Respiratory Viral Infections in Solid Organ and Hematopoietic Stem Cell Transplantation

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KEYWORDS

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

KEY POINTS

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

INTRODUCTION

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

GENERAL EPIDEMIOLOGY AND RISK FACTORS

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

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

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

GENERAL OUTCOMES AND COMPLICATIONS

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

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

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

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