

# Respiratory Viral Infections in Pediatric Solid Organ and Hematopoietic Stem Cell Transplantation

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**Abstract** Respiratory viruses are common in children, including pediatric recipients of both solid organ transplantation and hematopoietic stem cell transplantation. The prevalence and risk factors in each of these groups are reviewed. Furthermore, associated morbidity and mortality in pediatric transplant recipients with respiratory viral infections are addressed. The literature on specific prevention and treatment options for respiratory syncytial virus, adenovirus, influenza, and other respiratory viruses in pediatric solid organ and hematopoietic stem cell transplant recipients is reported.

**Keywords** Respiratory virus · Pediatric · Pediatric solid organ transplant · Pediatric hematopoietic stem cell transplant · Respiratory syncytial virus · Influenza

## Introduction

Respiratory viral infections (RVIs) in children can be caused by respiratory syncytial virus (RSV), adenovirus, rhinovirus, influenza virus, parainfluenza virus, human metapneumovirus (hMPV), and the emerging human coronaviruses and human bocaviruses. Although infection with these

pathogens often results in a mild, self-limiting illness, complications can arise. Immunocompromised children may experience significant morbidity and mortality related to RVIs, as compared with their otherwise healthy counterparts. We review the current literature regarding RVIs in immunocompromised children—specifically, recipients of hematopoietic stem cell transplantation (HSCT) or solid organ transplantation (SOT)—in order to appreciate the significance of these pathogens and to discuss the methods available to reduce RVI-associated morbidity and mortality in pediatric transplant recipients.

## Epidemiology

### RVIs in Immunocompetent Children

Respiratory illness is the leading cause of hospitalization in children with an incidence of approximately 30 % [1]. Furthermore, at least 40 % of these admissions are secondary to RVI [2]. In children presenting to the hospital with acute respiratory tract symptoms, antigen detection, viral culture, or PCR will identify a viral pathogen in as many as 87 % of episodes [3]. The most common viruses recovered include RSV, rhinovirus, adenovirus, influenza virus, parainfluenza virus, enterovirus, and hMPV. In over 25 % of events, multiple viruses have been isolated simultaneously [3]. Discovered in 2001, hMPV has been isolated in as many as 20 % of childhood lower respiratory tract infections [4]. Furthermore, influenza virus alone has been estimated to affect 90 million children under the age of 4 in a single year, with 20 million calculated to progress to lower respiratory tract infection [5]. Studies of RSV have estimated that 2 million children with RSV require medical attention each

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year, with increased risk for hospitalization in premature infants and younger children [6]. In summary, RVIs occur frequently and have a substantial impact on child health even in immunocompetent populations.

#### RVIs in Pediatric Solid Organ Transplant Patients

While RVIs have been commonly recognized in pediatric SOT recipients for decades, longitudinal prospective surveillance data in this population are currently lacking, particularly in nonlung SOT populations. Retrospective studies suggest that RVIs are the most common infectious episodes after pediatric kidney and liver transplantation, with 2.7 episodes per patient-year [7]. Overall, rhinovirus is reported as the most common respiratory viral pathogen in pediatric SOT recipients, with a seasonal peak in the spring and fall months similar to community patterns (Table 1). The largest reported experience is from the pediatric lung transplant population, where 13 %–51 % of children experienced an RVI in the first few months following transplantation [8–10]. The viruses isolated in this study were similar to those in immunocompetent individuals and included adenovirus, rhinovirus, RSV, and parainfluenza virus [9, 10]. These viruses were more likely to progress to lower respiratory tract infections (LRTIs), rather than remain limited to the upper respiratory tract (URTIs), in this cohort [9]. Younger patients and those receiving double lung transplants were at increased risk for RVI [10]. Further prospective investigation to assess the incidence and risk factors for RVI in pediatric SOT is needed, especially outside of the pediatric lung transplant population.

#### Complications of RVI in SOT

Although the rates of RVIs in transplant patients were comparable to those in their otherwise healthy peers [7, 11], the risk for RVI-associated complications may be more significant. For example, a 9-month-old liver transplant recipient developed severe respiratory failure with hMPV in the immediate posttransplant period [12]. Their and colleagues reported that up to 23 % of RVIs in kidney and liver transplant recipients were complicated by bacterial superinfection, including acute otitis media and sinusitis, and 15 % received multiple courses of antibiotics [7]. Furthermore, 18 % underwent surgical intervention for recurrent otitis media, which outpaces the rates in nontransplant recipients. In lung transplant recipients, where RVI directly affects the graft, complications are frequently reported. Most published studies to date have focused on adults, with acute decline in respiratory function or increased risk of acute rejection with RVI [8, 13]. Chronic graft rejection, known as bronchiolitis obliterans syndrome (BOS), following RVI has been reported in several cohorts [13–15]. However, to date, RVI

has not been found to be associated with increased incidence of acute rejection or BOS after pediatric lung transplantation [9, 10].

Influenza has been particularly prominent in the literature since the 2009 H1N1 pandemic. For example, a 12-year-old boy who was 8 years post-cardiac-transplant developed H1N1 influenza during this outbreak, complicated by respiratory failure requiring extracorporeal membrane oxygenation (ECMO) support for 24 days [16]. As compared with adults, pediatric patients had a lower incidence of ICU admission (12 % vs. 17 %) and mechanical ventilation (4 % vs. 12 %). Furthermore, there were no pediatric deaths in 83 cases, as compared with 10 in 154 adults (6 %) [17]. Interestingly, the pediatric population was more likely than adults to receive antiviral medications within 48 h of symptom onset, which may have affected outcomes and may reflect bias toward early intervention for pediatric SOT recipients with RVI symptoms.

Parainfluenza, influenza, and adenovirus were reported to impact mortality in the older pediatric literature; however, reports of mortality secondary to RVI have decreased in the recent transplant era. From 1987 to 1992, mortality from influenza and parainfluenza was 23 % and 15 %, respectively, in a single-center series from Pittsburgh [18]. Similarly, 2 of 16 pediatric lung transplant recipients who developed adenovirus expired secondary to their infection from 1994 to 1996 in Philadelphia [19]. However, more recent literature shows overall good prognosis in RVI after pediatric SOT. In liver, kidney, and lung transplant recipients, overall mortality has decreased significantly [7, 10, 20]. Further studies focusing on the impact of RVIs in pediatric SOT recipients, including changing patterns of morbidity and mortality, would benefit this population.

#### RVIs in Pediatric Hematopoietic Stem Cell Transplant Patients

Similar to pediatric SOT, pediatric recipients of HSCT experience RVIs in the posttransplant period. Rhinovirus is again among the most common pathogen recovered, infecting 20 % of some cohorts (Table 1). Acquisition of these viral infections occurs at equal frequencies among patients at various phases of immunologic recovery following transplant (neutropenic phase, early engraftment phase, and late engraftment phase) [21]. A significant proportion of HSCT patients who test positive for a single respiratory virus also test positive for other copathogens (viruses, bacteria, and fungi), further complicating treatment strategies [21–23].

Data suggest that URTIs are equally or more likely than LRTIs in HSCT children [21, 24]. Unlike SOT, where age and type of organ transplanted affect risk of RIV, age and source of transplanted cells (bone marrow, peripheral blood, or cord blood) do not appear to impact the development of

**Table 1** Frequencies and Seasonality of RVIs in Pediatric Transplantation

Respiratory virus	Frequency (%)	Seasonal peaks	Population
Solid organ transplantation			
Rhinovirus [9, 10•]	3–15	Spring, Fall	Pediatric
Influenza [8, 10•]	1–3	Spring, Winter	Pediatric
Respiratory syncytial virus [10•, 47]	3–11	Spring, Fall, Winter	Pediatric
Adenovirus [10•]	3	Spring	Pediatric
Parainfluenza virus [10•, 18]	3–6	Summer	Pediatric
Hematopoietic stem cell transplant			
Rhinovirus [23]	19–21	Fall	Pediatric and adult
Influenza [21, 28]	2–5	Spring, Fall	Pediatric
Respiratory syncytial virus [21, 22•, 94]	2–10	Winter	Pediatric and adult
Adenovirus [21]	2	Fall	Pediatric
Parainfluenza virus [21, 22•]	4–5	Summer	Pediatric and adult
Coronavirus [23]	10	Winter and Spring	Pediatric and adult
Human metapneumovirus [94, 95]	6–7	Winter and Spring	Pediatric and adult

RVIs in HSCT recipients [23]. Conversely, the type of transplant, autologous or allogeneic, may influence risk of RVI. Pediatric allogeneic HSCT was significantly associated with symptomatic parainfluenza viral infections, as compared with autologous HSCT [25]. It has been suggested that HLA compatibility and development of chronic GVHD may influence one's risk for developing a viral infection after HSCT, although data are limited and only 9 % of the infections in the reported cohort were RVI [26].

#### Complications of RVIs in HSCT

Complications of RVI in HSCT patients are similar to those in SOT recipients and include prolonged hospitalization, BOS, chronic lung disease, ECMO, mechanical ventilation, GVHD, and death [25, 27, 28]. During the 2009 H1N1 influenza A pandemic, hospitalization occurred more frequently in HSCT patients with influenza A and severe neutropenia (ANC < 500 K/uL) than in those with symptoms of RVI but normal neutrophil counts [28]. Although not routinely used for prognostic purposes, high viral loads in BAL samples have been found to be associated with subsequent mechanical ventilation in pediatric and adult HSCT recipients. The quantitative viral load in these BAL samples was not correlated with mortality; rather, presence of serum viral RNA put these patients at twofold increased risk for mechanical ventilation and death [22•]. Donor HLA mismatch, although potentially associated with initial infection, has not been linked with subsequent morbidity or mortality [25, 27]. Pretransplant conditioning, however, did impact clinical course following RVI; patients receiving total body irradiation experienced more complications than did those receiving a chemotherapy-based conditioning regimen [25, 27]. It appears that the complications of RVI in SOT and HSCT patients are quite similar; the risk of

complication, however, may depend closely on the protocols associated with each transplant.

#### Diagnosis

Current diagnostic tools allow for identification of a viral etiology for an upper respiratory tract infection in almost 60 % of cases collected from a nasal swab [29]. However, investigation of healthy infants within the first year of life demonstrated that viral isolation in asymptomatic children may also occur in nearly 25 % of nasopharyngeal specimens [30]. Thus, identification of high-risk groups likely to benefit from specimen sampling will continue to be an essential endeavor as diagnostic tests become more sensitive and specific.

One study created a symptom grade model to identify patients more likely to benefit from sampling. The authors of this study created four separate models, each utilizing qualitative measures of common RVI symptoms (rhinorrhea, cough, fever, and others) along with a quantitative assessment of symptom duration to assign severity scores to pediatric patients. The most successful model in this study (utilizing significant runny nose for 1–4 days and significant cough for 1–4 days) demonstrated a positive predictive value and a negative predictive value of 75 % and 70 %, respectively [29]. Furthermore, in younger children, where symptom quality and severity is less likely to be elicited, establishment of criteria was less useful. The utility of these models was not assessed in SOT or HSCT populations.

Investigations have moved toward optimizing testing protocols, since transplant patients are particularly susceptible to complications that arise from delayed or incomplete diagnosis. With the application of RT-PCR to identify viral

etiologies in immunocompromised children [31], there has been a 15 %–28 % improvement in detection [32, 33], as well as a 36 % expansion of viruses detected, as compared with conventional rapid viral culture and direct fluorescence antigen (viral culture/DFA) multiplex methods [33]. Additionally, PCR has been shown to detect viruses in samples with fewer viral copies than either of these conventional methods, as well as in patients with mild to absent respiratory symptoms [34]. PCR has recently been incorporated into the International Society of Heart and Lung Transplant's (ISHLT) guidelines for diagnosing RVIs in cardiothoracic transplant recipients; it has become a well-established tool for identifying a viral etiology, a step that is required to officially diagnose URTI or LRTI per these standards [35].

Recently, multiplex platforms that can test simultaneously for multiple viruses on a single respiratory sample have been approved for commercial use. Two of these platforms, the FilmArray Respiratory Viral Panel (FA-RVP; Idaho Technology, Salt Lake City, UT) and the Luminex xTAG Respiratory Viral Panel (xTAG-RVP; Luminex, Austin, TX), have been compared with regard to sensitivity, specificity, utility, and cost. The xTAG-RVP is one of the first FDA approved multiplex assays and detects 12 viruses: RSV A and B, influenza A (H1, H3, and untypable), influenza B, parainfluenza 1, 2, and 3, human metapneumovirus, adenovirus, and enterovirus. FA-RVP was approved in 2011 and identifies human coronaviruses NL63 and HKU1 and parainfluenza 4, in addition to those viruses identified by xTAG-RVP. A recent study looking at respiratory samples from pediatric cancer patients determined that the FA-RVP platform was better able to identify pathogens in nasopharyngeal samples than was the xTAG-RVP platform. Moreover, the FA-RVP protocol was faster than the xTAG-RVP protocol; however, xTAG-RVP was found to have a higher throughput and better reliability than FA-RVP [36]. The decision regarding the best platform will clearly depend on considerations for local populations, laboratory volumes, and the development of future platforms.

The ideal method of sampling has also come into question, since the yield of viral specimen may differ depending on the specimen source. A study investigating the quality of nasopharyngeal and oropharyngeal specimens in adults with RVIs demonstrated significant superiority of nasopharyngeal washes to both nasopharyngeal and oropharyngeal swabs [37]. However, when paired with nasopharyngeal swabs in children, oropharyngeal samples were able to increase the detection of respiratory viruses by 15 % over detection with nasopharyngeal swab alone [38]. While samples from the lower airways are often considered to have a higher yield than those in the upper airways, lower respiratory tract samples (such as bronchoalveolar lavage) are acquired through invasive procedures and may not be

available for all patients. One third of asymptomatic children tested positive for viral infection in a study examining bronchoalveolar lavage isolates, raising the question of whether all results from invasive testing are clinically significant [39]. Nevertheless, in patients who require lower respiratory tract investigation for alternative reasons, such as investigation of rejection episodes in lung transplant recipients or evaluation for bacterial or fungal pathogens, lower tract sampling may be warranted.

## Prevention Strategies

The prevention of RVIs in pediatric transplant patients has been a critical tool for minimizing both infections and their associated complications. Vaccination and antiviral prophylaxis will be discussed within the context of specific viruses; however, prevention strategies focusing on environmental factors and health-care delivery systems have also been investigated to reduce the incidence of RVIs. These precautions have included cohorting patients, applying contact or respiratory droplet precautions, assigning specific health-care staff to infected patients, and screening of visitors [40, 41]. Each of these infection prevention strategies has been shown to significantly decrease the incidence of nosocomial RVIs in HSCT patients and has subsequently been incorporated into the Center for Disease Control and Prevention (CDC) Healthcare Infection Control Practices Advisory Committee's recommendations to reduce health-care-associated pneumonia [42]. Methods for reducing RVIs in HSCT patients are also specifically addressed in collaborative guidelines by the CDC, the Infectious Diseases Society of America, and the American Society for Blood and Marrow Transplantation published in 2001 [43].

## Virus-Specific Prevention and Treatment

### Respiratory Syncytial Virus

#### *Prevention*

The pediatric transplant community has recognized the importance of RVI prophylaxis in susceptible patients for diminishing associated morbidity and mortality [44]. In 1998, the FDA approved palivizumab, a humanized monoclonal antibody against the fusion protein of the RSV virus, for the prevention of severe RSV infection in high-risk pediatric patients. Since that time, several studies have demonstrated the efficacy of palivizumab in suppressing the acquisition and spread of RSV in immunocompromised subjects [40, 45, 46]. A 2009 study reported on current RSV prophylaxis strategies found that U.S. pediatric

transplant centers offered RSV prophylaxis, mostly palivizumab (97 %), in 49 % of candidates and recipients of SOT [47]. Palivizumab was most often given to children under the age of 2 years, consistent with 2009 recommendations from the American Academy of Pediatrics [48].

The true efficacy of palivizumab in preventing RVI-associated morbidity in transplant patients is still up for debate. One decision analysis model of outcomes in pediatric HSCT patients given palivizumab for RSV prophylaxis predicted a 10 % increase in survival in patients offered immunoprophylaxis [49]. However, another analysis evaluated the use of palivizumab in preventing RSV progression to lower respiratory tract disease in 40 pediatric and adult allogeneic HSCT recipients and concluded that palivizumab did not impact RSV-associated morbidity or mortality [50]. Further investigation predicted a number needed to treat of 12–15 for palivizumab in high-risk children [49, 51]. Due to its high cost, some have expressed concern with offering palivizumab prophylaxis too widely. One study estimated that over \$150,000 would be required to prevent one patient admission secondary to RSV infection with palivizumab in the general pediatric population [51]. Therefore, risk assessment is now a common and appropriate step in determining the need for RSV prophylaxis in a particular pediatric patient and has been incorporated into the most current recommendations of the American Association of Pediatrics (AAP) for the use of palivizumab in RSV prevention [48].

### Treatment

For the treatment of RSV, the most studied antiviral has been ribavirin, a synthetic nucleoside analog FDA approved for the treatment of severe RSV pneumonia in children. Early studies investigating ribavirin's ability to clear RSV infection in immunocompromised patients were promising; however, these patients were identified shortly after infection, most not yet having become symptomatic [52]. These data likely cannot be generalized, since most pediatric transplant centers do not routinely test asymptomatic patients for RVIs and intervention is delayed until symptoms arise. In fact, several subsequent studies have suggested that effective ribavirin treatment is time dependent, with progression to LRTI representing a significant indicator of poor prognosis [53, 54]. In addition, alternative routes of delivery, including oral and intravenous ribavirin, have been investigated in adult lung transplant recipients, but these have not been reported in pediatric subjects to date [55–57]. Due to inconsistent results with ribavirin, especially in these children whose RSV infection extends into the lower respiratory tract, several studies have advocated for the concomitant use of immunoglobulin or palivizumab in high-risk children [58, 59]; palivizumab was not shown to decrease the risk of mortality or progression to lower tract

disease in at least one study of 40 patients [50]. Further investigation of novel treatment strategies is warranted.

### Adenovirus

Although adenoviral infection remains a significant threat in the pediatric transplant population, no formally approved and few effective treatment options exist. Several antiviral and replacement therapies have been attempted, including ribavirin, ganciclovir, vidarabine, cidofovir, intravenous immunoglobulin, and leukocyte transfusions, without definitive success.

Ribavirin has long since been identified as effective at clearing several viral infections, including adenovirus, in vitro [60]. Clinical studies of the efficacy of ribavirin in adenovirus have been less convincing, with only minimal to mild improvement of adenoviral infection with intravenous or aerosolized in small-population clinical studies [61, 62].

Cidofovir, originally approved to treat cytomegalovirus in HIV patients, is a phosphonate nucleotide analog that inhibits viral DNA polymerase that has more recently been shown to have broad-spectrum antiviral activity against several DNA viruses, including adenovirus [63]. Several studies have investigated the utility of cidofovir in pediatric transplant recipients with adenovirus and have shown overall efficacy and safety in this population [64–66]. Yet with an unfavorable toxicity profile, cidofovir remains an imperfect treatment, with deaths reported secondary to disseminated adenoviral infection in treated patients [67]. In an effort to optimize outcomes using cidofovir, a meta-analysis investigating adenoviral disease in HSCT patients suggests categorizing patients by level of risk [68]. Using this method, a dose of 1 mg/kg/day or 5 mg/kg/week has been proposed until viral load drops below 400 copies per milliliter in at least two consecutive samples [68]. Case series in pediatric lung transplantation have additionally reported successful treatment of adenovirus infection with low-dose cidofovir (1 mg/kg/dose every other day) in conjunction with probenecid, hydration, and intravenous immunoglobulin [20].

### Influenza

#### Prevention

Vaccination remains the public health sector's primary effort to prevent the acquisition and transmission of influenza. The seasonal influenza vaccine covers predicted widespread strains of both the influenza A and influenza B subtypes. During each influenza season, further antigenic characterization allows for specific strain identification and incorporation into the following year's preparation. Routes of administration for the seasonal influenza vaccine include

intramuscular, intradermal, and intranasal. For the pediatric population, two preparations are available in the United States: the trivalent inactivated intramuscular vaccine (6 months of age and older) and the live attenuated intranasal vaccine (2 years of age and older). Live attenuated vaccination is not recommended in posttransplant recipients [69]; however, it may be used in close contacts of transplant recipients if inactivated virus is not available.

Protection from influenza infection following vaccination occurs via antibody and cell-mediated immune responses. Although studies in pediatric transplant recipients have demonstrated a generally adequate antibody response to influenza vaccination in this population [70–72], cell-mediated responses may be suboptimal [70]. This finding is likely related to immunosuppression regimens in transplant recipients, which aim to minimize T-cell-mediated graft dysfunction. Details of the immunosuppression and vaccination protocols have also been investigated in an attempt to further optimize vaccination responses. For instance, steroid-sparing agents do not appear to offer an advantage over steroid-containing agents in terms of the magnitude of the antibody response to influenza vaccination, as demonstrated in a study of pediatric kidney transplant recipients [71]. Furthermore, additional booster doses of the influenza vaccine have not been shown to increase serological conversion rates in pediatric kidney and liver transplant recipients [71–73]. Vaccination against influenza is strongly suggested for family members and close contacts (including health-care workers) of SOT and HSCT recipients to create a “circle of protection” around the immunocompromised host [74].

The 2009 pandemic H1N1 influenza vaccine has received particular attention. Vaccination against the H1N1 strain has been shown to offer protection in pediatric transplant recipients, without significant adverse effects [72, 75–77]. Serologic conversion rates may be lower following H1N1 vaccination in pediatric transplant recipients than in healthy controls; however, administration in coordination with the seasonal influenza vaccine allowed for bolstered immune responses in this population [78]. Contrary to seasonal influenza vaccine, an additional booster dose of the H1N1 vaccination was shown to increase seroconversion rates from 62 % to 82.5 % in a group of pediatric liver transplant recipients [79]. However, the 2011 AST guidelines did not recommend booster vaccination, since data were still limited [69].

Aside from vaccination, prevention of influenza has been suggested through the use of prophylactic antivirals. Oseltamivir, a potent neuraminidase inhibitor used to treat influenza, has been studied as a prophylactic agent in pediatric cancer patients [80]. No cases of influenza were noted in the population offered oseltamivir for prophylaxis, and few minor side effects were reported. A recent study compared

oseltamivir prophylaxis with placebo in a cohort of mostly adult (96 %) SOT and HSCT recipients and reported a significant decrease in laboratory-confirmed influenza as determined by reverse transcriptase-PCR over the 12-week study period with oseltamivir prophylaxis (1.7 % vs. 8.4 % in placebo) [81]. Oseltamivir resistance in the immunocompromised population has surfaced [81, 82], reminding clinicians that the choice of a prophylactic antiviral should be determined on the basis of the properties of the current circulating influenza virus. Amantadine, another antiviral that interferes with viral uncoating, has been utilized less, due to resistance noted during the 2008–2009 season [83]. Recommendations regarding appropriate prophylactic agents are revised and published yearly by the CDC, WHO, and collaborating laboratories based on current resistance patterns of circulating influenza strains.

### *Treatment*

The pandemic novel influenza A/H1N1 strain in 2009 created a resurgence of literature evaluating antiviral treatment options for high-risk patients. The oral neuraminidase inhibitor oseltamivir is indicated for the treatment of uncomplicated influenza A or B infection in children 1 year and older who have been symptomatic for no more than 48 h. Dosing ranges from 30 to 75 mg twice a day based on weight. A primary goal in the treatment of influenza in transplant patients is to offer antiviral treatment as soon as possible after initial presentation. Oseltamivir has been shown to significantly reduce hospital stays in critically ill children infected with seasonal influenza [84], and SOT recipients with pandemic influenza A/H1N1 demonstrated a 60 % lower ICU admission rate in patients offered oseltamivir within 48 h of symptom onset [17••].

Zanamivir is an inhaled neurominidase inhibitor that has been less frequently utilized but may offer an alternative treatment for those unresponsive to oseltamivir [85]. Its indications are similar to those of oseltamivir, except that it is recommended for children 7 years and older. Dosing is 10 mg twice daily for 5 days, delivered via an oral inhalation disk. Peramivir is a neurominidase inhibitor that was granted emergency use authorization by the Federal Drug Association in 2009 for the treatment of influenza infection in hospitalized adult and pediatric patients requiring IV therapy following failure of oral and inhaled antiviral medications [86]. This was the first intravenous antiviral medication available for the treatment of influenza, although intravenous formulations of oseltamivir and zanamivir are under investigation (clinicaltrials.gov). Peramivir is licensed in Japan and South Korea and has been found to be effective against susceptible influenza A and B viruses. A phase 3 clinical trial is currently underway to examine the effect of adding peramivir to institutional standards of care in

improving symptoms and nasopharyngeal viral loads in adults and adolescents hospitalized with influenza infection (clinicaltrials.gov). Preliminary studies conducted in Japan have demonstrated improvement in symptoms and reduction of viral loads in pediatric patients given 10 mg/kg/day of peramivir infusion for influenza infection [87, 88]. Studies in transplant patients have not yet been reported. Despite the availability of several antiviral medications for the treatment of influenza, current management strategies focus on prevention of infection in susceptible hosts through vaccination, since complications arising from infection can be quite severe [89].

### Other Respiratory Viruses

Treatment of other respiratory viruses, including parainfluenza virus and human metapneumovirus, has been reported in the literature; however, these are generally case reports and not randomized clinical trials to gauge the efficacy of antiviral intervention. Ribavirin has been reported as a potential strategy for treating both parainfluenza virus and human metapneumovirus in the context of case reports and series of adult SOT and pediatric HSCT recipients, although successful responses have not been consistent [13, 25, 90–93]. However, supportive therapy without antivirals has also been successful in other reports, and further evaluation of potential treatment strategies for these common respiratory viral pathogens is warranted [12, 18, 21].

### Conclusion

Respiratory viral infections affect pediatric recipients of both SOT and HSCT. Prevalence appears similar to that for other children; however, increased risk of morbidity and mortality should influence care-givers to be vigilant about detecting RVIs in these children. Prevention is essential, including vaccination against influenza. Further investigation into treatment modalities is needed to expand treatment options.

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