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Respiratory Viral Infections in Transplant and Oncology Patients

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KEYWORDS

• Hematopoietic stem cell transplant • Solid organ transplant
• Influenza • Cancer

Respiratory viral infections (RVI) are a significant cause of morbidity and mortality in the immunocompromised host. In the last two decades, there has been significant advancement in the epidemiology and laboratory diagnosis of RVI with discoveries of new pathogens, such as bocavirus, KI and WU polyomaviruses, and novel coronaviruses (CoV). In addition, the clinical consequences of many respiratory viruses in the immunocompetent and immunocompromised host continue to be studied. Many therapeutics have also now become available, although their efficacy in transplant recipients remains uncertain. This section describes the current knowledge of RVI as it relates to solid organ transplant (SOT), hematopoietic stem cell transplant (HSCT), and oncology settings.

EPIDEMIOLOGY, TRANSMISSION, PATHOGENESIS

Respiratory viruses that are commonly recognized in the human host including the transplant recipient are influenza A and B, parainfluenza 1 to 4, respiratory syncytial virus (RSV), and adenovirus (AdV). Other viruses including CoV, enteroviruses, rhinovirus, and human metapneumovirus (hMPV) have gained importance in the past decade. In addition, bocavirus, parvovirus 4 and 5, polyomaviruses, and mimivirus have also been described, although there is limited literature in the transplant setting for these viruses. The prevalence of respiratory viruses in a given season depends on exposure, virulence of the virus, the types of circulating viruses, and detection methods used. Most respiratory viruses are transmitted by direct contact or aerosolized droplets.[1] Incubation periods range from 1 to 10 days, although those for newly described viruses (bocavirus, parvovirus 4 and 5, and mimivirus) are unknown.

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The incidence of RVI following HSCT has ranged from 3.5% to 29%.[2–5] Older studies are more likely to underestimate the incidence, however, because the RVI detection methodologies used were generally less sensitive and limited to fewer viruses.

The outcome of RVIs in HSCT recipients depends on several factors including whether the transplant was myeloablative versus nonmyeloablative, the presence of lymphopenia, and intensity of immunosuppression. In one series from a large cancer center, 343 RVIs in patients with hematologic malignancy and HSCT were identified over a 2-year period.[6] Progression to lower respiratory infection occurred in 35% of patients and did not depend on the type of infecting virus. Risk factors for progression included an underlying diagnosis of leukemia, age greater than 65 years, and severe neutropenia or lymphopenia. Lymphopenia as a risk factor in allogeneic and autologous HSCT has also been identified in other studies.[3,4] Lower tract infection is more common in those receiving myeloablative conditioning than in nonmyeloablative transplants.[7] Aside from direct morbidity and mortality, RVI may also be a risk factor for the development of invasive aspergillosis in allogeneic HSCT[8]; whether this represents an overall immunosuppressed state needs further study.

The incidence of RVI in SOT recipients is 7.7% to 64%.[9–13] Lung transplant recipients seem to have a greater frequency of RVI than other SOT recipients, likely because of the direct communication of the allograft with the environment and the poor immune response in the allograft. The risk of progression to lower tract disease is not well defined; however, it is likely dependent on time posttransplant and intensity of immunosuppression and the type of transplant. Because of poor immune responses in the allograft, lung transplant recipients likely have a greater risk of lower tract disease.

CLINICAL PRESENTATION AND COMPLICATIONS

There is significant overlap in the symptoms of respiratory viruses and it is difficult to distinguish clinically which respiratory virus is causing symptoms in a given patient. Common symptoms of upper respiratory tract illness include malaise, sore throat, coryza, cough, and fever. The presence of dyspnea may signal lower respiratory tract infection (LRTI) by the virus or bacterial superinfection. Chest radiograph may show diffuse interstitial infiltrates but can also show airspace disease. The most common chest CT finding is ground-glass attenuation; centrilobular nodules 3 to 10 mm in size including a tree-in-bud appearance can also be seen. Airspace consolidation can be present in up to one third of patients on CT chest scan.[14] A ''crazy-paving'' pattern has been described on high-resolution chest CT scan, which consists of interlobular and intralobular septal thickening superimposed on an area of ground-glass opacification. Although not specific for RVI, one study found that 70% of patients with this pattern had viral pneumonitis.[15] Progression from upper tract to lower tract infection can occur, although the incidence is quite variable. This is likely caused by the varying immunosuppressives, timing of infection from transplant, and other underlying diseases. Asymptomatic shedding of respiratory viruses has been shown to occur in both solid organ and HSCT recipients.[16] Transplant recipients have been postulated to be ''superspreaders'' of virus given the high viral loads of respiratory viruses found in respiratory secretions.[17] In addition, prolonged shedding of respiratory viruses is often noted. Transplant recipients may serve as sentinals for a given infection in the community, because they may be the first to become infected with an emerging virus signaling the beginning of an outbreak.

LABORATORY DIAGNOSIS

Traditionally, the laboratory diagnosis of respiratory viruses has been difficult and limited to relatively few viruses. In the past, acute and convalescent sera have been used to diagnose viral infections. In the transplant or oncology patient, however, humoral responses to viral infections are often not detectable or significantly delayed. Virus isolation in cell lines has also been used. Tube culture results are generally available in 8 to 10 days and lead to a delayed diagnosis. Direct fluorescent antibody (DFA) testing using a nasopharyngeal aspirate or swab is available in most clinical laboratories and provides a rapid result in 3 to 5 hours. This test is commonly limited, however, to influenza A and B; parainfluenza 1, 2, and 3; RSV; and AdV. It is also limited in its sensitivity of detection. With the recognition of other viruses, such as CoV (including severe acute respiratory syndrome [SARS]–associated CoV), hMPV, and rhinovirus as significant pathogens leading to disease, nucleic acid amplification testing (NAT) has taken a leading role in the diagnosis of RVIs. Multiplex polymerase chain reaction (PCR), microbead detection, or DNA microarrays have the capability of searching for several viruses in one test. Molecular detection of several respiratory viruses simultaneously using NAT-based assays is now being used in several clinical laboratories.[18] The detection and study of some viruses, such as human bocavirus, is dependent on NAT. In general, NAT testing is more sensitive than other methods.[19] One issue with such sensitive methods is the detection of asymptomatic viral infection. One study in HSCT recipients tested 688 nasal wash specimens from 131 patients in the first 100 days posttransplant by conventional DFA and PCR.[2] PCR significantly increased the yield of viruses; however, those viruses only detected by PCR had lower viral loads, many of which represented asymptomatic infections. Coinfection with two or more respiratory viruses may also be detected using such sensitive methods; in this case, it may be difficult to determine toward which virus treatment should be directed.

Influenza

Influenza is a negative sense, single-stranded RNA virus of the Orthomyxoviridae family. Influenza viruses undergo antigenic changes at a high frequency. Smaller antigenic changes are termed ‘‘antigenic drift’’ and produce minor variations in surface glycoproteins, such as substitutions in antibody-binding sites that can result in reinfection. Larger antigenic shifts can occur because of reassortment of genes, however, when two influenza viruses simultaneously infect one host. Antigenic shift can also occur as a result of direct mutation that allows for cross-species infection.

Complications of influenza infection seem to be common in HSCT and SOT populations. There seems to be a relatively high rate of progression to viral pneumonia in some reports, especially in lung transplant recipients and HSCT recipients.[20,21] In one study of organ transplant recipients over a 10-year period, the rate of influenza infection ranged from 2.8 cases per 1000 person years (liver transplant) to 41.8 cases per 1000 person years (lung transplant).[21,22] Complications including secondary bacterial pneumonia (17%) and extrapulmonary complications, such as myocarditis and myositis, were observed. This is in contrast to a report by Ljungman and colleagues[22] on 12 influenza cases in renal transplant recipients. Only one patient developed viral pneumonia and one had bronchitis. The remaining 10 patients recovered without complications. Severe disease has been commonly reported in HSCT recipients with attributable mortality rates as high as 43%.[20] A large review of 62 HSCT recipients with influenza showed that pneumonia developed in those who were infected sooner posttransplant and had lymphopenia.[23] In patients not treated with antivirals, 18% progressed to pneumonia. Shedding was longer in those on

steroid doses of greater than 1 mg/kg/d and it was suggested that oseltamivir may decrease this shedding. More recently, in a review of 19 patients with influenza, none with upper respiratory tract infection (URTI) progressed to LRTI and there was no mortality, although most patients were treated with oseltamivir. Shedding was present for a median of 12 days and correlated inversely with the presence of lymphopenia.[24] Lymphopenia (absolute lymphocyte count $\leq$200 cells/mL) was a specific risk factor identified for progression to influenza pneumonia.[6] Influenza A and B infection following autologous HSCT have also been associated with mortality.[4] In pediatric cancer patients, influenza was also an important cause of morbidity.[25]

The diagnosis of influenza can be made using several methods: serology, virus culture, DFA, and PCR. A nasopharyngeal swab or lower respiratory sampling can be used.

Therapy of influenza A or B with neuraminidase inhibitors (oseltamivir or zanamivir) is the mainstay of management (**Table 1**). In immunosuppressed hosts, oseltamivir can be started at any time during the course of the illness at an oral dose of 75 mg twice daily for five days. A dose of 150 mg twice daily has also been suggested by some experts, as has extending the therapeutic course for

Table 1
Suggested therapy for RVIs in transplant and oncology patients

Respiratory Virus	Diagnosis	Isolation Precautions[1]	Suggested Management
Influenza	DFA, NAT, serology, culture	Droplet Airborne for pandemic strains	Oseltamivir, 75–150 mg po bid $\times$ 5–10 d Zanamivir, 2 puffs bid $\times$ 5 d Amantadine, 100 mg bid Rimantadine, 100 mg bid
RSV	DFA, NAT	Droplet and contact	Ribavirin IVIg or RSV-Ig Palivizumab
Parainfluenza	DFA, NAT	Droplet	Ribavirin (aerosolized, po, IV)
Adenovirus	DFA, NAT	Droplet	Cidofovir, 3 mg/kg IV once weekly Ribavirin? IVIG
Coronavirus	NAT	Droplet Airborne for SARS-CoV	Supportive care Ribavirin (for SARS-CoV)
Human metapneumovirus	NAT	Droplet	Ribavirin? Supportive care
Rhinovirus	NAT	Droplet	Supportive care
Parvovirus B19	NAT, serology	Droplet	IVIG
Bocavirus	NAT	Droplet	Supportive care
WU/KI viruses	NAT	Droplet	Supportive care

Not all diagnostic tests are available in all clinical laboratories. Some diagnostic tests are primarily used for research purposes.

Doses of antivirals are standard doses for adults with normal creatinine clearance.

Abbreviations: DFA, direct fluorescent antibody; IVIG, intravenous immunoglobin; NAT, nucleic acid amplification testing; RSV, respiratory syncytial virus; SARS-CoV, severe acute respiratory syndrome associated coronavirus.

patients who remain symptomatic after 5 days. Zanamivir is a sialic acid analog that is available as an inhaled preparation and has been shown to be effective against influenza A in the general population when started within 48 hours of symptom onset.[26–28] Zanamivir has also been used successfully in HSCT recipients with influenza A or B.[29] The recommended dose of zanamivir is 10 mg (or two puffs) twice daily for 5 days. In the study by Johny and colleagues,[29] zanamivir was used until viral excretion ceased. Concerns have also been raised regarding the pulmonary bioavailability of zanamivir in immunocompromised patients.[30] Future clinical trials in this area and in the use of combination antivirals for the transplant population are needed. Resistance to oseltamivir has developed in a large proportion of influenza A–H1N1 viruses and some influenza A–H5N1 and influenza B viruses.[31] Conversely, H3N2 viruses have a high rate of resistance to zanamivir but remain susceptible to oseltamivir. The M2 inhibitor class (amantadine and rimantadine) can also be used in transplant recipients with influenza A but their use is limited because of side effects and antiviral resistance.[32] Ribavirin also has in vitro activity against influenza and could potentially be used in combination with other antivirals.[33,34] In addition, novel compounds, such as peramivir and combination antiviral therapies are also being studied in clinical trials.

The most commonly used trivalent inactivated subunit vaccine is revised annually and contains two influenza A and one influenza B strains. The vaccine is recommended for all transplant recipients, transplant candidates, their household contacts, and health care workers in contact with immunocompromised patients.[35–37] The immunogenicity of the vaccine is variable depending on the population studied. In HSCT recipients, vaccine responses are absent before 6 months posttransplant and it is recommended to wait until 6 months to administer the vaccine.[36] Similarly, in SOT recipients, vaccine can be administered any time after 3 to 6 months posttransplant. There are no data to support acute or chronic rejection as a consequence of vaccination in this population. The intranasal preparation is a live attenuated vaccine and is not recommended for the immunocompromised population.

Pandemic influenza is of particular concern in transplant and oncology centers. The current pandemic of swine origin H1N1 virus likely arose from cross-species adaptation of the virus from swine-to-human and successful human-to-human transmission. At the time of this writing, more than 168,000 persons were reported infected and more than 1150 deaths worldwide. Risk factors for severe disease include infants less than 1 year, underlying lung disease, diabetes, and pregnancy. Immunosuppressed patients are also at risk for severe disease, although there are no specific data on transplant or oncology patients; however, as greater knowledge becomes available, risk factors for severe disease or death will be more clearly defined. The impact on transplant programs in part depends on the virulence of the virus and the amount of resources required to manage critically ill patients.

Parainfluenza

Parainfluenza viruses (PIV) comprise a group of four serotypes (1–4) of single-stranded RNA paramyxoviruses. PIV occurs year-round and can cause a number of clinical syndromes including croup and bronchiolitis, the common cold, and pneumonia. In transplant recipients, the spectrum of PIV ranges from asymptomatic to respiratory failure and death. In a large retrospective review of HSCT patients in the 1990s, those with upper respiratory infection survived but those with pneumonia had a universal mortality despite ribavirin therapy.[38] Asymptomatic parainfluenza infection has been

detected in a surveillance study of HSCT patients and could be a possible mode of transmission in outbreaks.[5,39] PIV-3 in particular has caused nosocomial outbreaks on HSCT units as a result of person-to-person transmission.[39–44] Mortality rates up to 33% are seen in outbreak situations.[42,44] Other syndromes in transplantation associated with PIV include Guillain-Barré syndrome, acute disseminated encephalomyelitis, and parotitis.[45–47] In lung transplant recipients, the incidence of PIV has been estimated to be 5.3% of patients.[48] LRTI can occur in 10% to 66%. Bronchiolitis obliterans syndrome (BOS) can be a long-term consequence of this infection. Radiologic features can include peribronchial small nodules of less than 5 mm diameter on CT chest.[49] Intravenous and oral ribavirin have been used for therapy of infection in transplant recipients with conflicting results.[50–54]

Respiratory Syncytial Virus

RSV is possibly the most important cause of morbidity and mortality of all respiratory viruses affecting the transplant recipient. RSV causes severe lower respiratory tract disease in transplant patients. In one study risk factors for the progression of RSV were lack of RSV-directed antiviral therapy and age.[6] In pediatric studies, both lymphopenia and age less than 2 years have also been shown to be an important risk factors for progression.[55] RSV-related mortality in children treated for acute myeloid leukemia was 10%.[56] Diagnosis of RSV can be performed using standard DFA technique, culture, or NAT. The xTAG RVP assay has been reported to have a sensitivity of 100% for RSV detection with specificity ranging from 97% to 99%.[57] The primary therapy that has been most studied is aerosolized ribavirin given 2 g three times a day or 6 g over 18 hours. The logistical and cost issues with aerosol therapy limit its use in many centers. A negative pressure room must be used. The drug is teratogenic to those in close contact. A small randomized trial of aerosolized ribavirin versus standard care for upper respiratory RSV infection in HSCT recipients showed a decrease in viral load in the ribavirin arm but no difference in the progression to pneumonia.[58] Oral ribavirin has been suggested as an alternative. In a study of five lung transplant recipients, oral ribavirin and pulse solumedrol (10–15 mg/kg/d for 3 days) were given for RSV LRTI and was well-tolerated and seemed to be effective.[59] In a case series of 18 lung transplant recipients with RSV given intravenous ribavirin with corticosteroids, no mortality was seen although hemolytic anemia occurred.[60] Palivizumab is a monoclonal antibody specific for RSV. It has also been used in conjunction with antivirals in the treatment of RSV pneumonia.[61] A survey of pediatric SOT centers in the United States showed that 49% of centers used RSV prophylaxis, most of whom used palivizumab in infants up to 24 months.[62] Another humanized monoclonal antibody (motavizumab) is under investigation. In addition, an RNAi molecule (ALN-RSV01) that silences the nucleocapsid gene of the RSV genome is also in clinical trials. No vaccine is available, although clinical trials are ongoing.

Human Metapneumovirus

hMPV is a negative-sense nonsegmented RNA paramyxovirus closely related in structure to RSV. It is increasingly recognized as a cause of upper and lower respiratory infection during winter months. The incidence in HSCT patients is 2.7% to 7.2%.[5,63–65] Retrospectively, hMPV was found to be a cause of infection in 3% of HSCT patients diagnosed with idiopathic pneumonia.[63] It is unknown how often hMPV upper tract infection progresses to lower tract infection; however, fatal cases of progressive respiratory failure early posttransplantation have been described.[63,66] Persistent asymptomatic hMPV has also been recognized in HSCT recipients.[67] In lung transplantation, most hMPV infections seem to be symptomatic and can lead

to graft dysfunction.[68,69] The diagnosis of hMPV is based on nucleic acid detection. Supportive care is the mainstay of treatment. A reduction of immunosuppression may be of benefit. Ribavirin has shown activity in vitro and in animal models.[70–72] As well, there are reports of successful treatment of human cases with ribavirin with or without concomitant immune globulin.[73–75] Candidate vaccines for hMPV are being investigated in animal models.[76,77]

CoV Including SARS CoV

CoV have also emerged as important causes of upper and lower tract RVI in transplantation. The incidence of human CoV (hCoV) in transplant recipients has likely been underestimated because of the limitations of diagnostic testing. With the increasing use of NAT, however, the strains of hCoV described in transplant recipients now include OC43, 229E, NL63, SARS, and HKU1. A prospective study identified hCoV in 5.4% of bronchoalveolar lavage fluid specimens; transplantation (lung or liver) was the most common underlying medical condition occurring in almost half the patients.[78] In prospective studies of lung transplant recipients, coronavirus comprised 16.7% to 24% of specimens positive for respiratory viruses and lead to significant short- and long-term declines in forced expiratory pressure in 1 second.[11,79] Severe cases have also been described early post-HSCT.[80] Diagnosis of CoV is based on nucleic acid detection but culture using human hepatoma cell line (HUH7) and serology can also be used. There is no specific therapy for CoV infection.

In 2003, an outbreak of severe respiratory illness was described in China, Hong Kong, and Canada that eventually affected persons in several countries worldwide.[81–83] This was predominantly a health care–associated outbreak and significant mortality was seen in previously healthy persons. The etiologic agent was identified to be a CoV termed "severe acute respiratory syndrome–associated CoV" (SARS-CoV).[84] Common symptoms were fever, myalgias, and cough followed by dyspnea. Laboratory markers included lymphopenia, thrombocytopenia, and an elevated lactate dehydrogenase.[85] A characteristic viral pneumonitis was seen on chest radiograph. Several patients were given intravenous or oral ribavirin with corticosteroids often with adverse effects, such as hemolytic anemia (61%–76%) and hypocalcemia (58%).[85–87] A liver transplant recipient who acquired SARS following an outpatient hospital visit had a fatal outcome; he infected a significant number of health care workers.[88] In addition, tissue levels of SARS-CoV in a lung transplant recipient were several log-fold greater than in immunocompetent patients.[89] These observations in transplant recipients led to the term "super-shedders" of virus.[17] Although the spread of SARS-CoV was eventually controlled by effective infection control measures, the exercise in identification and management of an emerging virus provides important lessons for the future. Transplant patients are sentinals for emerging infections because of their immunosuppressed state and contact with the health care system. In addition, they generally have higher levels of virus in secretions. With widespread infections in the community, there is also a theoretical risk of transmission of a respiratory virus from a donor to a recipient, especially during lung transplantation but also theoretically from other organs and tissues.[88] Emerging viruses are also important for both HSCT and SOT programs and can lead to a complete halt of transplant activity, especially if resources need to be diverted for medical management of the general population.[17] Individual programs must review strategies for care of their transplant patients during respiratory virus outbreaks.

Adenovirus

AdV are nonenveloped DNA viruses with at least 52 known serotypes that are categorized into serogroups A to G. AdV are capable of causing a variety of illness in

immunocompetent and immunocompromised hosts.[90] This includes URTI and LRTI, conjunctivitis, keratoconjunctivitis and pharyngoconjunctival fever, enteritis, hepatitis, encephalitis, and disseminated disease. In HSCT recipients, an incidence of 5% to 47% has been reported. In SOT recipients, an incidence of 5.8% to 10% has been noted.[91–93] Variations in incidence depend on the type of diagnostic technique and type of transplant studied and age, with incidence being generally higher in the pediatric population.[94] Most likely, AdV in this population is acquired from the community but other possibilities are donor-derived infection or reactivation disease. Diagnosis can be made by indirect methods, such as serology, or methods that directly demonstrate the presence of virus, such as NAT and culture. DFA is not as sensitive a test for AdV as NAT.[95] In situ hybridization, immunohistochemistry, or PCR of fixed tissue can also identify adenovirus. Monitoring for AdV, similar to cytomegalovirus, may permit early detection in certain high-risk settings. Monitoring for AdV in peripheral blood seemed to predict disease in a cohort of allo-HSCT recipients[96] but was not beneficial in SOT recipients. In a surveillance study using blood PCR for AdV, it was found that self-limited adenoviremia can occur in 7% of SOT patients with 58% being asymptomatic.[91] Although AdV disease may manifest with these clinical syndromes in transplant patients, several cases of AdV-related hemorrhagic cystitis have also been described in HSCT and kidney transplant recipients. Hofland and colleagues[97] reviewed 37 cases of AdV hemorrhagic cystitis in kidney transplant patients. All cases occurred within the first year posttransplant and most presented with fever, dysuria, and hematuria. Graft dysfunction was present in most patients and viral changes or acute rejection may be seen in kidney biopsies. AdV species B predominates with serotypes 7, 11, 34, and 35 causing most disease. There is no specific therapy for AdV; acyclovir and ganciclovir generally do not have activity because AdV does not encode a thymidine kinase; vidarabine has in vitro activity against AdV and has also been used to treat AdV hemorrhagic cystitis[98]; however, clinical studies have focused on cidofovir and ribavirin. There are reports of successful treatment of disseminated disease with cidofovir.[99–101] Intravenous immunoglobulin (IVIg) has also been used in conjunction with antivirals[99]; however, IVIg may not contain sufficient quantity of antibody against all serotypes. Adoptive transfer of T cells has also been used with documented AdV-specific T-cell response in recipients.[102,103] Donor lymphocyte infusion has also been attempted. Overall AdV-related mortality was 19% in allogeneic stem cell transplant recipients despite antivirals[104] and especially high in those who received T-cell depleted grafts. Mortality rates are quite high (up to 75%) for adenoviral pneumonia or hepatitis. Lower, although significant, mortality rates (29%) for hemorrhagic cystitis or colitis are also seen.[105] Immune reconstitution plays an important role in the clearance of AdV; decreasing doses of immunosuppressive medication is important.

Rhinovirus

With the advancement of molecular diagnostic techniques for the detection of a broad-range of respiratory viruses, rhinovirus is likely the most frequently detected virus. Rhinovirus is a member of the Picornaviridae family and is well accepted as a major cause of URTI. LRTI can also occur especially in immunocompromised hosts. In one review of 15 patients with underlying hematologic malignancy and rhinovirus infection, lower respiratory tract involvement was present in 13% of cases at the onset of infection and progression to LRTI was seen in a further 13%.[106] Fatal cases in HSCT patients attributed to rhinovirus have also been described.[107] Persistent chronic infection with rhinovirus has also been described in lung transplant recipients and may lead to graft dysfunction.[108] Up to 20% of lung transplant recipients may have repeated detection of rhinovirus. In addition, the likelihood of rhinoviral persistence increases

if it is acquired soon after transplant.[109] Detection in asymptomatic patients, however, is common. A low-level viral load of rhinovirus was found in bronchoalveolar lavage specimens from many asymptomatic patients.[109] Pleconaril, a specific inhibitor of picornaviruses, seemed effective in clinical trials of immunocompetent persons with rhinovirus infection but is no longer available.[110] There is no specific therapy for rhinovirus and the management of a patient in whom rhinovirus is isolated is unclear. No intervention is likely necessary in the asymptomatic patient. If upper respiratory infection is present, many experts suggest decreasing exogenous immunosuppression if possible. For lower tract infection, immunosuppression should be reduced. There is no evidence that adjunct therapies, such as IVIg, corticosteroid therapy, or antibacterial prophylaxis, have a role to play in such infections.

Parvovirus B19

Parvovirus is a single-stranded DNA virus of the genus *Erythrovirus*. Although most infections are nonspecific flulike illnesses, specific clinical syndromes have been described. In children, parvovirus can cause a facial rash resembling "slapped cheeks"; adults with parvovirus can have a polyarthropathy syndrome. The virus can also lead to transient aplastic crisis in those with chronic hemolytic anemia and hydrops fetalis leading to intrauterine fetal death in pregnant women. Onset of parvovirus-associated syndromes can occur at any time posttransplant and has been described as early as 2 weeks. Acquisition of the virus is likely caused by inhalation of infected aerosols as in the immunocompetent host but also transmission from the donor is a possibility. It is also possible that parvovirus reactivates, although little is known about parvovirus latency or cellular reservoirs. Parvovirus B19 has been isolated from the lower respiratory tract of lung transplant recipients.[111] There are also reports of pneumonitis in transplant recipients.[112,113] Infection in transplant recipients is unlike that of immunocompetent patients in that viral replication can persist for prolonged periods of time.[114] Parvovirus has well-established association with hematologic abnormalities including pure red cell aplasia and acute or chronic anemia in transplant recipients. Because anemia is such a common problem in transplant recipients, it is important to search for parvovirus in cases of unexplained or recalcitrant anemia. Other cell lineages may also be affected and lead to leucopenia and thrombocytopenia. Serologic studies have limited use because they can be confounded by transfusion or immunoglobulin therapy. In addition, transplant recipients may not mount an antibody response. Instead, direct detection of virus by qualitative or quantitative DNA PCR is the most useful method. There is no specific antiviral therapy for parvovirus infection, although various management options have been suggested. These consist of a decrease in immunosuppression or IVIg. Various dose regimens of IVIg have been used and range from 0.4 to 1 g/kg for 4 to 10 days.

Bocavirus

Human bocavirus is a recently described member of the Parvoviridae family that also includes parvovirus B19 and parvovirus 4.[115] The first description of bocavirus was in 2005 by Allander and colleagues[116] in respiratory secretions of children. There have since been several studies worldwide in which seroprevalence has ranged from 1.5% to 19%. The virus has predominantly been found in children and many studies show its association with clinical upper and lower respiratory tract disease. It is found more frequently in symptomatic rather than asymptomatic individuals but has also been found as a copathogen with other respiratory viruses. Disseminated disease with bocavirus has been reported in a child with pulmonary infiltrates after HSCT where the virus was detected in respiratory, blood, and stool specimens.[117] Whether

bocavirus is pathogenic in adults is not well-established and descriptions in adults are rare.[118] Miyakis and colleagues[119] did not find bocavirus in bronchoalveolar lavage specimens from adult lung transplant recipients and symptomatic nontransplant controls. The detection of human bocavirus DNA is primarily based on PCR methodology using primers specific for viral genes NP1, NS1, and VP1/2 and remains a research tool. Serologic testing using antibody specific to human bocavirus' viral capsid proteins has also been described.[120,121] There are no readily available tests for bocavirus in the clinical setting, although these could potentially be added to existing multiplex platforms in the future. As with many of the respiratory viruses, there is no specific therapy for bocavirus.

KI and WU Polyomaviruses

KI and WU are recently described polyomaviruses that have also been associated with upper and lower respiratory tract disease. WU was first described in respiratory specimens from Australia and subsequently from respiratory specimens worldwide; most patients have been children, although a few adults are also among the cohorts.[122–127] The association of WU and KI viruses with disease has been debated in the literature especially given that coinfection with another respiratory virus is found in 70% to 80% of patients.[122,127] There is limited literature for these viruses in the transplant setting. In a study of 200 hospitalized patients with respiratory illness, KI was significantly more frequent in HSCT recipients (17.8% vs 5.1%; $P = .01$).[126] Another study used real-time PCR for polyomavirus detection in immunocompetent and immunocompromised patients.[128] KI virus was found in three immunocompromised patients, although two had coinfections making it difficult to interpret the extent to which the virus was pathogenic. PCR is generally the exclusive method for detection of these viruses. Further study will determine their significance in the immunocompromised host.

CLINICAL SIGNIFICANCE OF RVI IN LUNG TRANSPLANT RECIPIENTS

Community-acquired RVI occurring after lung transplantation has been associated with acute rejection and BOS. Several retrospective and prospective studies have shown this association.[11,79,129,130] One prospective study followed 50 lung transplant recipients with RVIs and compared them with 50 controls.[79] Those with RVIs had a greater incidence of acute rejection, BOS, and death. The risk of BOS was 25% in RVI-positive versus 9% in RVI-negative patients.[11] In most studies, no individual virus has been more associated with progression to BOS; however, a more recent study found that a significant percentage of lung transplant recipients with paramyxovirus infection progressed to BOS but not with rhinovirus or CoV.[11] In addition, when hMPV was compared with RSV infections in lung transplant recipients, 63% and 72% of patients, respectively, developed graft dysfunction; however, progression to BOS was seen in only those infected with RSV.[69] How viruses trigger rejection or the progression to BOS is unclear but the mechanism is likely a cytokine-mediated inflammatory cascade that recruits T cells to the allograft further resulting in intraluminal proliferation of fibroblasts.[131] The therapy of RVI post–lung transplant is variable. Most experts agree that if available, specific antiviral therapy should be given for symptomatic infections regardless of the duration of symptoms. In most circumstances, a decrease in immunosuppression is recommended for many posttransplant viral infections, including respiratory viruses. Many experts also use high-dose steroids (5–10 mg/kg/d for 3 consecutive days), however, in the presence or absence of specific antiviral therapy,

to prevent acute rejection and progression to BOS.[59,60] Whether specific antiviral therapy reduces the risk of progression to BOS-OB is controversial.[51,132]

INFECTION CONTROL MEASURES

General infection control measures for respiratory viruses include droplet precautions, which involves placing the patient in a single room. Persons entering the room should wear a gown, gloves, mask, and eye protection. In most situations, a surgical mask is appropriate; however, for more contagious viruses, a fit-tested N95 mask is required. When performing procedures, a face shield should be worn. Negative pressure isolation is also suggested for more virulent viruses. During an outbreak on a transplant unit, the following measures may reduce transmission and increase patient safety: temporarily discontinuing new transplants, discharging patients who are admitted for investigation or elective procedures, daily screening of staff for symptoms of respiratory illness, sending ill staff home promptly, and minimizing outpatient appointments and procedures for transplant patients. In an outbreak on a transplant ward, inpatients should be offered chemoprophylaxis if available. For example, during an influenza outbreak at a large HSCT center, oseltamivir prophylaxis, 75 mg daily, was shown to be safe and well-tolerated.[133]

SUMMARY

RVI continue to gain importance in transplant and oncology. New molecular techniques allow for rapid identification and identification of a greater number of viruses. The significance of newly found viruses in immunosuppressed patients continues to evolve. Treatment of RVI is limited and some infections, such as RSV, have a high mortality rate despite standard antiviral therapy. Prevention of infection with infection control measures and immunization against pathogens for which vaccines are available is important. Further research to improve diagnostics and therapeutic options in this population is needed.

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