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Changing Epidemiology of Respiratory Viral Infections in Hematopoietic Cell Transplant Recipients and Solid Organ Transplant Recipients

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Abstract

Purpose of review—New respiratory viruses have been discovered in recent years and new molecular diagnostic assays have been developed that improve our understanding of respiratory virus infections. This article will review the changing epidemiology of these viruses after hematopoietic stem cell and solid organ transplantation.

Recent findings—Respiratory viruses are frequently detected in transplant recipients. A number of viruses have been newly discovered or emerged in the last decade, including human metapneumovirus, human bocavirus, new human coronaviruses and rhinoviruses, human polyomaviruses, and a new 2009 pandemic strain of influenza A/H1N1. The potential for these viruses to cause lower respiratory tract infections after transplantation varies, and is greatest for human metapneumovirus and H1N1 influenza, but appears to be limited for the other new viruses. Acute and long term complications in hematopoietic and solid organ transplant recipients are active areas of research.

Summary—Respiratory viral infections are frequently associated with significant morbidity following transplantation and are therefore of great clinical and epidemiologic interest. As new viruses are discovered, and more sensitive diagnostic methods are developed, defining the full impact of emerging respiratory viruses in transplant recipients must be elucidated by well-designed clinical studies.

Keywords

Transplantation; human metapneumovirus; bocavirus; coronaviruses; rhinoviruses; polyomaviruses; influenza viruses

Introduction

Respiratory viruses cause potentially severe complications after solid organ (SOT) or hematopoietic stem cell transplantation (HCT). Within the last decade, new respiratory tract pathogens including human metapneumovirus (HMPV), human bocavirus (HBoV), new

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human coronaviruses (HCoV-NL63 and HCoV-HKU1), a new species of rhinovirus (HRV-C), and the KI and WU polyomaviruses (KIPyV and WUPyV) were discovered. However, epidemiologic and clinical characteristics of these viruses have yet to be fully described, particularly in transplant recipients. In addition, a new pandemic strain of influenza A/H1N1 emerged in 2009, which altered the usual seasonality of influenza and contributed to the changing epidemiology of influenza viruses after transplantation.

Advancement in the field of diagnostic virology has been significantly driven by the 2009 influenza A/H1N1 pandemic, as many clinical laboratories developed new molecular assays to diagnose respiratory viruses. Similarly, FDA approval in 2008 of the first multiplex PCR assay for detection of respiratory virus nucleic acids provided the opportunity for many laboratories that did not have expertise in traditional virology to diagnose a large number of viral pathogens [1]. Other multiplex panels and microarrays are being developed or are already available on the market as analyte-specific reagents (ASRs) [2**]. Comparative studies have shown increased sensitivity of real-time PCR assays and of these new multiplex panels compared with traditional viral culture and immunofluorescence testing [1, 3*, 4*].

Respiratory viral infections and outcomes among transplant recipients

Respiratory virus infections (RVIs) may present with a wide range of clinical syndromes among transplant recipients, from asymptomatic infection to severe pneumonia and death. Reported rates of infection and progression to lower respiratory tract disease vary by virus, and are in part dependent on viral detection methodology and study design.

Hematopoietic stem cell transplantation

Table 1 summarizes data from prospective and large retrospective published studies of RVIs among HCT recipients in the last 10 years, and **Figure 1** provides cumulative incidence estimates from a recent prospective study in allogeneic HCT recipients [22]. In general, rates of progression to lower respiratory tract infection and deaths attributable to infection have decreased compared with earlier studies from the previous decade. The reasons for this are likely multifactorial, including less immunosuppressive transplant regimens, improved supportive care, more sensitive diagnostics, and early treatment strategies. For example, some studies did not report pneumonia or progression to pneumonia with influenza or RSV, but did specifically note that early diagnosis and treatment of upper respiratory tract infection appeared to be effective in preventing lower tract disease [13, 16].

In HCT recipients, risk factors for disease progression to pneumonia include infection early after transplantation, graft-versus-host disease, allogeneic HCT, and myeloablative conditioning, although the main factor consistently found to confer increased risk is lymphopenia [7, 8, 14, 15, 18, 30]. These infections, independent of clinical symptoms and the specific virus, are often characterized by prolonged viral shedding, which may contribute to the emergence of antiviral resistance [31]. High rates of nosocomial acquisition have been described in outbreak situations, and co-infection with other viral, bacterial, or fungal agents can complicate infection with respiratory viruses [5, 9, 12, 18, 32, 33]. HCT recipients can potentially develop long-term sequelae including late airflow obstruction after RVIs [34].

Bronchiolitis obliterans syndrome (BOS) is a progressive lung alloreaction characterized by airflow obstruction that can occur following allogeneic HCT or allogeneic lung transplantation [35*]. Pneumonia with respiratory syncytial virus (RSV) or parainfluenza virus (PIV), and even upper respiratory tract infection with PIV, has been identified as a risk factor for BOS [34, 36]. A recent pediatric study in 104 HCT recipients found RVI to be a predictor of idiopathic pneumonia syndrome and BOS [37*]. Only one study has evaluated BOS prevalence and risk factors since 2005 NIH consensus criteria were defined to

standardize the diagnosis of BOS [38*]. In this analysis, the prevalence of BOS after HCT was higher using the new criteria definition, and there was no association with RVI [38*]. Additional investigation using the 2005 criteria will be necessary to further study whether RVI confers risk for the development of BOS.

Solid organ transplantation

Risk factors for disease progression have not been as well identified in solid organ transplant (SOT) recipients. Lung transplant recipients have the highest disease severity and long-term impact related to RVIs, but other organ transplant recipients may also have severe disease and complications. One study of RVIs in 152 SOT non-lung transplant recipients found the most complications among recipients of heart transplants (27.5%), followed by liver (10.7%) and kidney (7.8%) [39**]. A total of 3.7% of RVIs were complicated by pneumonia, and there was no relationship between infection and organ rejection [39**].

Table 2 provides an overview of recent relevant studies of RVIs in lung transplant recipients, highlighting short and long-term consequences. One study using Luminex technology to detect a respiratory virus in 14% of bronchoalveolar (BAL) samples from 52% of lung transplant recipients found an association between RVIs and acute rejection [42**]. Conversely, a similar study using PCR found a respiratory virus in 17% of BAL samples, but acute rejection was not associated with viral detection [46*]. However, detection of respiratory viruses in samples from patients with acute rejection was associated with worse lung function and slower recovery [46*]. Two retrospective pediatric studies showed no association between RVI and acute or chronic allograft rejection, but RVI was independently associated with decreased 1-year survival in one large multicenter cohort [43, 44*]. Thus far, a firm association has yet to be established between RVIs and either acute rejection or chronic allograft dysfunction after SOT, and large prospective studies with comprehensive viral testing and well-controlled multivariable models are needed to further evaluate these consequences.

Newly discovered respiratory viruses

With improved diagnostic methods, the significance of recently discovered respiratory viruses can be elucidated in the transplant population. Although viruses such as RSV and PIV are known to cause severe morbidity and mortality in immunosuppressed patients, we will limit discussion to recent updates regarding viruses that have been newly discovered or emerged in the last 10 years.

Human metapneumovirus

HMPV is most closely related to RSV and can cause both upper and severe lower respiratory tract infections after transplantation [49]. Asymptomatic shedding may potentially occur although this has not been consistently reported [50, 51]. One prospective study found that 40% of HMPV infections in 22 adults with hematologic malignancies progressed from upper respiratory infection to pneumonia, with case-fatality close to 14% [9]. Other studies in HCT recipients have shown pneumonia rates of 28% and mortality rates of 0-4% [19-21*]. Among 163 HCT recipients who underwent BAL for the work-up of pulmonary infiltrates, HMPV was detected in BAL samples from 5 of 163 (3%) patients; 4 of the 5 died with acute respiratory failure highlighting the potential severity of HMPV pneumonia [52].

In SOT recipients, the impact of HMPV has been mainly examined after lung transplantation, although case reports of severe disease have been described following liver and renal transplantation [53-55]. HMPV infection has been found in 4-6% of lung

transplant recipients but prevalence may be higher during nosocomial outbreaks [48*, 56, 57]. One study in the setting of a community outbreak identified HMPV in BAL samples from 9 of 26 (35%) patients; clinical presentation varied from asymptomatic infection to severe disease [56]. Acute allograft rejection was more frequent in the HMPV-infected group than in the non HMPV-infected group (33% vs. 6%, respectively; $p=0.0257$); and overall mortality was also higher (33% vs. 0%, respectively; $p<0.0025$) [56]. Another prospective study found HMPV infection to be as frequent as RSV after lung transplantation, and to cause as much pneumonia and acute allograft dysfunction (63% vs. 72%, respectively), but only RSV was associated with chronic allograft dysfunction at 6 months [41]. Similarly, another group reported that 25% of HMPV infections in lung transplant recipients were associated with acute allograft dysfunction compared with 88% for RSV [48*].

Human Bocavirus

HBoV, a small DNA virus, is a member of the parvoviridae family that was discovered in 2005 from respiratory samples [58]. HBoV has been identified in respiratory, blood, saliva, and stool samples from symptomatic immunocompetent children [59-61]. Seroepidemiologic studies have shown 90% seropositivity by age 5. Although some studies have reported that HBoV is more frequent in patients with respiratory symptoms than in asymptomatic individuals, the role of HBoV in respiratory illness remains controversial [62**].

A number of reports describe disseminated HBoV infection in immunocompromised patients, with virus detection in many sample types, including nasopharyngeal aspirate, serum, feces, and urine [63-65*]. In some patients, significant co-pathogens were also present and the clinical relevance of HBoV detection is unclear [63, 66]. Even detection of HBoV DNA in blood is of uncertain significance and appears to be not uncommon. In one study of 31 immuno-compromised children, HBoV DNA was detected in 2.6% of whole blood samples from 4 patients without respiratory symptoms [67]. Preliminary results of a large prospective study of HCT recipients found a day 100 cumulative incidence of HBoV detection in respiratory samples of 2.1% [26]. In this cohort, HBoV was also detected in 5 serum samples from 2 patients [26]. No patients had pneumonia or died, and respiratory symptoms were mild or absent when HBoV was detected, even in pediatric patients and when the quantity of viral shedding was high [26].

Fewer data are available regarding HBoV after SOT. In a study including 53 lung transplant recipients, 86 symptomatic and asymptomatic BALs were all negative for HBoV; in another study, HBoV was detected in BAL samples from 4 of 66 adults with respiratory insufficiency after transplantation (2 HCT, 1 lung, 1 liver) [68, 69]. One large prospective study of lung transplant recipients found 5 nasopharyngeal swabs but none of the simultaneous BAL samples to be positive for HBoV [46*]. In summary, additional data are needed to determine whether HBoV plays a pathogenic role after hematopoietic or solid organ transplantation.

Coronavirus

HCoVs are RNA viruses, members of the coronaviridae family. HCoV 229E and OC43 have long been known to be agents of the common cold. HCoV NL63 and HKU1 were discovered in 2004, and are associated with upper and lower respiratory tract infections in infants and older adults [70, 71].

Data on HCoVs in HCT recipients are limited. A recent report describes day 100 incidence for these 4 HCoVs of 11% (22 patients) among 215 allogeneic HCT recipients; 3 patients

had prolonged shedding for more than 12 weeks [22**]. Interestingly, in this study, HCoV infection was not associated with the presence of respiratory symptoms. HCoV-NL63 was detected in a BAL sample from 1 patient who died of respiratory failure, who also had influenza A and HMPV detected simultaneously. Four cases of lower respiratory tract infections have been described including a fatal HCoV-NL63 infection in an adult HCT patient [72, 73*, 74]. Thus, HCoVs may occasionally cause lower respiratory tract disease after HCT, but the overall progression rate seems to be very low.

HCoVs have been identified in SOT recipients but clinical outcomes have not been specifically investigated. In a study of mostly hospitalized children with respiratory symptoms, 5 children with hematologic malignancies and one kidney transplant recipient had HCoV detected as the sole respiratory pathogen [75]. In a prospective study of 279 adults hospitalized for respiratory disease, BALs were tested for the 4 non-SARS HCoVs and found positive for 29 patients, 12 of whom received a lung transplant [76]. Most patients had no other identified etiology for their respiratory symptoms. Other studies of lung transplant recipients found HCoVs in 2-15% of samples but no specific analysis of symptoms or outcomes was performed [40, 42**, 46*]. Further study is needed to understand the pathogenesis of HCoVs and the immune response in immunosuppressed SOT recipients.

Rhinovirus

HRVs are RNA viruses and members of the picornaviridae family. They can be divided into 3 groups (A, B and recently described C) and further subdivided into >100 subtypes. The new HRV-C group has been associated with higher rates of pneumonia and more asthma exacerbations in children; however, others have found that the illness severity for HRV-C is comparable to that of HRV-A [77-79].

In HCT recipients, rhinovirus has been described as a possible cause of LRTI and was found in BALs from 8% of 77 patients, although each case had significant co-pathogens [80, 81]. Two fatal cases have been reported with mortality directly attributed to RHV infection [82]. Of 28 pediatric patients with hematologic malignancy or HCT infected with HRVs, only one, infected with HRV-C, died of respiratory insufficiency [83]. In a large prospective study of 215 allogeneic HCT recipients, HRV day 100 cumulative incidence was 22.3% (45 patients); 22% of HRV-infected patients had a concurrent second respiratory virus [22**]. Median duration of viral shedding was 3 weeks, but 6 patients shed HRV for more than 3 months. A positive HRV sample within the last week was significantly associated with multiple respiratory symptoms. Progression to LRTI was uncommon compared with other respiratory viruses, but 2 patients were positive for HRV in BAL and subsequently died [22**].

A prospective study of 68 lung transplant recipients identified rhinovirus in BAL samples of 10 (14.7%) patients. Three patients were reported with persistent RHV shedding over 12 months. All three had allograft dysfunction and two died [84]. Another study found an HRV incidence of 18% among 67 adult lung transplant recipients [83]. The presence of low HRV amounts in BAL was not associated with clinical symptoms, which by contrast were consistently observed in the presence of high viral load [83]. Studies are needed to investigate risk factors for HRV disease severity in transplant recipients, and particularly for associations with HRV-C infection.

Human polyomaviruses, WU and KI

KIPyV and WUPyV, two new human polyomaviruses were described simultaneously in 2007, both detected from respiratory specimens [85, 86]. Seroprevalence for children and

adults is approximately 55-60% for both viruses, but no symptoms have yet been clearly associated with these viruses in the immunocompetent population [87].

Few data are available in transplant recipients, but it is suspected that these viruses establish latency, with reactivation under immunosuppression, similar to other polyomaviruses. In 31 HCT recipients with 126 serial nasopharyngeal aspirates, 2 samples were positive (one for each virus) without associated symptoms [28]. Another study reported a higher incidence of KiPyV of 17.8% in respiratory samples from 45 HCT recipients with acute respiratory illness; WUPyV was not detected [27*]. Preliminary results of a prospective study of 196 HCT recipients found KIPyV and WUPyV in nasal wash samples in 18.4% and 7.1% of patients, respectively. Although some positive episodes lasted many weeks, and the viruses were detected in high copy numbers in some patients, detection was not associated with the presence of serious respiratory symptoms in this cohort [29].

In a cohort of 24 lung transplant recipients with 53 BAL samples, KIPyV and WUPyV were detected in 6 (25%) and 7 (29.2%) patients, respectively, all with 1 positive sample, and an association was observed between the presence of either virus and acute rejection [88*]. Whether these viruses are a trigger for rejection, or whether rejection episodes lead to virus reactivation, remains to be clarified. Further investigation is needed to determine the significance of these viruses following transplantation.

Pandemic influenza A/H1N1 and transplant recipients

Since the emergence of the 2009 pandemic influenza A/H1N1 (pH1N1) strain, comparisons of virulence and transmissibility between seasonal H1N1 and pH1N1 in immunocompetent patients has not demonstrated significant differences [89-91]. In HCT recipients, the incidence of seasonal influenza has been reported between 1-4%, and can be significantly higher in outbreak situations [5-7, 12, 13, 92**]. Pandemic H1N1 has been described in HCT recipients and oncology patients from several studies and case series (**Table 3**). Case-fatality rates have ranged from 0 to 38% in various cohorts [95, 98-102, 104, 105].

Factors associated with severe disease included profound lymphopenia, increasing age, preexisting lung disease, bacterial co-infection, and delayed antivirals >48 hours after initial symptoms [93, 96, 114-119]. A recent study in HCT recipients found that, although there was no difference in mortality, pH1N1 infection was significantly associated with pneumonia, hypoxemia, and prolonged viral shedding compared with seasonal influenza A [93]. Importantly, in a multivariable model, even delayed administration of antivirals was shown to be protective in preventing pneumonia, and corticosteroids (< 1 mg/kg) were associated with a reduced risk for mechanical ventilation [93]. One case report describing the detection of influenza RNA in plasma of a patient with respiratory failure suggests that this may be a biomarker for severe disease [114].

Table 3 highlights studies describing pH1N1 in SOT recipients. Many case reports have highlighted the varied severity of pH1N1 disease among specific solid organ recipients [120-125]. In general; death rates appear consistently lower for SOT than HCT recipients, although one report describes significant mortality after lung transplantation [110]. Delayed antiviral therapy (>48 hours) and diabetes mellitus have been identified as risk factors for poor outcomes [108**, 112]. The largest SOT study included 237 patients from 26 centers with kidney, liver, lung, heart and other organ allograft transplantation [108**]. Adults had more risk of pneumonia and death than children, but children were significantly more likely than adults to receive antiviral therapy within 48 hours [108**]. In this study, complication rates were similar between lung and other organ transplant recipients.

Antiviral resistance and pH1N1

Influenza resistance to antiviral drugs is an important epidemiologic and clinical concern [31, 126, 127]. Cases of resistant pH1N1 quickly emerged during the 2009 pandemic [128]. Nearly all resistant strains had the same H275Y substitution in the neuraminidase protein, and this mutation was observed to develop within 48 hours of exposure to oseltamivir [129-131*]. Although oseltamivir resistance rates were estimated as <1% in the general population, resistance may have developed in up to half of HCT recipients, as indicated by studies in which serial positive influenza samples were tested and found to develop the H275Y mutation after initiation of therapy [105, 132, 133*]. A variety of outcomes among HCT recipients with oseltamivir-resistant pH1N1 have been described, from benign upper respiratory infection to severe and fatal pneumonia [133*]. Community and nosocomial transmission of H275Y-mutant pH1N1 has been described in immunocompetent and immunocompromised populations [134*, 135*].

Conclusion

Newly discovered respiratory viruses, such as HMPV, HBoV, and human polyomaviruses, and new viruses such as 2009 pandemic influenza A/H1N1, cause a spectrum of illness in patients after transplantation. With advancements in molecular diagnostics, data are rapidly emerging regarding the overall morbidity associated with these infections. HMPV appears to cause a similar spectrum of disease as RSV, with the potential for severe pneumonia. Recent studies suggest that lower respiratory tract disease appears to be uncommon, although possible, with coronavirus and rhinovirus, and even rarer with bocavirus and polyomavirus infections. Further study is needed to determine long-term sequelae of respiratory virus infections after transplantation, and to define the clinical manifestations associated with new viruses such as HBoV, KIPyV, and WUPyV. Delayed antiviral therapy and lymphopenia were consistently associated with severe disease from 2009 pH1N1, and pH1N1 seemed to cause increased disease severity compared with seasonal influenza A in HCT recipients. The development of oseltamivir-resistant pH1N1 in immunocompromised patients is of concern, and highlights the need for optimized management with early and aggressive therapy and close monitoring. Well-designed studies are essential to fully characterize the epidemiology and long-term sequelae of respiratory viruses so that treatment and prevention strategies can be developed for highly immunosuppressed transplant recipients.

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Key points

- New molecular diagnostic assays greatly improve our understanding of the impact of respiratory virus infections in hematopoietic stem cell and solid organ transplant recipients.
- Human metapneumovirus infections have similar outcomes to RSV infection in hematopoietic stem cell transplant recipients, including potentially severe and fatal pneumonia.
- Rhinovirus and coronavirus infections are very frequent in transplant recipients; lower respiratory tract disease can occasionally occur but is uncommon.
- Human bocavirus and the new human polyomaviruses, WUPyV and KiPyV, are present in the respiratory tract of transplant recipients but their significance in respiratory illness and overall clinical impact are still unknown.
- Pandemic H1N1 has the potential for rapid emergence of oseltamivir resistance, and is associated with significant morbidity in highly immunocompromised transplant recipients, particularly in patients with lymphopenia and delayed antiviral therapy.
- The association between respiratory virus infections and acute or chronic allograft rejection in lung transplant recipients remains controversial.

Figure 1. Cumulative incidence of first respiratory virus infection episodes in 215 allogeneic HCT recipients

At 100 days post-transplantation, the cumulative incidence estimates and 95% confidence intervals were 22.3% (16.5–28.1%) for HRVs; 11.1% (6.7– 15.4%) for HCoVs; 6.5% (3.1– 10.0%) for RSV and PIV (1, 2, 3 or 4); 5.5% (2.3–8.6%) for HAdV, 2.6% (0.3–4.8%) for influenza A or B; and 1.5% (0–3.1%) for HMPV.

HRV – Human rhinoviruses, HCoV– Human coronaviruses, RSV – Respiratory syncytial virus, PIV – Parainfluenza virus, HAdV – Human adenoviruses, Flu – Influenza, HMPV – Human metapneumovirus

Table 1

Respiratory virus infections among cohorts of asymptomatic and/or symptomatic patients with hematopoietic stem cell transplantation and/or hematologic malignancy.

Virus (References)	Study design of selected references	Laboratory methods used for viral testing ^a	Incidence ^b (%)	Proportion of LRTI ^c (%)	URTI progression to LRTI ^c (%)	Deaths associated with LRTI ^c (% of LRTI)	Deaths related to overall infection ^d (% total positive)
Influenza virus [5-10**, 11-14]	Prospective & retrospective	Traditional or PCR	1-4 ^e	7-44	7-35	15-28	0-15
Respiratory syncytial virus [5, 6, 8-10**, 11, 12, 14-17]	Prospective & retrospective	Traditional or PCR	1-12	17-70	18-55	7-33	0-18
Parainfluenza [5, 6, 8-10**, 11, 14, 15, 18]	Prospective & retrospective	Traditional or PCR	0.2-18	12-50	13-43	12-50	0-14
Metapneumovirus [5, 9, 10**, 19-21*]	Prospective & retrospective	PCR	3-7	27-41	21-40	33-40	0-14
Adenovirus [5, 6, 9, 22**, 23]	Prospective	Traditional or PCR	1-19 ^f	36-42	22-25	40-50	0-18
Rhinoviruses [5, 22**]	Prospective	Traditional or PCR	2-22		<5	NA	<5
Coronaviruses [22**]	Prospective	PCR	11	<5	<5	NA	<5
Bocavirus [24-26]	Prospective	PCR	1-3	NA	NA	NA	NA
KI polyomavirus [27*-29]	Prospective	PCR	3-22	NA	NA	NA	NA
WU polyomavirus [27*-29]	Prospective	PCR	0-7	NA	NA	NA	NA

LRTI: lower respiratory tract infection; URTI: upper respiratory tract infection; NA: Not available;

^aTraditional laboratory methods include viral culture and direct fluorescent antibody testing

^bIncidence reported when available. In some cases, the frequency of respiratory virus infection is reported over the total observation period.

^cStudies that did not report lower respiratory tract disease cases or progression rates were not included in the results.

^dIncludes all studies, including those that did not report cases of lower respiratory tract disease.

^eMay be higher during outbreaks [5,6,12,13].

^fReflects detection in respiratory samples, and not other possible sites of disseminated adenovirus infection.

Table 2

Outcomes associated with respiratory virus infections in lung transplant recipients

Author (Ref)	Study period	Population; Number of patients; Study design	Symptoms present with RV testing	Sample type	Laboratory testing method	RV detection (proportion positive)	Comments and outcomes associated with RV1
Gottlieb [40]	2005-2007	Adult N=388 Prospective	Symptomatic and asymptomatic	NPS and BAL	IF, culture, PCR (PCR for 40% of pts)	8% of patients	<ul style="list-style-type: none"> • BOS at 1 year: 27% RV-positive vs 9% RV-negative patients (P=0.01) • Predominance of paramyxoviridae (RSV, PIV, HMPV) • No patient with HRV or HCoV developed BOS
Hopkins [41]	2003-2006	Adult N=89 Prospective	All symptomatic	NPS and BAL	IF, HMPV PCR	9% of RTI	<ul style="list-style-type: none"> • Acute graft dysfunction: 63% of HMPV-infected vs 72% of RSV-infected patients • Chronic rejection in patients with acute graft dysfunction: 0% of HMPV-infected vs 38% of RSV-infected patients • No testing for HRV or HCoV
Kumar [42**]	2003-2005	Adult N=93 Prospective	Symptomatic and asymptomatic	BAL only	Luminex, IF, culture	52% of patients; 14% of samples	<ul style="list-style-type: none"> • Biopsy-proven acute rejection or significant decrease in FEV1: 33% of RV-positive vs 7% of RV-negative patients (P=0.001) • Predominance of HRV, HCoV, and PIV
Liu [43]	1988-2005	Pediatric N=576 Retrospective	All symptomatic	NPS, BAL, sputum, tracheal aspirate	Culture, IF, PCR (mostly culture)	14% of patients	<ul style="list-style-type: none"> • No association with acute or chronic rejection • RVI associated with decreased 1-year survival (HR 2.6) • Predominance of HRV, ADV, PIV, and RSV
Liu [44*]	2002-2007	Pediatric N=55 Retrospective	All symptomatic	NPS, BAL, sputum, tracheal aspirate	Culture, IF, PCR (mostly culture)	51% of patients	<ul style="list-style-type: none"> • No association with chronic rejection or mortality • Predominance of HRV, ADV, PIV
Mistone [45]	1999-2000	Adult N=50 Prospective	All symptomatic	NPS, BAL	Culture, PCR, serology, antigen tests	34% of patients	<ul style="list-style-type: none"> • No association with acute or chronic rejection • Predominance of RSV and influenza
Soccal [46*]	2003-2006	Adult N=77 Prospective	Symptomatic and asymptomatic	NPS, BAL	PCR	29% of NPS, 17% of BAL	<ul style="list-style-type: none"> • No association of RVI with biopsy-proven acute rejection • 66% of viruses in BAL were HRV or HCoV

Author (Ref)	Study period	Population; Number of patients; Study design	Symptoms present with RV testing	Sample type	Laboratory testing method	RV detection (proportion positive)	Comments and outcomes associated with RVI
Vilchez [47]	1990-2000	Adult N=454 Retrospective	All symptomatic	BAL only	Culture	5% of patients PIV-positive	<ul style="list-style-type: none"> • 82% of PIV-infected patients developed biopsy-proven acute rejection • 32% of PIV-infected patients developed chronic rejection
Weinberg [48*]	2005-2007	Adult N=60 Prospective	All symptomatic	NPS, BAL	PCR, culture	46% of RTI	<ul style="list-style-type: none"> • Clinically-diagnosed acute rejection: 45% of RV-positive vs 21% of RV-negative patients (P=0.002) • Chronic rejection: 25% of RV-positive vs 18% of RV-negative patients • Predominance of PIV, influenza, RSV

NPS: nasopharyngeal specimen; BAL: bronchoalveolar lavage; IF: immunofluorescence, includes direct fluorescent antibody and enzyme immunoassay; RTI : respiratory tract infection based on symptoms; RVI : respiratory virus infection based on positive detection; FEV1 : forced expiratory volume in 1 second; BOS : bronchiolitis obliterans syndrome

Table 3

Summary of epidemiologic studies of pandemic 2009 influenza A/H1N1 among populations of hematopoietic stem cell transplant and solid organ transplant recipients.

Author (Reference)	Population	Number of patients	LRTI (%)	Overall deaths (%)	Deaths related to H1N1 (%)
A. Hematopoietic stem cell transplant recipients					
Choi [93]	HCT	18	56	17	17
Ditschkowski [94]	HCT	10	NR	20	20
George [95]	HCT	13	39	31	15
Ljungman ^a	HCT	286	33	9	6
Protheroe [96]	HCT	60	35	23	13
Rihani [97]	HCT	39	21	5	5
Taplitz [98]	HCT	27	52	43	22
Caselli [99]	Cancer, HCT (pediatric)	62	16	3	0
Cost [100]	Cancer, HCT (pediatric)	30	10	3	3
Garland [101]	Cancer, HCT	13	54	38	31
Lalayanni [102]	Cancer, HCT (H)	8	63	38	25
Liu [103]	Cancer, HCT	9 Cancer 18 HCT	44 33	22 6	22 6
Redelman-Sidi [104]	Cancer, HCT	24 Cancer 21 HCT	8 29	4 0	0 0
Tramontana [105]	Cancer, HCT (H)	16 Cancer 16 HCT	44 69	6 38	6 38
Vigil [106]	Cancer, HCT	69	24	11	NR
A. Solid organ transplant recipients					
Fox [107]	Lung transplant	10	40	0	0
Kumar [108**]	SOT	154 Adults 83 Children	39 16	7 0	6 0
Low [109]	SOT (H)	22	23	5	5
Ng [110]	Lung transplant	24	75	25	21
Ridao-Cano [111]	Renal transplant	13	23	0	0
Smud [112]	SOT	77	49	8	8

Author (Reference)	Population	Number of patients	LRTI (%)	Overall deaths (%)	Deaths related to H1N1 (%)
Vazquez-Alvarez [113]	Heart transplant (pediatric)	11	NR	0	0

H: Hospitalized cohort; ILI: Influenza-like illness; LRTI: Lower respiratory tract infection; NR: Not reported

^aUnpublished data