Respiratory Viral Pathogens in Solid Organ and Hematopoietic Stem Cell Transplant Recipients

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Abstract

Respiratory viruses are among the most common causes of infection among solid organ and hematopoietic stem cell transplant recipients. Respiratory viruses, such as influenza and respiratory syncytial virus, can cause a range of disease from asymptomatic shedding, upper respiratory infections, to life threatening pneumonia. In addition, respiratory viruses may be associated with chronic sequelae, including devastating late complications such as chronic rejection in lung transplant recipients and late airflow obstruction among hematopoietic stem cell transplant recipients. Currently only influenza has an available vaccine and licensed antivirals are limited to influenza and RSV. However, there are a number of novel vaccine candidates, preventative therapies, and antiviral drugs currently in development for the treatment and prevention of other clinically important respiratory viruses. Due to the limitation in currently available treatment options and the increased risk of transmission among high-risk transplant patients, infection prevention and control efforts remain the cornerstone to prevention during respiratory virus season and outbreaks. In this chapter, we will review the epidemiology, clinical presentation, prevention strategies, and management options for respiratory viruses in solid organ and hematopoietic stem cell transplant recipients.

Keywords

Influenza · Respiratory syncytial virus · Parainfluenza virus · Rhinovirus · Coronavirus · Adenovirus · Bocavirus · Enterovirus · Hematopoietic cell transplant · Solid organ transplant · Respiratory virus

Abbreviations

2019-nCoV	2019 novel Coronavirus
AdV	Adenovirus
BAL	Bronchoalveolar lavage
BoV	Bocavirus
CLAD	Chronic lung allograft dysfunction
CoV	Coronavirus
CT	Computed tomography
EV	Enterovirus
GVHD	Graft-versus-host disease
hMPV	Human metapneumovirus
hRhV	Human rhinovirus
HSCT	Hematopoietic stem cell transplant

ICU	Intensive care unit
IV	Intravenous
LRTI	Lower respiratory tract infection
MDR	Multidrug resistance
MERS-CoV	Middle Eastern Respiratory Syndrome Coronavirus
PCR	Polymerase chain reaction
PFT	Pulmonary function tests
PIV	Parainfluenza
RSV	Respiratory syncytial virus
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SOT	Solid organ transplant
URI	Upper respiratory infection

Introduction

Despite significant advances in surgical and medical therapies, infections remain a significant risk for morbidity and mortality among patients who have undergone both solid organ (SOT) and hematopoietic stem cell transplantation (HSCT). Respiratory viruses, including influenza A and B, respiratory syncytial virus (RSV), parainfluenza viruses (PIV), human metapneumovirus (hMPV), human rhinovirus (hRhV), coronaviruses (CoV), adenoviruses (AdV), and bocavirus (BoV), are among the most common causes of posttransplant infections (Fig. 1) [1].

Fig. 1 Common respiratory viruses seen in transplant patients are those seen in normal populations and during seasonal outbreaks. Although most are community acquired pathogens, adenoviruses are often viruses that can reactivate from latent reservoirs in the host or be newly acquired from exposures. *Bocavirus is more often considered a gastrointestinal pathogen, and many multiplex PCR panels may not include this for routine testing. †These four Coronaviruses are human strains see as common community strains, and do not include outbreak strains such as MERS-CoV, SARS-CoV, and 2109-novel CoV. Abbreviations: RSV-respiratory syncytial virus

Clinically, it is challenging to differentiate specific respiratory viruses based on symptoms or presentation. In transplant recipients, a high-index of suspicion is needed as these patients can present with a myriad of infections and inflammatory conditions associated with sinopulmonary symptoms (e.g., idiopathic pneumonia syndrome, cryptogenic organizing pneumonia) [2]. In addition, symptoms may be minimal to absent in many immunosuppressed patients [3]. As a result, it is crucial that the early diagnostic workup include an evaluation for respiratory viruses in order to identify and guide therapy. There are currently approved agents for the prevention and treatment of influenza and RSV. Although emerging experimental therapies [4–6] are becoming more available for other respiratory viruses, alternate antiviral agents which are licensed for other viral infections (e.g., ribavirin) have been used particularly among those with severe disease [7, 8]. In this chapter, we will review the general approach to respiratory viruses and then discuss approaches to the common respiratory viruses with a focus on prevention and treatment.

Respiratory Virus Epidemiology Among Transplant Patients

Multiple contemporary studies of SOT and HSCT patients using molecular diagnostics have helped to define the epidemiology of respiratory viruses in this population. Patients early after their transplant, particularly lung transplant recipients, allogeneic HSCT, and pediatric transplant recipients consistently, have higher rates of clinically significant respiratory viral infections and a higher rate of progression to lower tract disease. Other risk factors associated with more severe and progressive illness include recent use of lymphocyte depleting agents, lymphopenia <300 cells/ μL , use of high-dose glucocorticoids, and severe hypogammaglobulinemia (≤ 4.5 g/mL) [1]. Seasonal epidemics of respiratory viruses in transplant recipients follow the local seasonal patterns, although disease may be first recognized among immunosuppressed populations [1]. For the northern hemisphere, influenza and RSV are most common November–April; hRhV and CoV are most common in the fall and spring; and there is less seasonal variation with PIV and AdV. HRhV consistently is the most commonly identified pathogen, followed by coronavirus, RSV, PIV viruses, influenza, AdV, human hMPV, and BoV [9]. While cases are more severe among the most immunosuppressed transplant patients, such as those immediately posttransplant or those undergoing treatment of rejection, infections from respiratory viruses can occur at any time after transplant.

Clinical Presentations of Respiratory Viral Pathogens in Transplant Recipients

Transplant patients develop symptoms commonly described with respiratory viral infections, including rhinorrhea, sore throat, cough, and fever; however, presentation is much more varied among these patient populations ranging from asymptomatic shedding to severe lower respiratory tract infections. However, it has been

Table 1 Common respiratory viruses in transplantation

Virus	Isolation recommendations	Prophylactic options	Therapeutic options
Influenza	Contact and droplet	Inactivated influenza vaccine seasonal NAI	NAI
RSV	Contact and droplet	Palivizumab	Ribavirin ± immunoglobulin
hMPV	Contact and droplet	None	Ribavirin ± immunoglobulin
PIV	Contact and droplet	None	Ribavirin ± immunoglobulin
Rhinovirus	Contact and droplet	None	None (^a DAS181)
Coronavirus	Contact and droplet ^a 2019 novel CoV, MERS, or SARS which require contact, droplet and airborne precautions	None	None
Adenovirus	Contact & droplet	None	Cidofovir, (^a brincidofovir)
Bocavirus	Contact & droplet	None	None

Contact Precautions: gown, gloves; Droplet: Mask and Eye protection

Abbreviation: NAI, Neuraminidase inhibitor (oseltamivir, peramivir, or zanamivir); RSV, Respiratory Syncytial virus; hMPV, Human metapneumonvirus; PIV, Parainfluenzas; CoV, Coronavirus; MERS, Middle East respiratory syndrome-related Coronavirus; SARS, Severe acute respiratory syndrome-related Coronavirus

^aunapproved agents currently in clinical trials

demonstrated that transplant patients are more likely to present with less prominent early signs and symptoms, for example, rhinorrhea, reduced PFTs, or fever may be the sole presenting signs of a respiratory viral infection in lung transplant recipients [1, 9–11]. Similarly, HSCT recipients are more apt to have atypical symptoms, such as fever only, and many patients present with limited symptoms. As a result, clinicians must have a low index of suspicion for testing patients and considering early therapy (Fig. 1, Table 1) [3]. A recent large study of SOT and HSCT recipients with influenza clearly demonstrated the paucity of classic symptoms with only 64% presenting with fever, 35% with a sore throat, and 40% with myalgias [12].

Importantly, immunosuppressed patients are more likely to present with severe life-threatening lower tract infections such as pneumonia [12]. Patients with more severe lower tract disease presentations are more likely to present with shortness of breath, hypoxia, and severe respiratory symptoms that require intubation and ICU level support. Any transplant patient presenting with acute respiratory distress, particularly those with diffuse infiltrates on radiologic assessment, should have common respiratory viral infections included in their early differential diagnosis.

With the development of molecular techniques for detection of respiratory viruses, several studies have also noted that transplant patients can present with asymptomatic infections. These studies which screen patients prospectively

demonstrate that patients have documented viral detection (by PCR) but a lack of clinical symptoms [13]; some patients never develop clinical evidence of disease [3]. In part due to atypical symptoms and the potential for asymptomatic shedding, nosocomial transmission in HSCT clinic and hospital settings has been well described. Even well organized, careful infection prevention and screening programs targeted to these high-risk patients mitigate but cannot eliminate the risk of respiratory viruses and the development of clinical disease [14, 15].

Disease Progression and Complications

Respiratory viral infections can become life threatening as patients are more likely to progress from upper tract infections to lower tract infections. Rates of progression vary between virus, ranging from 5% to 50% depending on the pathogen and the level of immunosuppression in the host [16]. Among HSCT recipients, a number of factors have been identified to be associated with an increased risk of progression from upper to lower respiratory tract involvement. Commonly identified risk factors include neutropenia (≤ 500 neutrophils/mL), lymphopenia (≤ 200 lymphocytes/mL), age ≥ 40 years, presence of graft-versus-host disease (GVHD), use of glucocorticoids within 2 weeks of infection, myeloablative chemotherapy within 1 year of infection, cumulative antibiotic exposure, and infection early, especially within 1 year, of HSCT [16, 17]. Other factors include a history of smoking, nosocomial acquisition, hypoxia at diagnosis, use of matched unrelated or mismatched donor, prior autologous HSCT, and cord blood transplant [5, 18, 19]. Two risk scores have been developed to risk stratify HSCT recipients with respiratory viruses and predict response to therapy [7, 18–20].

In transplant populations with respiratory viruses, bacterial infections are a known but infrequent complications linked to these infections, with *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, and other common oral and aerodigestive tract bacterial species commonly seen as co-pathogens. Multidrug resistant (MDR) infections such as methicillin-resistant *Staphylococcus aureus* and MDR gram negative infections may also be more likely in these patients due to significant prior hospitalization and antibiotic exposures [21–23].

In addition to disease specific complications, emerging reports have linked respiratory viruses with rejection, particularly among lung transplant recipients. While there remains controversy about the role of respiratory viruses in triggering acute rejection, there is a clear association with an increased risk of developing chronic rejection or chronic lung allograft dysfunction (CLAD) and infectious complications, including aspergillosis, among lung transplant recipients [24–27]. Risk of CLAD appears to be greatest with infection with the pneumoviruses (RSV and HPMV) and with lower respiratory tract involvement (HR 3.0, 95% CI 1.5–5.9) [28, 29]. Although data suggests that this association is linked to symptomatic infections, additional studies on the role of asymptomatic respiratory viral infections on lung transplant patients are needed [24]. Lower respiratory tract involvement with the respiratory viruses is associated with late onset airflow

obstruction and infectious complications, including invasive aspergillosis, in HSCT recipients as well [30–32]. Transplant patients may develop encephalitis, myocarditis, or other rare complications that have been reported seen in patients with influenza infection.

Diagnostic Overview

As with most respiratory infections, patients with signs and symptoms of pneumonia should undergo radiologic evaluation. Although patients with upper tract symptoms do not routinely need imaging, patients with lower tract disease symptoms (e.g., cough or shortness of breath) should undergo imaging to evaluate the extent of lower tract involvement [33]. Chest x-rays can be a useful test (Fig. 2a), but among immunosuppressed transplant patients, noncontrast CT scans have increased sensitivity for lower tract disease manifestations and are often the preferred method for radiologic evaluation (Fig. 2b). Transplant patients with lower tract respiratory viral infections most commonly present with diffuse or patchy ground glass infiltrates, tree-in-bud findings, and/or consolidation on CT scans (Fig. 3).

It is nearly impossible to clinically distinguish infection due to one respiratory virus from another. Making a diagnosis among SOT and HSCT recipients is critical not only for infection prevention purposes, but also to enable the treating physician to select the optimal therapy for the patient. While a range of diagnostic methods are available, including serology, culture, and antigen detection, nucleic acid testing (PCR) has become the gold standard for the diagnosis of respiratory viruses. There are a range of molecular diagnostics, including a number multiplex panels that allow for concurrent screening of multiple pathogens from a single sample, and most of the currently available assays provide rapid results. In general, immunocompromised patients with any upper respiratory tract symptoms and/or fever should have upper

Fig. 2 Allogeneic transplant patient who presented with worsening hypoxia, fever and dry cough, documented to have lower tract human metapneumovirus. Human metapneumovirus documented by multiplex PCR from nasal wash and by bronchoalveolar lavage. A. Posterior anterior chest radiograph demonstrating a diffuse interstitial pattern. B. CT scan of the chest demonstrating diffuse multifocal lung infiltrates

Fig. 3 Transplant patient with multifocal ground glass (yellow arrow) infiltrates and consolidations (black arrow) from documented Influenza A

Transplant patient with multifocal ground glass (yellow arrow) infiltrates and consolidations (black arrow) from documented Influenza A.

airway samples (nares or nasopharyngeal) sent for multiplex PCR testing for respiratory viruses. False negative testing from the upper respiratory tract samples can occur from inadequate sample collection or among patients who have progressed to lower respiratory tract involvement. In one recent study, upper respiratory tract samples failed to detect a pathogen present in lower airway samples in 14.8% of patients [34]. Failure to detect a pathogen using upper respiratory samples, particularly in patients with symptoms of lower tract involvement, should prompt collection of lower airway samples, by deep tracheal aspirate or preferably by bronchoalveolar lavage (BAL); BAL samples should be tested using by similar multiplex PCR methods [5, 35]. Sampling lower tract specimens also helps determine if patients with respiratory viral infections have associated co-infections, which may require additional targeted therapy.

Common and Uncommon Respiratory Viral Pathogens

Respiratory viruses present with similar findings, but outcomes, complications, and treatment for various viruses are unique. In the following section, we describe specific epidemiologic details of individual viruses and describe available methods for treatment.

Influenza

Influenza viruses are *Orthomyxoviridae* enveloped and segmented RNA viruses, and Influenza A and B cause the vast majority of infections in transplant patients. Influenza results in seasonal epidemics typically from November to May in the

northern and May to October in the southern hemisphere, respectively. Influenza A typically occurs early in the season, followed by Influenza B, however seasonal variation can shift normal patterns. Seasonal epidemics are triggered by viruses that have antigenically drifted, with minor changes in which hemagglutinin or neuraminidase proteins are altered slightly so that preexisting antibodies present in the population no longer neutralize the virus. Far less frequently, an antigenic shift can occur when a novel hemagglutinin or neuraminidase that has not circulated in the human population for a long period of time emerges (e.g., H1N1 Swine influenza) and causes transmission, often associated with significant morbidity and mortality [36].

Among SOT patients, patients present most frequently with cough (85%) and fever (64%) but other cardinal symptoms, such as sore throat (35%) and myalgias (40%), are less common. Twenty-two percent have radiologic evidence of pneumonia on initial evaluation although proven bacterial superinfections are less frequently reported. While most patients in one large study were hospitalized, the length of stay was short (median 6 days), only 11% required ICU-level care, and even fewer required mechanical ventilation (8%) [12]. Among HSCT recipients, symptom presentations are similar, with cough as the most common symptom in most studies, appearing in 70–90% of patients [12, 18, 37]. Reported rates of fever range from 30% to 70% in these same studies, while myalgias are less frequently reported (5–39%). Importantly, rhinorrhea, sore throat, and other URI symptoms can also be among the only presenting symptoms in HSCT patients with influenza [38]. Additionally, patients who develop influenza in the early post-HSCT period may have less frequent and or prominent symptoms [3]. Hospitalizations and ICU level admission rates appear to be similar to SOT patient populations [12]. Presentations in transplant patients may vary from mild to severe, and this variation is likely related to host immunity, symptom distribution which may also shift between seasons, and unique characteristics of new seasonal strains [18, 39].

Treatment

Currently, there are three classes of antivirals approved for the treatment of influenza: M2 ion channel inhibitors (amantadine and rimantadine), neuraminidase inhibitors (oseltamivir, peramivir, and zanamivir), and the polymerase inhibitor (baloxavir marboxil). Due to widespread resistance in all circulating strains, the M2 ion channel inhibitors are not recommended for the prevention or treatment of influenza. While the polymerase inhibitor baloxavir marboxil is associated with improved activity against influenza B and is associated with much more rapid reduction in viral replication, clinical studies are only available in immunocompetent patients [40–42]. Resistance among these immunocompetent emerged quickly in ~10% of adults and up to 40% of children treated with baloxavir marboxil. Resistance was seen more commonly in those with poor preinfection immunity and in individuals infected with A/H3N2 viruses. The resistant variants are transmissible and associated with longer durations of clinical symptoms and viral

shedding in many of the patients [43–50]. As such, routine use of baloxavir is not recommended for transplant patients. If considered for use, it should always only be used in combination with a neuraminidase inhibitor and likely requires repeat dosing; the pharmacokinetics to inform optimal timing for repeat dosing are currently being studied (ClinicalTrials.gov: NCT03684044) [36].

Prospective studies have not been performed in the transplant setting to define the optimal dose, route, or duration of antiviral NAI therapy, or the role of combination therapies. NAI therapy is associated with reduced mortality, reduced progression to pneumonia, reduced duration of shedding, and among lung transplant recipients, reduced risk of development of chronic lung allograft dysfunction [51, 52]. Early therapy, defined as initiation in <48 h after symptom onset, is associated with the best outcomes [53]. Nonetheless, therapy appears to be beneficial in this population beyond 48 h and all symptomatic patients should be treated. Unless diagnostic testing results are readily available, antiviral therapy should be initiated as soon as influenza is suspected in a transplant patient presenting with symptoms during influenza season, even if diagnostics are pending; patients without evidence of lower tract disease with negative testing can have therapy discontinued. Viral replication is prolonged with the average duration of shedding being significantly longer than 5 days in HSCT and SOT patients [12, 20]. As such, most experts recommend at least 10 days of therapy with longer therapy in patients that remain symptomatic and have ongoing shedding beyond 10 days. Higher than usual doses (i.e., oseltamivir 150 mg p.o. BID) may be associated with reduced risk of resistance emergence [54] or considered for treatment of patients with influenza B infections (ClinicalTrials.gov: NCT00545532), but recommendations vary about the utility of routine use of high-dose therapy in transplant patients [55–57].

Patients that have persistent symptoms with sustained or worsening viral replication after 5 days should be considered to have virologic resistance, which is more frequently detected among transplant recipients. Not all contemporary multiplex assays provide surrogates for estimating viral loads (i.e., mean fluorescence or cycle threshold (CT) values or viral loads), but if available, an increasing viral load among patients on therapy is often evidence of virologic failure. Additionally, resistance assays are available at specific centers, the CDC, and some State Health Departments. If your assay does not provide these surrogate endpoints, it is recommended that repeat testing with assays that provide such data can help discern whether the patient is experiencing virologic failure. At medical centers without such tools, patients with prolonged viral detection and progression of symptoms while on therapy should also be considered to potentially have antiviral resistant infection.

If resistance is considered or documented by molecular techniques, most recommend a switch to an alternative therapy (ideally a combination of two active drugs). Resistance testing of clinical samples is recommended, if not already sent. Since most centers use oseltamivir as primary therapy, a switch to zanamivir is often recommended if possible as some resistant strains maintain susceptibility to zanamivir [58]; however, resistance to oseltamivir is more likely to be associated with cross resistance to peramivir [59]. Caution should be used with zanamivir in patients with reactive airways and among those intubated and receiving respirator

support, as the drug is inhaled. Transplant patients with mutations conferring multidrug resistance have been described, so consideration for dual therapy (NA inhibitor and another agent) is often recommended in those failing therapy [60]. The most effective combination therapies have not been studied except in small case series [61]. Most commercially available assays only detect the most common H275Y mutation that is relevant for oseltamivir resistance in influenza A/H1N1 viruses; if other agents or other viruses require testing, samples can be sent to CDC through state or local health departments in the USA or through local public health agencies.

Prevention

Although screening and contact precautions can help prevent healthcare associated transmission, prevention is best accomplished through use of the inactivated influenza vaccine. Current guidelines recommend annual influenza vaccination in all transplant patients, their close contacts, and healthcare workers caring for them. Ideally, vaccination should happen 3–6 months posttransplant, but earlier vaccination should be considered if there is an ongoing local epidemic [5, 35]. A number of different formulations of influenza vaccine are available. Although studies have generally been small, all formulations of inactivated vaccine have been demonstrated to be effective in preventing influenza [62]. In general, live-attenuated influenza vaccine (Flumist®) should be avoided in transplant patients because of the theoretical risk of developing clinical disease from the vaccine, unless the live attenuated vaccine is the only option for vaccinating the patient during a period where the potential risk outweighs the benefit of vaccination (e.g., center level outbreak). The CDC and others also recommend that family members should not receive the live virus vaccine, but if live vaccine receipt occurs, close contacts should be separated from the transplant recipient for at least one week [63, 64].

In general, transplant patients have less robust responses to influenza vaccine than normal hosts even when considering seasonal variance in vaccine responses [65]. Poor responses have been demonstrated with vaccine within 6 months of HSCT, in patients with active GVHD, in patients who are on ≥ 2 g of daily mycophenolate mofetil (MMF) and who are ≥ 65 years [66–69]. All standard dose inactivated vaccines are quadrivalent (currently containing the influenza A/H1N1, A/H3N2, B/Victoria and B/Yamagata strains), including the egg-based, cell culture based, and recombinant HA vaccines. The high dose and MF59 adjuvanted influenza vaccine currently are only approved in trivalent forms (both lack the B/Yamagata strain); a quadrivalent high dose vaccine was recently approved and will become commercially available during the 2020–2021 season. Adjuvanted vaccine did not appear to result in improved responses compared to unadjuvanted vaccine in HSCT and SOT recipients [70–72]. Among HSCT patients, lower seroconversion was associated with use of calcineurin inhibitors ($P < 0.001$) and shorter duration from transplantation, as well as GVHD [68, 72].

Two commonly studied approaches to improve vaccine responses include giving a booster vaccine 4–8 weeks after initial vaccine or the use of high-dose influenza vaccine. Booster dosing has been most commonly utilized in individuals needing vaccination shortly after transplant. This approach is associated with a consistent but modest improvement in seroconversion and seroprotective humoral responses (10–12% increased seroprotection with the second vaccine) [73]. The European Conference of Infections in Leukemia (ECIL) recommend a second dose of inactivated vaccine administered 3–4 weeks after the first dose should be considered in patients with severe GVHD or low lymphocyte counts. Additionally, they recommend early vaccination at 3 months post-HSCT during outbreaks, followed by an additional dose 3–4 weeks later [74]. Current US guidelines recommend single dose inactivated influenza vaccine at 6 months post-HSCT, or a dose at 3 months followed by a second dose 3–4 weeks later [64].

Inactivated high-dose influenza is a trivalent vaccine that contains 4 times the hemagglutinin protein and has also been studied in various transplant populations. In the largest study to date, high-dose vaccine was associated with an improved seroconversion rate in SOT recipients (A/H1N1: 40.7% vs. 20.5%; A/H3N2: 57.1% vs. 32.5%; B: 58.3% vs. 41.6%) although there were no significant difference in seroprotection, likely due to high prevaccine titers [75]. A pilot study in adult HSCT patients demonstrated that high dose vaccine was found to be safe and associated with a higher percentage of individuals with titers $\geq 1:40$ and a higher geometric mean titer (GMT) against the H3N2 strain compared with that of the standard dose group [76]; a randomized clinical trial comparing standard dose or high-dose followed by boosting at 4 weeks post-HSCT has currently completed enrollment but final study results are pending at the time of this update. Without Advisory Committee of Immunization Practices, support for routine use in immunosuppressed patients access may be limited due to costs and insurance restrictions, so high-dose vaccine is generally only given to patients ≥ 65 years of age for which it is specifically indicated [77]. None-the-less, current guidelines in SOT recommend the routine use of high-dose vaccine in all SOT recipients; available HSCT guidelines have not supported routine use, other than to those ≥ 65 years of age, due to the limited data available in this population [35, 78].

For patients who would be predicted to have a poor influenza vaccine response, seasonal antiviral prophylaxis can be considered, particularly during large outbreaks and is supported by a randomized clinical trial. In this trial, patients were given oseltamivir 75 mg once daily or placebo for 12 weeks when influenza was first recognized in the community. Such an approach was associated with reduced incidence of PCR positive (1.7% vs. 8.4%) and culture-confirmed ($<1\%$ vs. 3.8%) viral breakthrough infections, yet without evidence of NAI resistance mutations in viruses that failed prophylaxis [79]. While generally well tolerated, clinical experience demonstrates challenges in drug approvals from health insurance carriers and a high incidence of discontinuation because of intolerance.

Postexposure prophylaxis using the lower prophylactic dose (daily vs. twice daily) is not recommended for those with documented household or nosocomial exposures since transmission may have already occurred and the risk of clinical and

virologic influenza breakthrough should be clearly avoided, especially in immunocompromised patients where resistance is a major concern [36]. Instead, empiric treatment using the therapeutic dosing (i.e., 10 days of twice daily oseltamivir) should be restricted to high risk transplant recipients (HSCT within 6 months of transplant or unvaccinated lung transplant recipients). Low-risk patients should be monitored closely and started on early full dose treatment if they develop any symptoms. If used, therapy should be started as soon as the diagnosis is confirmed in the contact but should not be started if there has been >48 h of exposure to a symptomatic contact; in such situations active symptom monitoring with proactive treatment is recommended.

Respiratory Syncytial Virus

RSV was reclassified in 2016 into the family *Pneumoviridae*, genus *Orthopneumoviridae* [80, 81]. RSV is an enveloped, nonsegmented, negative sense, single-stranded RNA virus which encodes 11 proteins: 2 nonstructural and 9 structural [82]. RSV isolates are divided into two major antigenic groups A and B, each of which are further divided into 13 RSV A genotypes and 20 RSV B genotypes [80, 81].

Studies involving SOT recipients have demonstrated significant mortality in lung transplant patients where LRTIs with RSV can be a risk factor for CLAD and for death (mortality rate up to 20%) [83, 84]. Local inflammation and enhanced exposure of the immune system to pulmonary antigens lead to injury in the airway epithelial cells and sub-epithelial structures, leading to obliteration of the small airways, and subsequently CLAD [85].

Among adult HSCT recipients with RSV infection, progression from URTI to LRTI occurs in 40–60% of cases and LRTI is associated with mortality rates up to 80% [86–89]. Two available risk scores (see Table 2) are helpful in predicting outcomes for RSV.

In the first scoring system, patients with more than 2 SID (Severe Immunodeficiency) factors (VSID, Very Severe Immunodeficiency) were found with RSV-attributed mortality rates of 18% [7]. The immunodeficiency scoring index RSV (ISI-RSV) score demonstrates an increasing risk of progression from upper to lower tract disease (7%, 15% and 48%, respectively) and mortality (0%, 3%, and 29%, respectively) across the 3 risk levels [19]. These scores have been proposed as tools for determining need for hospital admission and antiviral therapy.

Treatment

The standard of care for the management of RSV infection in adults is mainly limited to supportive care with bronchodilators, supplemental oxygen, intravenous fluid, and antipyretics [90]. Ribavirin and immunoglobulin preparations are the therapies most

Table 2 Risk score for HSCT recipients with RVI to predict risk of progression to lower tract disease and death

(a) Severe immunodeficiency score		
Moderate immunodeficiency (MID)	Severe immunodeficiency (SID)	Very severe immunodeficiency (VSID)
≥1 factor present	Only 1 factor present	≥ 2 factors present
	Neutropenia <0.5 10 ⁹ /L	Neutropenia <0.5 10 ⁹ /L
	Lymphopenia <0.1 10 ⁹ /L	Lymphopenia <0.1 10 ⁹ /L
	Allo-HSCT <6 months ago	Allo-HSCT <6 months ago
GVHD<2 or limited GVHD	GVHD ≥2 or requiring treatment	GVHD ≥2 or requiring treatment
T-cell depletion >3 months	T-cell depletion <3 months	T-cell depletion <3 months
B-cell depletion >3 months	B-cell depletion <3 months	B-cell depletion <3 months
	Hypo-γ-globulinemia <4.5 g/L	Hypo-γ-globulinemia <4.5 g/L
(b) Immunodeficiency Score Index (ISI)		
Factor	Score	
Neutropenia <0.5 10 ⁹ /L	3	
Lymphopenia <0.2 10 ⁹ /L	3	
Pre-engraftment or Allo-HSCT <1 months	1	
GVHD (acute/chronic)	1	
Corticosteroids	1	
Myeloablative conditioning	1	
Age > 40 years	2	
Interpretation: 0–2: Low risk; 3–6: Moderate risk; 7–12: High risk		

commonly utilized and are generally limited to HSCT and lung transplant recipients [82]. Ribavirin is a guanosine analogue that is FDA approved, in its aerosolized formulation, for the treatment of RSV in infants and young children only. Intravenous ribavirin is not commercially available in most parts of the world. Due to challenges in drug delivery and the high cost of aerosolized ribavirin, many centers utilize oral ribavirin off-label for the treatment of immunocompromised patients despite a lack of prospective efficacy data [91–93].

Available studies suggest that if therapy is to be used, it is of greatest benefit when started early to prevent progression to lower tract disease [94–96]. When used for lower tract disease, ribavirin has been shown to be less effective [97]. Furthermore, a comprehensive review of the available literature shows that patients treated with aerosolized ribavirin and an antibody preparation, including standard intravenous immune globulin (IVIG), RSV immunoglobulin, or palivizumab had the lowest risk of progression to lower tract disease and death [16, 89]. If aerosolized ribavirin is used, continuous dosing (6 g over 18 h daily) has been shown to be equally effective in preventing progression to LRTI compared to intermittent dosing (2 g over 3 h every 8 h) [98].

Oral ribavirin is increasingly used among transplant centers globally due to ease and cost considerations [92]. A range of doses have been utilized across centers,

although aggressive dosing is likely needed to approach the drug concentration needed in alveolar lung fluid to treat RSV; dosing approaches must be balanced with adverse effects such as hemolytic anemia [93, 99–119]. Most studies in HSCT recipients that have compared oral to inhaled ribavirin have demonstrated similar efficacy, although none have been randomized and none included a placebo arm. Among lung transplant recipients, IV ribavirin has been associated with 100% survival rate with only 5% developing post-RSV BOS, a rate lower than historical data [120]. Several retrospective observational studies of oral ribavirin have consistently shown similar outcomes compared with IV or inhaled ribavirin in lung transplant patients. The majority of studies have not been placebo controlled. However, two recent studies of novel RSV drugs found that when ribavirin was utilized in transplant patients, it was not shown to convincingly improve outcomes compared to patients that did not receive ribavirin [6, 121]. These data, the lack of availability of intravenous ribavirin, the cost of inhaled ribavirin, and the lack of placebo-controlled studies in transplant patients highlight the challenges and ongoing need for safety and efficacy studies of ribavirin in the transplant population.

The current approach used in most centers is the use of aerosolized or oral ribavirin for treatment of RSV in HSCT and lung transplant recipients; antibody preparations are often added to ribavirin in HSCT recipients with more severe disease [5, 35, 82, 122]. Most centers will utilize standard intravenous immunoglobulin (IVIG) for the antibody preparation. Recently, a high titer RSV immunoglobulin (RI-002) was approved by the FDA without a specific RSV indication but in a compassionate use study was associated with a high survival rate in HSCT recipients (73%) [123]. Limited data on treatment in adults suggests reduced progression to lower tract disease with early combination therapy using IV palivizumab and ribavirin [16, 124, 125]. However, use of palivizumab in combination therapy was not found to decrease mortality in a large retrospective study of patients with RSV pneumonia and is not recommended by most centers [126]. The largest single-center study utilizing palivizumab in younger adults (median age 16 years old) with HSCT also failed to show significant impact on outcome as assessed by progression to LRTI, early mortality rate, and 1-year overall survival rate [124].

Two investigational agents provide further insight into antiviral therapy in this population but did not meet prespecified study endpoints. The first, ALN-RSV01, is a small interfering RNA (siRNA) that was studied to assess its impact on prevention of BOS in lung transplant patients. Two completed studies in lung transplant patients demonstrated a statistically nonsignificant decrease in new or progressive BOS at day 180 (13.6% vs. 30.3%, $p = 0.058$) but no impact on viral parameters or symptom scores. Early therapy was associated with greatest impact [127]. Although this agent is no longer under clinical development, it demonstrated the ability to use CLAD as a potential endpoint in studies in lung transplant recipients. The second, presatovir (oral GS-5806), is an oral small molecule fusion inhibitor that has been studied in lung and HSCT recipients. Unfortunately, despite excellent data in human challenge models and a clear safety profile in clinical studies, presatovir did not achieve the clinical or virologic endpoints in the transplant studies [6, 121, 128]. A small effect was noted in patients with significant lymphopenia with upper

respiratory tract illness [121]. Several other experimental therapies (JNJ-53718678: ClinicalTrials.gov Identifier NCT03379675, NCT03656510; RV521: ClinicalTrials.gov Identifier NCT03782662; and MDT-637) are undergoing clinical development, including some studies in the transplant setting [82].

Prevention

Prevention of RSV is limited by the lack of an approved vaccine to protect against the virus. Palivizumab is an RSV-specific monoclonal F antibody that is currently approved by the FDA and European Medicines Agency for the prevention of RSV only in pediatric patients at high risk of RSV disease. In high risk infants, palivizumab is 55% effective at reducing rates of pediatric hospitalization and has been shown to reduce morbidity although not mortality [129]. Given cost constraints, there are limited data on the use of palivizumab as preventative therapy in immunosuppressed patients and the elderly (cost per adult dose of >\$10,000 in the United States) [130]. Palivizumab has been successfully utilized to prevent an outbreak of nosocomial RSV transmission in a single adult HSCT unit [131]. Palivizumab is used by some but not all pediatric lung transplant programs based on a recent survey [132].

Human Metapneumovirus

Human metapneumovirus (hMPV) is a negative-sense, single-stranded RNA virus in the Paramyxoviridae family. There are two subtypes with two subgroups of each (A1, A2, B1, and B2). Much like other members of the Paramyxoviruses, hMPV has a propensity to cause LRTI and has been associated with high mortality. There are limited data in SOT, with the preponderance of data in lung transplant recipients. hMPV is symptomatic in about half of patients and two-thirds go on to develop LRTI [11]. hMPV has also been associated with development of CLAD and additional infectious complications including CMV reactivation in these patients [133–135].

There have been few HSCT patient studies focused on hMPV but those suggest that approximately 25% of patients develop LRTI progression at a median of 7 days after initial symptom onset (range 2–63 days). Progression to LRTI is associated with steroid use ≥ 1 mg/kg prior to URI diagnosis (HR, 5.10; $P = 0.004$), low lymphocyte count (HR, 3.43; $P = 0.011$), and early onset of HMPV infection after HSCT (before day 30 after HSCT; HR, 3.54; $P = 0.013$) [136]. Interestingly, baseline viral load was not associated with risk of LRTI progression. Mortality rates at 100 days in some studies have been high (reported as high as 43%), and mortality has been associated with steroid therapy, oxygen requirement >2 L, or mechanical ventilation, and bone marrow as stem cell source [137]. Reports also suggest higher attack rates in pediatric and adolescent HSCT populations [138].

Treatment and Prevention

Based on in vitro activity, some centers use inhaled, intravenous, or oral ribavirin with and without immunoglobulin for the treatment of hMPV [139–145]. Since there are no comparative studies, the clinical benefit of this approach cannot be assessed particularly since the majority of patients who receive treatment are those with severe LRTI disease; due to lack of other treatment options, these remain in clinical use [145, 146]. There are few novel drugs in the market that target hMPV, but a novel sialidase inhibitor, DAS-181, has shown some promise in animal models of hMPV infection [147]. There are no currently available vaccines to prevent hMPV and no prophylactic treatments approved that target hMPV.

Parainfluenza Viruses

PIVs are negative sense single stranded RNA viruses in the Paramyxoviridae family. There are four different serotypes (PIV-1, -2, -3, -4) [148]. The envelope is studded with two different glycoproteins; one contains hemagglutinin-neuraminidase (HN protein) activity while the other is involved in the fusion mechanism (F protein) [149]. The HN is responsible for attachment to sialic acid-containing receptors on respiratory epithelial cell surfaces. The four different serotypes of PIV also show remarkably different seasonal patterns, but together lead to a nearly yearly presence of PIV infections. PIV-1 follows a biennial pattern, marked by a dramatic increase in cases in the months of September to December of odd-numbered years [150]. Outbreaks of PIV-3 infections occur yearly, primarily in the months of April to June. During the absence of endemic PIV-1, PIV-3 shows increased activity, either as a longer spring season or as a second but milder season in the months of November to December [151]. Similar to PIV-3, outbreaks of infection with PIV-2, which are smaller in magnitude, occur on an annual basis [151]. Data on PIV-4 is less clear, as it is less frequently tested for and isolated, making it difficult to draw conclusions on the seasonality of this serotype [150, 151].

Together PIV infections pose a large infectious burden on HSCT and lung transplant recipients [152, 153]. In multiple studies investigating the incidence of PIV infection in adult and pediatric HSCT patients, an overall incidence of 4% (0.2–30%) was identified, with an estimated 3–7% of patients becoming infected with PIV within the first 100 days of transplantation [154]. PIV-associated mortality is highest in patients with LRTI disease, who often progress to multiorgan failure, and in those who develop pulmonary co-pathogens, with an average mortality rate of 27% (0–62%) [152].

Treatment and Prevention

There are currently no approved vaccines for the prevention of PIV [155]. Likewise, there are currently no FDA approved treatments for PIV infection. Ribavirin is active

against paramyxoviruses through the depletion of intracellular GTP pools secondary to the inhibition of IMP dehydrogenase [156]. However, ribavirin and IVIG have been studied in transplant patients without convincing efficacy in most retrospective nonrandomized studies. Oral, aerosolized, and intravenous ribavirin have been administered in the management of PIV but studies have not demonstrated significant improvement in viral shedding or mortality (77.3% aerosolized ribavirin vs. 86.3% no treatment) among patients with PIV-associated pneumonia when compared to no treatment [155]. Despite the negative data, ribavirin $\pm$ IVIG therapy are recommended for the treatment of severe PIV infection in transplant patients in current guidelines, due to the lack of other available therapies [35, 122].

DAS181 is a novel inhaled host-active antiviral composed of the *Actinomyces viscosus* sialidase catalytic domain linked to the human AR glycosaminoglycan-binding sequence [157]. DAS181 selectively cleaves host cell sialic acids, which are required by influenza and PIV for binding of the virus to the host cell [158]. DAS181 showed promise when used as treatment for patients who received the drug through compassionate use access to the drug, where DAS181 resulted in improved pulmonary function and reduced viral loads in most, but not all of the patients [159–165]. Nonresponders frequently had co-infections and typically died of the infection [165]. A randomized, placebo-controlled study of DAS181 in HSCT recipients with PIV was recently conducted (Clinicaltrials.gov identifier: NCT01644877). DAS181 was well tolerated but the study failed to demonstrate superiority in terms of the primary endpoint (clinical stability survival, defined as being alive with normalization of vital signs and resolution of supplemental oxygen requirements, at day 45 after randomization; 39.2% DAS181 vs. 31.4% placebo, $p = 0.29$). Post hoc analysis demonstrated a trend to higher rates of return to room air in patients with lower tract PIV infection who did not require mechanical ventilation [166]. Based on this post hoc analysis and being granted Breakthrough Therapy Designation by the US FDA, a phase 3 trial is currently enrolling nationally (Clinicaltrials.gov identifier: NCT03808922).

Rhinovirus

Human rhinoviruses (hRhV) are *Picornaviridae* in the genus *Enterovirus*. They are small enveloped single-stranded positive sense RNA viruses [167]. While there are a large number of recognized hRV types (over 160), they can all be classified into three species (A–C). hRVs are the most commonly isolated viruses among both SOT and HSCT recipients and are associated with prolonged shedding, which can occur for months posttransplant [11, 168–171]. A high baseline viral load has been associated with more prolonged shedding for all 3 species [169]. Among lung transplant recipients, hRV is not convincingly associated with acute or chronic rejection but may be associated with an increased risk of bacterial co-infections [10, 172]. Despite a sense by many treating transplant patients that hRV infections are a nuisance, fatal cases of LRTI hRV infections have been described and reports suggest that mortality rates associated with LRTI are similar to other respiratory viruses [173, 174]. More

recently, a risk score that incorporates the risk of low lymphocyte count, low albumin, positive cytomegalovirus serostatus, recipient statin use, and steroid use ≥ 2 mg/kg/day has been developed that predicts progression to LRTI among HSCT patients [175].

Treatment and Prevention

Unfortunately there are no active vaccines for hRhV, and while several drugs have been studied against hRhV, none have been licensed to date; there are no current trials of investigational agents in transplant patients [176].

Coronavirus

CoVs are a broad group of respiratory pathogens that span animal and human strains. The most common circulating human CoVs, HCoV-229E, and -NL63, and HCoV-OC43 and -HKU1, are large, enveloped single-stranded RNA viruses that are common causes of respiratory infection in transplant recipients [171]. Clinically, most patients have mild upper respiratory tract infections often with a prolonged period of asymptomatic shedding [171, 177–180]. Clinical symptoms of LRTI appear to be less frequent than other respiratory viruses among SOT and HSCT patients, but often when present co-infection is noted in patients with severe lower tract signs or symptoms. Data among HSCT recipients with clinical signs and symptoms of LRTI and detection of CoV in the lower tract demonstrate increased oxygen requirements (60%) at presentation and mortality rates within 90 days (54%) of diagnosis were high [179].

Animal CoV of clinical significance to humans, MERS-CoV, SARS-CoV, and the recently emergent SARS-CoV-2, have resulted in high rates of mortality in regional epidemics and global pandemics [181, 182]. Data on outcomes in transplant patients are uncertain with these pandemic CoVs as few patients have been affected by MERS-CoV or SARS-CoV. When infection has been described with these emerging CoV, patients may have atypical infection or a prolonged period of asymptomatic shedding [183–185]. Data on transplant patients affected by the emergent COVID-19 are still undergoing study at this time but slightly worse outcomes have been described clinically [186–188].

Treatment and Prevention

There are no known vaccine candidates for human or emergent animal CoVs, and there are no currently available therapies which are approved for treatment. Respiratory etiquette and infection prevention strategies remain the foundation of CoV prevention. Importantly, for MERS-CoV, SARS-CoV, and COVID-19,

airborne, droplet, contact, and standard precautions are recommended; eye protection is recommended for aerosol-generating procedures [189].

Adenovirus

Human adenoviruses (AdV) are divided into seven species (A–G) with over 80 serotypes [190]. They are double-stranded, nonenveloped DNA viruses. AdV can cause a range of clinical manifestations including infections of the central nervous system, the eye, the gastrointestinal tract, the genitourinary tract, and the respiratory tract; disseminated disease, defined as ≥ 2 sites of infection typically with viremia, is more common among HSCT patients and associated with the highest risk of mortality (Fig. 4). Asymptomatic AdV viremia is common in SOT recipients [191, 192]. Adenoviral hepatitis, typically caused by AdV 1, 2, or 5, is most common among liver transplant recipients and can be diagnosed by detection of viremia, elevated liver function tests, or visualization of viral intranuclear inclusions on liver biopsy [1]. AdV enterocolitis occurs in small bowel transplant recipients and may mimic rejection [193]. Adenoviral pneumonia is associated with graft loss, death, or progression to obliterative bronchiolitis in lung transplant recipients. AdV causes hemorrhagic cystitis with or without interstitial nephritis in kidney transplant recipients. Such patients typically present with fever, hematuria, and new-onset renal

Fig. 4 Locations of adenovirus disease among transplant patients. (Most common locations for AdV disease among transplant patients include the gastro-intestinal tract, genitourinary tract and respiratory tract. This figure does not represent isolated viremia or disseminated disease (with multiple organ sites and associated viremia). Image courtesy of Kyoko Kurosawa)

dysfunction [194]. AdV DNA in biopsy specimens is associated with worse outcomes among pediatric heart transplant patients [195, 196]. AdV in SOT patients is most common in pediatric transplantation, small bowel recipients, and those who receive lymphocyte depletion [1].

Among HSCT recipients, AdV is most common among those with an allogeneic transplant, cord blood transplant, cell-depleted graft, receipt of alemtuzumab, and patients with acute graft-versus-host disease. Severe lymphopenia (<300 cells/ μ L) has been associated with disseminated disease. Although disseminated disease only affects 1–7% of HSCT recipients, it is associated with a significant risk of mortality (8–26%) [1]. Similar to SOT recipients, AdV can present as a number of manifestations, including pneumonia/pneumonitis, CNS disease, colitis, hepatitis, cystitis, and nephritis, and can be seen as isolated viremia in some patients (Fig. 4) [197, 198]. While the majority of AdV cases are associated with reactivation from latent infection in the recipient, patients can also develop community-acquired upper and lower respiratory tract infections, and there are reports of outbreaks of AdV on HSCT units [199]. Since early detection of AdV in stool and blood predicts disease, especially in pediatric HSCT patients, screening is often utilized to identify patients in whom interventions may reduce risk of disease progression [200–204]. A threshold of $5 \log^{10}$ copies/g feces has been shown to be predictive of developing adenoviremia in one study [200].

Treatment and Prevention

No antiviral agents are currently FDA approved for the treatment of AdV. Ribavirin has not shown clear clinical benefit, despite having activity in vitro [190, 205]. Cidofovir has demonstrated clinical utility using either 5 mg/kg weekly or 1 mg/kg three times a week in combination with probenecid and hydration, but significant nephrotoxicity and bone marrow toxicity limit its long term treatment of severe infections; toxicity also makes routine use of preemptive Cidofovir challenging for pediatric hematopoietic stem cell transplantation patients with persistent or rising AdV viral loads [1, 190, 205, 206]. Brincidofovir, a lipid conjugate of cidofovir available in tablet and liquid form, appears more potent against AdV than cidofovir with less bone marrow and renal toxicity [207]. The one significant toxicity that is associated with Brincidofovir is GI toxicity which often presents as diarrhea and can mimic GVHD [208, 209]. In clinical studies and case series, brincidofovir appears to be associated with antiviral and clinical benefit among HSCT and SOT patients who have been treated [207, 210–212]. Unfortunately, clinical development of the drug for AdV has been suspended although the drug remains available for compassionate use until current supplies of the drug are expended (ClinicalTrials.gov Identified: NCT02596997).

A newer approach using AdV- and multivirus-specific T cells is also being studied in prospective trials (ClinicalTrials.gov Identified: NCT03425526, NCT03378102,

NCT03266627, NCT02532452, NCT02510417, NCT02007356, NCT01945814) [203, 213]. While these agents remain experimental, early studies suggest significant clinical benefit.

Bocavirus and Other Uncommon Respiratory Viruses

Bocaviruses (BoV) are single stranded nonenveloped DNA viruses of the Parvovirinae in the virus family Parvoviridae that are associated with both respiratory and GI infections. Data on prevalence and outcomes in transplant patients are limited, but among those with a documented respiratory pathogen BoV may make approximately 8% of all detected viruses. These same data suggest that BoV patients with active symptoms are more likely to have a co-pathogen when detected [214]. Increased detection among HSCT recipients in stool may be evidence that the GI tract is the more common location for this pathogen [215]. Novel enterovirus (EV), such as EV-D68, are infrequent but are known to lead to clinical illness among transplant patients that varies between mild URI to severe respiratory disease [216].

Infection Control Practices to Protect Transplant Patients from Respiratory Viruses

Transplant centers should develop standard respiratory virus protocols which can be implemented throughout floors, units and clinics where high risk immunosuppressed patients receive care. In order to track such efforts and plan for interventions, Infection Prevention teams should set up surveillance systems among transplant patients, as outbreaks of multiple respiratory virus pathogens have been seen in these populations [14, 217, 218]. Policies should target high level compliance with hand hygiene, and protocols aimed at early identification of patients with active respiratory symptoms. Enhanced Infection Control strategies, for respiratory virus prevention including recommended contact and droplet precautions for many of these pathogens; most centers isolate patients with active respiratory symptoms (Table 1) [189]. Eye protection should be routinely used (face shield or goggles) and consideration for use of N95-level protection is recommended for aerosol-generating procedures (Fig. 5) [189]. Airborne isolation, droplet, and contact isolation (including placement in negative pressure rooms) are required for patients who are diagnosed with MERS-CoV, SARS-CoV, or 2019-nCoV due to high risk for transmission.

Placing patients with active respiratory symptoms into single rooms, masking symptomatic patients on units while outside of their rooms, shifting efforts to rapid molecular testing and implementing early treatment protocols, particularly for influenza, are targeted efforts that can help limit the spread of respiratory viruses. In addition, actively screening those who enter the unit or clinic for respiratory symptoms on arrival can assure early detection and isolation of patients and prevent

Respiratory virus prevention should include personal protective equipment for contact and droplet precautions with a surgical mask (with goggles or face shield to protect eyes), a gown and gloves. Red: For some high-risk invasive procedures, such as bronchoalveolar lavage, interventionalists may want to consider wearing a fit-tested N-95 mask for infections such as Influenza. It is critical to remember that N-95 or Powered Air Purifying Respirator (PAPR) is required for emerging coronaviruses, such as MERS-CoV, SARS-CoV and 2019-nCoV.

Fig. 5 Personal protective equipment for patients with respiratory viruses. Respiratory virus prevention should include personal protective equipment for contact and droplet precautions with a surgical mask (with goggles or face shield to protect eyes), a gown and gloves. Red: For some high-risk invasive procedures, such as bronchoalveolar lavage, interventionalists may want to consider wearing a fit-tested N-95 mask for infections such as Influenza. It is critical to remember that N-95 or Powered Air Purifying Respirator (PAPR) is required for emerging coronaviruses, such as MERS-CoV, SARS-CoV and 2019-nCoV. (Image courtesy of Kyoko Kurosawa)

transmission from caregivers or hospital staff with symptoms [15]. Some centers also restrict access to high-risk units to young children, to help limit possible exposures.

Standardized CDC guidelines recommend contact and droplet precautions (masks with face shields or goggles) for staff caring for patients during the duration of clinical illness [189]. Masking of symptomatic patients can help limit production of secretions and help limit spread of respiratory viruses; however, routine use among patients and staff remains controversial. Many centers consider routine masking during high risk respiratory virus season (November–April), while others target all inpatients regardless of season. Older studies gave conflicting data on the utility of wearing gowns and masks to decrease nosocomial transmission, but two recent studies demonstrate a potential correlation with universal mask use, particularly for providers who come in contact with HSCT patients; albeit nonrandomized longitudinal single center comparison studies may be biased by seasonal variations [219–223]. Routine masking can help address those who are contagious prior to development of symptoms (e.g., influenza) or patients with asymptomatic shedding.

It is also critical for centers to assure staff, caregivers, and visitors avoid entering units or clinics while symptomatic. Efforts to avoid presentism can be critical as health care workers can both be affected by and possibly be linked to outbreaks in such units [15, 224]. Since outpatient care for transplant patients is often through transplant clinics, organized outpatient prevention programs are needed in clinic

spaces where patients cohort together [15]. As discussed above, efforts to assure high-level influenza vaccine compliance and dedicated vaccination campaigns among healthcare workers and families/caregivers can also provide additional protection for high risk patients [225, 226]. Furthermore, dedicated educational efforts targeted towards patients and their caregivers to promote active hand hygiene, appropriate respiratory hygiene, and awareness of the risks of respiratory viruses are important.

Unique Donor and Recipient Issues

Respiratory viruses raise unique concerns of donor-derived infectious disease transmission to the recipient. In general, viremia is not a significant concern for most respiratory viruses, so risk of disease transmission is generally limited to lung donors. As such, lung donors with proven influenza, RSV, hMPV, PIV, or AdV infections are generally excluded from infection. Although current guidelines do not recommend the use of influenza-infected donors and infection has been demonstrated to be transmitted to recipients, some centers will consider the use of these organs with the concurrent use of oseltamivir in the recipient, especially if the donor has received therapy as well [35, 227–229]. Viremia and disseminated infection can occur with novel influenza viruses, including avian viruses, as well as AdV. As such, donors with these viruses generally should not be used. Donors with other respiratory viruses can generally be considered for nonlung donation without significant risk of disease transmission.

In the setting of HSCT, one controversial issue is how to proceed with transplant in recipients who have symptomatic infections at the time of induction. Symptomatic patients with viruses detected pre-HSCT had increased mortality (unadjusted HR 3.5, 95% CI 1.0–12.1, $p = 0.05$); asymptomatic patients with detected virus had no increased mortality risk [37]. As such, most experts recommend testing patients with symptoms of a URI prior to induction and delaying transplant if virus, even hRhV, is detected if feasible [5].

Conclusions

Respiratory viral pathogens remain common complications among SOT and HSCT recipients. Despite progress in improved diagnostics, transplant immunosuppression, and prevention strategies, respiratory viral pathogens are a still major cause of morbidity and mortality among transplant patients, particularly among the most immunosuppressed. Respiratory viruses often present with fever, cough, and upper respiratory symptoms, but classic symptoms seen in normal hosts may be missing in these patients, and they are more likely to progress to life-threatening pneumonia. Only influenza viruses have approved therapies, but emerging trials may provide future options for treatment for other respiratory viruses. Influenza vaccination for patients and their close contacts and infection prevention practices to prevent person-

to-person transmission remain critically important to limit outbreaks and clusters in transplant centers.

Key Points

- Respiratory viruses are common causes of morbidity and mortality among transplant patients.
- Patients with respiratory viruses may present with atypical or less prominent clinical symptoms, despite being at high risk for progression to lower tract disease.
- Awareness and early diagnosis are key to managing and isolating patients with active respiratory viral symptoms.
- All patients with influenza should be treated with antiviral agents, but treating teams should be aware of increased risk for the development of resistance.
- Influenza vaccine should be promoted to all patients, caregivers/family, and staff at transplant centers.
- Aggressive infection prevention policies aimed at early detection, isolation, and treatment of patients is key to prevent outbreaks in transplant populations.

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