



Respiratory Viral Infections in Transplant Recipients

40

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Introduction

Respiratory viral infections (RVIs) are common causes of illness in humans. While such infections tend to be mild and self-limiting in healthy individuals, severe or even life-threatening disease can be seen in immunocompromised hosts, as well as the very young and the elderly. In particular, RVIs are frequently associated with significant morbidity following hematopoietic stem cell transplantation (HSCT) or solid organ transplantation (SOT). A number of RNA and DNA viruses can cause respiratory tract infections. This chapter focuses on the epidemiology, clinical manifestations, diagnosis, treatment and prevention of respiratory syncytial virus (RSV), parainfluenza viruses (PIVs), human metapneumovirus (HMPV), influenza viruses, human coronaviruses (HCoV), and human rhinoviruses (HRV).

The respiratory viruses are associated with a wide range of clinical syndromes in the general population, including the common cold, pharyngitis, tracheobronchitis, laryngo-tracheobronchitis (croup), bronchiolitis, and pneumonia. For transplant recipients, disease spectrum similarly spans from asymptomatic or mild infections to life-threatening lower respiratory tract involvement, although severe complications tend to be more frequent. The severity and outcome of infection largely depend on the type of virus as well as host factors, including the type of transplantation and the degree of immunosuppression at the time of infection. Coinfections with other pulmonary pathogens including bacteria or fungi,

e.g., *Aspergillus* species, *Pneumocystis jiroveci*, or other viruses like CMV or more than one respiratory viruses, are also common and can further complicate treatment and lead to poorer outcomes [1–3]. For HSCT recipients, most RVIs occur in 1–10% of the patients during the first 100 days post-transplantation [1, 4, 5], with cumulative incidence varying from a few percent (e.g., HMPV, influenza, RSV, PIVs) to 11–22% such as HCoV and HRV [5]. Infections with RSV, influenza, HMPV, PIVs, and adenovirus have a higher risk of progression from upper respiratory tract infection (URTI) to lower respiratory tract infection (LRTI) and tend to cause the most serious disease, with mortality rate of up to 40–60% among those with LRTI [6–9]; HRV and HCoV infections tend to be mild, but severe LRTI from these viruses can rarely occur [10]. Risk factors for disease progression to LRTI include pre-engraftment status, allogeneic transplant, myeloablative conditioning, graft-versus host disease, and lymphopenia [1, 2, 6, 11–15].

SOT recipients can also suffer from severe disease and complications from RVI. Risk factors for disease progression are not as well defined, but those with lung and heart-lung transplant are particularly vulnerable. Cumulative rates of RVIs in lung transplant recipients range from 8% to 21% in retrospective studies of 5–7 years [16, 17], and a high incidence of progression to LRTI up to 26% has been reported [18]. In contrast, the incidence of RVIs among heart, liver, and kidney transplant recipients is similar to that of the general population, although complications are more frequent [19].

In addition to direct effects from viral infection, RVIs may promote immunologically mediated lung injury in HSCT or lung transplant recipients, potentially leading to acute allograft rejection in the case of lung transplant recipients and/or the development of bronchiolitis obliterans syndrome (BOS), which is characterized by progressive circumferential fibrosis of the small terminal airways histopathologically, resulting in fixed airflow obstruction [20, 21]. BOS is the major limiting factor for long-term survival after lung transplantation [22–28]. The reported incidence of BOS associated with RVIs ranges from 6% to 42% [17, 23], while

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the incidence of acute rejection associated with RVIs varies from 16% to as high as 82% [25, 28–30]. For HSCT, BOS is often observed in the setting of chronic graft-versus-host disease, but it has also been associated with RVIs [31–34]. Among the respiratory viruses, RSV, PIV, HMPV, and influenza have all been associated with BOS [30, 35, 36], and mortality associated with these viruses can be up to 20% in lung transplant patients [37]. For heart, liver, or kidney transplantation, no relationship between RVI and rejection has been noted [19].

Paramyxoviruses

RSV, PIVs, and HMPV are members of the *Paramyxoviridae* family. The epidemiology, clinical manifestations, and treatment of each of these viruses are discussed separately.

Respiratory Syncytial Virus (RSV)

Epidemiology and Clinical Manifestations

RSV has two subtypes, A and B, with the former typically causing more severe disease. While both subtypes can simultaneously circulate during outbreaks, a few distinct genotypes of each subtype can predominate within a community. The dominant strains can also shift yearly. This shifting of viral strains, along with the waning protective immunity from natural infection, might account for frequent re-infections throughout life [38].

RSV usually causes mild and self-limited URTI in healthy older children and nonelderly adults, but certain patient populations are at risk for developing severe RSV infection, including premature or very young infants, elderly patients with comorbidities, or immunocompromised hosts [39–41]. RSV has been associated with apnea in young or preterm infants [42] and can cause severe LRTI in children including bronchiolitis, pneumonia, and acute respiratory failure [42]. Among adults infected with RSV, more than 80% are symptomatic, and lower respiratory tract signs and symptoms can occur in a quarter of the patients [43]. Signs of URTI include cough, rhinorrhea, and conjunctivitis, and compared to influenza, RSV is more frequently associated with nasal congestion, ear and sinus involvement, productive cough, and longer duration of illness [43].

RSV Infection in Transplantation

For transplant patients, RSV is a leading cause of viral respiratory tract infections [44, 45]. Among HSCT recipients, the incidence may be as high as 10% during winter months [6]. URTI precedes pneumonia in 80–90% of patients, and approximately 30–40% of patients with URTI progress to pneumonia after a median of 7 days [46]. Attributable mor-

tality among HSCT patients ranges from 7% to 83% [47, 48], with more recent studies showing mortality rates of about 20–35% [49–54]. Risk factors for the development of LRTI include allogeneic transplant, mismatched or unrelated transplant, presence of graft versus host disease, myeloablative regimens, advanced age, prolonged lymphopenia, relapse of malignancy, and lack of engraftment [1, 6, 8, 9, 12, 13, 15, 55, 56].

For SOT recipients, RSV-associated mortality rate is significantly lower than that experienced in HSCT [57] although mortality rates among lung transplant patients of up to 20% have been reported [17, 37]. While there have been some reports of favorable outcomes in lung transplant recipients even in the absence of specific antiviral treatment [58], other studies suggest that up to 33% of RSV-infected patients develop long-term pulmonary dysfunction [23, 24, 37] and up to 60% have worsening of BOS stage [58].

Treatment of RSV

Available Agents for RSV Treatment

Treatment modalities for RSV are limited to ribavirin with or without the addition of immunomodulatory agents and/or corticosteroids. Currently, the only Food and Drug Administration (FDA)-approved therapy for RSV is aerosolized ribavirin (1- β -D-ribofuranosyl-1,2,4-triazole-3-carboximide), which was licensed in 1986 for the treatment of RSV LRTI in hospitalized high-risk infants and young children [59]. Ribavirin is a synthetic nucleoside analog with a broad spectrum of activities against many RNA and DNA viruses in vitro and in vivo. It competitively inhibits inosine monophosphate dehydrogenase and can be incorporated into the viral genome, leading to lethal mutagenesis [60]. The drug also has immunomodulatory properties that might contribute to its efficacy in vivo [61, 62].

The standard regimen of aerosolized ribavirin consists of a daily dose of 6 g delivered at a concentration of 20 mg/ml of sterile water for 18 h/day. Due to potential teratogenicity, the drug is usually administered to patients within a scavenging tent and preferably in a negative pressure room to prevent environmental contamination. After administration, the room needs to be cleaned to minimize secondary exposure to health care workers and visitors [48]. Women of childbearing potential should not care for or visit patients receiving aerosolized ribavirin. For ease of administration and improved compliance, the drug is often delivered with an intermittent dosing schedule at 2 g administered for 2–3 h every 8 h [63, 64]. In a randomized trial of 50 subjects, patients receiving intermittent vs continuous dosing had a lower incidence of progression from URTI to LRTI [65]. The reported duration of treatment is variable in the literature; the 4th European Conference on Infections in Leukaemia (ECIL-4) guidelines recommend a duration of 7–10 days [66].

Side effects of aerosolized ribavirin treatment include cough, dyspnea, bronchospasm, rash, nausea, headache, and conjunctival irritation. Patients can also experience claustrophobia and deterioration of pulmonary function. Ribavirin can also be administered intravenously or orally, with major side effects including hemolytic anemia, leukopenia, and hyperbilirubinemia [47].

Intravenous RSV-specific immunoglobulin (RSV-IVIG and palivizumab [PVZ]) were licensed initially for prevention of serious complications from RSV infection in high-risk children (refer to section “Immunoprophylaxis”) [67], but they have also been employed for RSV treatment [68–72]. Intravenous immunoglobulin (IVIG) is also frequently used for the treatment of RSV and other severe viral infections in transplant recipients. The efficacy of these agents for prophylaxis or treatment among transplant patients has not been evaluated in randomized controlled trials although in an observational study of HSCT patients with RSV LRTI, multivariate analysis did not find any effect of antibody-based therapies on treatment outcomes [73].

Treatment of RSV in HSCT

The evaluation of any treatment modalities for RSV, or any other respiratory viruses, has been limited by the fact that most published studies are small observational studies which lack standardized definitions of URTI and LRTI, use different dosages and duration of therapy, and are subject to selection and publication bias. Among dozens of reports on the treatment of RSV in HSCT patients, there have only been two small randomized clinical trials. One study of aerosolized ribavirin was discontinued due to slow accrual, after enrollment of 14 patients in 5 years [69]. The other trial enrolled 50 patients and found that an intermittent dosing schedule of aerosolized ribavirin for treatment of RSV URTI was more effective than a continuous dosing schedule for prevention of progression to LRTI [64].

Two pooled analyses of published studies between 1980 and 2010 suggest that treatment of RSV URTI and LRTI with aerosolized ribavirin and IVIG reduces the risk of progression to LRTI in individuals with URTI and reduces mortality [47, 48]. When compared to no treatment, aerosolized ribavirin decreased the rate of progression to LRTI and mortality with the greatest impact observed when aerosolized ribavirin was given in combination with an immunomodulator. Specifically, when comparing aerosolized ribavirin treatment alone with no treatment, progression to LRTI was decreased from 47% to 25% and the mortality rate was reduced from 89% to 50% [47]. The addition of immunomodulators such as PVZ, IVIG, and/or RSV-IVIG to ribavirin compared to no treatment decreased progression to LRTI from 45% to 12% and mortality rate from 77% to 24%. There are paucity of reports on the use of intravenous or oral ribavirin, but the combined data suggest a benefit compared to no treat-

ment. It is important to recognize that neither of these systematic reviews represented formal meta-analyses; there was no adjustment for confounders, and thus, results should be interpreted with caution. The only trial to date that evaluated PVZ as monotherapy for the treatment of RSV infection in HSCT recipients showed no benefit in prevention of progression to LRTI or mortality [74].

Overall, these analyses show a trend toward improved outcomes with regard to progression to LRTI and mortality among HSCT recipients treated with a combination of aerosolized ribavirin and immunomodulators than those treated with aerosolized ribavirin alone or with intravenous/oral ribavirin, or those given no treatment. However, the use of aerosolized ribavirin is cumbersome and very costly with the price increase in 2015 to \$30,000 per day [75]. In addition, the aerosolized form of ribavirin is not available in all countries, and the intravenous form is not commercially available in the United States. The experience with oral ribavirin in HSCT is limited and warrants further evaluation, but some studies suggest that it may be a safe and effective alternative to aerosolized ribavirin for the treatment of RSV [51, 76–78]. In a retrospective study of 124 HSCT recipients with RSV infection, there was no difference in rates of progression to LRTI and mortality among patients receiving oral compared to aerosolized ribavirin [51]. The optimal dose of oral ribavirin for treatment of RSV is unclear and quite variable in the literature [79]. Commonly described dosing strategies include a fixed dose of 600–800 mg two or three times a day or a loading dose of 10 mg/kg followed by 20 mg/kg/day divided into three doses, adjusted for renal failure [51, 77, 79].

Treatment of RSV in SOT

Similar to the HSCT population, the mainstay of treatment for paramyxoviral infections in SOT populations has been aerosolized ribavirin [37, 80]. In an observational study, a combination of aerosolized ribavirin, IVIG, and corticosteroids was found to be safe and effective in preserving lung function in lung transplant recipients after RSV or PIV infections [29]. Few studies have examined the role of oral ribavirin. Pelaez et al. [81] reported treatment of five lung transplant patients with RSV infection using oral ribavirin in combination with methylprednisolone and found this regimen well tolerated and effective with mean forced expiratory volume in 1 s (FEV1) returning to baseline with treatment. In a prospective observational study, oral ribavirin treatment in 38 patients with RSV, PIV, or HMPV infection was associated with earlier recovery of graft function and prevention of BOS as compared to 29 patients with only supportive care including corticosteroids [82]. In one study that evaluated lung transplant patients who received either aerosolized or oral ribavirin for RSV infection, no significant differences in 6-month outcomes were noted between the two groups,

but variations in their adjunctive therapies, e.g., use of corticosteroids, IVIG, and/or montelukast, might have altered the patients' clinical response [83]. Intravenous ribavirin was also found to be a safe and cost-effective treatment among 18 patients with RSV after lung transplantation [84].

Overall, these studies support the use of ribavirin in treating RSV infection among SOT recipients although it is important to recognize that the evidence is limited to small, uncontrolled studies. There are significant variabilities among these studies regarding the dose and duration of treatment as well as the use of immunomodulating agents such as corticosteroids, IVIG, or PVZ as adjunctive measures.

More recently, a new agent presatovir (GS-5806), an orally bioavailable antiviral agent that inhibits fusion of RSV with host cell membranes, is being developed for treatment of RSV infection. Phase II clinical trials studying HSCT and lung transplant recipients were completed, and the data on lung transplant recipients has been published [85]. In this Phase 2b randomized controlled trial that enrolled a total of 61 lung transplant patients with RSV, presatovir was apparently well tolerated, but its use did not result in improved viral or clinical outcomes.

Parainfluenza Viruses (PIVs)

Epidemiology and Clinical Manifestations

There are four distinct serotypes of PIVs, namely, PIV-1 to -4. These viruses can circulate throughout the year in most communities, although PIV-3, the dominant serotype affecting transplant populations, seems to have the highest prevalence during spring and summer seasons [38]. PIVs cause a spectrum of respiratory tract infections similar to RSV, but most are URTIs and result in fewer hospitalizations. PIV-1 and, to a lesser extent, PIV-2 are the principal causative agents of croup or laryngotracheobronchitis, primarily in children between the ages of 6 and 48 months. PIV-3 is most frequently associated with pneumonia and bronchiolitis; neonates, immunocompromised, and the elderly are at particular risk for severe disease. PIV-4 is infrequently detected and is thought to cause mostly asymptomatic or mild infections.

PIV Infection in Transplantation

Symptomatic PIV infection affects about 3–7% of HSCT recipients [2, 64, 86, 87] and approximately 3–5% of lung transplant recipients [28, 88]. LRTI can develop in up to 50% of PIV-infected HSCT patients, with associated mortality rate ranging from 12% to 57% [2, 8, 64, 86, 87, 89, 90]. Two large retrospective studies have evaluated PIV infections in HSCT and found that most patients (70–87%) presented with URTI, but 13–24% subsequently progressed to LRTI [2, 64]. Among those with LRTI, overall mortality at 30 days

was 17–35% [2, 64]. Independent risk factors for progression to LRTI included receipt of corticosteroids at the time of URTI diagnosis, neutropenia, an APACHE II score >15, and respiratory coinfections. Independent predictors of death included relapsed or refractory underlying cancer, APACHE II score >15, and high-dose corticosteroid use considered in patients given cumulative dose of prednisolone >600 mg within 4 weeks of PIV diagnosis [2, 14]. Whether steroids are still important if adjusted for lymphopenia requires further study. While RSV infections are always symptomatic, asymptomatic shedding is present in about 1/3 of PIV-infected HSCT patients [91]. In a surveillance study of lung transplant recipients, asymptomatic PIV infection was present in 70% of patients [28].

PIV LRTI has also been associated with a significantly increased risk of severe airflow decline after HSCT when compared to RSV [31]. For lung transplant patients, PIV has been associated with acute rejection and BOS [18, 28, 88, 92, 93].

Treatment of PIV

A number of studies reported treatment of PIV with ribavirin (see section "Treatment of RSV"), but most are limited to case reports or small series. For HSCT, both aerosolized [2, 86, 87, 94, 95] and oral ribavirin [96, 97] have been employed, although some patients received intravenous ribavirin when they did not respond to aerosolized or oral treatment [86, 98]. In a series that included 55 patients with PIV-3 LRTI, 31 were treated with aerosolized ribavirin with or without IVIG in a nonrandomized fashion. Such therapy did not appear to alter mortality from PIV-3 pneumonia or decrease the duration of viral shedding [2]. A more recent retrospective study evaluated 173 HSCT recipients with PIV infection [90]. Forty-one patients with LRTI were treated with aerosolized ribavirin with or without IVIG, but 100-day mortality of this group was similar to those with LRTI not treated with ribavirin. Overall, there is no convincing evidence that ribavirin is effective for treatment of PIV upper or lower tract disease in HCT recipients. Effective prophylaxis and treatment for PIV in HSCT population are desperately needed.

Successful treatment of PIV LRTI has been reported in heart transplant recipients with aerosolized ribavirin or with intravenous ribavirin plus methylprednisolone [99, 100] as well as in a kidney transplant recipients with aerosolized ribavirin and IVIG [101] although none of these studies included controls.

DAS181 is a novel sialidase fusion protein with activities against multiple strains of influenza and PIVs. It has been used for PIV treatment in a small number of HSCT and lung transplant recipients. The drug was found effective in most of these cases and was well tolerated [102–106]. A phase II, randomized, double-blind, placebo-controlled study to

examine the effects of DAS181 in immunocompromised hosts with LRTI by PIV has been completed, but no results have been published to date.

Human Metapneumovirus (HMPV)

Epidemiology and Clinical Manifestations

HMPV was first described in 2001 among Dutch children with bronchitis [107], although serological studies indicate that it has been a cause of human infection since 1958 [108]. There are two subgroups of HMPV, A and B, and each with two clades, A1, A2, B1, and B2. All four subtypes co-circulate, while a single subtype tends to dominate each year [109]. HMPV has a worldwide distribution; it circulates in late winter to early spring in temperate climates and in late spring to summer in tropical regions [108].

HMPV may contribute to 12–20% of all previously virus-negative LRTI [110]. When compared to RSV, infection with HMPV tends to occur in slightly older children and cause milder symptoms, but severe disease can occur among small children, elderly, and those with immunosuppression or chronic medical conditions [111]. Clinical manifestations range from mild URTIs to severe pneumonia. Elderly patients are much more likely to experience dyspnea and wheezing than young adults, and hoarseness is a more common complaint when compared to other paramyxoviruses [112]. Among hospitalized patients and recipients of HSCT, wheezing is prominent and noted in up to 80–90% of patients [113, 114].

HMPV Infection in Transplantation

For patients with hematologic malignancies or HSCT, HMPV is responsible for approximately 3–14% of RVIs [114–117]. A systematic review of HMPV infections among HSCT recipients and hematologic malignancy patients found that despite lack of directed antiviral therapy, overall mortality rates are low (6%) unless patients progress to LRTI (27%) [118]. Approximately one-third of patients with HMPV URTI develop LRTI [119].

In lung transplant recipients, HMPV is responsible for 14–30% of RVIs with a similar morbidity when compared to other community-acquired respiratory viruses [3, 35, 36, 120]. Acute HPMV infection has been associated with allograft rejection [36]. In a study [120] of 89 lung transplant patients who presented with RVIs, HMPV and RSV were equally prevalent and had similar clinical manifestations, although severe bronchospasm was less common with HMPV. A significant number of patients with either HMPV or RSV infection developed graft dysfunction (63% and 72%, respectively), but onset or progression of BOS occurred only in patients with RSV (38%) at 6 months and in none with HMPV. Another study of 60 lung transplant

patients also showed that HMPV infection increased the risk of acute graft rejection without associated chronic rejection or BOS [3, 120].

Treatment of HMPV

Treatment for HMPV is largely supportive, as there is currently no antiviral therapy licensed for this virus. Ribavirin is active against HMPV *in vitro* and in animal models [121, 122]. In clinical settings, there have been scattered reports in the literature describing HMPV cases treated successfully using aerosolized, oral, or intravenous ribavirin given with or without IVIG [3, 120, 123–126]. However, these studies did not include any untreated control groups, and the efficacy of these regimens cannot be determined. Some have suggested that ribavirin with IVIG may be considered as a treatment option for patients with severe disease [125], but this approach is not routinely used.

Several new approaches for treatment of HMPV are in development, including monoclonal antibodies against the fusion protein [127, 128] or synthetic peptides with antiviral activities [129]. Their efficacies against HMPV have been demonstrated *in vitro* and in animal models, but studies in human have not been reported.

Diagnosis of Paramyxoviruses

Radiographic Evaluation

LRTI by respiratory viruses produces a spectrum of imaging findings; with the most common high-resolution chest computed tomography (HRCT) scan, observations include small, poorly defined centrilobular nodules or tree-in-bud opacities, ground-glass opacities, bronchial wall thickening, and air-space consolidations, which may be difficult to differentiate from other causes of pulmonary consolidation [130–137]. There is considerable overlap in the imaging appearance of viral, bacterial, mycobacterial, and fungal respiratory tract infections in transplant population. The findings such as tree-in-bud opacities, bronchial wall thickening, and peribroncholar consolidation may suggest a viral etiology [138]. HRCT findings between immunocompetent and immunocompromised patients are relatively similar [139], but infection with co-pathogens is common among transplant recipients, thus complicating interpretation of radiographic findings. Correlation with patient immune status, recent treatment, and exposure history, as well as epidemiologic factors, are essential to help narrow the list of possible etiologies both infectious and noninfectious and to guide diagnostic testing and appropriate therapy [130].

Laboratory Diagnosis of Paramyxoviruses

Laboratory diagnosis of respiratory viruses is usually made by analysis of respiratory secretions. Samples can

be obtained as a nasal wash, nasopharyngeal or throat swab, bronchoalveolar lavage, or, for those incubated, tracheal aspirate. Detection of the virus in the respiratory samples can be performed by cell culture, antigen testing, and PCR.

Viral isolation by cell culture used to be the gold standard for diagnosis but has largely been replaced by molecular studies. Reverse transcriptase (RT)–PCR is now routinely used for respiratory viral diagnosis for the detection of RNA viruses in respiratory secretions [140] and has higher sensitivity than either viral culture or antigen detection assays, particularly in immunocompromised patients [91, 140]. Compared with culture, the sensitivity and specificity of RT-PCR techniques can reach 100% and 95–98%, respectively [141–143]. PCR-based tests for respiratory viral detection are often designed as part of a multiplex PCR assay that can allow detection of multiple respiratory pathogens simultaneously [144], and rapid point-of-care tests are being developed as well [145, 146].

Transmission and Prevention of Paramyxovirus Infection

The modes of transmission of PIVs and HMPV are not as well studied as RSV, but these respiratory viruses are mostly transmitted by direct person-to-person contact, through exposure to nasopharyngeal secretions from infected individuals such as respiratory droplets or by self-inoculation after touching contaminated surfaces has also been described [147, 148]. Outbreaks of RSV, PIVs, or HMPV have been reported in outpatient clinics, in long-term care facilities, and in hospitals, including hematology and HSCT units [94, 149–153]. To prevent transmission of respiratory viruses in health care setting, policies and procedures regarding patients with respiratory viruses should be formulated; in particular, compliance with proper hand hygiene and contact precautions are of paramount importance. Other infection control measures include isolating infected patients in private room, cohorting patients, and/or limiting transport of patients from their rooms. During a nosocomial outbreak, personnel caring for infected patients should be restricted from caring for uninfected high-risk patients if possible [154–156].

Immunoprophylaxis

PVZ is a RSV-specific humanized monoclonal antibody directed against the F glycoprotein of RSV and is FDA approved for immunoprophylaxis against RSV in high-risk children. Data for its use in immunocompromised adult patients are limited [48, 68], with only one uncontrolled study in the literature reporting the use of PVZ as immu-

noprophylaxis during an RSV outbreak in an adult HSCT unit [150]. RSV-IVIG prophylaxis has also been studied in high-risk adult HSCT recipients; an increase in antibody titers against RSV was demonstrated, but the study was underpowered to evaluate its efficacy [157]. There are several monoclonal antibodies against RSV under development.

Vaccines

Despite the major clinical importance of paramyxoviruses, there is currently no vaccine approved for these viruses in humans. Using various strategies for vaccine development, those tested in animal models include live-attenuated virus vaccines including chimeric and recombinant variety, inactivated virus vaccines, and subunit vaccines. A number of them are currently in phase I–II clinical trials [158–161].

Other Strategies

In a retrospective study of 37 HSCT patients with pretransplant RSV URTI, 34 patients had their transplant delayed or conditioning aborted [162]. Overall, RSV pneumonia occurred in 1 of 34 patients for whom HSCT was delayed, compared with two of three patients for whom there was no delay. This study suggested that for HSCT candidates with pretransplant RSV URTI, a delay of HSCT might reduce the risk of developing RSV pneumonia. Thus, the strategy of delaying transplantation to prevent progression of a viral URTI to LRTI is recommended unless precluded by progression of underlying malignancy. There are limited data for other respiratory viruses [66, 147] although some proposed guidance is available (Table 40.1) [163].

Orthomyxovirus: Influenza

Influenza belongs to the family *Orthomyxoviridae* with three types, influenza A, influenza B, and influenza C virus. Influenza A viruses are further classified into subtypes based on their hemagglutinins (HA) and neuraminidases (NA). One of the unique features of influenza virus is the frequency by which antigenic variation occurs which is the reason that influenza continues to be a cause of major epidemics. Annual variation of the influenza virus is due to relatively minor antigenic changes within the HA and/or NA and is known as antigenic drift. Major changes in HA or NA through genetic reassortment or a major mutation are known as antigenic shift and occur once every 10–30 years. This results in an entirely novel strain to which the population has no immunity, leading to an unhindered global spread; the last pandemic occurred in 2009 with the emergence of a novel strain of influenza A/H1N1.

Table 40.1 Recommendations for respiratory viral infections prior to hematopoietic stem cell transplantation

Virus	Recommendation for URTI	Recommendation for LRTI
RSV	Delay transplant if possible If not possible to delay, consider oral ribavirin	Delay transplant; consider ribavirin if delay is not feasible (anecdotal data)
Influenza virus	Delay transplant if possible and treat If not possible to delay, treat	Delay transplant and treat
Parainfluenza virus	Delay transplant if possible If not possible to delay, supportive care	Delay transplant; consider ribavirin if delay is not feasible (anecdotal data)
Metapneumovirus	Delay transplant if possible	Delay transplant; no data on ribavirin
Rhinovirus	No delay needed for URTI	Delay transplant for allogeneic transplant if feasible
Coronavirus	No data	No data
Bocavirus	No data	No data

Adapted from Waghmare et al. [163]

Table 40.2 Role of corticosteroid treatment in progression of respiratory viral illnesses

Virus	Progression				Mortality			
	Steroid dose per day		HR (95% CI)	P-value	Steroid dose per day		HR (95% CI)	P-value
RSV	>2 mg/kg	+	1.4 (0.4–5.2)	0.19 ³	>2 mg/kg	+++	3.3 (1.7–6.3)	<0.001 ¹¹
Influenza	≥1 mg/kg	+/-	0.8 (0.2–2.4)	0.60 ⁴⁶	≥1 mg/kg	+/-	1.1 (0.3–3.5)	0.87 ⁴⁶
PIV	>2 mg/kg	+++	4.6 (1.2–17.0)	0.02 ⁷⁴	>2 mg/kg	+++	3.2 (1.5–7.2)	0.004 ¹³
HMPV or RSV	No data				Any steroid	+++	5.0 (1.8–14)	0.002 ¹⁶
					≥1 mg/kg	++++	7.1 (2.3–22)	<0.001 ¹⁶

Adapted from Waghmare et al. [163]

RSV respiratory syncytial virus, PIV parainfluenza virus, HMPV human metapneumovirus, HR hazard ratio

Epidemiology

Influenza is a significant cause of morbidity and mortality in transplant patients. In recipients of solid organ transplantation, up to 42% of URTIs and 48% of LRTIs may be due to influenza infection and the annual between 1% and 4% [164]. During the 2009 H1N1 pandemic, mortality rates ranged from 0 to 8% in most case series [4] although one study reported a mortality rate of 21% among lung transplant recipients [165]. Of the organ transplants, lung transplant recipients appear to be at the highest risk; in one study, the incidence of influenza was 10–15 times higher in recipients of lung transplantation compared with recipients of other solid organs such as kidney or liver [166].

The incidence of influenza among HSCT ranges between 1% and 4% with 7–44% of such patients may develop LRTI. Death rates associated with influenza in HSCT recipients are higher than in SOT. Among patients with LRTI, mortality rates ranged from 15% to 28% and case fatality rates during the 2009 H1N1 pandemic ranged from 0 to 38% [4]. The main risk factor for disease progression to LRTI was lymphopenia; allogeneic HSCT, infection during early post-transplant period, presence of graft-versus-host disease, myeloablative preparatory regimen, and delayed initiation of antiviral therapy were other risk factors [1, 11, 12, 167]. Of interest, concomitant corticosteroid use has not been associ-

ated with an increased risk for progression to LRTI, a need for mechanical ventilation, or infection associated death; however, patients given systemic higher doses (≥1 mg/kg) of corticosteroids may be predisposed to prolonged viral shedding [11, 168]. The potential role of corticosteroids in influencing risk of progression to LRTI and mortality of influenza and other respiratory viral infections is summarized in Table 40.2 [163].

Clinical Manifestations

Clinical manifestations of influenza are similar to those in immunocompetent patients. In a multicenter cohort study of 242 organ transplant patients during the 2009 H1N1 pandemic, the most common presenting symptoms were cough (91%), fever (85%), myalgias (51%), gastrointestinal symptoms (44%), rhinorrhea (43%), and sore throat (43%) [169]. In a multicenter cohort study of 286 HSCT recipients during the 2009 H1N1 pandemic, the most common presenting symptoms were cough (85%), fever (81%), rhinorrhea (49%), myalgias (29%), and sore throat (23%) [170]. However, atypical presentations may occur in those with significant immunosuppression, which may include fever as the only presenting symptom or afebrile patient with rhinorrhea alone. It is speculated that corticosteroid use and blunting of the cytokine response associated with

acute influenza infection in these patients may contribute to the reduction or absence of systemic symptoms in selected patients.

The primary complication of influenza infection in transplant patients is progression from URTI to LRTI which can lead to acute lung injury and death. Morbidity and mortality appear to be greatest among HSCT and lung transplant recipients. While diffuse or peribronchial ground-glass opacity is the typical radiographic appearance in patients with LRTI, centrilobular nodules and frank lower lobe consolidation can also be observed [171]. Coinfection with other viral, bacterial, or fungal pathogens may occur and was reported in 29% of patients in a multicenter study of SOT recipients with pandemic influenza A/H1N1 [172]. Compared to those with viral co-pathogens, patients with bacterial or fungal coinfections had worse outcomes [11, 172]. Although uncommon, influenza can also cause a variety of extrapulmonary complications including myocarditis, myositis, encephalopathy, renal failure, severe diarrhea, and pneumomediastinum [166, 173, 174]. Virus-associated hemophagocytic syndrome has been reported as a severe complication of pandemic H1N1 leading to multiorgan failure [175]. As discussed previously, several studies suggest an association between RVIs including influenza and allograft rejection/BOS in the case of lung transplants, while others have not; a prospective study is needed to better characterize the impact of these infections on long-term sequelae [19, 44, 172, 176].

In healthy adults, seasonal influenza virus shedding ranges from 5 to 7 days and may extend beyond 1 week in hospitalized patients [177, 178] and even longer in transplant recipients. The median duration of viral shedding among allogeneic HSCT recipients was between 11 and 12 days compared to 1 week among recipients of autologous transplants [11, 179]. Prolonged viral shedding beyond 2 weeks and, in some cases, for months has been described in HSCT recipient. Risk factors for prolonged viral shedding include the use of corticosteroids at dosages ≥ 1 mg/kg per day and use of bone marrow and cord blood versus peripheral blood stem cell.

Diagnosis

There are several methods available for detection of influenza including rapid antigen, direct immunofluorescence antibody (DFA), viral culture, and PCR. As for other respiratory viruses, molecular tests have largely replaced these other testing modalities. In a study evaluating test characteristics of four different diagnostic assays during the 2009 H1N1 pandemic, PCR was found to have the greatest sensitivity and specificity. Given their improved sensitivity and specificity over other methods, PCR or other nucleic acid-based detection assays are preferred for the diagnosis of influenza

infection in this susceptible patient population. Multiplex PCRs have the added advantage of identifying other causes of respiratory viral infections as well.

Treatment

Currently, there are two major classes of antiviral agents with activity against influenza: adamantanes which block the viral M2 protein ion channel, thereby preventing fusion of the virus with host cell membranes, and neuraminidase inhibitors which prevent the release of progeny virus from infected cells. While the adamantanes, amantadine, and rimantadine are only active against influenza A, the neuraminidase inhibitors oseltamivir and zanamivir are active against both influenza A and B viruses, although reduced effectiveness of oseltamivir has occasionally been reported for influenza B virus [180]. The development of resistance to the adamantanes among influenza A virus has substantially limited their utility in clinical practice. Although 2008–2009 seasonal H1N1 remained susceptible to the adamantanes, resistance emerged among seasonal H3N2 in 2003 and was widespread among 2009 pandemic H1N1 viruses. Oseltamivir resistance first emerged in 2007 among seasonal H1N1 viruses and was described during the 2009 H1N1 pandemic [181]. Oseltamivir resistance is primarily conferred by the H275Y mutation which does not result in cross-resistance to zanamivir. PCR testing is available for the detection of the H275Y mutation. In 2010, the S247 N mutation was detected in strains of 2009 pandemic H1N1 collected in Asia and was found to confer low to moderate oseltamivir and zanamivir resistance [182]. Otherwise, there has been very little zanamivir resistance reported to date, and thus, it is recommended for the treatment of oseltamivir-resistant influenza infection.

Because resistance patterns evolve over time, clinicians should become familiar with local patterns of influenza circulation in their communities throughout each influenza season and refer to the Centers for Disease Control and Prevention (CDC) influenza website (<http://www.cdc.gov/flu>) [183] for updated information regarding antiviral resistance and recommendations regarding antiviral use. In addition, antiviral resistance appears to occur more commonly among severely immunocompromised patients likely due to prolonged viral shedding [184, 185]. During the 2009 H1N1 pandemic, the majority of patients with oseltamivir-resistant virus reported to the CDC were HSCT recipients or patients who had a hematologic malignancy receiving chemo- or immunosuppressive therapy [186].

There have been no randomized clinical trials of antiviral therapy for influenza in transplant patients. All randomized trials have included healthy adult outpatients who were treated within 48 h after symptom onset and, in aggregate, demonstrate a reduction in duration of symptoms by ~1 day

and time to return to normal activity [180]. Although further study is needed regarding the role of antiviral therapy >48 h of symptom onset, the 2009 IDSA guidelines for management of seasonal influenza suggest that antiviral therapy initiated >48 h after symptom onset may be beneficial in hospitalized patients based on a prospective cohort study [167, 180, 187]. Observational studies suggest that early antiviral therapy of HSCT recipients with influenza URTI is effective in preventing progression to LRTI [8, 11, 168, 179, 188]. Among SOT recipients, a multicenter study found that early antiviral therapy was associated with a lower incidence of hospitalization and likelihood of ICU admission as compared to delayed (>48 h after symptom onset) therapy [169]. Although antiviral therapy may have its greatest value when initiated early, it is felt that symptomatic transplant patients may benefit even beyond 48 h if they have evidence of viral replication, and in general, treatment of all symptomatic transplant patients is recommended regardless of the duration of symptoms [189–191].

The optimal dose and duration of antiviral therapy in transplant patients has not been established. Oseltamivir has been studied at doses of 75 mg or 150 mg twice daily in immunocompetent patients with seasonal influenza; there was no significant advantage of the higher dose although a slightly higher rate of adverse effects was observed [192, 193]. However, due to concerns over higher viral loads, prolonged viral shedding, and uncertain drug absorption particularly in those patients undergoing chemotherapy or with gastrointestinal graft-versus-host disease, some experts suggest using the higher dose in transplant patients particularly if absorption is uncertain, in those patients with severe LRTI or who are critically ill [189–191]. Based on clinical studies in healthy adults, the recommended duration of treatment of influenza in immunocompetent patients is 5 days [180].

However, transplant patients may need longer durations of therapy due to prolonged viral shedding. Some experts recommend treating all SOT recipients until viral replication has ceased; authors recommend checking PCR once a week and treat until negative [190, 191]. Others have suggested a 10-day course for HSCT recipients and extending treatment in those patients with pneumonia, ongoing symptoms, or viral shedding [189]. Resistance testing should be considered in those patients with persistent viral shedding or who progress despite antiviral therapy.

While most literature in transplant recipients has focused on oseltamivir, inhaled zanamivir appears to be a reasonable alternative. IV zanamivir is currently available for compassionate use, and there is limited published experience among transplant recipients where it has been used with some benefit among patients with oseltamivir-resistant influenza or severe disease [194].

Peramivir, a parenteral neuraminidase inhibitor, was FDA approved in 2014 for the treatment of uncomplicated influenza infection in adults who have been ill for ≤ 2 days. There are limited data regarding the use of peramivir in transplant recipients. Of note, the H275Y mutation which confers oseltamivir resistance also confers cross-resistance to peramivir.

There are currently no data that indicates a clear clinical benefit of combination antiviral therapy over single drug therapy. A randomized, double-blind, multicenter phase 2 trial found that combination antiviral therapy with oseltamivir, amantadine and ribavirin reduced day 3 viral shedding compared to oseltamivir monotherapy, but there was no difference in clinical outcomes including resolution of symptoms or fever or time to recovery after illness [195].

Table 40.3 summarizes antiviral options for treatment of influenza.

Table 40.3 Antiviral options for the treatment of influenza

Antiviral agent	Dose	Parenteral formulation?	Side effects	Remarks
Oseltamivir	75 mg PO twice daily	Yes, investigational	Gastrointestinal: nausea, vomiting, diarrhea Neurologic: confusion, delirium, depressed consciousness (mostly reported among Japanese adolescents and adults)	Some experts recommend higher doses (150 mg PO BID) in transplant patients who are critically ill with LRTI
Zanamivir	2 puffs (10 mg) inhaled twice daily	Yes, investigational	Bronchospasm, cough, headache, dizziness, sinusitis, nausea, diarrhea	Little cross-resistance with oseltamivir
Peramivir	600 mg IV once daily	Yes (only available as parenteral formulation)	Gastrointestinal: nausea, vomiting, diarrhea Neutropenia	Cross-resistance with oseltamivir exists.
Amantadine	100 mg PO twice daily	No	Neurologic: insomnia, lethargy, inability to concentrate, dizziness Gastrointestinal: nausea	No longer routinely recommended due to high incidence of resistant influenza unless circulating strain known to be susceptible
Rimantadine	100 mg PO twice daily	No	Gastrointestinal Neurologic (less common than amantadine): lightheadedness, insomnia, inability to concentrate, nervousness	No longer routinely recommended due to high incidence of resistant influenza unless circulating strain known to be susceptible

Prevention

Annual influenza vaccination is a key component of infection prevention among HSCT and SOT recipients. There are several types of influenza vaccines: standard-dose inactivated influenza vaccines (IIV), available either as a trivalent or quadrivalent injection, high-dose IIV (available as a trivalent injection), live attenuated influenza vaccine (LAIV), intradermal IIV, and recombinant egg-free IIV. All vaccines are modified annually based on the anticipated circulating strains during the upcoming influenza season. The LAIV is contraindicated in immunocompromised patients and should not be used in transplant recipients. The intradermal IIV has not been evaluated in transplant recipients.

For HSCT recipients, influenza vaccination is recommended ≥ 6 months post-transplant and beginning 4 months following transplant if there is a community influenza outbreak [196]. If the vaccine is administered earlier than 6 months after HSCT, a second dose should be considered. The timing of vaccine administration appears to predict response with one study demonstrating that influenza immunization at least 6 months after HCT was 80% effective in preventing influenza [197]. The high-dose trivalent IIV is FDA approved for individuals ≥ 65 years of age and was found in a multicenter randomized clinical trial to induce higher antibody responses and improved protection against influenza compared to standard dose IIV [198]. In a phase I trial, HSCT recipients randomized to receive high-dose trivalent IIV had evidence of greater immunogenicity when compared to those receiving standard-dose trivalent IIV [199]. There was a higher frequency of injection site reactions, but most were mild. There are ongoing studies to further evaluate the role of high-dose IIV in HSCT.

For SOT recipients, influenza vaccination is recommended 3–6 months after transplant [164]. The immunogenicity of influenza vaccine following SOT is variable depending on the type of transplant, time from transplant, and immunosuppressive regimens. Among SOT recipients, overall responses based on seroprotection or seroconversion have ranged from 15% to 93% with greater responses observed several years after kidney transplant and lower responses seen in lung transplant [164]. Although there is a theoretical concern that influenza immunization may be associated with early allograft rejection or allosensitization of patients after transplant, this has not been observed in clinical trials [200]. In a randomized, double-blind trial of 172 SOT recipients, high-dose influenza vaccine demonstrated significantly better immunogenicity than the standard-dose vaccine [201]; no increased risk of rejection was reported although the study was not powered to address this outcome.

Immunization of health care workers and household contacts of transplant recipients is a critical component of

influenza prevention and is strongly recommended in published guidelines [147, 164]. A systematic review suggests that vaccination of healthcare workers reduces influenza-like illness and all-cause mortality in the elderly [202]. Due to the theoretical risk of transmission of LAIV, the CDC recommends that IIV not be used for household members and health care workers who have close contact with severely immunosuppressed patients such as recipient of hematopoietic stem cell allograft transplantation during those periods in which the patient requires care in a protective environment. Those persons who receive LAIV should avoid providing care for and contact with such patients for 7 days after vaccination.

Although influenza vaccination is the primary tool for influenza prevention, antiviral chemoprophylaxis may be considered as a prevention strategy in selected situations. The 2009 IDSA Guidelines for Management of Seasonal Influenza recommends consideration of antiviral chemoprophylaxis in high-risk patients during the 2 weeks after vaccination before an adequate immune response develops if influenza is circulating in the community [180]. It should also be considered among transplant recipients following exposure within the previous 48 h to an individual with influenza, particularly among those for whom the vaccine is contraindicated, unavailable, or expected to have low effectiveness such as patients with severe immune suppression. The choice of chemoprophylactic agent depends on the susceptibility pattern of the circulating influenza strain.

Human Coronaviruses (HCoV) and Human Rhinoviruses (HRV)

Epidemiology

HRVs and HCoVs are also common causes of RVIs in human, classified into the *Picornaviridae* family (genus *Enterovirus*) and the *Coronaviridae* family, respectively. Approximately 100 serotypes of HRV have been identified. In comparison, HCoV-229E and HCoV-OC43 were the only two known HCoVs for >40 years. In 2004, a new HCoV was identified as the causative agent of the outbreak of Severe Acute Respiratory Syndrome (SARS) and was named SARS-CoV. Subsequently, two other new HCoVs, NL63 and HKU1, were discovered in 2004 and 2005, respectively. In the latter part of 2012, another novel CoV was identified as the cause of severe respiratory illness in two adults from the Middle East [203] and was termed Middle East respiratory syndrome coronavirus (MERS-CoV). Similar to SARS-CoV, this virus can also cause severe, life-threatening disease. The ability of these emerging HCoVs to cause major outbreaks can be a potential threat to global public health and economy [204].

HCoV and HRV in Transplantation

In immunocompetent hosts, HRVs and HCoVs usually cause URTIs, but HCoVs can also cause croup, wheezing, as well as pneumonia, which can be severe with significant mortality, as in the case of SARS. The significance of HRV and HCoV in transplant populations has not been well established. According to a prospective study of HSCT recipients [5], infection with these viruses appears common in the first 100 days after allogeneic transplant, with day 100 cumulative incidence estimated as 22% for HRV and 11% for HCoV. HRV infection was associated with URTI signs and symptoms, but HCoV infection was asymptomatic. More than half of the infected patients had prolonged viral shedding for more than 3 weeks, and about 13% shed virus for more than 3 months [5]; only a few patients developed LRTI in that study. Fatal pneumonia associated with HRV and HCoV have been reported among HSCT recipients [205–207]. Recent studies suggested that HRV and HCoV LRTI with viral detection in the BAL are associated with mortality rates similar to those seen with RSV, PIV, or influenza viruses [10, 208].

For SOT, HRV and HCoV are frequently isolated among lung transplant patients [23, 25, 28], but a majority of these patients can be asymptomatic, according to a prospective surveillance study [28]. As discussed previously, RVI can increase the risk for developing acute rejection and/or BOS even with asymptomatic infections [23, 25, 28], but whether HRV or HCoV infection confer the same level of risk as compared to the paramyxoviruses or influenza cannot be delineated from these studies.

Currently, there are no specific agents licensed for the treatment of HRV and HCoV, but antiviral therapy for enteroviruses is under intense research.

Conclusions and Future Directions

Respiratory viral infections are common and associated with significant morbidity and mortality among patients undergoing hematopoietic stem cells and solid organ transplantation. The optimal management of these infections is limited by insufficient randomized treatment data as well as a limited new and novel antiviral drugs being investigated for potential clinical use. Large, preferably multicenter prospective, randomized trials are essential to (1) assess preferred therapy for life-threatening infections such as RSV, (2) define the role of combination antivirals for influenza virus infections, and (3) determine the use of adjunctive immunomodulatory therapy and/or corticosteroids in the management of these infections among the highly susceptible transplant population. The evaluation of novel long-lasting potent monoclonal antibodies for prevention may be warranted.

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