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REVIEW

Update in the treatment of non-influenza respiratory virus infection in solid organ transplant recipients

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ABSTRACT

Introduction: Despite the improved outcomes in solid organ transplantation with regard to prevention of rejection and increased patient and graft survival, infection remains a common cause of morbidity and mortality. Respiratory viruses are a frequent and potentially serious cause of infection after solid organ transplantation. Furthermore, clinical manifestations of respiratory virus infection (RVI) may be more severe and unusual in solid organ transplant recipients (SOTRs) compared with the non-immunocompromised population.

Areas covered: This article reviews the non-influenza RVIs that are commonly encountered in SOTRs. Epidemiologic and clinical characteristics are highlighted and available treatment options are discussed.

Expert opinion: New diagnostic tools, particularly rapid molecular assays, have expanded the ability to identify specific RVI pathogens in SOTRs. This is not only useful from a treatment standpoint but also to guide infection control practices. More data are needed on RVIs in the solid organ transplant population, particularly regarding their effect on rejection and graft dysfunction. There is also a need for new antiviral agents active against these infections as well as markers that can identify which patients would most benefit from treatment.

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1. Introduction

Each year respiratory viruses account for significant morbidity and mortality worldwide [1,2]. Furthermore, viruses such as influenza A and B, parainfluenza (PIV), respiratory syncytial virus (RSV), and adenovirus (AdV) often cause more severe manifestations in immunocompromised individuals, including solid organ transplant recipients (SOTRs) [3]. While influenza infection is known to cause significant morbidity and mortality in immunocompromised as well as immunocompetent populations [4], there are fewer data on the other viruses that cause respiratory infection in SOTRs. In recent decades, more effective and sustained immunosuppressive therapy has been developed and incorporated into antirejection regimens, decreasing the incidence and degree of rejection episodes in this population [2]. However, simultaneous with enhanced immunosuppression is the increased risk for infection, including that due to respiratory viruses.

The reported rates of respiratory virus infections (RVIs) among SOTRs vary widely in the literature [2]. For example, among lung SOTRs, the incidence of RVIs in published reports ranges from 1.4% to 60%, likely due to the heterogeneity of the types of patients screened, including whether patients are symptomatic or asymptomatic at the time of screening [5,6]. Furthermore, most studies may select for cases of more severe disease by including only hospitalized patients or those being seen by a healthcare provider in the outpatient setting. Patients with milder respiratory symptoms may be less inclined to seek medical attention. Another problem is that even those hospitalized with respiratory infection may not undergo appropriate procedures to make a diagnosis. Until recently, identifying specific respiratory pathogens was difficult, given the similarity in clinical presentation among potential pathogens and the time-consuming nature of available microbiologic techniques such as cell culture or serologic assays. Molecular diagnostics now available in most laboratories can provide more rapid and reliable diagnoses compared to older techniques including antigen detection [3,7,8]. In addition, molecular diagnostics have led to the identification of respiratory tract viruses not previously recognized to be common or important pathogens, including, for instance, bocavirus, certain enteroviruses and coronaviruses [8,9].

Despite the relative dearth of knowledge about RVIs in SOTRs, several studies have revealed some important information. Aside from perhaps PIV, RVIs in SOTRs tend to parallel the seasonal nature of infections in the immunocompetent [3,10,11]. However, SOTRs may have atypical presentations, including few or no symptoms at onset with subsequent progression to severe life-threatening disease [3,10,12–15]. SOTRs may also shed virus for very prolonged periods of time even in the absence of symptoms and thus can spread viruses nosocomially to a greater degree, with potentially devastating consequences to other hospitalized SOTRs [16,17]. Co-infection with bacteria and fungi are also more commonly seen in transplant recipients with RVIs [18].

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Article highlights

- Respiratory viral infections are a significant complication among solid organ transplant recipients and lung transplant recipients are especially prone to complications from these infections.
- In solid organ transplant recipients with respiratory viral infection, bacterial and/or fungal coinfection is more common than in immunocompetent individuals.
- Solid organ transplant recipients with respiratory viral infection are more likely to shed virus for a longer duration compared to immunocompetent patients.
- Timing of respiratory viral infections in transplant recipients largely parallels infection in the community.
- All solid organ transplant recipients with suspected respiratory viral infection should have a nasopharyngeal sample tested by PCR.
- Adenovirus infection may be due to reactivation or new infection in immunocompromised patients.
- Currently, antiviral treatments are limited, but several new therapies are being studied for respiratory viral infections.

This box summarizes key points contained in the article.

Despite the serious consequences of RVIs in immunocompromised hosts, there are few US FDA-approved therapies available. Even so, it is important to identify the presence of specific viruses to determine if antiviral therapy may benefit a patient. In addition, decreasing immunosuppression may be feasible in order to speed up the resolution of a viral infection, and appropriate isolation precautions must be instituted in the hospital setting to limit spread [17]. As noted above, molecular diagnostics are a mainstay of diagnosis of RVIs, and multiplex polymerase chain reaction (PCR) assays using multiple primer pairs to detect a variety of different target sequences can be an efficient and cost-effective means for diagnosis [2,3,9,19]. Of note, Preikasaitis et al. recently demonstrated the feasibility of patient-collected nasopharyngeal swabs for diagnosis of RVI in SOTRs [20].

Compared to other SOTRs, lung transplant recipients are uniquely susceptible to respiratory viral infection due direct exposure of the allograft to the pathogen as well as impaired mucociliary function, lymphatic drainage, and cough reflex due to denervation of the allograft [5,21]. In addition, respiratory viral infections are thought to be a risk factor for the development of rejection and/or bronchiolitis obliterans syndrome (BOS) among lung SOTRs, although this is not consistently demonstrated in the literature [5,11,22–24]. A cohort of 100 lung transplant recipients, 50 with RVI and 50 without RVI, was followed for 3 months and demonstrated an acute rejection rate of 16% in the RVI group compared to 0% in those without RVI, and greater decline in forced expiratory volume in 1 s (FEV1) in the RVI group [23]. However, in a pooled analysis, Vu et al. (2011) were unable to confirm the link between acute rejection and RVI and there were not sufficient numbers to assess the association of RVI and BOS [5]. McCurdyet al. reported no association between RVI treated with ribavirin (RBV) and BOS [25]. Fuehner et al., however, found a protective effect of RBV treatment among lung SOTRs who received the drug for paramyxovirus infection (5% BOS among RBV recipients, 24% BOS among non-RBV recipients, $p = 0.02$) [26]. Finally, a recent prospective cohort study of 98 lung transplant recipients demonstrated that RVIs were significantly associated with acute rejection and a decline in lung function at 1 and 3 months [6]. Definitive assessment of the association between RVIs and acute and chronic rejection will require further study with larger cohorts of patients.

2. Diagnosis

Since RVIs may have overlapping clinical presentations and may cause upper respiratory tract infection (URTI) as well as LRTI, efforts should be made to identify the causative pathogen as the treatment options, if available, differ by virus. In general, all SOTRs suspected of having an RVI should have a nasopharyngeal swab, wash, or aspirate obtained and sent for rapid testing, ideally with PCR-based assays using nucleic acid amplification that can detect a broad range of respiratory pathogens [3]. Culture, antigen detection, and serology have largely been replaced by more sensitive PCR methods. Multiplex PCRs, which are widely used by most transplant centers [27], identify a variety of pathogens not detected by conventional methods [3,8] but may vary in sensitivity and specificity for the detection of AdV [3,7,28]. Quantitative AdV PCR from blood may also be obtained to aid in diagnosis. The features and possible pharmacologic therapies for important non-influenza RVIs in the SOTR population are discussed below and summarized in Table 1.

3. Adenovirus

3.1. Clinical manifestations and epidemiology

AdV is a non-enveloped, double-stranded DNA virus with over 50 serotypes classified into subgroups A–G. AdV causes a variety of usually self-limited infection manifestations in immunocompetent individuals, and AdV is more common in children in both the immunocompetent and immunocompromised populations. Certain AdV serotypes have a predilection for causing pulmonary infection, including subgroups B1 (serotypes 3, 7, 16, 21, 50), B2 (serotypes 11, 14, 34, 35), C (serotypes 1, 2, 5, 6), and E (serotype 4) [29]. Immunocompromised patients can become ill from newly acquired infection or reactivation of latent virus from prior infection [14,29,30]. AdV infection in SOTRs typically occurs within the first year after transplant [14,29,31] and tends to cause more frequent and severe disease in lung transplant recipients [29,32]. Humar et al. reported finding AdV in 19 of 263 SOTRs (7.2%) [14], although none were lung transplant recipients. Viremia was universal and some were asymptomatic. All patients in this cohort recovered from their infection with no consequences. In a cohort of lung transplant recipients, the reported incidence of AdV infection was 22.5%, with most being asymptomatic and no association with rejection or decline in pulmonary function [31]. However, others have reported pediatric and adult SOTRs with severe necrotizing pneumonia (Figure 1) and AdV-associated mortality [13,14,32–34]. Patients who receive antilymphocyte antibodies are at an increased risk of developing AdV infection, and an increase in AdV-specific T lymphocytes has been associated with resolution of AdV in blood and lungs [35,36].

Table 1. Non-influenza respiratory viruses and their treatment.

Virus	Classification	Treatment	US FDA Approval Status
AdV	Non- enveloped, double-stranded DNA virus	Cidofovir	Approved but off-label for AdV
		Brincidofovir	Not approved
		Ribavirin	Approved but off-label for AdV
		Ganciclovir	Approved but off-label for AdV
		IVIG	Approved but off-label for AdV
		AdV-specific T lymphocytes	Not applicable
RSV	Enveloped, single- stranded RNA paramyxovirus	Ribavirin	Aerosolized ribavirin is approved for RSV; IV/PO ribavirin approved but off-label for RSV
		IVIG	Approved but off-label for RSV
		RSV-IVIG	Removed from market in 1998
		Palivizumab	Approved for RSV prophylaxis
		Motavizumab	Not approved
		RI-001	Not approved
		Presatovir	Not approved
		ALS-008176	Not approved
		ALN-RSV01	Not approved and no longer in development
hMPV	Enveloped, single-stranded RNA paramyxovirus	Ribavirin	Approved but off-label for hMPV
		IVIG	Approved but off-label for hMPV
PIV	Enveloped, single-stranded RNA paramyxovirus	Ribavirin	Approved but off-label for PIV
		DAS181	Not approved
HRV	Non-enveloped, single-stranded, RNA picornavirus	Plecoranil	Not approved
		Vapendavir	Not approved
		Recombinant human interferon-α1b	Approved but off-label for HRV
		Subcutaneous interferon-α2a	Approved but off-label for HRV
		Inhaled interferon-β1a	Approved but off-label for HRV
		SNG001	Not approved
		OC459	Not approved
		Omalizumab	Approved but off-label for HRV
HCoV	Enveloped, RNA virus	Ribavirin	Approved but off-label for HCoV
		Interferon-α-2a	Approved but off-label for HCoV
		Interferon-α-2b	Approved but off-label for HCoV
		Oseltamivir	Approved but off-label for HCoV
		Lopinavir/ritonavir	Approved but off-label for HCoV
		Plasma from patients who recently recovered from MERS-CoV	Not applicable

AdV: adenovirus; HCoV: human coronavirus; hMPV: human metapneumovirus; HRV: human rhinovirus; IV: intravenous; IVIG: intravenous immunoglobulin; MERS-CoV: Middle East Respiratory Syndrome coronavirus; PIV: parainfluenza virus; PO: oral; RSV: respiratory syncytial virus.

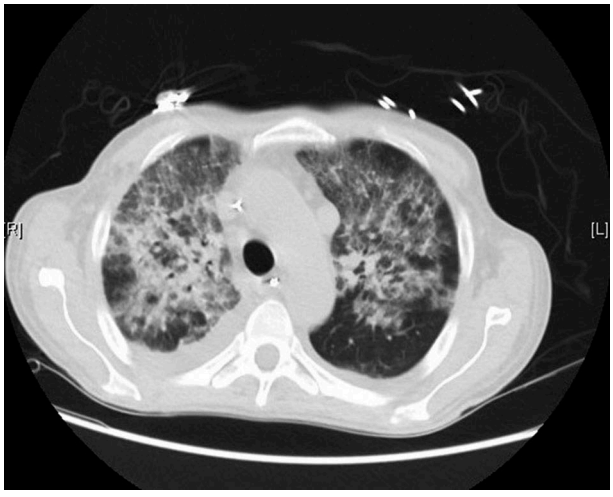


Figure 1. Chest CT image of liver transplant recipient with bilateral adenovirus pneumonia showing interstitial and airspace opacities of the upper lobes.

3.2. Treatment

3.2.1. Cidofovir

There are no FDA-approved antivirals for the treatment of AdV infection. Therefore, the mainstays of therapy for AdV pneumonia are reduction in immunosuppression and supportive care [30]. However, cidofovir, a cytosine analog that interrupts AdV replication *in vitro*, is often used for treatment of more severe infections [30,33,35]. The intracellular diphosphate form of cidofovir acts as an AdV DNA polymerase substrate that is preferred over other cellular substrates, and cidofovir possesses *in vitro* activity against all AdV serotypes [30,37,38]. No prospective controlled trials have been conducted using cidofovir for AdV infection, and its efficacy remains uncertain. Data come from non-randomized series and case reports (mostly in hematopoietic stem cell transplant [HSCT] recipients [HSCTRs] and for various sites of infection including cystitis and enteritis), with varying results including failures [39] as well as clearance of viremia and possible mortality benefit [13,33,40–44]. Monitoring AdV PCR viral load may help in assessing recovery [45], although case reports have also reported apparent early clinical and virologic improvement with subsequent respiratory failure and death [16,33]. Some centers, particularly those caring for pediatric HSCTRs, may perform regular AdV blood PCR for preemptive monitoring, with initiation of cidofovir at the onset of viremia to try to prevent disease [39].

Cidofovir must be administered intravenously as its bioavailability is poor and only 10% of a dose is taken up intracellularly [40]. In addition, cidofovir treatment is frequently

associated with severe nephrotoxicity, even when used as recommended with intravenous normal saline hydration and the renoprotective agent probenecid [46]. The usual dosing is 5 mg/kg/wk for 2 weeks as induction therapy followed by 5mg/kg every 2 weeks with careful monitoring of renal function [30]. Alternate dosing is 1 mg/kg three times weekly [33,35].

3.2.2. Brincidofovir

Brincidofovir (BCV, Chimerix, Durham, NC) is a cidofovir derivative with a lipid moiety that augments cellular uptake of the drug. Once intracellular, cidofovir is released and does not easily get removed from the cells [38]. It has *in vitro* activity against numerous double-stranded DNA viruses and, unlike cidofovir, is not a substrate for organic anion transporter 1, which causes cidofovir accumulation in renal tubules, so BCV lacks the severe nephrotoxicity of cidofovir [47]. BCV received Fast Track status by the FDA for AdV infection, and enrollment was recently completed for a phase 3 clinical trial of BCV in several cohorts: (1) HSCTRs with asymptomatic or limited AdV infection; (2) HSCTRs with disseminated AdV infection; and (3) other immunocompromised patients with AdV infection (the AdVise Study) [38,48]. The primary outcome of the study was 24-week mortality. This open-label non-randomized study included patients aged 2 months to 75 years, and BCV was administered twice a week for 12 weeks [48]. Preliminary data from HSCTRs have demonstrated mixed results. There were improved outcomes in pediatric patients compared to adults with disseminated infection (19% mortality vs. 43% mortality, respectively), and a rapid decline in viral load was noted for many patients as well as improved overall survival among those with an antiviral response [49]. However, BCV was discontinued due to adverse events (primarily gastrointestinal) in 20% of pediatric and 29% of adult subjects [49], and there was no difference in survival between those treated with BCV compared to historical controls, a finding that investigators believed was due to baseline differences in the two cohorts [50].

Florescu and colleagues reported on the safety and efficacy of BCV as salvage therapy in 13 immunocompromised patients with severe AdV infection. They noted that nine patients showed virologic response by 8 weeks, and these patients had longer survival compared to those who did not exhibit a viral response (196 days vs. 55 days) [51].

3.2.3. Other antivirals

RBV is a guanosine analog with activity against DNA and RNA viruses. Data regarding its efficacy for AdV infection have been equivocal and limited to a small number of case reports [35,52]. It appears to have *in vitro* activity only against subgroup C serotypes [41], although serotype analysis is not typically performed on clinical samples. Ganciclovir (GCV) has *in vitro* activity against AdV; however, it has not prevented AdV infection among patients receiving CMV prophylaxis with GCV or valganciclovir [14,53].

3.2.4. Immunoglobulin therapy

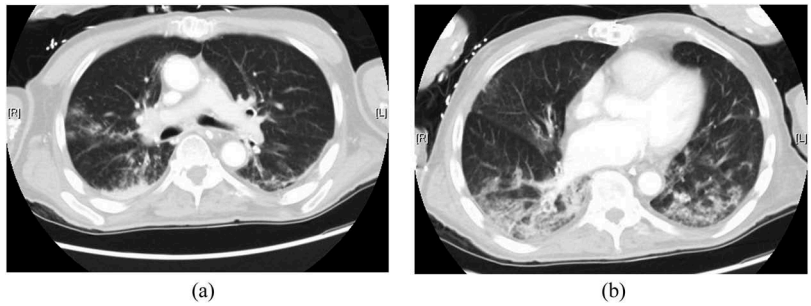
There are numerous reports in the literature citing the use of intravenous immunoglobulin (IVIG) as part of therapy for viral infections in immunocompromised patients [13,33,43,54]. Although hypogammaglobulinemia is associated with an increased risk of opportunistic infections, Noell did not find an effect of hypogammaglobulinemia on community-acquired RVI in a cohort of lung transplant recipients, and few of the infections noted in these patients were due to AdV [54]. Because reconstitution of the immune system appears to be important in overcoming AdV infection [55], other forms of immunotherapy, including transfer of AdV-specific T lymphocytes, are under investigation [56].

4. Respiratory syncytial virus

4.1. Clinical manifestations and epidemiology

RSV is an enveloped, single-stranded RNA paramyxovirus responsible for seasonal annual epidemics worldwide, although it may have a prolonged season in temperate climates [57]. Transmission occurs through inhalation of infectious droplets or through contact with infectious fomites, emphasizing the importance of appropriate infection control practices, especially among hospitalized SOTRs [3]. RSV is the most common cause of childhood acute URTI and LRTI [58–60], with the highest prevalence among children less than 2 years of age [59]. The incidence of RSV infection in SOTRs is unclear but reported in the literature to range from 2% to 22%, with most reporting less than 5% [5,21,22,61].

RSV infection may occur at any time posttransplant, but recent reports have found a mean onset of 2–6 years after SOT [62–65]. RSV infection typically manifests as an URTI in SOTRs with cough as the predominant symptom followed by



(a) (b)

Figure 2 (a) and (b). Chest CT images of a heart transplant recipient with bilateral RSV pneumonia showing scattered reticulonodular infiltrates and lower lobe consolidation.

dyspnea and fever [58,65,66]. RSV infection progresses to LRTI in 27–67% of SOTRs (Figure 2(a,b) [58,65,66]. In addition, SOTRs with RSV infection may have difficulty clearing the infection due to immunosuppression, resulting in prolonged viral shedding [58,67]. Mechanical ventilation has been required in up to 25% of SOTRs with RSV infection but mortality in this population, even in the absence of antiviral therapy, is relatively low in published series, 0–13% [26,52,58,62,66,68–70]. Of note, in one series where appreciable RSV-related mortality was noted (4/30, 13% overall), mortality was 22% among 18 SOTRs more than 1 year after SOT compared to 0% among 12 SOTRs within 1 year of SOT [66].

4.2. Treatment

4.2.1. Ribavirin

There are limited treatment data for RSV in SOTRs. Similar to AdV infection, the primary therapy consists of supportive care and reduction in immunosuppression [3]. RBV is a nucleoside analog with demonstrated *in vitro* activity against RSV [71] and aerosolized RBV is FDA-approved for RSV treatment. However, the majority of published clinical data in immunocompromised patients are in HSCTRs [72,73], where it has been shown to decrease progression to LRTI when given to patients with URTI [73].

Among SOTRs, the most experience with RBV is in lung transplant recipients. Early reports of aerosolized RBV for RSV infection in lung SOTRs largely described successful outcomes but given the lack of comparators in these reports it is unknown if patients would have responded without treatment [74,75]. In a larger case series, Liu et al. described 23 episodes of RSV among lung or heart/lung SOTRs [64]. Patients were given aerosolized RBV 2 gm every 8 h for 15 doses, methylprednisolone 500 mg once daily for 3 days, and one dose each of IVIG 0.5 mg/kg and palivizumab 15 mg/kg. No patients with URTI progressed to LRTI, and no treatment episodes required mechanical ventilation. No adverse effects were noted, and one patient died of worsening preexisting liver failure unrelated to RSV infection. Average FEV_1 values declined by 5.7% at the time of infection but were not significantly different than baseline in the 6 months after treatment.

Inhaled RBV is difficult to administer. It must be given with a small particle nebulizer at a dose of 6 gm daily, aerosolized continuously over 18 h, or 2 gm every 8 h over 2 h each [72,73]. During this time, the patient is confined to an oxygen hood or drug-scavenging tent to protect health-care workers and other patients from RBV exposure due to its teratogenic potential [73,76]. In addition to the logistically complicated administration, the drug is associated with serious toxicities such as hemolytic anemia [3,26,52,62].

Intravenous (IV) or oral (PO) RBV may be given as alternative to aerosolized RBV. Glanville et al. gave IV RBV 33 mg/kg in three divided doses on day 1 followed by 20 mg/kg in three divided doses to 18 lung SOTRs with RSV LRTI [63]. RBV was given in combination with prednisolone 1 mg/kg/day (up to 60 mg) weaned by 5 mg every other day until at baseline steroid dose. Treatment was continued until repeat nasopharyngeal swab was negative for RSV. No patient required mechanical ventilation, and there was no mortality. The same group of investigators gave the aforementioned IV loading dose of RBV followed by PO RBV 20 mg/kg in two divided doses (rounded to nearest 200 mg) to 52 lung SOTRs with 56 episodes of RSV LRTI for a median duration of therapy of 8 days [62]. RBV was given in combination with prednisolone 1 mg/kg/day with a taper as in the IV study. Worsening anemia was noted in 23 of 33 episodes among patients with preexisting anemia and *de novo* anemia in 5 of 21 episodes. No patient required mechanical ventilation, and there was no infection-related mortality although there were four late deaths unrelated to infection. One and two patients, respectively, had new-onset BOS at 3 and 6 months afterward.

Other authors have reported comparable outcomes with PO RBV. Peleaz et al. gave PO RBV 15–20 mg/kg in three divided doses for 10 days with methylprednisolone 10–15 mg/kg/day for 3 days to five lung SOTRs [69]. No patient required mechanical ventilation and there was no mortality. One patient developed mild anemia that did not require treatment. In a larger cohort, Fuehner et al. described 67 lung or heart/lung SOTRs with paramyxovirus infection including 43 with RSV infection; half of all patients had LRTI [26]. Of the 43 patients, 24 received PO RBV 15–20 mg/kg/day in two divided doses for 14 days. Outcome results were pooled for all viruses (RSV, PIV, and human metapneumovirus [hMPV] infection). Graft function recovery at 30 days was more common among RBV recipients compared to those receiving supportive care (84% vs. 59%, $p = 0.02$), and new-onset BOS occurred less frequently in the RBV group (5% vs. 24%, $p = 0.02$). A high rate of RBV recipients (26%) required premature drug discontinuation due to adverse effects (5 hemolysis, 4 renal failure, 1 nausea). Li et al. compared the outcomes of six lung SOTRs who received PO RBV (400 mg 3 times daily) to 15 lung SOTRs who received aerosolized RBV (6 gm over 12 h) for RSV infection [68]. Over 50% of patients in both groups had LRTI, and there were no significant differences in 6-month outcomes based on the route of administration.

More recent cohort studies have reported the outcomes of RBV treatment for RSV infection among non-lung SOTRs. Ariza-Heredia et al. described their experience with 12 SOTRs (5 kidney, 4 liver, and 3 lung transplant recipients) with RSV infection [58]. Eight of 12 had LRTI and were given either aerosolized (6 gm over 18 h) or PO RBV at doses of 600–1800 mg/day in two to three divided doses. Three patients with LRTI also received palivizumab, and two of these also received IVIG. One patient with URTI received PO RBV. Although 25% required mechanical ventilation, there was no mortality associated with the infection. Subsequent investigators have given PO or aerosolized RBV to non-lung SOTRs for RSV infection, but the numbers are relatively small and in some reports have been pooled with lung SOTRs and/or HSCTRs, which makes it difficult to determine the drug's utility in non-lung SOTRs [65,66].

A recent meta-analysis by Gross et al. [52] pooled data among all populations who received PO RBV for RVIs. The mortality among lung SOTRS who received PO RBV was 1/108 (0.9%). Hemolysis (ranging in severity from mild anemia to severe hemolytic anemia and lactic acidosis) was the most common side effect, occurring in 14% (54/375) of PO RBV recipients. Therapy was prematurely discontinued in 4% (15/

375) due to adverse effects. Despite the limited data to support the efficacy of RBV in SOTRs, oral and inhaled RBV are still commonly employed for SOTRs with URTI or LRTI RSV infection, especially lung SOTRs [27].

4.2.2. Immunoglobulin therapy

Experts recommend considering the addition of an antibody preparation to RBV with or without corticosteroids for severe RSV infection in SOTRs, although there are limited data to support this recommendation [3]. As described above, there are a small number of case series that report the use of IVIG and/or palivizumab in combination with RBV, but antibody therapy has not been studied as a stand-alone treatment [58,64,66]. RSV–IVIG was removed from the market in 1998 due to the introduction of palivizumab, a monoclonal antibody against the RSV fusion (F) protein. It is FDA-approved for the prophylaxis of RSV in high-risk infants during RSV season [77]. As above, Liu et al. and Aziza-Heredia et al. reported giving palivizumab in combination with RBV ± IVIG and/or methylprednisolone [58,64]. Grodin et al. reported the successful treatment of a 70-year-old heart transplant recipient who received one dose of palivizumab (7.5 mg/kg = 900 mg) in combination with aerosolized RBV, IVIG, and methylprednisolone [78]. Palivizumab prophylaxis is frequently given outside of RSV season to pediatric SOTRs (93% of centers give to infants up to 12 months and 79% to infants up to 24 months) [79], although it has not been studied for this indication. Motavizumab (MedImmune, LLC/AstraZeneca, Wilmington, DE) is a second-generation humanized monoclonal antibody with ~70-fold higher affinity for the RSV F protein and 20-fold greater neutralizing capacity than palivizumab [80]. When compared to palivizumab for RSV prophylaxis in high-risk children, motavizumab demonstrated 26% fewer RSV-associated hospitalizations and a 50% decrease in outpatient RSV LRTIs [81]. Concerns about increased nonfatal hypersensitivity reactions led the FDA to deny the drug's licensed approval, and development for that indication has ceased [82]. A recent report described the use of high-titer anti-RSV neutralizing antibody (RI-001, ADMA Biologics, Inc, Ramsey, NJ) for the treatment of 15 patients with hematologic malignancy or hematopoietic stem cell transplantation and RSV LRTI [83]. Eleven of 15 patients survived, and survivors had a shorter time from RSV diagnosis to initiation of RI-001.

4.2.3. Other antivirals

Presatovir (GS-5806, Gilead Sciences, Inc., Foster City, CA) is a potent and selective RSV fusion inhibitor [84,85] and is currently being studied in a phase 2b placebo-controlled RCT in lung SOTRs with RSV infection. ALS-008176 (Janssen Research & Development, LLC, Raritan, NJ) is a nucleoside inhibitor of the RSV RNA polymerase; it inhibits RSV replication *in vitro* and was effective in a healthy adult inoculation study [86]. Treatment with ALS-008176 was associated with more rapid RSV clearance and decreased disease severity compared to placebo treatment. It is being studied in a randomized, placebo-controlled phase 2b trial of adults hospitalized with RSV infection [87].

ALN-RSV01 (Alnylam Pharmaceuticals, Cambridge, MA) is a small interfering RNA directed against the mRNA of RSV nucleocapsid (N) protein (RNA interference therapy). Eighty-five healthy volunteers were experimentally infected with wild-type RSV and randomized to receive ALN-RSV01 nasal spray or placebo for 2 days before and 3 days after RSV inoculation. The proportion of culture-confirmed RSV infections was 71% and 44% among placebo and active drug recipients, respectively ($p = 0.009$), with a similar safely profile between medications [88]. ALN-RSV01 has since been studied in lung SOTRs with RSV infection [89]. Subjects were randomized to receive active drug or placebo daily for 5 days. The primary outcome was progression to BOS, found in 14% of ALN-RSV01 recipients compared to 30% of placebo controls ($p = 0.058$). The treatment effect was enhanced when ALN-RSV01 was started less than 5 days from symptom onset independent of RBV administration. However, the compound is no longer in development [90].

5. Human metapneumovirus

5.1. Clinical manifestations and epidemiology

hMPV is an enveloped, single-stranded RNA virus in the paramyxovirus family. hMPV was newly discovered as recently as 2001, but found through serologic studies to be present in the population in the 50 years prior [9,91]. Initially, it was described as the cause of URTI and LRTI in immunocompetent children under 5 years of age but is now known to cause infection in older adults and immunocompromised individuals [91] with a seasonality similar to influenza [9]. A retrospective study of lung transplant recipients found that hMPV accounted for 6% of RVIs [24]. In addition, although many studies report no mortality due to hMPV infection among transplant recipients, there are also descriptions of fatal hMPV LRTIs despite treatment with RBV and IVIG [12,24,91–94]. Shahda reported death related to hMPV infection in two of four lung transplant recipients and worse lung function in the two surviving recipients [15]. Allograft rejection has been reported in up to 25% of SOTRs with hMPV infection [24].

5.2. Treatment

There is no approved drug for the treatment for hMPV respiratory infection. Supportive therapy is the main treatment [12,19,24,91], although RBV alone or with IVIG has been given to SOTRs [12,15,92–94]. Shahda reported recovery of two HSCTRs with hMPV pneumonia after transplant with oral and aerosolized RBV and IVIG [15]. Kitanovski reported rapid recovery from hMPV pneumonia in an immunocompromised 2-year-old after treatment with oral RBV and IVIG [94]. However, Chu et al. reported mortality due to hMPV pneumonia in their cohort despite therapy [12]. There are no sponsored clinical trials underway addressing therapy for hMPV in immunocompromised patients, but monoclonal antibodies potentially effective in clinical hMPV infection are in development [95].

6. Parainfluenza

6.1. Clinical manifestations and epidemiology

Similar to RSV and hMPV, PIV is an enveloped, single-stranded RNA paramyxovirus classified into four types (1–4). Types 1 and

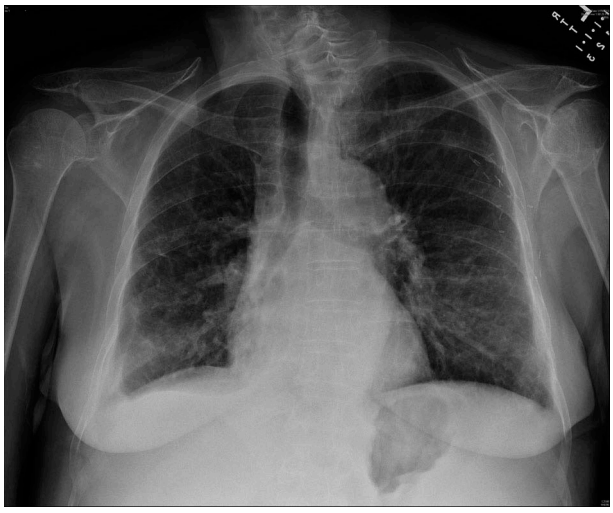


Figure 3. Chest x-ray image of a liver transplant recipient with PIV-4 pneumonia showing bilateral interstitial infiltrates of the lower lungs.

2 tend to circulate in the fall and winter while PIV-3 circulates year-round but has the highest incidence in the late spring and summer [96,97]. PIV-4 is uncommon (Figure 3). There are significantly fewer data on PIV infection in SOTRs compared to HSCT recipients, and most data in SOTRs are in lung transplant recipients. A review of 32 PIV infections in 24 lung transplant recipients over 10 years revealed that infection occurred a median of 2 years after transplant (range 0.6–5 years); respiratory failure developed in 21% and BOS in 32% [98]. Most infections were caused by PIV-3; this type also causes the majority of infections in HSCTRs [26]. URTI is the most common manifestation although it can progress to LRTI, resulting in fatal infection; there was an 8% mortality in the review of lung transplant recipients noted above [98]. PIV infection may be most serious in pediatric SOTRs as well as lung SOTRs of any age. And, of the respiratory viruses, PIV is most strongly associated with the development of BOS in lung SOTRs [3,23].

6.2. Treatment

6.2.1. Ribavirin

Supportive care is the mainstay of PIV treatment. RBV has demonstrated *in vitro* activity against PIV [99] and has been used as monotherapy [25,26,75] and in combination with IVIG and corticosteroids [64] to treat lung SOTRs with PIV infection. In all of these relatively small, retrospective cohort studies of lung transplant recipients, outcome data were pooled with other paramyxovirus and RBV was associated with variable responses.

6.2.2. Other antivirals

A novel recombinant sialidase fusion protein administered by oral inhalation, DAS181 (Ansun Biopharma, San Diego, CA), has *in vitro* activity against PIV by binding to respiratory epithelial cells and removing the cell-surface sialic acid residues necessary for PIV attachment and cell entry [100]. DAS181 has demonstrated efficacy against PIV in a compassionate-use protocol conducted in 16 HSCTRs [101]. Eleven of the 16 patients were hypoxic, and after 5–10 days of DAS181 9/16 (56%) had a complete clinical response and 4/16 (25%) had a partial response, but there were also three deaths (19%). There are additionally two anecdotal reports on the successful use of DAS181 in lung SOTRs [102,103]. The drug is currently being studied in phase 2 clinical trials for the treatment of PIV in SOTRs and HSCTRs [104]. Finally, similar to AdV immunotherapy, McLaughlin et al. generated PIV-3-specific T cells from healthy donors but their use has not yet been reported in humans [105].

7. Rhinovirus

7.1. Clinical manifestations and epidemiology

Human rhinoviruses (HRVs), members of the *Enterovirus* genus and hence known as respiratory enteroviruses, are non-enveloped, single-stranded RNA picornaviruses capable of causing URTI and LRTI. They display a peak incidence in the spring and fall and the highest occurrence is in children who may act as reservoirs [3,106]. HRVs are the most frequent cause of the 'common cold' in children and adults as well as the most frequent cause of RVI in SOTRs [5,97,107]. HRVs have historically been classified into two species, HRV-A and HRV-B, until the recent discovery of a new species, HRV-C [108]. HRV-C has since been deemed the most prevalent HRV species and although it still most commonly causes URTI in children it also causes LRTI in adults. The epidemiology of HRV-C in SOTRs is not well described in the literature.

The most common manifestation of HRV infection is URTI, and symptoms are more often absent or milder compared to PIV and RSV infections [97,107]. The role of HRVs in LRTI has been debated given the frequency of detection in asymptomatic persons. A review of bronchoalveolar lavage specimens from 36 lung transplant recipients showed a detection rate of 41.7% compared with approximately 14% in other immunocompromised individuals and in immunocompetent patients, demonstrating a high rate of LRTI in lung transplant recipients [109]. However, there was also a high rate of co-infection by other viral or nonviral pathogens (86% of patients), and the minority of patients had signs or symptoms of pneumonia. One lung transplant recipient with HRV isolated as a single agent did experience respiratory failure.

7.2. Treatment

7.2.1. Capsid-binding agents

There are no approved antivirals for the treatment of rhinoviruses. Pleconaril (Merck Sharp & Dohme, Corp., Kenilworth, NJ), which binds the HRV capsid proteins surrounding the RNA genome and interferes with HRV binding to cellular receptors, has been shown to have broad antienteroviral activity [110]. Hayden et al. reported in two randomized, double-blind studies that pleconaril reduced the duration of illness by 1 day among 1363 adults with HRV infection [111], although data in infants revealed drug accumulation and increased adverse effects [112]. FDA approval for treatment of the common cold was rejected due to safety issues and concerns about antiviral resistance [113]. Subsequently, the drug has been in development as a

nasal spray aimed to reduce common cold symptoms and asthma exacerbations following HRV infection [114] and as an oral formulation for treatment of enteroviral sepsis in neonates [115].

BTA-798, vapendavir (Aviragen Therapeutics, Alpharetta, GA), another capsid-binding agent, was found to be 10-fold more potent than pleconaril [116] and is in development for the treatment of HRV. A phase 2 study in adults with HRV and asthma was recently completed [117], but the drug has not been studied in SOTRs.

7.2.2. Other antivirals

Recombinant human interferon-α1b was recently shown to improve healing and clearance time among children with hand, foot, and mouth disease caused by EV71 [118]. Subcutaneous interferon-α2a is being studied among patients with hypogammaglobulinemia and HRV infection [119]. Inhaled interferon-β1a (SNG001, Synairgen Research Ltd., Southampton, UK) was studied in a randomized trial of 147 patients with asthma and HRV infection to assess whether it can reduce virus-related asthma exacerbations [120]. Patients received inhaled SNG001 or placebo within 24 h of developing cold symptoms. Treatment had no significant effect on preventing or attenuating asthma symptoms in the entire cohort but a subanalysis of more difficult-to-treat asthmatics showed that treatment was associated with improved asthma control [120].

OC459 (Atopix Therapeutics Ltd., Abingdon, Oxon, UK) is a CRTh2 (chemoattractant receptor homolog on Th2 cells) antagonist that decreases Th2 cell and eosinophil chemotaxis and inhibits the release of Th2-type cytokines [121]. It is designed to improve lung function in patients with eosinophilic asthma and is being studied in a phase 2 trial of adults with asthma and HRV infection [122]. Omalizumab, a humanized antibody that binds free IgE and is approved for use in treatment of asthma, is being studied in mild asthmatics with HRV infection [123]. Additional compounds with *in vitro* activity against viral targets such as HRV protease, helicase, and RNA polymerase are being investigated for the treatment of HRV infections [124].

8. Coronavirus

8.1. Clinical manifestations and epidemiology

Human coronaviruses (HCoVs) are enveloped RNA viruses that tend to occur in a seasonal manner [21,89] and have a similar clinical presentation to HRV infection. They generally result in self-limited disease but may progress to LRTI in young children and older adults [125,126]. The most common types of HCoV are OC43, 229E, HKU1, and NL63. Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) are novel coronaviruses that have been responsible for recent acute respiratory syndrome epidemics [127]. MERS-CoV is a zoonotic virus with camels as the most likely source of transmission [128]. The epidemiology of HCoV infections in SOTRs is limited, but there was a recent report describing two renal SOTR recipients with MERS-CoV infection. One patient had progressive respiratory and renal failure and died, while the other patient had respiratory symptoms but remained stable and recovered from the infection despite receipt of antithymocyte globulin one month prior [129].

8.2. Treatment

8.2.1. Ribavirin and interferon-α

There are no antivirals licensed for the treatment of HCoV infections, and therapy consists of supportive care. There is great interest in developing effective treatments for MERS-CoV given its prevalence in the Middle East and apparent high fatality rate, 36.3% in one review [128]. The effect of RBV in combination with interferon-α-2a on MERS-CoV has been reported in two publications. Omrani et al. retrospectively compared a treatment group of 20 patients with MERS-CoV LRTI to 24 control patients who received supportive care [130]. Over 90% of patients in both groups required mechanical ventilation. After 14 days, 14/20 (70%) of antiviral recipients had survived compared to 7/29 (17%) of controls ($p = 0.004$), but the treatment effect was no longer statistically significant at 28 days (30% vs. 17%, $p = 0.054$). Al-Tawfiq et al. reported a case series of five critically ill adults who received PO RBV, interferon-α-2b, osteltamivir, and corticosteroids for MERS-CoV LRTI [131]. None of the patients responded to therapy, and all patients died although the median time from admission to RBV and interferon was 19 days (range 10–22 days). Use of this combination has not been reported in SOTRs.

8.2.2. Other antivirals

Lopinavir/ritonavir, approved for treatment of HIV infection, and interferon-β1b both have *in vitro* activity against MERS-CoV and are active in a marmoset model of infection [12]. There is a phase 2/3 placebo-controlled study being conducted in Saudi Arabia assessing the efficacy of a combination of the two drugs given for 14 days in hospitalized adults with MERS-CoV [132]. There is also a phase 2 trial in Saudi Arabia of convalescent plasma for MERS-CoV infection using plasma obtained from patients who recently recovered from MERS-CoV, health-care workers with exposure, and other volunteer donors [133].

9. Conclusion

AdV, RSV, hMPV, PIV, HRV, and HCoV are common causes of non-influenza respiratory infection in SOTRs, and our knowledge of the epidemiology and spectrum of these pathogens has expanded with the use of newly available rapid molecular diagnostic tools. RVIs may cause severe morbidity with respiratory failure and may be fatal in immunocompromised hosts, and some studies have shown an association between RVIs and long-term allograft dysfunction. The main therapy for many consists of reduction in immunosuppression and supportive care. More treatment options are needed as is additional research dedicated to the epidemiology of RVIs in SOTRs and risk factors associated with poor outcomes.

10. Expert opinion

The number of SOTRs continues to increase, leaving a large population vulnerable to potentially severe RVIs. There clearly is a need for new effective and non-toxic antiviral compounds with activity against community-acquired respiratory viruses. This article highlights available therapies as well as some compounds in later stages of development. However, further work is needed in this area since clinically available treatments are limited, toxic, unproven, or unavailable, depending on the virus in question. Novel antivirals such as DAS-181 and brincidofovir have been highly anticipated, but the latter's future is uncertain given its mixed results in recent studies of immunocompromised patients with CMV infection [134] and AdV infection [49]. Broad-spectrum antivirals possessing activity against multiple RVIs and a high barrier to the development of resistance could provide great benefit.

One of the major questions clinicians face in treating SOTRs with available antivirals, such as cidofovir or RBV, is when to intervene with therapy. Not all SOTRs will develop LRTI or respiratory failure, and the adverse effects of these medications may be significant. Having predictors of poor outcomes would be extremely useful. Some studies have shown a correlation of viral loads with severe disease due to RVIs [86,135], but more work is needed to identify viral load cutoffs that predict LRTI or respiratory failure and whether quantification of upper respiratory tract viral loads predict viral burden in the lower respiratory tract [136]. As noted above, the strategy of preemptive therapy for AdV infection via monitoring quantitative viral loads in blood has been advocated in allogeneic HSCT recipients [30], but such strategies have yet to be established as beneficial in SOTRs [30].

Manipulation of the immune system is an additional tool that could combat RVIs. Immune reconstitution is an important factor in recovery from infection in organ transplantation and, as noted above, the use of specific immunotherapies such as virus-specific T cells, particularly those that are simultaneously active against multiple viruses, may be a significant advance in antiviral therapy. To allow for broad application of this technology, it would be optimal if such cells could be made from donors who are seronegative (e.g. using cord blood-derived cytotoxic T lymphocytes) or derived from other third parties as 'off-the-shelf' therapy [137].

At the same time, inflammatory responses may sometimes be deleterious in RVIs, and rather than targeting viral proteins or enzymes, targeting host proteins involved in the pathogenesis of RVI infection is an additional potential treatment approach. CRTh2 antagonists mentioned above can diminish harmful immune responses prompted by RVIs. In addition, inhibitors of cyclophilin, such as cyclosporine, can prevent inflammatory cytokine production and have shown activity against HCoVs [138,139]. Development of more accurate measures of immune function would also be quite helpful in stratifying SOTRs at the highest risk of serious RVI or complications from RVI. Finally, the development of effective vaccines for RVIs is a high priority given the prevalence of these infections and their impact on immunocompetent and immunocompromised individuals.

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