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TRANSPLANT AND ONCOLOGY (M ISON AND N THEODOROPOULOS, SECTION EDITORS)

# Respiratory Syncytial Virus in Hematopoietic Stem Cell Transplantation and Solid-Organ Transplantation

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**Abstract** Respiratory syncytial virus (RSV), one of the most common causes of respiratory infections in immunocompetent individuals, can cause significant pulmonary morbidity and mortality in hematopoietic stem cell (HSCT) and less often in solid-organ transplant recipients. Early diagnosis and medical intervention prior to the progression from upper to lower respiratory tract viral involvement is essential to positively affect the clinical course. The greatest risk of disease progression from upper to lower respiratory tract disease is during the early posttransplant period for HSCT recipients, with lymphopenia being an important risk factor. Polymerase chain reaction has become the preferred method for rapidly diagnosing infection in this population because of higher sensitivity compared to traditional viral culture and direct viral antigen methods. Despite the lack of prospective randomized trials, retrospective pooled analyses have suggested that systemically delivered ribavirin (either aerosolized, oral, or IV; with or without immunomodulator therapy) can decrease the risk of progression of disease. Additionally, there are a number of clinical trials currently in process to evaluate several new agents that target RSV in the high-risk HSCT patient population.

**Keywords** Respiratory syncytial virus · Transplant · Ribavirin

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## Introduction

Respiratory syncytial virus (RSV), an enveloped single-stranded RNA virus of the family *Paramyxoviridiae*, is a common cause of seasonal upper respiratory virus infections in infants and young children. It is also the most common cause of lower respiratory viral disease (LRD) among young children worldwide, presenting as bronchiolitis or viral pneumonia. RSV causes significant morbidity and mortality annually in the US population, with an estimated hospitalization rate of 55.3 per 100,000 person-years and death rate of 4.3 per 100,000 persons per year [1]. Although virtually all children have experienced a primary RSV infection by the age of 2, it is clear that initial infection does not confer durable protective immunity and symptomatic reinfection can occur throughout life [2]. In immunocompetent adults, symptomatic RSV reinfections typically consist of upper respiratory disease (URD) including rhinorrhea, pharyngitis, sinusitis, cough, and fever lasting 2–5 days. More severe RSV infections may be seen in the elderly and immunocompromised [3]. In immunocompromised patients, such as those who have undergone hematopoietic stem cell transplantation (HSCT) or solid-organ transplantation (SOT), RSV can also progress to severe and life-threatening lower respiratory tract disease (LRD) with hypoxemia, dyspnea, and new or changing infiltrates on chest radiography.

## Immunopathogenesis and Disease Severity

T cells are known to play a critical role in containing and clearing RSV from the respiratory tract. Therefore, it is likely that the iatrogenic depletion of T cells required to prevent graft rejection (both in HSCT and SOT settings) contributes to the delayed viral clearance and chronic RSV viral shedding often

observed in immunosuppressed patients. However, the specific immunopathogenesis of severe RSV infection is complex and remains poorly understood [4]. It is not clear whether severe disease relates to an overly exuberant immune response or a paucity of immune effects. In fact, it has been generally observed that subjects with intact immune responses develop bronchiolar infiltrates and wheezing, whereas immunocompromised patients are more prone to developing alveolar infiltrates, less prominent wheezing, and prolonged periods of asymptomatic viral shedding suggesting that more potent immunoreactivity might correlate with disease status [5, 6]. More recently, T helper (Th) lymphocytes that produce interleukin 17 (IL-17), known as Th17 lymphocytes, have been identified as playing a central role in RSV pathogenesis [7]. The Th17 responses, however, appear to represent the proverbial "double edged sword": in addition to being protective by stimulating cytokine cascades that promote viral clearance by effector cells, they can also cause deleterious pathology by recruiting an influx of neutrophils into the lung during early RSV infection and by inducing excessive mucous production by goblet cells. A limited Th17 cellular response is associated with better prognosis in most infected individuals but increased Th17 responses may cause excessive inflammation and adverse effects in others.

## Diagnosis

Several different types of laboratory tests are available for diagnosis of RSV infection. Rapid methods that allow for direct viral antigen or nucleic acid detection from clinical specimens have almost completely replaced traditional viral culture for identification of RSV. Culture methods were limited by low sensitivity due to the thermolability of virus in cells, labor intensity, and incubation times upwards of 1 week. Although antigen detection methods from nasal wash/throat swab specimens have a much faster turnaround time, they do not provide reliably accurate results, especially in immunocompromised adults where sensitivity is in the range of 20 % or lower [8, 9].

Accordingly, polymerase chain reaction (PCR) is the preferred method for diagnosing viral infections, including RSV and other respiratory viral infections. Multiplex PCR viral panels now offer the ability to identify numerous respiratory pathogens within hours of sample collection allowing for quick identification and subsequent patient isolation [10]. Appropriate clinical samples for rapid respiratory virus testing by PCR include nasal washes, nasopharyngeal swabs, and fluid obtained from bronchoalveolar lavage. Although detectable RSV RNA in plasma or serum appears to be a marker for lung injury and poor outcomes in HSCT recipients with LRD, this testing is investigational and not widely available [11•]. However, plasma or serum detection of RSV RNA is not routinely available clinically. Serologic tests using paired acute- and convalescent-phase sera to demonstrate a significant rise in antibody titer to RSV may be important for epidemiologic studies but cannot be used to guide patient care due to the length of time required for results to become available [12].

## HSCT

### Epidemiology and Clinical Disease

RSV infections are recognized as a significant cause of morbidity and mortality particularly in allogeneic HSCT recipients. The incidence of RSV in the HSCT population has been reported from 2–17 % with a mortality of 7–33 % [2–10, 11•, 12–21]. Infection with RSV can occur anytime throughout the transplant process, though most commonly it is seen in the outpatient setting where more exposure occurs, especially during the respiratory viral season [11•]. RSV usually presents with URD, but it can progress to LRD in 18–55 % of patients [15]. The frequency of progression to RSV pneumonia is higher during the pre-engraftment neutropenic period than during the post-engraftment. Once pneumonia develops, the overall mortality is reported at over 60 % [19, 22]. Autologous transplant recipients have a much lower incidence of clinically significant respiratory tract infections compared with allogeneic recipients, and severe or fatal infections appear to be much less frequent [16].

In HSCT recipients, URD is often defined as detectable RSV in the nasopharynx, throat, or sinuses; whereas, LRD requires radiographic as well as clinical evidence of pneumonia in the presence of RSV detection in either upper or lower respiratory secretions and exclusion of other causes [23]. Risk factors for acquiring symptomatic RSV URD have included male sex, allogeneic transplantation, cytomegalovirus seropositivity, and pre-engraftment status [21–23]. Pulmonary involvement increases the likelihood of a fatal outcome from RSV infection, so it is important to identify risk factors that contribute to disease progression from localized upper respiratory symptoms to pneumonitis or LRD. T cell immunity is essential to the control and clearance of RSV infection, and therefore it is not surprising that lymphopenia, particularly when $<100/mm^3$, is associated with a greater rate of progression to LRD [24]. Furthermore, a gradual risk increase in lung involvement has been observed as the lymphocyte count at initial RSV diagnosis decreased among HSCT recipients [24, 25•]. Interestingly, an absolute lymphocyte count of $>1.0\times 10^9$/l at diagnosis was noted to be completely protective against progression to lower respiratory tract disease. Thus, the absolute lymphocyte count seems to correlate with risk stratification and could serve as one tool for choosing which patients should receive drug therapy [24, 25•].

Further risk factors (Table 1) that have been associated with LRD progression in the alloHSCT patient include graft-versus-host disease, pre-engraftment or early posttransplant status (<1 month), older age, myeloablative conditioning, conditioning with high-dose total body irradiation, and transplant from a mismatched or unrelated donor [21–24, 25•, 26]. Smoking is also a risk for LRD [24]. Delayed engraftment and graft failure have rarely been described as a complication of RSV infection in 8.2–15.4 % of patients [27, 28]. The mechanism of how RSV would lead to graft failure is unclear and given the small numbers of patients reported, it is uncertain if a true association exists.

Risk factors for virus-related mortality include steroid therapy, oxygen requirement >2 l or mechanical ventilation, and bone marrow or cord blood as transplant cell source [29, 30]. Pre-engraftment status is an important risk for RSV-attributable morality [31]. Among those who survive RSV or other respiratory viral infection in the first 100 days following HSCT, significant pulmonary dysfunction measured at 1 year is a frequent complication [32, 33].

## Prevention and Treatment

Management of RSV infection in HSCT needs to begin in the pre-transplant period. While there is controversy in the literature about the need for delayed conditioning in patients with active RSV infection, one study clearly demonstrated that delaying the conditioning regimen was associated with a lower risk of developing pneumonia when compared with situations in which delay was not possible [34]. Therefore, the Centers for Disease Control and Prevention/American Society of Blood and Marrow Transplantation recommend that HSCT be delayed on the basis of URD symptoms due to symptomatic infection attributable to respiratory viruses, rather than waiting for virologic confirmation [35, 36]. All HSCT candidates or recipients with symptoms consistent with URD/LRD should be isolated to prevent possible transmission to other patients while awaiting virologic confirmation.

Once RSV infection is identified in individuals undergoing or who have undergone HSCT, supportive care is the mainstay of management but antiviral therapy may be considered for some patients. Ribavirin, a nucleoside analogue with broad-spectrum antiviral activity against RNA and DNA viruses, has in vitro activity against RSV and has often been used to treat RSV infections in the immunosuppressed population for many years. Nonetheless, there remains no consensus on precise dosage, route of delivery, or clinical indications for ribavirin therapy in these patients. In fact, the efficacy of the drug for RSV infection has not been firmly established by a large clinical trial.

**Table 1** Risk factors for RSV progression from URD to LRD in HSCT

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|---|
| Lymphopenia (<100/mm$^3$) |
| Pre-engraftment period |
| Early post-engraftment period (≤1 month) |
| Mismatched or unrelated donor |
| High-dose total body irradiation |

Ribavirin comes in oral and inhaled (aerosol) formulations in the USA, and an intravenous form is also available in Europe. Inhaled ribavirin is the most commonly employed route, requiring a small particle aerosol generator (SPAG) unit that generates aerosol particles in the range of 1.0 to 1.3 μm, thus enabling delivery of the drug into the lower respiratory tract. Both continuous (6 g/day at 20 mg/ml for 18 h) and intermittent (6 g/day at 60 mg/ml for 2 h every 8 h) aerosolization dosing schedules have been described and are thought to be of equal efficacy [37, 38]. Since the drug is a known rodent teratogen, concerns about human fetal exposure to ribavirin by aerosolization have led to strict administration protocols aimed at limiting occupational exposure of healthcare workers [39, 40]. However, registry data from a ribavirin pregnancy exposure registry have not suggested human teratogenicity [41]. Bronchospasm, eye irritation, and anemia are important adverse effects of inhaled ribavirin.

In adults, the utility of ribavirin therapy in HSCT recipients remains controversial. However, there are some data to suggest that early-inhaled ribavirin may reduce morbidity and mortality. Only one randomized controlled multicenter trial has attempted to compare inhaled ribavirin to supportive care alone in those with URD but was hampered by poor enrollment of only 14 patients. Available results showed that preemptive ribavirin tended to decrease viral load over time, but there was no difference in outcome [42]. In a recent retrospective analysis of 280 allogeneic HSCT recipients with RSV infection at MD Anderson Cancer Center, it was observed that receipt of aerosolized ribavirin at time of URD was a critical factor in reducing the risk for progression to RSV lower respiratory disease, RSV-related mortality, and all-cause mortality [23]. The use of ribavirin in HSCT recipients is also supported by a systematic review demonstrating a reduced risk for lower respiratory tract disease and improved outcomes of RSV pneumonitis when ribavirin treatment is given at the upper respiratory virus stage [19]. Substantial limitations of this review included the fact that most of the studies were non-randomized, very small in number, biased toward inclusion of sicker patients, and extremely variable with regard to therapeutic regimens and duration of treatment, making treatment endpoint evaluations unclear. Thus, in the absence of convincing data for efficacy, the financial and logistic burdens of inhaled ribavirin treatment for patients with URD have prompted some centers to abandon its use in stem cell transplant populations.

Oral ribavirin is being increasingly employed in HSCT recipients with RSV due to its simplicity of administration

and paucity of adverse events. There is an emerging evidence that ribavirin delivered orally may have some efficacy for treatment of RSV [43•, 44]. However, an effective role of oral ribavirin for RSV treatment has not been established by a larger randomized controlled trial. A recent observation of five allogeneic HSCT recipients with URD RSV infection had no progression to LRD when treated with oral ribavirin [45]. Similarly, in a study of 96 adults with PCR-proven RSV infection, 34 were moderately to severely immunocompromised and received oral ribavirin treatment (600–800 mg twice daily) with or without IVIG (500 mg/kg IV q48 h), the drug was well tolerated, and no RSV-related deaths were seen in the 34 patients described [44]. Likewise, oral ribavirin appeared to have a protective effect against LRD mortality during an outbreak in a hematology and transplant unit (23 vs. 69 %, treated vs. non-treated, respectively; $n=56$) [46]. In contrast, in a very carefully executed propensity-matched case-control study in 145 hematologic patients with paramyxovirus infections, there was no significant difference in 30-day mortality between those with and without oral ribavirin treatment, suggesting that there may be little value to giving it for RSV or parainfluenza virus infections in those patients [47]. Dosing of oral ribavirin has not been clearly established, but one study found that when utilizing dose escalation, a starting dose of 10 mg/kg/day was not sufficient to prevent progression from URD to LRD in seven patients and recommend a starting dose of 20 mg/kg/day increasing to a maximum dose of 60 mg/kg/day [48]. A systematic review of retrospective studies identified that any form of ribavirin-based therapy (alone (oral or inhaled) or in combination with immunomodulators) was effective in preventing URD from progressing to LRD (from 45 to 16 %) and mortality (from 70 to 35 %) in adult HCT recipients compared with no antiviral therapy, though there was a trend toward better outcomes in those patients treated with aerosolized ribavirin and an immunomodulator than aerosolized ribavirin alone [20]. Thus, solid guidance about ribavirin treatment is lacking, but it seems reasonable to consider some form of ribavirin treatment in HSCT patients with URD, especially in the setting of severe lymphopenia ($<100/mm^3$) in particular. Similarly, for documented LRD, some clinicians would be inclined to use either oral or inhaled ribavirin in the absence of strong data to the contrary.

Additional therapies, including intravenous immunoglobulin (IVIG), RSV hyperimmunoglobulin, and palivizumab (a monoclonal RSV IgG), have been utilized for RSV infection with mixed efficacy in immunocompromised patients [31, 49–51]. Early studies suggested that ribavirin plus RSV-IVIG (RespiGam/MedImmune), a hyperimmune globulin preparation with high concentrations of RSV-neutralizing antibody, conferred a mortality advantage over ribavirin alone in RSV-infected pediatric HSCT patients with LRD; however, RSV-IVIG has since been removed from the market because alternatives now exist to this human plasma-derived product (RespiGam) [52]. Palivizumab, an engineered RSV monoclonal antibody, currently approved for the prophylaxis of RSV infection in a select group of high-risk infants and children younger than 24 months of age who are profoundly immunocompromised during the RSV season. However, this recommendation is not strongly supported by the American Academy of Pediatrics [53]. Palivizumab was used as prophylaxis in an adult HSCT unit following an RSV outbreak in which 16 RSV-negative patients received the drug in combination with strict infection control measures, and none acquired the virus [50]. In contrast, a case series of 40 allogeneic HSCT patients infected with RSV received treatment with palivizumab, but this did not seem to have any impact on the progression to LRD or mortality [54]. Given the questionable efficacy, it is difficult to justify the high cost of palivizumab (15 mg/kg in 70 kg adult >$22,000) as a treatment option [51]. The routine use of immunoglobulin preparations for RSV infection alone in HSCT recipients with established LRTI due to RSV is not recommended due to lack of efficacy data, though the combination of aerosolized ribavirin plus immunoglobulin therapy has trended toward better outcomes [19].

There are several new agents in early clinical trials for RSV. ALN-RSV01 (Alnylam Pharamecutiicals, Cambridge, MA) is a compound that inhibits replication of RSV by interrupting synthesis of the viral nucleocapsid protein (N-protein) and has shown promising results in phase 2 clinical trials. Aerosolized ALN-RSVO1 versus placebo in combination with standard of care (ribavirin, corticosteroids, IVIG/palivizumab) in lung transplant recipients with RSV infection showed a significant reduction in the cumulative daily symptom score and incidence of new or progressive bronchiolitis obliterans syndrome (6.3 vs. 50 %, $P=0.027$) [55]. MDT-637 (MicroDose Therapeutx, Inc. and Gilead Sciences) is an antiviral fusion inhibitor, which is delivered utilizing a dry inhalation powder is undergoing phase 2 trials to assess safety and tolerability in healthy adults (http://clinicaltrials.gov/show/NCT01355016). A second fusion inhibitor GS-5806 (Gilead Sciences) has shown promising results in a phase 2 RSV challenging study in healthy adults [56]. There are currently two phase 2b trials recruiting HSCT patients with RSV URD or LRD (http://clinicaltrials.gov/show/ NCT02254408 and NCT02254421) to evaluate antiviral effects, pharmacokinetics, safety and tolerability.

## SOT

### Clinical Disease and Epidemiology

The epidemiology of RSV in SOT is less well described than in HSCT, most likely because it is far less problematic in most SOT populations. The majority of the literature is derived from heart and lung transplantation, where it can occasionally

contribute to respiratory compromise. Few studies exist of respiratory virus infections in abdominal organ transplant recipients, where it appears to be more of a nuisance than a frequent cause of morbidity and mortality.

The cumulative incidence of RSV infection in lung transplant over 5–7 years has varied from 8 to 21 % in several retrospective series, with an annual incidence describe of 2–16 % [57–64]. Mortality attributable to LRD with RSV in this population has been reported from 10 to 20 % [57, 60]. A prospective study identified only 2 of 51 adult liver transplant recipients with RSV, and both had only mild upper respiratory symptoms [65]. Similarly, a large retrospective study of 493 pediatric liver transplant recipients found only 17 episodes (3.4 %) of RSV infection; respiratory failure and morality were only 1 and 0.4 % (5/493 and 2/493), respectively [66]. In contrast, mortality was as high as 40 % in a separate small retrospective study evaluating pediatric abdominal organ transplant recipients where 5 of 30 patients with upper respiratory symptoms had RSV isolated and the two with progression to LRD died [67]. In a study of RSV infection among pediatric liver transplant recipients, acquiring infection in the early posttransplant period (<20 days), preexisting lung pathology, and age <3 months were associated with a more severe clinical course [66]. Thus, RSV infection may have greater clinical significance in pediatric recipients compared to adults.

Presentation of RSV disease is similar to that described in HSCT patients, with the majority of patients initially demonstrating fever, cough, and dyspnea [60, 68, 69]. The incidence of mild RSV infection is probably underestimated considerably since diagnostic tests are rarely sent for patients with symptoms of a "common cold." As seen in HSCT recipients, an association between lower lymphocyte count (mean 580 cells/mm$^3$) and RSV progression to LRD has been noted in SOT patients [68]. Late complications of early-onset RSV lower respiratory tract infection in lung transplant patients has been of greatest concern due to a possible link with development of bronchiolitis obliterans syndrome (BOS), a typically progressive fibrotic process that limits long-term survival in this population. In a large prospective cohort study, paramyxovirus infection increased the risk for new onset of BOS, but not progression of disease [57]. Conversely, a recent meta-analysis did not find an association between respiratory viral infections in lung transplant patients and development of BOS, although the number of studies analyzed was small ($n$=4) [70]. When rhinovirus was excluded from a cohort of respiratory viral infections in lung transplant patients, there was a trend toward increased incidence of acute rejection though this did not reach statistical significance. The authors suggested an association between respiratory viral infection and the development of BOS, even in the absence of acute rejection, after finding significantly decreased allograft function (decreased FEV1) post infection [71]. Needless to say, further investigation into the impact of RSV and other paramyxoviruses in the lung transplant population would help determine the risk and range of detrimental effects and thus direct any therapeutic interventions.

### Prevention and Treatment

Supportive care remains the mainstay of therapy for SOT recipients found to have RSV infection with the role of antiviral agents or immunomodulators not well established. In a series of 13 adult lung transplant recipients treated for RSV infection with continuous aerosolized ribavirin, only two developed BOS in follow-up; any possible benefit of ribavirin cannot be adequately assessed by this tiny, noncomparative trial, however [60]. An Australian series of 18 adult lung transplant recipients infected with RSV received both IV ribavirin and oral prednisolone 1 mg/kg/day with only one patient developing BOS and all surviving [62]. Several additional small adult and pediatric series have been described in the literature utilizing multipronged approaches with ribavirin, steroids, and IVIG, but the data is inadequate and inconsistent to be able to draw substantive conclusions [65, 71–74]. As prevention is the key in the approach to this infection, the AAP also suggests prophylaxis with palivizumab for SOT recipients younger than 24 months of age who are profoundly immunocompromised during the RSV season despite the lack of evidence to support this [53]. A survey of pediatric SOT centers revealed that prophylaxis is provided to the majority of infants aged 0–12 months (93 %) [75].

## Summary

Identification and isolation of HSCT and SOT patients with upper respiratory symptoms is the first step in the management of this infection. Multiplex PCR systems now allow for the reliable and rapid identification of a number of respiratory pathogens, including RSV. As the mortality associated with RSV LRD in HSCT patients is high, it is recommended that patients with URD who are in the pre-engraftment or early posttransplant period and have significant lymphopenia (<100 cells/mm$^3$) should receive combined ribavirin (inhaled or oral) and immunomodulatory therapy at the time of diagnosis with the goal of prevention of progression from URD to LRD. While the evidence is less supported in SOT, ribavirin use should also be considered in those recipients in the early posttransplant period with evidence of lymphopenia; especially in lung transplant patients where there has been some association noted between LRD and allograft dysfunction or BOS. Prophylaxis with palivizumab should be considered in children <24 months during the RSV season who remain severely immunocompromised. Future multicenter prospective studies

should be undertaken to assess the best management on these complicated populations.

**Compliance with Ethics Guidelines**

**Conflict of Interest** Kari Neemann has no relevant disclosures. Alison Freifeld reports other from Astellas, other from Merck, outside the submitted work.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by the authors.

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