post-induction chemotherapy neutropenia and leukopenia have also been shown to increase the risk of progression to LRTI.^{22,24} In a recent retrospective study, neutropenia and lymphopenia were not independently associated with progression of disease in HM patients, but the combination of the two factors was associated with a higher risk of progression.³⁷ However, time from last chemotherapy was not shown to play a role in progression to LRTI in HM patients.³⁷ On the other hand, lack of ribavirin therapy was associated with progression of dis-

Table 2. Risk factors for progression to respiratory syncytial virus lower respiratory tract infections among hematopoietic cell transplant recipients and patients with hematologic malignancies.

Risk factors for progression to RSV LRTI	
HCT recipients	Patients with hematologic malignancies
Neutropenia ≤ 500 cells/mL	Neutropenia ≤ 500 cells/mL
Lymphopenia ≤ 200 cells/mL	Lymphopenia ≤ 200 cells/mL
Age ≥ 40 years	
HCT within 1 year of infection	
Myeloablative chemotherapy within 1 year of infection	
Presence of GvHD	
Use of steroids within 2 weeks of infection	
History of smoking	
Nosocomial infection	
Hypoxia	
Matched unrelated donor transplant/mismatched donor source	
Prior autologous HCT	
Cord blood as transplant cell source	

RSV: respiratory syncytial virus; LRTI: lower respiratory tract infection; HCT: hematopoietic cell transplant; GvHD: graft *versus* host disease.

Table 3. Outcome data stratified by respiratory syncytial virus-Immunodeficiency Scoring Index from three different cohorts.

ISI risk stratification	Shah <i>et al.</i> 2014 ⁵³			Wang <i>et al.</i> 2016 ¹²			Damlaj <i>et al.</i> 2015 ⁵⁶		
	Low n=69	Medium n=147	High n=21	Low n=17	Medium n=20	High n=7	Low n=11	Medium n=28	High n=6
Mortality rate, %	0	3	29	0	20	14	0	4	50
Rate of progression to LRTI, %	7	15	42	6	15	29	NA	NA	NA

ISI: Immunodeficiency Scoring Index; LRTI: lower respiratory tract infection.

ease in HCT recipients and HM patients with RSV infections.^{37,53,58} The protective benefits of ribavirin are discussed further in the treatment section.

Long-term complications of respiratory syncytial virus infection

Certain long-term complications after RSV infection have been described in HCT recipients, with the most widely described long-term complication being a reduction in pulmonary function.^{24,43,59-61} Delayed engraftment after RSV infection is less commonly described, with an uncertain association in small numbers of patients.^{45,46,62}

A decrease in forced expiration in 1 second (FEV₁) by more than 5% from baseline after HCT has been associated with poor outcomes.⁶³ In fact, previous studies have shown that a decrease in FEV₁ of 10% or greater is associated with the development of bronchiolitis obliterans.⁶⁴ However, the relationship between respiratory viruses (RSV in particular) and changes in FEV₁ or other markers of pulmonary function is not fully understood.

There are limited data on HCT recipients and pulmonary function (including changes in FEV₁ and oxygen diffusion capacity) after an RSV infection. Avetisyan *et al.* showed that, compared to a control group, HCT recipients with RSV infections were more likely to develop mild or marked changes in vital capacity or diffusion capacity during pulmonary function tests.²⁴ Subsequently, Seo *et al.* described significant decreases in patients' diffusion capacity 3 months after RSV infection, which persisted for a year.⁴⁵ There were some indications that FEV₁ and total lung capacity were also affected, but the sample size was too small to draw definite conclusions. Another study compared the effects of different viruses on pulmonary function in HCT recipients;⁶⁰ RSV and parainfluenza were associated with FEV₁ decreases of at least 10%. It was postulated that subclinical shedding of these viruses may augment airway inflammation, leading to airway restriction. In comparison, lung transplant recipients who are infected with respiratory viruses are at increased risk of developing bronchiolitis obliterans, with an associated mortality of up to 29%.⁶⁵ Similarly, HCT recipients with prior respiratory viral infections were more likely to develop bronchiolitis obliterans or changes in FEV₁,^{59,66} with a higher mortality rate than that of patients without bronchiolitis obliterans (HR: 2.7).⁵⁹

Delayed or failed engraftment of stem cells during or after acute RSV infection has been reported; however, it is an uncommon complication with a total of only seven patients having been described in a few case series.^{45,46,62} This association was first described in 1999 by McCarthy *et al.*, who noted that four patients with graft failure had had an RSV infection in the pre-engraftment period,⁴⁵ with no other identified infections. Furthermore, during an RSV outbreak in a hematologic unit in Australia, delayed neutrophil and platelet engraftment occurred in two autologous HCT recipients and graft failure occurred in one allogeneic HCT recipient with an RSV infection.⁶² On the other hand, a study by Waghmare *et al.* showed no significant changes in lymphocyte count dynamics in HCT recipients who experienced progression to RSV LRTI compared to patients who did not.⁴⁶ Overall, there are very limited data supporting that RSV infection *per se* leads to graft failure or contributes to a delay in engraftment.

Mortality and associated risk factors

High mortality rates have been reported in HM patients and HCT recipients with RSV infection. RSV-attributable mortality rates in HCT recipients vary between 0% in outbreak situations,^{48,62,67} in which some patients received reduced-intensity conditioning regimens,⁶² and 43% in other circumstances.^{5,20,22,24,25,42-51} When HCT recipients develop RSV LRTI, the mortality rate can range from 21% to 83%.^{4,31,42,43,45,46,48,68} Of note, when HCT recipients with RSV infections were classified into those with possible RSV LRTI (only radiological evidence of chest abnormalities and negative or no bronchoscopy data) or proven RSV LRTI (RSV detected in the lower respiratory tract),³¹ the mortality rate increased from 0% to 26%, respectively.³¹ Multiple other risk factors for mortality from RSV have been identified, most of which are host-related, including neutropenia and lymphopenia, time from transplant to infection, cell source, older age, steroid exposure, graft-versus-host disease, hypoxia, and the use of myeloablative chemotherapy.^{25,42,43,46,47} The RSV-ISI has been validated to predict mortality risk in HCT recipients^{12,53,56} (Table 2). Based on the derivative cohort of allogeneic HCT recipients with RSV infections, the predicted mortality for patients with high RSV-ISI was 29%⁵³ and 50% in one of the validation cohorts.⁴⁴ Interestingly, some studies showed that ribavirin may have a protective effect in HCT recipients and HM patients.^{37,42,44,53,58} This is discussed further in the treatment section.

Delaying transplant in patients diagnosed with RSV or other respiratory viruses prior to HCT was shown to improve survival.⁶⁹ Campbell *et al.* reviewed 116 patients who had pre-transplant respiratory viral infections and found that, regardless of the virus, they had a higher 100-day mortality rate than did those without infections.⁷⁰ At our institution, HCT is delayed for approximately 2 weeks when patients are diagnosed with RSV infections prior to transplantation.

Among HCT recipients with RSV infections, mortality was considerably lower in pediatric patients than in adults. Mortality varied from 0 to 5% among all pediatric HCT recipients with RSV infections^{39,41} and is higher in patients with LRTI (up to 15%).

The mortality rate amongst HM patients with RSV can be as high as 18%.^{4,50} The mortality rate in a small study conducted in the mid-1990s was 80% among leukemia patients with RSV LRTI who had recently undergone myelosuppressive chemotherapy.⁵⁷ More recent studies of HM patients with RSV LRTI found mortality rates of 8% to 17%.^{37,38,58} This better outlook could be explained in part by the improvement in supportive care over the years and the use of ribavirin for the treatment of RSV in this population of patients.^{37,58} Risk factors associated with mortality in RSV-infected leukemia patients include neutropenia (≤ 500 neutrophils/mL), lymphopenia (≤ 200 lymphocytes/mL), and a high APACHE II score at diagnosis.^{37,58} These host factors reflect the patients' immune status and its ability to curtail the impact of RSV infections. The severity and stage of the infection (URTI vs. LRTI) or the virulence of the RSV may also affect mortality. In HM patients with proven LRTI, the 30-day mortality rate was reported to be 36% compared to 14% in patients with possible LRTI.³⁸ In a recent retrospective analysis, patients with HM, including HCT recipients, in whom respiratory viral infections were detected in the intensive care unit

had a higher intensive care unit mortality rate, with the association being strongest when influenza, parainfluenza or RSV was detected.¹⁰

Treatment options for respiratory syncytial virus infection in patients with hematologic malignancies and in hematopoietic cell transplant recipients

The current treatments for RSV infections in immunocompromised adult patients are ribavirin, in different formulations [although it has not been approved by the Food and Drug Administration (FDA) for this purpose], and immuno-modulators, such as conventional IVIG or RSV monoclonal antibodies (palivizumab).

Ribavirin

Ribavirin is a nucleoside analog that is active against a broad spectrum of RNA viruses. It acts through intercalation into the RNA virus, enhancing its mutation rate. Ribavirin is available in aerosolized, oral, and intravenous formulations. Aerosolized ribavirin was approved by the FDA for the treatment of RSV LRTI in hospitalized infants and young children in 1985 and is the most studied formulation in HCT recipients.^{4,5,24,42,44,45,49,53,58,71-77} The conventional dosing regimen is 6 g delivered over 18 h through a small particle aerosol generator, with patients in a scavenger tent to decrease environmental contamination and exposure to healthcare workers (ribavirin is teratogenic). In an alternative regimen, the same total dose of ribavirin is given but is divided into three doses per day (2 g over 3 h, 3 times a day). This intermittent regimen was shown to be equivalent to the conventional continuous regimen in an adaptive randomized trial.⁷³

Most of the studies on the use of ribavirin for RSV infections in HCT recipients and HM patients are retrospective in nature, lacking a comparison or control group.^{26,45,73,74,79,80} Yet cumulative evidence, albeit not from clinical trials, suggests a better outcome when ribavirin is used in HCT recipients with early disease or URTI.^{4,46,71,78,81-83} A decrease in the rate of progression from RSV URTI to LRTI after aerosolized ribavirin therapy in HCT recipients with RSV infections was pronounced (from 59% to 20%) in one study.⁴ A randomized control trial that was halted before completing enrollment for different reasons, including slow accrual, showed a trend towards a lower rate of progression to LRTI when aerosolized ribavirin was used.⁷¹ Of the nine patients who were treated with ribavirin, only one experienced progression compared to two of the five patients who were not treated.

A systemic review of the treatment of RSV infections in adult HCT recipients showed an overall reduction in the rate of progression to LRTI, from 45% to 16%, and a reduction in the rate of RSV-related mortality in patients with LRTI, from 70% to 35%, after early treatment with aerosolized ribavirin.⁸⁴ In the largest retrospective study to date of the impact of aerosolized ribavirin therapy in HCT recipients (n=280) with RSV infections,⁴² early ribavirin therapy at the URTI stage reduced the risk of progression to LRTI. In addition, a lack of ribavirin therapy was associated with an increased mortality rate (odds ratio: 2.4).

Data on the use of ribavirin in HM patients with RSV infections are limited. Several retrospective studies demonstrated that early use of aerosolized ribavirin

reduced the mortality rate in leukemia patients with RSV infections.^{57,58} A large retrospective study of 181 HM patients showed better outcomes with aerosolized ribavirin.³⁷ On the other hand, Vakil *et al.* found that ribavirin use, at either the URTI or LRTI stage, did not reduce overall mortality,³⁸ but the objective of this study was to assess risk factors for mortality and not the role of ribavirin in HM patients. Although some of these studies showed a positive trend towards a benefit from therapy with ribavirin, specific recommendations cannot be made at present.

Despite our experience with aerosolized ribavirin for the treatment of RSV infections in adult HCT recipients and its increase in popularity over the years, a major shift to the oral formulation occurred around 3 years ago, at least at our institution, when the cost of ribavirin increased drastically.⁸⁵ Oral ribavirin has been used to treat RSV URTI or LRTI in both HCT recipients and HM patients.^{79,81,82,86-88} The dosing regimens vary between a weight-based regimen of 15 mg/kg to 60 mg/kg to a standardized dosage of 600 mg-800 mg twice daily or 600 mg three times daily for a maximum of 1800 mg/day. Oral ribavirin is more readily available than is aerosolized ribavirin and is well tolerated, on the basis of data on its long-term use in patients with hepatitis C virus infections.⁸⁹ In a retrospective analysis of our experience with aerosolized ribavirin and the recent switch to oral ribavirin, we found no significant differences in outcomes, including progression to LRTI and day 30 or 60 all-cause mortality, in HCT recipients with RSV infections.⁹⁰ On the basis of the results of a recent analysis, we propose the use of oral ribavirin as a viable alternative to aerosolized ribavirin (Figure 1). At our institution, we implemented a decision-making treatment algorithm as guidance for our clinical providers. HCT recipients are stratified on the basis of their RSV-ISI score and stage of RSV diagnosis (URTI vs. LRTI).

Side effects associated with oral and aerosolized ribavirin have been reported in prior publications. One of the common side effects associated with aerosolized ribavirin is that patients often complained of feeling “lonely” and seeing “hail” while they were in the scavenger tent.⁵⁷ There have been a few reports of hepatotoxicity associated with the use of aerosolized ribavirin.^{76,91} In a randomized, placebo-controlled trial assessing the use of aerosolized ribavirin for the treatment of RSV in HCT recipients, the rates of hepatotoxicity were similar in the two groups, although the sample size was small;⁷¹ no other side effects were noted in the trial. Hepatotoxicity was reported in association with the use of oral ribavirin for the treatment of hepatitis C virus.⁹² However, the observed hepatotoxicity was probably due to the co-administration of interferon therapy.⁹² In a retrospective study assessing the use of oral ribavirin in immunocompromised patients, including HCT recipients,⁷⁹ only one of the 38 patients who received oral ribavirin developed hemolytic anemia and lactic acidosis. The latter was thought to be due to severe gastrointestinal graft-versus-host disease. In a recent retrospective analysis comparing outcomes of HCT recipients with RSV infections who received either aerosolized or oral ribavirin,⁹⁰ two of 29 (6.9%) patients on oral ribavirin developed new-onset grade 3 or more anemia at day 14 compared to two of 41 (4.9%) patients who received the aerosolized formulation. These studies demonstrate that both aerosolized and oral ribavirin have similar safety profiles.

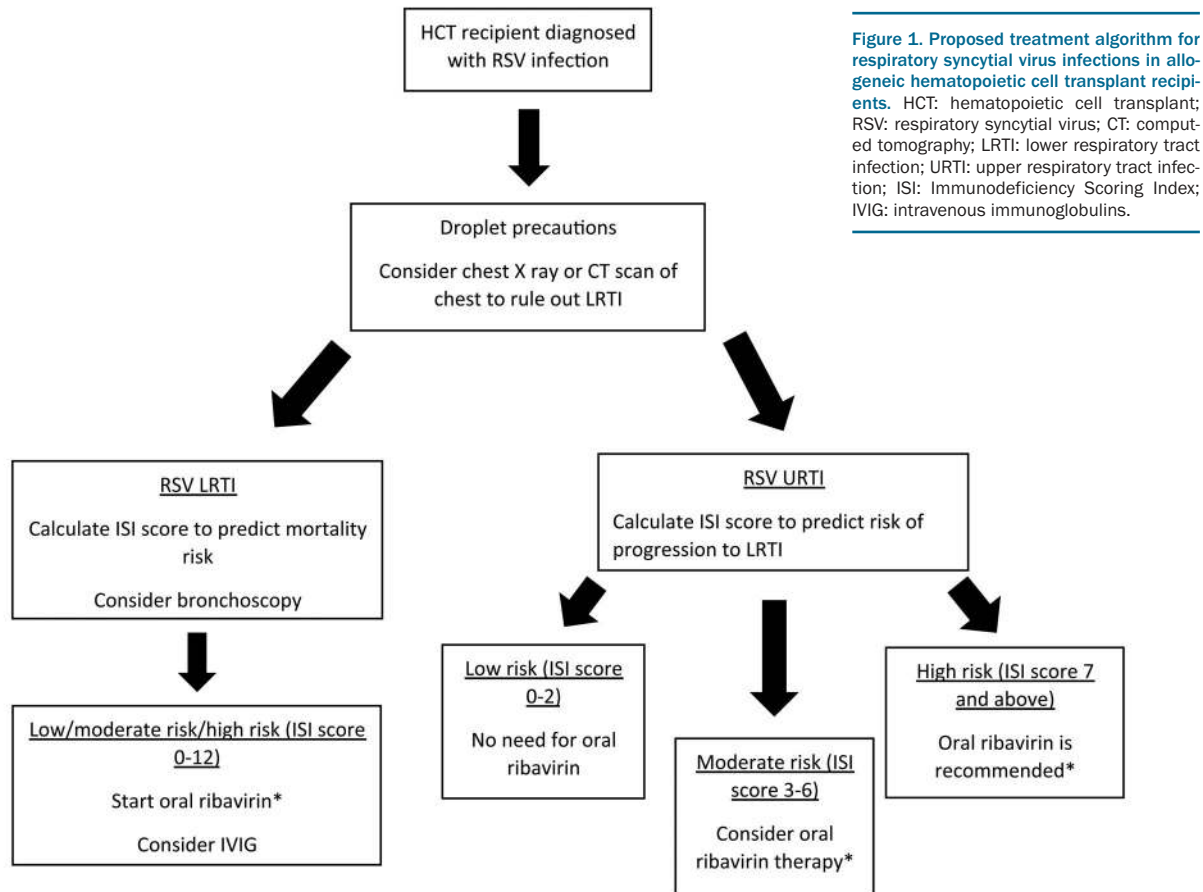


Figure 1. Proposed treatment algorithm for respiratory syncytial virus infections in allogeneic hematopoietic cell transplant recipients. HCT: hematopoietic cell transplant; RSV: respiratory syncytial virus; CT: computed tomography; LRTI: lower respiratory tract infection; URTI: upper respiratory tract infection; ISI: Immunodeficiency Scoring Index; IVIG: intravenous immunoglobulins.

*If patient is unable to take oral ribavirin, it can be substituted with the aerosolized formulation.

Intravenous ribavirin has been used to treat RSV infection in HCT recipients.^{24,45,49,80} The most common regimen used is a single 33 mg/kg loading dose, followed by 16 mg/kg four times a day for 4 days with a maintenance dose of 8 mg/kg three times a day until symptoms resolve. The intravenous formulation of ribavirin is not readily available in the USA due to the lack of FDA approval; however, it can be acquired through the FDA for emergency or compassionate use.

Adjunctive therapies

Many immunomodulators have been used as adjunctive therapy for RSV infections in adult HM patients and HCT recipients. There have been no randomized control trials comparing the benefits of adding IVIG to ribavirin therapy. Many retrospective analyses have reported variable results for this combination.^{22,42,45,46,49,53,85,93,94} Shah *et al.* suggested a minimal benefit in HCT recipients with RSV infections;⁴² all 51 HCT patients who were treated with combination therapy survived, and only one of 61 patients treated with ribavirin alone died. This was not evaluated in multivariate analysis. Another study showed no clinical benefit in HCT recipients who received weekly or high-dose IVIG as adjunctive therapy for RSV infections.⁴⁶ It was hypothesized that humanized IVIG lacks sufficient specific antibodies to RSV, which would explain the mixed results seen in retrospective studies.

RSV-specific monoclonal antibodies, such as palivizumab, have also been evaluated for the treatment of RSV infections in HCT recipients and HM patients. Originally, palivizumab was approved for the prevention of RSV infections in neonates and children. Experience with palivizumab as treatment in HCT recipients with RSV is very limited. Several studies showed no survival benefit when comparing palivizumab as adjunctive therapy to ribavirin as monotherapy for RSV infections in adult HCT recipients.^{42,46,83,95,96} In a recent retrospective study of a mixed population of adult HCT recipients and patients with HM,⁹⁷ those treated with palivizumab for RSV infections showed a trend towards better 90-day survival compared to the control group, with mortality rates of 11% compared to 17%, respectively.⁹⁷ However, this difference was not statistically significant and recommendations for the routine use of palivizumab in this population of patients cannot be made.

Investigational agents

As previously discussed, there are limited therapeutic options for RSV infections and new therapies are desperately needed. Presatovir is an oral RSV fusion inhibitor with selective anti-RSV activity *in vitro*. In a phase I, first-in-human, single- and multiple-ascending dose study,⁹⁸ presatovir had an excellent safety profile, despite having an extended half-life. The oral bioavailability was also

good, regardless of prandial state.⁹⁸ Although clinical trials on RSV infections in transplant recipients have been challenging due to low recruitment,⁷¹ two phase II trials on presatovir in HCT recipients with RSV infections were recently completed^{99,100} (*ClinicalTrials.gov* number NCT02254408). To overcome potential low recruitment, 189 HCT recipients with RSV infections limited to the upper respiratory tract were recruited from a total of 43 centers in nine countries over 2.5 years.^{99,100} Preliminary data showed that presatovir was not effective at reducing nasal RSV viral load over time or at reducing the incidence of lower respiratory tract complications. However, in an exploratory analysis, presatovir did reduce the rate of progression to lower respiratory tract complications in patients with lymphopenia relative to the rate in placebo-treated patients. Furthermore, presatovir was not effective at reducing nasal RSV viral load, supplemental oxygen use or all-cause mortality in another phase II trial in HCT recipients with RSV LRTI.^{99,100} Several lessons were learned from the two trials. HCT recipients with one or more risk factors (i.e. lymphopenia, neutropenia, or infected within a year from transplant) for poorer outcomes from RSV infections may benefit the most from an effective antiviral therapy. On the other hand, time from symptom onset and time before the development of lower respiratory tract complications are probably critical factors in determining the effectiveness of fusion inhibitors.

The development of another novel agent, ALX-0171, was recently stopped and the drug may not enter clinical trials on RSV infections in HCT recipients. This inhaled agent is a trivalent nanobody that inhibits RSV replication by binding the F-protein on the surface of the virus and thereby neutralizes RSV by blocking virus uptake into cells. A recent phase 1 trial in infants with RSV infections was prematurely terminated due to lack of efficacy (*ClinicalTrials.gov* identifier: NCT03418571).

Prevention of respiratory syncytial virus infection

The prevention of RSV in HM patients and HCT recipients is limited to infection control measures and interventions. There are many reports of outbreaks in these popu-

lations of patients,^{15-18,101,102} and the emphasis has been on multifaceted interventions, including compliance with hand hygiene, contact precautions with gowns and the use of gloves, screening visitors and healthcare workers for respiratory symptoms and restricting visitors and healthcare workers if they are symptomatic, grouping RSV-infected patients together, and sometimes screening asymptomatic patients in the same treatment areas. These interventions have been shown to be effective in mixed adult and pediatric patients.^{19,103,104} At our institution, we place all patients diagnosed with respiratory viral infections on contact and droplet precautions.¹⁰⁵

Interestingly, the use of chemoprophylaxis with palivizumab was described during an outbreak¹⁵ in patients who were at high risk of acquiring RSV infections in a bone marrow transplant ward. Sixteen asymptomatic patients were given one prophylactic dose of palivizumab during the outbreak, and none developed an RSV infection. These results warrant further investigation into the use of palivizumab in an outbreak; however, no definite recommendation can be made at this time. Finally, an RSV vaccine for children or adults is not available at present. Multiple trials in children and healthy adults are in progress (*www: ClinicalTrials.gov*). Whether immunization for RSV would be beneficial in immunocompromised patients is uncertain.

Conclusions

RSV is a common respiratory viral infection in adult HM patients and HCT recipients. Its incidence is affected by its seasonality and geography and the diagnostic method used. The mortality rate associated with RSV can be high in severely immunocompromised patients with LRTI. The use of an ISI is helpful to stratify HCT recipients into risk categories; a similar scoring system is needed for HM patients. Ribavirin, with or without IVIG, may mitigate the impact of RSV infections in this population of patients. The further development of new antiviral agents or other treatment modalities is of the utmost importance to have a greater impact on rates of progression to LTRI and mortality in adult HM patients and HCT recipients.

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