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Respiratory Viral Infections in Solid Organ and Hematopoietic Stem Cell Transplantation

Grant C. Paulsen, MD*, Lara Danziger-Isakov, MD, MPH

KEYWORDS

• Respiratory virus • Solid organ transplant • Hematopoietic stem cell transplant

KEY POINTS

- Respiratory viral infections are common causes of infection in solid organ and hematopoietic stem cell recipients.
- Respiratory viral infections can cause significant morbidity and mortality in immunocompromised patients.
- Treatment options for respiratory viruses are limited and prevention is vital following transplants.

INTRODUCTION

Common respiratory viral infections (RVIs) are an important cause of morbidity and mortality following solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT).[1,2] RVIs are typically caused by respiratory syncytial virus (RSV), influenza, parainfluenza, rhinovirus, adenovirus, and human metapneumovirus (hMPV). There is also increasing recognition of human coronavirus and human bocavirus in these populations. In addition, in SOT and HSCT patients, respiratory infections can be caused by viruses less commonly associated with the respiratory tract, such as cytomegalovirus (CMV), human herpesviruses (herpes simplex virus [HSV] 1, HSV2), and varicella zoster virus (VZV). This article focuses on the epidemiology, outcomes, and specific prevention and treatment options for RVIs in SOT and HSCT patients.

GENERAL EPIDEMIOLOGY AND RISK FACTORS

RVIs are a well-recognized cause of morbidity and mortality following SOT, especially within the thoracic transplant population. Recent prospective surveillance of 98 lung transplant recipients in Spain found an overall rate of respiratory viruses, asymptomatic and symptomatic, of 0.76 per patient-year and a significantly higher rate of 2.1 RVIs per patient-year in symptomatic patients.[3] Nasopharyngeal swabs collected from asymptomatic patients were positive 11.5% of the time compared with 55.4% positive in symptomatic patients. The most frequently detected RVIs in symptomatic patients were picornaviruses, such as rhinovirus and enterovirus, at 43%, followed by coronavirus (16.7%) and influenza (16.7%). Symptomatic RVI detection progressed to lower respiratory tract infection (LRTI)

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Division of Infectious Diseases, Cincinnati Children's Hospital Medical Center, S8.216 MLC 7017, 3333 Burnet Avenue, Cincinnati, OH 45229, USA
* Corresponding author.
E-mail address: Grant.paulsen@cchmc.org

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in 40% of patients.[3] A prospective Swiss study reported similar results with an RVI incidence of 0.83 per patient-year, detection of respiratory viruses in 14% of those screened and 34% of symptomatic patients, and rhinovirus/enterovirus as the most common RVI.[4] Human bocavirus, identified in 2005, has been reported to cause upper respiratory infection (URI), fevers, wheezing, LRTI, and diarrhea in normal hosts, and plays an unclear role in SOT recipients.[5] Parainfluenza, RSV, hMPV, and influenza were the most frequently found viruses in LRTI and were associated with higher rates of hospitalization. Analyses of RVI in lung transplant recipients have reported a rate of infection from 1.4% to 60%, with detection 5 times more frequent if symptoms were present (**Table 1**).[6,7] Reported risks for RVI in lung transplant patients include increased calcineurin inhibitor levels, age less than 15 years, and underlying cause for transplant other than cystic fibrosis.[4,8]

As noted for SOT patients, RVIs in HSCT recipients have been well-characterized causes of significant morbidity and mortality. Reported incidences of RVI in HSCT recipients vary between 4% in earlier reports using antigen detection and culture[9] and 20% to 40% using polymerase chain reaction (PCR) testing (see **Table 1**).[2,10–12] Bocavirus, as mentioned earlier, also plays an unclear role in the HSCT population, with 1 report of disseminated bocavirus in a pediatric HSCT recipient.[13] Risk factors for progression to LRTI include age greater than 65 years, lymphopenia, neutropenia, alternative/nongenoidentical sibling donor, and chronic graft-versus-host disease (GVHD).[10,14]

GENERAL OUTCOMES AND COMPLICATIONS

Several publications have attempted to delineate morbidity and mortality following RVI in thoracic transplant recipients, specifically with respect to acute rejection and chronic lung allograft dysfunction (CLAD)/bronchiolitis obliterans syndrome (BOS). In the study from Spain mentioned earlier, LRTI was associated with significant change in lung function (forced expiratory volume in 1 second [FEV_1]) at 1 and 3 months following infection and nested case-control analysis reported a significant association between RVI within 3 months and acute rejection (hazard ratio [HR], 6.54; confidence interval [CI], 1.47–29.08; $P = .01$).[3] Alternatively, the Swiss study with similar incidence rates found no such association.[4] CLAD compromises long-term survival following lung transplant and although an association with previous viral infection has been explored in published literature, a definitive link remains unclear. Pooled incidence rates for CLAD in the meta-analysis mentioned earlier for virus-positive cases were 18% (9 out of 50 cases) compared with 11.6% (37 out of 319) in virus-negative cases, but because of limited number of overall events a link could not be confirmed.[6] However, there are published epidemiologic links between RVI and CLAD as well as data on biologically plausible mechanisms underlying a causal relationship.[5,15–17] In addition, a recent large retrospective cohort (n = 250) of lung transplant recipients found an independent association between RVI and development of CLAD within 3 the next months (HR, 4.8; CI, 1.9–11.6; $P<.01$).[18]

Table 1
Classification and distribution of respiratory viral infections in solid organ transplant and hematopoietic stem cell transplant

			Distribution of RVIs (%)		
Respiratory Virus	**Family**	**Type of Nucleic Acid**	**SOT**	**HSCT**	**Seasonality**
Rhinovirus/Enterovirus	Picornaviridae	RNA	21–62	22–34	Spring, summer, fall
Coronavirus	Coronaviridae	RNA	13–29	3–11	Spring, winter
RSV	Paramyxoviridae	RNA	6–20	19–31	Spring, fall, winter
Adenovirus	Adenoviridae	DNA	1–25	2–6	Spring
Parainfluenza	Paramyxoviridae	RNA	3–18	19–27	Summer
Influenza	Orthomyxoviridae	RNA	2–16	13–33	Spring, winter
Human metapneumovirus	Paramyxoviridae	RNA	4–7	4–11	Spring, winter
Bocavirus	Parvoviridae	DNA	1	—	—

Data from Refs.[2–4,7,8,11,12,14,38,161]

Published attributable mortality caused by LRTI in HSCT from a respiratory virus varies, up to 28% to 30% in some reports, most commonly involving influenza, RSV, adenovirus, and hMPV.[10,19] Important risk factors for mortality in the HSCT population include lymphopenia, corticosteroids (>1 mg/kg), and viral or bacterial coinfection.[11] BOS following allogeneic stem cell transplant is also associated with significant morbidity and mortality. The most recognized risk factor for BOS following HSCT is GVHD, but there is some evidence that RVIs may play a role as well.[20,21]

DIAGNOSIS

The array of diagnostic tools for RVIs in immunocompromised patients has greatly increased over the last few years, providing increased sensitivity as well as decreased processing times.[22] In general, testing for RVIs has moved away from viral antigen and culture methods and now relies heavily on molecular methods. Real-time quantitative and qualitative reverse transcription PCR testing is a well-established method for identifying viral infection and is now incorporated into many of the guidelines in use.[23] Multiplex platforms that test for multiple viruses simultaneously from a single sample are now common.

As the sensitivity of molecular diagnostic tools has improved, the issues of asymptomatic viral shedding and sampling methods have become more relevant than ever. As noted earlier, asymptomatic viral shedding is seen frequently, including reports of asymptomatic RSV shedding in HSCT recipients for 35 to 80 days and persistent rhinovirus detection for 8 to 15 months in lung transplant recipients.[3,18,24,25] The ability of current molecular testing methods to detect virus in samples with few viral copies combined with prolonged viral shedding in SOT and HSCT recipients can create a challenge for clinicians trying to determine whether a positive molecular test indicates a true pathogen.[26] The source or sampling method used is an important consideration. Respiratory samples are routinely obtained from aspirates/washes or swabs from the nasopharynx (NP) or oropharynx (OP) as well as more invasive collection methods such as bronchoalveolar lavage (BAL). However, the choice of upper respiratory sample collection methodology for optimal viral recovery is uncertain. In children hospitalized because of respiratory infections, sensitivity of RVI detection with NP aspirates of 86% to 100% have been reported versus nasal swab sensitivity of 67% to 95%.[27] A similar comparison of NP swabs with or without OP swabs in immunocompetent children found a higher sensitivity of NP swabs for RVI of 91% to 100%, which was greater than or equal to OP swabs (83%–98%), with combined testing increasing detection by 2% to 9%, depending on the virus.[28] Investigation in adults reported higher sensitivity with NP washes (85%) than NP swabs (73%) or OP swabs (54%), and noted that maximal sensitivity was achieved through a combination of all 3 methods.[29]

GENERAL PREVENTION

RVI prevention is a key component to minimize infections and subsequent complications. Interventions can be patient specific, such as antiviral prophylaxis following transplant and immunization both before and following transplant. For the most common RVIs, immunization is only available for influenza, as discussed later. Vaccines for many of the other RVIs are still under development and not commercially available. In addition, interventions at the level of the health care system decrease the incidence of RVI, including the appropriate use of respiratory or contact precautions, screening of visitors, and immunization of health care staff.[30,31] These interventions are included in the general US Centers for Disease Control and Prevention (CDC) recommendations to reduce health care–associated pneumonia.[32] Prevention of RVI in HSCT recipients is also addressed in the joint CDC, Infectious Diseases Society of American (IDSA), and American Society for Blood and Marrow Transplantation guidelines as well (http://asheducationbook.hematologylibrary.org/content/2001/1/392.long).[33] Other interventions, such as universal mask use for all health care staff and visitors on an HSCT unit, strict isolation of all patients, mandatory hand washing, and visitor restriction for children less than 12 years of age, have been shown to significantly reduce the incidence of RVIs and are used at some centers.[34–36]

VIRUS-SPECIFIC OUTCOMES, PREVENTION, AND TREATMENT

Respiratory Syncytial Virus

Epidemiology, risk, and attributable mortality

RSV has long been recognized as a concerning pathogen in immunocompromised hosts, with increased mortality if the infection involves the lower respiratory tract.[19]

In the solid organ population, lung transplant recipients are at increased risk for RSV-related mortality and morbidity compared with the other organs.[37,38] Incidence of RSV in lung transplant recipients is variable and accounts for roughly 6% to 12% of RVI infections.[4] Risk factors for morbidity and mortality are not clearly defined, with reports

of young age (<2 years), recent transplant, preexisting lung disorder, recent rejection, and multivisceral transplant as risk factors.[39,40]

RSV infection following HSCT depends on several factors, including patient age and type of transplant. Incidence of RSV infection following HSCT has been reported at 7% to 9% for allogeneic and 1.5% for autologous, with pediatric patients at the greatest risk of RSV.[41,42] Several risk factors have been reported for RSV as well as progression to LRTI or severe infection. In HSCT, risk factors for RSV include less than 1 month posttransplant (preengraftment), both younger (<2 years) and older (>60 years) age, GVHD, relapsed disease, and smoking.[40,43] Risks for presenting with LRTI or progression to LRTI include lack of RSV-directed therapy, high-dose total body irradiation, respiratory coinfection, absolute neutrophil count less than 500 cells/mm^3, and an absolute lymphocyte count (ALC) less than 100 to 200 cells/mm^3.[42,44] In contrast, an ALC greater than 1000 cells/mm^3 was protective against progression to LRTI.

Attributable mortality in RSV infection has been reported in several publications; with mortality approaching 80% in untreated HSCT patients and decreased to 6% to 25% with prompt supportive care and/or treatment.[40] More recent assessment of adult hospitalized patients reported 5% to 16% mortality in HSCT and 10% to 13% in SOT recipients in the setting of ribavirin treatment.[39,45,46] Age greater than 60 years and lymphopenia were risk factors for mortality and compared with nontransplant patients. A recent report in pediatric HSCT recipients also showed better outcomes than historical reports, with only 19% progression to LRTI and no mortality, with a primary treatment modality of intravenous immunoglobulin (IVIG) supplementation.[42] Although transplant patients are likely at increased risk for morbidity and mortality, especially those with LRTI, pediatric patients presenting in clinic with upper respiratory tract infection (URTI) symptoms have also been managed with good outcomes in the outpatient setting.[47] Therefore, although RSV infection in SOT and HSCT populations is associated with increased morbidity and mortality, precise determination of its impact remains elusive, but overall outcomes seem to be improving over time.

Prevention

In addition to the general preventive measures reviewed earlier, the only US Food and Drug Administration (FDA)–approved agent for the prevention of severe RSV infection is palivizumab. Palivizumab is a humanized monoclonal antibody targeting the F glycoprotein of RSV, and is approved for prevention of RSV in high-risk patients less than 2 years of age. Recommendations were published in 2014 by the American Academy of Pediatrics for palivizumab prophylaxis for infants and children less than 24 months of age with specific predisposing conditions.[48] With respect to immunocompromised children, no specific recommendations were made, aside from considering prophylaxis in profoundly immunocompromised patients younger than 24 months of age. A more recent multidisciplinary consensus conference in Italy, referencing the lack of adequate clinical trials and statistical power, recommended against palivizumab for children with primary or acquired immunodeficiencies.[49] In practice, the use of palivizumab for RSV prophylaxis in immunocompromised patients varies widely. Approximately 50% of surveyed pediatric SOT centers used palivizumab for prophylaxis, in both candidates and recipients, with 93% of those targeting infants 0 to 12 months old and 79% extending use to 0 to 24 months.[50] Only 10% provided palivizumab for patients 2 to 4 years old and 7% gave palivizumab for patients more than 4 years of age. This variability in practice is likely caused by the limited data on the efficacy of palivizumab prophylaxis in immunocompromised patients. In a retrospective pediatric HSCT cohort from Memorial Sloan Kettering Cancer Center (n = 275), nearly half of the high-risk patients received intravenous (IV) palivizumab. In the palivizumab treatment group, 30% developed RSV compared with only 4% of those who did not receive prophylaxis.[51] Similarly, an approach limiting palivizumab only to those HSCT pediatric patients younger than 12 months with either a chronic oxygen requirement or severe combined immunodeficiency, pretransplant to 100 days posttransplant, found no increase in the incidence of RSV or patient outcomes compared with historical controls with wider use of palivizumab.[52]

If time allows, delaying HSCT has also been reported to be an effective strategy to prevent serious RSV infection in HSCT candidates with RSV URTI before conditioning.[53,54] One reported strategy delayed transplant until symptom resolution and negative repeat RSV testing, resulting in a significant reduction in RSV pneumonia following transplant and improved mortality compared with those patients whose transplants were not delayed.[53] Careful thought must be given to the underlying disease process, risk of progression, as well as type of transplant before making the decision to delay HSCT.

Treatment

Several management options for RSV have been considered and reported in the literature, and although there are reports of improved outcomes, no placebo-controlled trial has clearly delineated the indication for and efficacy of treatment. The only randomized controlled trial accrued 14 HSCT patients over 5 years and reported that aerosolized ribavirin decreased RSV viral load compared with supportive care but did not significantly improve outcomes.[55] Ribavirin is a broad-spectrum nucleoside analogue with activity against DNA and RNA viruses. Reported toxicities of inhaled ribavirin include bronchospasm, cough, nausea, rash, and decreased pulmonary function. IV ribavirin adverse effects include hemolysis, hyperbilirubinemia, and leukopenia, whereas oral ribavirin can cause anemia and rash.[56] At present, aerosolized ribavirin remains the only FDA-approved drug for the treatment of severe RSV infection, and it is only approved for use in children.[57] Immunomodulators that have also been investigated include IVIG and anti-RSV monoclonal antibody (palivizumab).

Because of the lack of clear evidence of efficacy, wide variation in management of RSV exists.[58] Recommendations and guidelines have been published for HSCT and SOT patients, and although based on the best available data, they are not strong recommendations in many cases. For example, the SOT recommendations for RSV LRTI are for consideration of aerosolized ribavirin in combination with RSV IVIG or palivizumab.[59] Because of the increased mortality in HSCT patients, recommendations for treatment within this population are stronger.

Based on published reports as well as self-reported treatment strategies in surveys from SOT centers, lung and heart-lung recipients are often treated for URTI or LRTI with RSV; LRTIs may be treated in non–lung transplant SOT recipients, although this is inconsistent.[58] Retrospective and prospective studies report improved outcomes in symptomatic lung transplant patients treated with IV ribavirin plus corticosteroids[60]; oral ribavirin plus corticosteroids[61]; oral or IV ribavirin[62,63]; and inhaled ribavirin plus corticosteroids, IVIG, and palivizumab,[64] highlighting the lack of consensus on treatment strategies in this population.

Recommendations for HSCT patients from the Infectious Diseases Working Party of the German Society for Haematology and Medical Oncology recommend IVIG in general and ribavirin in particular for RSV in patients with cancer, largely based on data in HSCT recipients.[65] Guidelines from the United Kingdom recommend inhaled ribavirin and IVIG for allogeneic HSCT recipients with either LRTI or URTI and risk factors for progression to LRTI; they also suggest oral ribavirin if the inhaled form is not available.[66] Outside of guidelines and recommendations, several prospective and retrospective studies have been published on the treatment of RSV in HSCT patients, and, despite the available literature, there is no commonly accepted approach. Reports of improved outcomes in the treatment of RSV in HSCT patients can be found for inhaled, oral, or IV ribavirin,[46,67,68] as well as combinations of ribavirin with IVIG, palivizumab, and/or RSV-specific IVIG[56]; most support treatment at the URTI stage, before progression to LRTI. A systematic review of the available retrospective studies in 2011 reported that any form of ribavirin, alone or in combination with an immunomodulatory agent, was effective in preventing progression of URTI to LRTI, with a trend toward better outcomes with inhaled ribavirin plus an immunomodulator.[56] Although negative studies are potentially less likely to achieve publication, there are data available suggesting that adjunctive corticosteroid use and palivizumab alone do not improve outcomes.[69,70]

Complicating the assessment of RSV treatments in SOT and HSCT patients are recent reports of good outcomes with minimal intervention, such as the 54 immunocompromised pediatric patients diagnosed with symptomatic RSV without any mortality despite only 8 (15%) receiving directed therapy.[47] Another analysis of 32 pediatric HSCT recipients with RSV reported no attributable mortality with no ribavirin therapy; all patients were managed either with supportive care alone or immunoglobulin therapy.[42]

Investigational respiratory syncytial virus therapies

Although it is unclear which, if any, RSV-specific treatment is the most effective intervention, there are potentially effective investigational drugs being developed. Treatment with aerosolized ALN-RSV01 (Alnylam Pharmaceuticals, Cambridge, MA), a small interfering RNA that targets the RSV nucleocapsid messenger RNA, has shown some early promise in potentially preventing BOS in lung transplant recipients with RSV.[71] Another agent, RI-001 (ADMA Biologics, Inc, Ramsey, NJ) contains standardized levels of high-titer anti-RSV neutralizing antibody. In a report of compassionate use in 15 patients with RSV LRTI already receiving treatment with ribavirin, RI-001 was well tolerated and showed at least a 4-fold increase in geometric mean titer of RSV antibodies.[72] RI-002 (ADMA Biologics, Inc, Ramsey, NJ) is a new immunoglobulin formulation that

was developed using plasma collected from individuals tested to have high-titer anti-RSV antibodies, and in early trials showed a significant increase in anti-RSV neutralizing antibodies when administered to primary immunodeficient patients.[73] In addition, there are several other small molecule therapies in various stages of development, including early clinical trials.[74] One such molecule, GS-5806, an oral RSV entry inhibitor, was reported to have significantly lower viral load, total mucus weight, and total symptom score versus placebo in a healthy adult challenge.[75] Phase 2b trials with the same novel small molecule in lung transplant recipients and bone marrow transplant (BMT) patients have completed enrollment, with results pending (NCT02534350, NCT02254421).

Influenza

Epidemiology, risk, and attributable mortality

The impact of influenza infection in SOT patients can be particularly severe, especially in lung transplant recipients. Rates of severe influenza in lung transplant patients have been reported in 16% to 20% of those infected, with an attributable mortality of 4% to 8%; even higher mortalities of 21% caused by the 2009 H1N1 infection in lung transplant recipients with preexisting BOS grade 3 were reproted.[76–78] A report of Australian lung transplant recipients with H1N1 influenza noted a 16% FEV_1 decline at presentation and 39% of patients had prolonged allograft dysfunction.[78] Reports of the most severe infections are largely based on outcomes following the 2009 H1N1 pandemic; however, a recent retrospective cohort study of Brazilian renal transplant recipients with influenza A between 2009 and 2014 reported a 14% incidence of both intensive care unit (ICU) admission and mortality, which is higher than expected.[79]

Similar to solid organ recipients, influenza infection in HSCT patients causes significant morbidity and mortality. Progression from URTI to LRTI varies widely depending on the report, but has been found in 23% to 30% of adult HSCT patients or patients with hematologic malignancy, with overall mortality of 4% to 12%.[14,80,81] Risk factors for either presentation with LRTI or progression to LRTI include an ALC less than 100 to 200 cells/mL, lack of influenza-directed therapy, increased creatinine level, and delay in seeking care. There is a significant survival benefit if treated with influenza-directed therapy, with 9% mortality in treated patients versus 27% mortality in untreated patients.[14,80,81]

Prevention

Vaccination remains the primary focus and most strongly recommended method of influenza prevention.[82] Seasonal influenza vaccines cover either 3 or 4 strains of influenza based on antigenic characterization of the previous year's circulating strains. In general, quadrivalent vaccines cover an additional influenza B strain compared with the trivalent vaccines without interfering with vaccine response.[83] Influenza vaccines are available in inactivated (intramuscular or intradermal administration) and live, attenuated (intranasal) formulations. The live, attenuated vaccine is not recommended for immunocompromised recipients, and the inactivated vaccine is preferred for household contacts.[82,84] Overall influenza vaccine response in SOT and HSCT patients remains variable based on the population.

The optimal timing of vaccination following SOT has not been precisely determined, with guidelines from the American Society of Transplantation Infectious Diseases Community of Practice and the IDSA recommending vaccination between 2 and 6 months after transplant.[85,86] Reports of immunogenic response to influenza vaccine in SOT show a wide variation depending on the organ transplanted and the year assessed, with historical ranges between 15% and 93% protection.[82] Seroprotective responses have been reported between 19% and 43% in lung transplant recipients,[87–89] 19% and 55% in adult renal transplant recipients,[90] and greater than 75% in pediatric liver recipients.[91] Various adjuvants and dosing strategies have been evaluated in an effort to increase immunogenicity, with variable results. High-dose influenza vaccine contains 4 times the antigen dose of the standard influenza vaccine, and in early trials has been reported to increase the percentage of pediatric SOT patients who achieved an increase in protective titers.[92]

There are several likely explanations behind the reported variability in response, including the organ transplanted, duration of time from transplant, and degree of immunosuppression. The impact of immunosuppression on immunogenicity shows mycophenolate mofetil as most consistently associated with a decrease in response, whereas sirolimus has been associated with an increase in vaccine responsiveness.[87,93]

Because of concerns about the potential development of human leukocyte antigen alloantibodies following the adjuvanted pandemic H1N1 influenza vaccine, evaluations of acute rejection following influenza immunization have been conducted.[94–96] A subsequent postauthorization safety study following the 2009/2010 pH1N1 vaccine found no increased risk of acute rejection associated with vaccination.[97] Further, seasonal influenza immunization from 2006 to 2009 also found no increased risk of acute rejection.[98]

Similar to SOT patients, influenza immunization is recommended for HSCT recipients and is less effective compared with healthy controls. Again, response rates to influenza in HSCT vary based on time from transplant, influenza season/year studied, and degree of immunosuppression. Rates of seroconversion of 30% to 40% are typical.[99,100] In addition, there are encouraging reports of increased immunogenicity with high-dose inactivated influenza vaccine compared with standard dose.[101]

Although inactivated influenza vaccination is strongly recommended for SOT and HSCT recipients, other approaches have been suggested to prevent infection. In addition to use for treatment of influenza, oseltamivir and zanamivir are also approved for influenza chemoprophylaxis. A prospective study, predominantly in adult SOT recipients, found that daily oseltamivir for 12 weeks during seasonal influenza circulation significantly reduced the incidence of laboratory-confirmed influenza as determined by reverse transcription PCR.[102] Oseltamivir, given for 7 to 10 days, has also been reported to be effective in prevention of influenza infection in a hematology/HSCT inpatient unit during a nosocomial H1N1 outbreak.[103]

Treatment

Early treatment with antiviral drugs has been shown to improve outcomes and reduce hospital admissions and mechanical ventilation use.[77,80,81,104] The mainstay of treatment of influenza are the neuraminidase inhibitors (NAIs), oseltamivir, peramivir, and zanamivir. The influenza A M2 protein inhibitors amantadine and rimantadine are active against influenza A only, but are no longer recommended because of significant resistance in circulating influenza strains.[76] Literature on the treatment of influenza in SOT and HSCT are reliably reproducible with maximum benefit seen the earlier in the course that virus-specific therapy is initiated.[81] During the 2009 pandemic H1N1 season, SOT recipients treated with antiviral agents within 48 hours of symptom onset were significantly less likely (8% vs 22%) to require ICU admission.[77] Although treatment within 24 to 48 hours is optimal, benefit has been shown even with delayed treatment.[80] Most experts therefore endorse influenza-specific antiviral treatment of SOT and HSCT patients with influenza at any point in their illness.

Oseltamivir is an oral NAI indicated for the treatment of influenza A and B in adults and children more than 2 weeks of age. Recommended duration of treatment is 5 days in immunocompetent children and adults. In general, treatment recommendations and practice in SOT patients with influenza are for 5 days of oseltamivir as well.[105,106] Although 5 days of oseltamivir is the typical treatment duration, there are reports of treatment for 10 days or longer in patients with persistent symptoms.[107] A clinical trial also investigated conventional-dose versus double-dose oseltamivir for 10 days in immunocompromised patients, with no results yet released (clinicaltrials.gov, NCT00545532). Zanamivir is an inhaled NAI approved for treatment of influenza A and B in adults and children 7 years of age and older. Zanamivir is used less frequently than oral oseltamivir, likely because of the delivery route and rare reports of inhaled zanamivir failure.[108]

Peramivir is active against influenza A and B and currently is the only IV NAI approved for clinical use in patients aged 18 years and older. IV formulations of both zanamivir and oseltamivir are under investigation in clinical trials.[109,110] There is generally less experience with peramivir compared with oral oseltamivir, but published reports of clinical effectiveness and reduction in viral load are encouraging. Peramivir is a viable treatment option, especially in those patients in whom oral or inhaled antivirals are not the optimal route.[111,112]

The pandemic 2009 H1N1 influenza strain was also notable for an increased frequency of NAI resistance in up to 14% of strains.[113] However, NAI resistance is currently uncommon, with an overall incidence of 0.5% to 1.9% of isolates, but does remain an area of growing concern.[114] The most frequent neuraminidase mutation is the H275Y substitution, which results in high-level oseltamivir resistance, reduced peramivir susceptibility, and generally preserved zanamivir activity.[110,114] Options for oseltamivir-resistant influenza are limited. Inhaled zanamivir may have activity in many, but not all, cases. Peramivir has been reported to be effective in patients with oseltamivir-resistant influenza and has shown encouraging results in preventing lethality in mouse models of NAI-resistant H5N1/avian influenza models.[115,116] DAS181 (Ansun BioPharma, San Diego, CA) is a recombinant fusion protein that removes the sialic acid receptor for influenza binding and entry into the cell, potentially inhibiting influenza and parainfluenza infection. DAS181 has shown promising in vitro results of activity against oseltamivir-resistant influenza strains, and additional testing versus several NAI-resistant strains is ongoing.[117,118]

Aside from advances in supportive care, no specific adjunctive therapies are routinely recommended. Corticosteroids have been shown to decrease the need for mechanical ventilation and progression to LRTI but at the cost of prolonged viral shedding.[80] Therefore, although corticosteroids are not routinely recommended, if corticosteroids are

indicated for another reason, such as rejection or GVHD, worsening infection with influenza is not clear reason to withhold steroids.

Adenovirus

Epidemiology, risk, and attributable mortality

Adenovirus is a double-stranded DNA virus made up of 52 immunologically distinct types, with serotypes 1 and 2 most commonly associated with pneumonia.[119] In nonimmunocompromised patients, adenovirus typically causes self-limited disease, such as URI, conjunctivitis, and/or gastroenteritis. Adenovirus infection in immunocompromised patients can range from asymptomatic viremia to significant localized or disseminated disease. In contrast with many of the other community-acquired respiratory viruses, adenoviral infection can occur from primary acquisition or through reactivation of virus. In 1 study, viral reactivation was linked to the timing of immune reconstitution and CD4+ T-cell counts.[120] Depending on patient factors, clinical disease in immunocompromised patients can include pneumonia, hepatitis, colitis, hemorrhagic cystitis, and encephalitis.[5] In a 1993 to 2006 retrospective cohort of RVIs in pediatric SOT, HSCT, and oncology patients, adenoviral infection was associated with the greatest length of stay, and was the only specific virus that increased the risk of morbidity and mortality related to RVI (odds ratio, 3.7; CI, 1.1–12.6; $P = .03$).[1]

Adenoviral infections have been reported in renal, liver, small bowel, lung, and heart transplant recipients, and although most are asymptomatic, they can be associated with severe disease.[121–126] Although adenoviral infection in HSCT is more likely to cause severe disease than in SOT, there are reports of graft infection and rejection with adenovirus in essentially all SOT populations.[123,127,128] Infection in lung recipients is common (up to 22% in 1 series) and there are multiple reports of severe infection, including graft loss, progression to BOS, and death.[125,129–132]

Infection in HSCT recipients can be severe and associated with significant mortality. In 14 adult HSCT recipients with adenovirus viremia, most of whom were treated with antivirals, almost 50% developed invasive adenoviral disease and 23% died of the infection.[133] Adenoviral LRTI and disseminated disease generally carry the greatest mortality in pediatric and HSCT patients (up to 80% in some reports).[134–136]

Treatment

Treatment options for adenoviral infection or disease are limited because there are currently no approved antiviral agents for treatment. Reports of recovery with reduced immune suppression alone make the need for therapy and optimal timing for intervention uncertain.[124] As for most viral infections in SOT and HSCT patients, immunosuppression reduction is recommended if possible. Cidofovir, approved for treatment of CMV retinitis in patients with acquired immunodeficiency syndrome, has been the most common antiviral used for treatment. Cidofovir is a nucleotide analogue that inhibits viral DNA polymerase with broad antiviral activity against DNA viruses, such as herpesviruses and adenovirus. Although cidofovir has in vitro activity against adenovirus and is generally accepted as the standard of care, cidofovir treatment efficacy is controversial.[135,137,138] Dosing of cidofovir is generally 5 mg/kg IV once every 7 days, or 1 mg/kg IV 3 times per week, often in conjunction with probenecid and hydration.[129] Cidofovir nephrotoxicity, which is not dose dependent, is the most common reason for discontinuation of therapy.[137] Alternative therapies, including ribavirin and combination cidofovir plus IVIG, have been reported with limited data, and these are not routinely recommended for use.[119,122,139]

Investigational adenovirus therapies

Because of new antiviral development and alternative treatment modalities, there may be additional options in the future. Brincidofovir is an orally bioavailable lipid conjugate of cidofovir that has potent in vitro activity against adenovirus, and has shown promising results for both treatment of serious invasive adenovirus infections and asymptomatic viremia.[140,141] Recognizing the vital role of T-cell immunity in control of viral infections and the loss of this immunity during HSCT and SOT, the use of adoptive T-cell immunity is promising as well. Adoptive T-cell immunity uses donor virus-specific T-cells to treat infection, and has been reported to be safe and effective when performed early in the course of the infection.[134,142] Adoptive T-cell transfer has generally been limited to a few centers and predominantly in HSCT recipients, because of both the time and the expertise needed for cell preparation, but more recent methods may allow shorter generation time and more access to this therapy.[143,144]

Parainfluenza

Epidemiology, risk factors, and attributable mortality

Parainfluenza virus (PIV) is a single-stranded, enveloped RNA virus with 4 distinct serotypes (types 1–4). Serotypes vary in seasonality and disease, with PIV3 associated with pneumonia and bronchiolitis, and year-round activity that peaks in spring

and summer. PIV1 and PIV2 are commons causes of pediatric laryngotracheobronchitis (croup) and typically peak in fall and winter.[5] PIV4 infection is rarely associated with disease.

A retrospective analysis of RVI in pediatric immunocompromised patients reported that 26% of RVIs in SOT patients were caused by PIV. Parainfluenza infections presented more commonly as URTI with or without LRTI symptoms, and less frequently as LRTI alone.[1] Although there are previous reports of significant mortality in SOT recipients caused by PIV (up to 15% in 1 series[145]), more recent publications in lung and other organ recipients report decreased mortality.[8,146]

Retrospective reports place the incidence of PIV infection following HSCT between 2% and 7%, with greater incidence in children than in adults.[147–149] LRTI after HSCT is associated with high morbidity and mortality. Risk factors for LRTI caused by PIV are lymphopenia (<300 cells/mm^3), neutropenia (<500 cells/μL), APACHE (Acute Physiology and Chronic Health Evaluation) II score greater than 15, myeloablative conditioning, high-dose corticosteroids for GVHD, and coinfection.[104,150] Reported risk factors for mortality in HSCT include LRTI, early infection, mismatched related donor, APACHE II score greater than 15, new oxygen requirement at diagnosis, low monocyte counts (<100 cell/μL), and high-dose steroid use (>2 mg/kg/d).[149,151,152] In a series of 28 HSCT patients with PIV LRTI, mechanical ventilation was necessary in 29% and attributable mortality was 46%.[150] Other recent publications report 17% to 37% mortality in HSCT recipients with probable or proven parainfluenza LRTI.[149,151,152]

Treatment

There are no currently FDA-approved antiviral treatments for parainfluenza disease. Treatment is supportive and includes reduction in immunosuppression. Ribavirin and/or IVIG have been used, off label, in parainfluenza infections with variable results and no definitive evidence of efficacy.[147,149–155]

Investigational parainfluenza virus therapies

DAS181, as discussed previously for NAI-resistant influenza, can potentially inhibit PIV binding to respiratory epithelial cells. DAS181 is an inhaled treatment typically administered via a dry powder inhaler for 5 to 10 days, and has been used under compassionate use and clinical trial protocols in HSCT and SOT recipients, including 2 lung transplant patients. In published reports, DAS181 has shown encouraging results, including reduction in PIV quantitative viral load and overall outcomes.[156–159] In addition, there are intriguing studies examining the impact of cholesterol reducing agents such as gemfibrozil and lovastatin on disrupting viral assembly in PIV, RSV, and influenza.[160] Reports of parainfluenza-specific T-cell generation from healthy donors may also ultimately lead to effective adoptive T-cell therapy for PIV.[161]

Human Metapneumovirus

Epidemiology, risk factors, and attributable mortality

Human metapneumovirus (hMPV) is an RNA virus identified in 2001, in the same paramyxovirus family as RSV and parainfluenza, that typically causes a self-limited URTI in immunocompetent persons. hMPV is found worldwide and occurs predominantly in the late winter and spring months, often following the RSV season.[162] As with many of the other community-acquired RVIs in SOT and HSCT patients, progression from the upper respiratory tract to the lower respiratory tract is associated with increased morbidity and mortality.

hMPV has been a well-documented cause of symptomatic and asymptomatic infection in lung transplant recipients. In a retrospective population of 49 symptomatic adult lung transplant recipients, 25% were hMPV positive via nasopharyngeal aspirate or BAL.[163] As with most RVIs, up to 20% can be asymptomatic, whereas others develop severe pneumonia or acute graft dysfunction. Rhinorrhea, cough, and sputum production are the most frequently reported symptoms, with mortality caused by acute respiratory distress syndrome and graft rejection also reported.[4,164] Identification of replicating hMPV in respiratory samples has been seen with simultaneous biopsy-proven graft rejection, suggesting a potential association between hMPV and acute rejection.[163]

Infection in HSCT patients is variable as well, with recent reviews reporting an overall incidence of 5% to 7%.[165,166] The same analysis found that LRTI occurred in 34% of hMPV infections in HSCT recipients, with a mortality of 6%, greatest in those with LRTI. Mortalities caused by hMPV infection have been reported to be as high as 39%.[167] Progression from URTI to LRTI is seen in up to 60% of HSCT recipients and has been associated with steroid use (>1 mg/kg), low lymphocyte count (<300 cells/mm^3), and onset of infection less than 30 days from HSCT.[168]

Treatment

There are no currently approved antivirals for the prevention or treatment of hMPV. As with RSV, ribavirin has reported in vitro activity against hMPV.[169] The efficacy of ribavirin for hMPV

infection has not been reliably shown. There are reports in lung transplant recipients of oral ribavirin resulting in quicker return to baseline and decreased incidence of subsequent BOS, and case reports of survival with IV and inhaled ribavirin.[170,171] However, most reports are from small single-centered studies and do not include a control population. In addition, other studies have not been able identify a similar beneficial effect of ribavirin for hMPV treatment.[167,172]

Investigational human metapneumovirus therapies

Adoptive T-cell transfer has not yet been achieved, but hMPV-specific T cells have been generated, with further work ongoing.[173] There are also reports in vitro and in mouse models of a human monoclonal antibody for prophylactic and therapeutic hMPV infections.[174]

Cytomegalovirus

Epidemiology, risk factors, and attributable mortality

Cytomegalovirus (CMV) is a β-herpesvirus well recognized as a significant pathogen in immunocompromised patients. CMV has been reported to affect from 12% to 80% of heart and lung transplant recipients and 50% of HSCT patients.[175–177] Although CMV can cause a wide array of infections, from asymptomatic to tissue-invasive disease, CMV pneumonitis/pneumonia is of particular concern for thoracic transplant recipients. The diagnosis of proven CMV pneumonitis is based on compatible clinical signs and/or symptoms and documented CMV in lung tissue. Traditionally, tissue-invasive CMV is based on histopathologic or immunohistochemical (IHC) findings consistent with tissue invasion on biopsy.[178,179] CMV cultures or quantitative nucleic acid amplification testing of tissue samples are difficult to interpret because a positive finding could indicate tissue-invasive disease, shedding in the setting of active viremia, or both.[178] Recent updates to the definition of CMV pneumonia now include proven, probable, and possible CMV pneumonia. Proven disease still relies on identification of viral antigens or inclusion bodies via immunohistochemistry in biopsy material, but probable CMV pneumonia is defined as compatible symptoms plus CMV detection via viral isolation, culture, or quantitation of CMV DNA in BAL fluid.[180] There is no definitive cutoff for CMV DNA load in the setting of CMV pneumonia; however, some reports suggest greater than 500 to 5500 IU/mL as a possible cutoff.[180,181] Possible CMV pneumonia has been suggested based on positive quantitative PCR performed on biopsy tissue.

Risk factors for CMV disease have been reported as advanced age and reduced-dose valganciclovir.[179] Delayed-onset CMV pneumonitis (>100 days posttransplant), donor with positive CMV serology, asymptomatic CMV infection, and CMV disease at any time have been associated with increased mortality in lung transplant recipients.[182–184]

CMV in HSCT patients can also cause a wide array of clinical manifestations, with CMV pneumonia being the most serious, resulting in a mortality of approximately 30%.[185,186] CMV reactivation alone is associated with lower overall mortality following HSCT.[187] Incidence of CMV pneumonia is unclear, largely because of the difficulties with definitive diagnosis, but an autopsy study of 999 patients with cancer and HSCT reported an incidence of CMV pneumonia of 3%.[176] Risk factors associated with CMV-attributable mortality include female sex, lymphopenia, and mechanical ventilation at onset.[185,188] Diagnostic classification of CMV pneumonia/pneumonitis is the same as discussed earlier for SOT.

Prevention

IV ganciclovir (GCV) and oral valganciclovir, with or without CMV immunoglobulin (CMVIg), are the agents recommended for prophylaxis of CMV infection in SOT recipients.[178] The most common strategies used are universal prophylaxis versus preemptive therapy, with consensus recommendations favoring universal prophylaxis for high-risk heart and lung recipients. Risk stratification in organ transplant recipients relies heavily on donor and recipient CMV serologic results before transplant. Donors who are CMV immunoglobulin (Ig) G positive (D+) paired with recipients who are IgG negative (R−) are considered the highest risk group. Recipients who are CMV D−/R− are generally considered low risk, although community-acquired infection can occur posttransplant, and R+ patients are variably classified as intermediate-risk or high-risk, often center dependent. Recommended duration of prophylaxis varies based on organ system and risk stratification. For D+/R− heart transplant recipients, the recommended minimum duration of CMV prophylaxis is between 3 and 6 months. For D+/R− lung transplant recipients the minimum recommended duration is between 6 and 12 months, with some advocates for longer, even indefinite, prophylaxis. Centers using indefinite prophylaxis for lung transplant recipients report low incidence of CMV infection, which must be balanced against reports of association between GCV-resistant CMV and prolonged CMV prophylaxis, with an

incidence of 10% to 50% GCV-resistant infection in some cases.[177,189,190] For R+ recipients the minimum duration in lung is 6 months, and 3 months in heart recipients. In D−/R− populations the routine use of CMV prophylaxis is not generally recommended.[178] There are several published reports of potential benefit to the addition or sole use of CMVIg for prophylaxis, but, because of the limited data to support routine use, the addition of CMVIg is not routinely recommended.[178,191] The most recent consensus guidelines note that some experts add CMVIg for intermediate and higher-risk recipients, but there are no randomized studies indicating that CMVIg is any better than GCV or valganciclovir alone.

As opposed to SOT recipients, HSCT patients with positive CMV serology (R+) before transplant are at higher risk for reactivation and non–relapse-related mortality.[192] Preventive strategies following HSCT are similar and generally consist of either universal prophylaxis for at least 100 days following HSCT or a preemptive approach, with the latter as the more commonly reported practice.[192,193] There are also reports that suggest immunosuppression choice alters CMV infection risk. Lower incidences of CMV infection are reported in patients treated with regimens including a mammalian target of rapamycin (mTOR) inhibitor.[194–197] Although these results are not consistently reproducible, some experts recommend considering the use of mTOR inhibitors in the presence of clinically relevant, recurrent, or GCV-resistant CMV infection.[198–200] Further, CMV vaccination is under evaluation with several candidate vaccines assessed in clinical trials, including live attenuated; recombinant glycoprotein B (gB); DNA plasmid; and virus-like particle systems.[201] Investigations in immunocompromised patients have reported on the safety of a CMV DNA vaccine candidate (ASP0113) and a chimeric peptide vaccine (PF03512676) in HSCT, with some early evidence of potential clinical benefit as well.[202,203] Similarly, a phase 2 trial of an adjuvanted gB vaccine versus placebo in pretransplant liver and kidney patients showed reduced CMV viremia and days of GCV therapy following transplant, with the greatest effect seen in CMV seronegative patients.[204] Therefore, although the current CMV vaccine candidates are not yet ready for clinical use, the available data plus the number of clinical trials either planned or ongoing in immunocompromised patients are very encouraging.

Treatment

IV GCV and oral valganciclovir are the most commonly used treatments for CMV infection or disease.[178,205] Foscarnet and cidofovir are active agents as well, but are generally reserved for GCV-resistant infection or those HSCT recipients with concern for potential bone marrow suppression caused by of GCV, such as during the preengraftment period.[178,185] CMVIg has been reported to be effective in several publications and may have a role in certain settings.[188,206] CMVIg is often used for CMV pneumonia in HSCT recipients, although a recent analysis failed to find significant improvement with adjunctive IVIG or CMVIg administration in that population.[185] The consensus guidelines on CMV treatment in SOT recipients recommend consideration of adjunctive IVIG or CMVIg for recurrent CMV disease in thoracic organ recipients as adjunctive therapy in cases of hypogammaglobulinemia.[178]

Investigational cytomegalovirus therapies

Investigational drugs and therapies for CMV prevention and treatment are currently being developed and/or tested in clinical trials. Letermovir interacts with UL56, a component of viral DNA cleavage and packaging, and has been reported to be effective in reducing CMV infection in HSCT recipients and reducing viral load in SOT patients.[207,208] Maribavir is a competitive inhibitor of UL97 that failed to show noninferiority of CMV prevention in liver transplant patients and HSCT recipients, but is currently under investigation for use in CMV infections that are refractory to GCV, valganciclovir, foscarnet, or cidofovir (clinicaltrials.gov, NCT02931539).[209,210] Brincidofovir, referenced earlier for adenovirus, has been shown to reduce CMV events compared with placebo in HSCT recipients.[211] In addition, adoptive T-cell therapy for CMV disease has been reported to be effective in a lung transplant recipient and as well as in several HSCT recipients.[212–214]

Herpes Simplex Virus and Varicella Zoster Virus

HSV1 and HSV2 are α-herpesviruses and common causes of infection in immunocompetent and immunocompromised persons. In immunocompromised patients, HSV can cause a wide variety of clinical infection from asymptomatic oropharyngeal shedding to mucocutaneous and disseminated disease, including pneumonitis. HSV pneumonitis is uncommon in the era of antiviral prophylaxis, but thoracic transplant and HSCT recipients are reportedly at greatest risk.[215–217] Similar to CMV pneumonitis, the recommended diagnostic test for HSV pneumonitis is tissue histopathology with IHC for HSV. Positive BAL PCR testing for HSV may represent contamination or oropharyngeal shedding.[218] IV acyclovir is the

treatment of choice for severe, disseminated HSV, including pneumonitis. It is recommended to continue IV acyclovir until resolution, or 14 days, at which time oral medication may be given.[218]

VZV, another herpesvirus, can also cause significant disease in SOT and HSCT recipients. The most common manifestations of VZV are primary varicella, or chickenpox, in susceptible seronegative patients or herpes zoster, or shingles, in those with previous VZV infection or vaccination.[219] Visceral dissemination is more common in HSCT and less common in SOT. Disseminated disease includes infection of lung tissue resulting in VZV pneumonia with significant morbidity and mortality.[220,221] Risk of dissemination is increased in acute and chronic GVHD, as well as increased immunosuppresion.[219,220] IV acyclovir is also the recommended treatment of disseminated or invasive VZV for at least 7 days, and potentially longer in patients with extensive involvement.[219]

SUMMARY

RVIs are common in SOT and HSCT recipients and cause a broad array of infections, ranging from asymptomatic to significant virus-associated mortality. Although there are some potential new and/or novel therapeutic options under evaluation, current treatment options remain limited in immunocompromised patients and generally consist of supportive care; reduction of immunosuppression; and, if available, antiviral medications. Preventive measures with infection control and appropriate immunization remain vital.

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