Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
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. Incubation periods range from 1 to 10 days, although those for newly described viruses (bocavirus, parvovirus 4 and 5, and mimivirus) are unknown.
The incidence of RVI following HSCT has ranged from 3.5% to 29%. 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. 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. Lower tract infection is more common in those receiving myeloablative conditioning than in nonmyeloablative transplants. Aside from direct morbidity and mortality, RVI may also be a risk factor for the development of invasive aspergillosis in allogeneic HSCT, whether this represents an overall immunosuppressed state needs further study.

The incidence of RVI in SOT recipients is 7.7% to 64%. 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. 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. 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. Transplant recipients have been postulated to be “superspreaders” of virus given the high viral loads of respiratory viruses found in respiratory secretions. In addition, prolonged shedding of respiratory viruses is often noted. Transplant recipients may serve as sentinels 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. 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. 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. 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. 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). 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 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%. A large review of 62 HSCT recipients with influenza showed that pneumonia developed in those who were infected sooner posttransplant and had lymphopenia. 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. Lymphopenia (absolute lymphocyte count ≤ 200 cells/mL) was a specific risk factor identified for progression to influenza pneumonia. Influenza A and B infection following autologous HSCT have also been associated with mortality. In pediatric cancer patients, influenza was also an important cause of morbidity.

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

| Respiratory Virus          | Diagnosis               | Isolation Precautions | Suggested Management            |
|----------------------------|-------------------------|-----------------------|---------------------------------|
| Influenza                  | DFA, NAT, serology, culture | Droplet Airborne for pandemic strains | Oseltamivir, 75–150 mg po bid × 5–10 d Zanamivir, 2 puffs bid × 5 d Amantadine, 100 mg bid Rimantadine, 100 mg bid |
| RSV                       | DFA, NAT                | Droplet and contact   | Ribavirin IVlg 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 immunoglobulin; 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. Zanamivir has also been used successfully in HSCT recipients with influenza A or B. The recommended dose of zanamivir is 10 mg (or two puffs) twice daily for 5 days. In the study by Johny and colleagues, zanamivir was used until viral excretion ceased. Concerns have also been raised regarding the pulmonary bioavailability of zanamivir in immunocompromised patients. 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. 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. Ribavirin also has in vitro activity against influenza and could potentially be used in combination with other antivirals. 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. 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. 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. Asymptomatic parainfluenza infection has been
detected in a surveillance study of HSCT patients and could be a possible mode of transmission in outbreaks.\textsuperscript{5,39} PIV-3 in particular has caused nosocomial outbreaks on HSCT units as a result of person-to-person transmission.\textsuperscript{39–44} Mortality rates up to 33\% are seen in outbreak situations.\textsuperscript{42,44} Other syndromes in transplantation associated with PIV include Guillain-Barré syndrome, acute disseminated encephalomyelitis, and parotitis.\textsuperscript{45–47} In lung transplant recipients, the incidence of PIV has been estimated to be 5.3\% of patients.\textsuperscript{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.\textsuperscript{49} Intravenous and oral ribavirin have been used for therapy of infection in transplant recipients with conflicting results.\textsuperscript{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.\textsuperscript{6} In pediatric studies, both lymphopenia and age less than 2 years have also been shown to be an important risk factors for progression.\textsuperscript{55} RSV-related mortality in children treated for acute myeloid leukemia was 10\%.\textsuperscript{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\%.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{60} Palivizumab is a monoclonal antibody specific for RSV. It has also been used in conjunction with antivirals in the treatment of RSV pneumonia.\textsuperscript{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.\textsuperscript{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\%.\textsuperscript{5,63–65} Retrospectively, hMPV was found to be a cause of infection in 3\% of HSCT patients diagnosed with idiopathic pneumonia.\textsuperscript{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.\textsuperscript{53,66} Persistent asymptomatic hMPV has also been recognized in HSCT recipients.\textsuperscript{67} In lung transplantation, most hMPV infections seem to be symptomatic and can lead
to graft dysfunction.\textsuperscript{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.\textsuperscript{70–72} As well, there are reports of successful treatment of human cases with ribavirin with or without concomitant immune globulin.\textsuperscript{73–75} Candidate vaccines for hMPV are being investigated in animal models.\textsuperscript{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.\textsuperscript{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.\textsuperscript{11,79} Severe cases have also been described early post-HSCT.\textsuperscript{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.\textsuperscript{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).\textsuperscript{84} Common symptoms were fever, myalgias, and cough followed by dyspnea. Laboratory markers included lymphopenia, thrombocytopenia, and an elevated lactate dehydrogenase.\textsuperscript{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\%).\textsuperscript{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.\textsuperscript{88} In addition, tissue levels of SARS-CoV in a lung transplant recipient were several log-fold greater than in immunocompetent patients.\textsuperscript{89} These observations in transplant recipients led to the term “super-shedders” of virus.\textsuperscript{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 sentinels 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.\textsuperscript{86} 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.\textsuperscript{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. 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. 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. 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. 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 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. 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 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; however, clinical studies have focused on cidofovir and ribavirin. There are reports of successful treatment of disseminated disease with cidofovir. Intravenous immunoglobulin (IVIg) has also been used in conjunction with antivirals; 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. Donor lymphocyte infusion has also been attempted. Overall AdV-related mortality was 19% in allogeneic stem cell transplant recipients despite antivirals 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. 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%. Fatal cases in HSCT patients attributed to rhinovirus have also been described. Persistent chronic infection with rhinovirus has also been described in lung transplant recipients and may lead to graft dysfunction. 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.\textsuperscript{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.\textsuperscript{109} Pleconaril, a specific inhibitor of picornaviruses, seemed effective in clinical trials of immunocompetent persons with rhinovirus infection but is no longer available.\textsuperscript{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 polyarthritis 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.\textsuperscript{111} There are also reports of pneumonitis in transplant recipients.\textsuperscript{112,113} Infection in transplant recipients is unlike that of immunocompetent patients in that viral replication can persist for prolonged periods of time.\textsuperscript{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.\textsuperscript{115} The first description of bocavirus was in 2005 by Allander and colleagues\textsuperscript{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.\textsuperscript{117} Whether
Bocavirus is pathogenic in adults is not well-established and descriptions in adults are rare. Miyakis and colleagues 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. 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. 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. 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%; \( P = .01 \)). Another study used real-time PCR for polyomavirus detection in immunocompetent and immunocompromised patients. 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. One prospective study followed 50 lung transplant recipients with RVIs and compared them with 50 controls. 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. 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. 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. 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. 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.\textsuperscript{59,60} Whether specific antiviral therapy reduces the risk of progression to BOS-OB is controversial.\textsuperscript{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.\textsuperscript{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.

**REFERENCES**

1. Siegel JD, Rhinehart E, Jackson M, et al. 2007 Guideline for isolation precautions: preventing transmission of infectious agents in health care settings. Am J Infect Control 2007;35:S65.
2. Kuypers J, Campbell AP, Cen A, et al. Comparison of conventional and molecular detection of respiratory viruses in hematopoietic cell transplant recipients. Transpl Infect Dis 2009;11(4):298–303.
3. Ljungman P, Ward KN, Crooks BN, et al. Respiratory virus infections after stem cell transplantation: a prospective study from the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant 2001;28:479.
4. Martino R, Porras RP, Rabella N, et al. Prospective study of the incidence, clinical features, and outcome of symptomatic upper and lower respiratory tract infections by respiratory viruses in adult recipients of hematopoietic stem cell transplants for hematologic malignancies. Biol Blood Marrow Transplant 2005;11:781.
5. Peck AJ, Englund JA, Kuypers J, et al. Respiratory virus infection among hematopoietic cell transplant recipients: evidence for asymptomatic parainfluenza virus infection. Blood 2007;110:1681.
6. Chemaly RF, Ghosh S, Bodey GP, et al. Respiratory viral infections in adults with hematologic malignancies and human stem cell transplantation recipients: a retrospective study at a major cancer center. Medicine (Baltimore) 2006;85:278.

7. Schiffer JT, Kirby K, Sandmaier B, et al. Timing and severity of community acquired respiratory virus infections after myeloablative versus non-myeloablative hematopoietic stem cell transplantation. Haematologica 2009;94:1101.

8. Martino R, Pinana JL, Parody R, et al. Lower respiratory tract respiratory virus infections increase the risk of invasive aspergillosis after a reduced-intensity allogeneic hematopoietic SCT. Bone Marrow Transplant 2009;44(11):749–56.

9. Bonatti H, Pruett TL, Brandacher G, et al. Pneumonia in solid organ recipients: spectrum of pathogens in 217 episodes. Transplant Proc 2009;41:371.

10. Garbino J, Soccal PM, Aubert JD, et al. Respiratory viruses in bronchoalveolar lavage: a hospital-based cohort study in adults. Thorax 2009;64:399.

11. Gottlieb J, Schulz TF, Welte T, et al. Community-acquired respiratory viral infections in lung transplant recipients: a single season cohort study. Transplantation 2009;87:1530.

12. Lopez-Medrano F, Aguado JM, Lizardoain M, et al. Clinical implications of respiratory virus infections in solid organ transplant recipients: a prospective study. Transplantation 2007;84:851.

13. Milstone AP, Brumble LM, Barnes J, et al. A single-season prospective study of respiratory viral infections in lung transplant recipients. Eur Respir J 2006;28:131.

14. Franquet T, Rodriguez S, Martino R, et al. Thin-section CT findings in hematopoietic stem cell transplantation recipients with respiratory virus pneumonia. AJR Am J Roentgenol 2006;187:1085.

15. Marchiori E, Escuissato DL, Gasparetto TD, et al. Crazy-paving patterns on high-resolution CT scans in patients with pulmonary complications after hematopoietic stem cell transplantation. Korean J Radiol 2009;10:21.

16. van Kraaij MG, van Elden LJ, van Loon AM, et al. Frequent detection of respiratory viruses in adult recipients of stem cell transplants with the use of real-time polymerase chain reaction, compared with viral culture. Clin Infect Dis 2005;40:662.

17. Kumar D, Humar A. Pandemic influenza and its implications for transplantation. Am J Transplant 2006;6:1512.

18. Mahony JB. Detection of respiratory viruses by molecular methods. Clin Microbiol Rev 2008;21:716.

19. Fox JD. Nucleic acid amplification tests for detection of respiratory viruses. J Clin Virol 2007;40(Suppl 1):S15.

20. Ison MG, Hayden FG. Viral infections in immunocompromised patients: what's new with respiratory viruses? Curr Opin Infect Dis 2002;15:355.

21. Vilchez RA, McCurry K, Dauber J, et al. Influenza virus infection in adult solid organ transplant recipients. Am J Transplant 2002;2:287.

22. Ljungman P, Andersson J, Aschan J, et al. Influenza A in immunocompromised patients. Clin Infect Dis 1993;17:244.

23. Nichols WG, Guthrie KA, Corey L, et al. Influenza infections after hematopoietic stem cell transplantation: risk factors, mortality, and the effect of antiviral therapy. Clin Infect Dis 2004;39:1300.

24. Khanna N, Steffen I, Studt JD, et al. Outcome of influenza infections in outpatients after allogeneic hematopoietic stem cell transplantation. Transpl Infect Dis 2009;11:100.
25. Tasian SK, Park JR, Martin ET, et al. Influenza-associated morbidity in children with cancer. Pediatr Blood Cancer 2008;50:983.
26. Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group. Lancet 1998;352:1877.
27. Hayden FG, Osterhaus AD, Treanor JJ, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenzavirus infections. GG167 Influenza Study Group. N Engl J Med 1997;337:874.
28. Makela MJ, Pauksens K, Rostila T, et al. Clinical efficacy and safety of the orally inhaled neuraminidase inhibitor zanamivir in the treatment of influenza: a randomized, double-blind, placebo-controlled European study. J Infect 2000;40:42.
29. Johny AA, Clark A, Price N, et al. The use of zanamivir to treat influenza A and B infection after allogeneic stem cell transplantation. Bone Marrow Transplant 2002;29:113.
30. Medeiros R, Rameix-Welti MA, Lorin V, et al. Failure of zanamivir therapy for pneumonia in a bone-marrow transplant recipient infected by a zanamivir-sensitive influenza A (H1N1) virus. Antivir Ther 2007;12:571.
31. Sheu TG, Deyde VM, Okomo-Adhiambo M, et al. Surveillance for neuraminidase inhibitor resistance among human influenza A and B viruses circulating worldwide from 2004 to 2008. Antimicrob Agents Chemother 2008;52:3284.
32. Monto AS. Antivirals and influenza: frequency of resistance. Pediatr Infect Dis J 2008;27:S110.
33. Ilyushina NA, Hay A, Yilmaz N, et al. Oseltamivir-ribavirin combination therapy for highly pathogenic H5N1 influenza virus infection in mice. Antimicrob Agents Chemother 2008;52:3889.
34. Smee DF, Hurst BL, Wong MH, et al. Effects of double combinations of amantadine, oseltamivir, and ribavirin on influenza A (H5N1) virus infections in cell culture and in mice. Antimicrob Agents Chemother 2009;53:2120.
35. Guidelines for vaccination of solid organ transplant candidates and recipients. Am J Transplant 2004;4(Suppl 10):160.
36. Ljungman P, Avetisyan G. Influenza vaccination in hematopoietic SCT recipients. Bone Marrow Transplant 2008;42:637.
37. Ljungman P, Engelhard D, de la Camara R, et al. Vaccination of stem cell transplant recipients: recommendations of the Infectious Diseases Working Party of the EBMT. Bone Marrow Transplant 2005;35:737.
38. Elizaga J, Olavarria E, Apperley J, et al. Parainfluenza virus 3 infection after stem cell transplant: relevance to outcome of rapid diagnosis and ribavirin treatment. Clin Infect Dis 2001;32:413.
39. Nichols WG, Erdman DD, Han A, et al. Prolonged outbreak of human parainfluenza virus 3 infection in a stem cell transplant outpatient department: insights from molecular epidemiologic analysis. Biol Blood Marrow Transplant 2004;10:58.
40. Cortez KJ, Erdman DD, Peret TC, et al. Outbreak of human parainfluenza virus 3 infections in a hematopoietic stem cell transplant population. J Infect Dis 2001;184:1093.
41. Hohenthal U, Nikoskelainen J, Vainionpaa R, et al. Parainfluenza virus type 3 infections in a hematology unit. Bone Marrow Transplant 2001;27:295.
42. Jalal H, Bibby DF, Bennett J, et al. Molecular investigations of an outbreak of parainfluenza virus type 3 and respiratory syncytial virus infections in a hematology unit. J Clin Microbiol 2007;45:1690.
43. Piralla A, Percivalle E, Di Cesare-Merlone A, et al. Multicluster nosocomial outbreak of parainfluenza virus type 3 infection in a pediatric oncohematology unit: a phylogenetic study. Haematologica 2009;94:833.

44. Zambon M, Bull T, Sadler CJ, et al. Molecular epidemiology of two consecutive outbreaks of parainfluenza 3 in a bone marrow transplant unit. J Clin Microbiol 1998;36:2289.

45. Au WY, Lie AK, Cheung RT, et al. Acute disseminated encephalomyelitis after para-influenza infection post bone marrow transplantation. Leuk Lymphoma 2002;43:455.

46. Lange T, Franke G, Niederwieser D. Parotitis associated with a parainfluenza virus type 3 infection during aplasia after unrelated allogeneic stem cell transplantation. Leuk Lymphoma 2006;47:1714.

47. Rodriguez V, Kuehnle I, Heslop HE, et al. Guillain-Barre syndrome after allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 2002;29:515.

48. Vilchez RA, Dauber J, McCurry K, et al. Parainfluenza virus infection in adult lung transplant recipients: an emergent clinical syndrome with implications on allograft function. Am J Transplant 2003;3:116.

49. Ferguson PE, Sorrell TC, Bradstock KF, et al. Parainfluenza virus type 3 pneumonia in bone marrow transplant recipients: multiple small nodules in high-resolution lung computed tomography scans provide a radiological clue to diagnosis. Clin Infect Dis 2009. [Epub ahead of print].

50. Chakrabarti S, Collingham KE, Holder K, et al. Pre-emptive oral ribavirin therapy of paramyxovirus infections after haematopoietic stem cell transplantation: a pilot study. Bone Marrow Transplant 2001;28:759.

51. McCurdy LH, Milstone A, Dummer S. Clinical features and outcomes of paramyxoviral infection in lung transplant recipients treated with ribavirin. J Heart Lung Transplant 2003;22:745.

52. Nichols WG, Gooley T, Boeckh M. Community-acquired respiratory syncytial virus and parainfluenza virus infections after hematopoietic stem cell transplantation: the Fred Hutchinson Cancer Research Center experience. Biol Blood Marrow Transplant 2001;7(Suppl):11S.

53. Shima T, Yoshimoto G, Nonami A, et al. Successful treatment of parainfluenza virus 3 pneumonia with oral ribavirin and methylprednisolone in a bone marrow transplant recipient. Int J Hematol 2008;88:336.

54. Wright JJ, O’Driscoll G. Treatment of parainfluenza virus 3 pneumonia in a cardiac transplant recipient with intravenous ribavirin and methylprednisolone. J Heart Lung Transplant 2005;24:343.

55. El Saleeby CM, Somes GW, DeVincenzo JP, et al. Risk factors for severe respiratory syncytial virus disease in children with cancer: the importance of lymphopenia and young age. Pediatrics 2008;121:235.

56. Sung L, Alonzo TA, Gerbing RB, et al. Respiratory syncytial virus infections in children with acute myeloid leukemia: a report from the Children’s Oncology Group. Pediatr Blood Cancer 2008;51:784.

57. Mahony J, Chong S, Merante F, et al. Development of a respiratory virus panel test for detection of twenty human respiratory viruses by use of multiplex PCR and a fluid microbead-based assay. J Clin Microbiol 2007;45:2965.

58. Boeckh M, Englund J, Li Y, et al. Randomized controlled multicenter trial of aerosolized ribavirin for respiratory syncytial virus upper respiratory tract infection in hematopoietic cell transplant recipients. Clin Infect Dis 2007;44:245.
59. Pelaez A, Lyon GM, Force SD, et al. Efficacy of oral ribavirin in lung transplant patients with respiratory syncytial virus lower respiratory tract infection. J Heart Lung Transplant 2009;28:67.

60. Glanville AR, Scott Al, Morton JM, et al. Intravenous ribavirin is a safe and cost-effective treatment for respiratory syncytial virus infection after lung transplantation. J Heart Lung Transplant 2005;24:2114.

61. Chavez-Bueno S, Mejias A, Merryman RA, et al. Intravenous palivizumab and ribavirin combination for respiratory syncytial virus disease in high-risk pediatric patients. Pediatr Infect Dis J 2007;26:1089.

62. Michaels MG, Fonseca-Aten M, Green M, et al. Respiratory syncytial virus prophylaxis: a survey of pediatric solid organ transplant centers. Pediatr Transplant 2009;13:451.

63. Englund JA, Boechk M, Kuypers J, et al. Brief communication: fatal human metapneumovirus infection in stem-cell transplant recipients. Ann Intern Med 2006;144:344.

64. Kamboj M, Gerbin M, Huang CK, et al. Clinical characterization of human metapneumovirus infection among patients with cancer. J Infect 2008;57:464.

65. Oliveira R, Machado A, Tateno A, et al. Frequency of human metapneumovirus infection in hematopoietic SCT recipients during 3 consecutive years. Bone Marrow Transplant 2008;42:265.

66. Evasheuk KM, Forgie SE, Gilmour S, et al. Respiratory failure associated with human metapneumovirus infection in an infant posthepatic transplant. Am J Transplant 2008;8:1567.

67. Debiaggi M, Canducci F, Sampaolo M, et al. Persistent symptomless human metapneumovirus infection in hematopoietic stem cell transplant recipients. J Infect Dis 2006;194:474.

68. Gerna G, Vitulo P, Rovida F, et al. Impact of human metapneumovirus and human cytomegalovirus versus other respiratory viruses on the lower respiratory tract infections of lung transplant recipients. J Med Virol 2006;78:408.

69. Hopkins P, McNeil K, Kermeen F, et al. Human metapneumovirus in lung transplant recipients and comparison to respiratory syncytial virus. Am J Respir Crit Care Med 2008;178:876.

70. Hamelin ME, Prince GA, Boivin G. Effect of ribavirin and glucocorticoid treatment in a mouse model of human metapneumovirus infection. Antimicrob Agents Chemother 2006;50:774.

71. Wyde PR, Chetty SN, Jewell AM, et al. Comparison of the inhibition of human metapneumovirus and respiratory syncytial virus by ribavirin and immune serum globulin in vitro. Antiviral Res 2003;60:51.

72. Wyde PR, Moylett EH, Chetty SN, et al. Comparison of the inhibition of human metapneumovirus and respiratory syncytial virus by NMSO3 in tissue culture assays. Antiviral Res 2004;63:51.

73. Bonney D, Razali H, Turner A, et al. Successful treatment of human metapneumovirus pneumonia using combination therapy with intravenous ribavirin and immune globulin. Br J Haematol 2009;145:667.

74. Raza K, Ismailjee SB, Crespo M, et al. Successful outcome of human metapneumovirus (hMPV) pneumonia in a lung transplant recipient treated with intravenous ribavirin. J Heart Lung Transplant 2007;26:862.

75. Safdar A. Immune modulatory activity of ribavirin for serious human metapneumovirus disease: early I.V. therapy may improve outcomes in immunosuppressed SCT recipients. Bone Marrow Transplant 2008;41:707.
76. Herfst S, Fouchier RA. Vaccination approaches to combat human metapneumovirus lower respiratory tract infections. J Clin Virol 2008;41:49.
77. Herfst S, Schrauwen EJ, de Graaf M, et al. Immunogenicity and efficacy of two candidate human metapneumovirus vaccines in cynomolgus macaques. Vaccine 2008;26:4224.
78. Garibino J, Crespo S, Aubert JD, et al. A prospective hospital-based study of the clinical impact of non-severe acute respiratory syndrome (Non-SARS)-related human coronavirus infection. Clin Infect Dis 2006;43:1009.
79. Kumar D, Erdman D, Keshavjee S, et al. Clinical impact of community-acquired respiratory viruses on bronchiolitis obliterans after lung transplant. Am J Transplant 2005;5:2031.
80. Pene F, Merlat A, Vabret A, et al. Coronavirus 229E-related pneumonia in immunocompromised patients. Clin Infect Dis 2003;37:929.
81. Drosten C, Gunther S, Preiser W, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med 1967;348:2003.
82. Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med 2003;348:1953.
83. Rota PA, Oberste MS, Monroe SS, et al. Characterization of a novel coronavirus associated with severe acute respiratory syndrome. Science 2003;300:1394.
84. Adachi D, Johnson G, Draker R, et al. Comprehensive detection and identification of human coronaviruses, including the SARS-associated coronavirus, with a single RT-PCR assay. J Virol Methods 2004;122:29.
85. Booth CM, Matukas LM, Tomlinson GA, et al. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. JAMA 2003;289:2801.
86. Chiou HE, Liu CL, Buttrey MJ, et al. Adverse effects of ribavirin and outcome in severe acute respiratory syndrome: experience in two medical centers. Chest 2005;128:263.
87. Knowles SR, Phillips EJ, Dresser L, et al. Common adverse events associated with the use of ribavirin for severe acute respiratory syndrome in Canada. Clin Infect Dis 2003;37:1139.
88. Kumar D, Tellier R, Draker R, et al. Severe Acute Respiratory Syndrome (SARS) in a liver transplant recipient and guidelines for donor SARS screening. Am J Transplant 2003;3:977.
89. Farcas GA, Poutanen SM, Mazzulli T, et al. Fatal severe acute respiratory syndrome is associated with multiorgan involvement by coronavirus. J Infect Dis 2005;191:193.
90. Echavarria M. Adenoviruses in immunocompromised hosts. Clin Microbiol Rev 2008;21:704.
91. Humar A, Kumar D, Mazzulli T, et al. A surveillance study of adenovirus infection in adult solid organ transplant recipients. Am J Transplant 2005;5:2555.
92. McGrath D, Falagas ME, Freeman R, et al. Adenovirus infection in adult orthotopic liver transplant recipients: incidence and clinical significance. J Infect Dis 1998;177:459.
93. Michaels MG, Green M, Wald ER, et al. Adenovirus infection in pediatric liver transplant recipients. J Infect Dis 1992;165:170.
94. Ljungman P. Treatment of adenovirus infections in the immunocompromised host. Eur J Clin Microbiol Infect Dis 2004;23:583.
95. Fox JD. Respiratory virus surveillance and outbreak investigation. J Clin Virol 2007;40(Suppl 1):S24.
96. Lion T, Baumgartinger R, Watzinger F, et al. Molecular monitoring of adenovirus in peripheral blood after allogeneic bone marrow transplantation permits early diagnosis of disseminated disease. Blood 2003;102:1114.

97. Hofland CA, Eron LJ, Washecka RM. Hemorrhagic adenovirus cystitis after renal transplantation. Transplant Proc 2004;36:3025.

98. Bordigoni P, Carret AS, Venard V, et al. Treatment of adenovirus infections in patients undergoing allogeneic hematopoietic stem cell transplantation. Clin Infect Dis 2001;32:1290.

99. Doan ML, Mallory GB, Kaplan SL, et al. Treatment of adenovirus pneumonia with cidofovir in pediatric lung transplant recipients. J Heart Lung Transplant 2007;26:883.

100. Refaat M, McNamara D, Teuteberg J, et al. Successful cidofovir treatment in an adult heart transplant recipient with severe adenovirus pneumonia. J Heart Lung Transplant 2008;27:699.

101. Ribaud P, Scieux C, Freymuth F, et al. Successful treatment of adenovirus disease with intravenous cidofovir in an unrelated stem-cell transplant recipient. Clin Infect Dis 1999;28:690.

102. Feuchtinger T, Matthes-Martin S, Richard C, et al. Safe adoptive transfer of virus-specific T-cell immunity for the treatment of systemic adenovirus infection after allogeneic stem cell transplantation. Br J Haematol 2006;134:64.

103. Leen AM, Christin A, Myers GD, et al. Cytotoxic T lymphocyte therapy with donor T cells prevents and treats adenovirus and Epstein-Barr virus infections after haploidentical and matched unrelated stem cell transplant. Blood 2009;114(19):4283–92.

104. Neofytos D, Ojha A, Mookerjee B, et al. Treatment of adenovirus disease in stem cell transplant recipients with cidofovir. Biol Blood Marrow Transplant 2007;13:74.

105. Symeonidis N, Jakubowski A, Pierre-Louis S, et al. Invasive adenoviral infections in T-cell-depleted allogeneic hematopoietic stem cell transplantation: high mortality in the era of cidofovir. Transpl Infect Dis 2007;9:108.

106. Parody R, Rabella N, Martino R, et al. Upper and lower respiratory tract infections by human enterovirus and rhinovirus in adult patients with hematological malignancies. Am J Hematol 2007;82:807.

107. Gutman JA, Peck AJ, Kuypers J, et al. Rhinovirus as a cause of fatal lower respiratory tract infection in adult stem cell transplantation patients: a report of two cases. Bone Marrow Transplant 2007;40:809.

108. Kaiser L, Aubert JD, Pache JC, et al. Chronic rhinoviral infection in lung transplant recipients. Am J Respir Crit Care Med 2006;174:1392.

109. Gerna G, Piralla A, Rovida F, et al. Correlation of rhinovirus load in the respiratory tract and clinical symptoms in hospitalized immunocompetent and immunocompromised patients. J Med Virol 2009;81:1498.

110. Hayden FG, Herrington DT, Coats TL, et al. Efficacy and safety of oral pleconaril for treatment of colds due to picornaviruses in adults: results of 2 double-blind, randomized, placebo-controlled trials. Clin Infect Dis 2003;36:1523.

111. Costa C, Terlizzi ME, Solidoro P, et al. Detection of parvovirus B19 in the lower respiratory tract. J Clin Virol 2009;46(2):150–3.

112. Beske F, Modrow S, Sorensen J, et al. Parvovirus B19 pneumonia in a child undergoing allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 2007;40:89.

113. Janner D, Bork J, Baum M, et al. Severe pneumonia after heart transplantation as a result of human parvovirus B19. J Heart Lung Transplant 1994;13:336.
114. Waldman M, Kopp JB. Parvovirus-B19-associated complications in renal transplant recipients. Nat Clin Pract Nephrol 2007;3:540.
115. Allander T. Human bocavirus. J Clin Virol 2008;41:29.
116. Allander T, Tammi MT, Eriksson M, et al. Cloning of a human parvovirus by molecular screening of respiratory tract samples. Proc Natl Acad Sci U S A 2005;102:12891.
117. Schenk T, Strahm B, Kontny U, et al. Disseminated bocavirus infection after stem cell transplant. Emerg Infect Dis 2007;13:1425.
118. Kupfer B, Vehreschild J, Cornely O, et al. Severe pneumonia and human bocavirus in adult. Emerg Infect Dis 2006;12:1614.
119. Miyakis S, van Hal SJ, Barratt J, et al. Absence of human Bocavirus in bronchoalveolar lavage fluid of lung transplant patients. J Clin Virol 2009;44:179.
120. Kantola K, Hedman L, Allander T, et al. Serodiagnosis of human bocavirus infection. Clin Infect Dis 2008;46:540.
121. Lindner J, Karalar L, Schimanski S, et al. Clinical and epidemiological aspects of human bocavirus infection. J Clin Virol 2008;43:391.
122. Bialasiewicz S, Whiley DM, Lambert SB, et al. Presence of the newly discovered human polymaviruses KI and WU in Australian patients with acute respiratory tract infection. J Clin Virol 2008;41:63.
123. Bialasiewicz S, Whiley DM, Lambert SB, et al. A newly reported human polymavirus, KI virus, is present in the respiratory tract of Australian children. J Clin Virol 2007;40:15.
124. Gaynor AM, Nissen MD, Whiley DM, et al. Identification of a novel polymavirus from patients with acute respiratory tract infections. PLoS Pathog 2007;3:e64.
125. Le BM, Demertzis LM, Wu G, et al. Clinical and epidemiologic characterization of WU polymavirus infection, St. Louis, Missouri. Emerg Infect Dis 2007;13:1936.
126. Mourez T, Bergeron A, Ribaud P, et al. Polymaviruses KI and WU in immunocompromised patients with respiratory disease. Emerg Infect Dis 2009;15:107.
127. Norja P, Ubillos I, Templeton K, et al. No evidence for an association between infections with WU and KI polymaviruses and respiratory disease. J Clin Virol 2007;40:307.
128. Bialasiewicz S, Whiley DM, Lambert SB, et al. Detection of BK, JC, WU, or KI polymaviruses in faecal, urine, blood, cerebrospinal fluid and respiratory samples. J Clin Virol 2009;45:249.
129. Billings JL, Hertz MI, Savik K, et al. Respiratory viruses and chronic rejection in lung transplant recipients. J Heart Lung Transplant 2002;21:559.
130. Khalifah AP, Hachem RR, Chakinala MM, et al. Respiratory viral infections are a distinct risk for bronchiolitis obliterans syndrome and death. Am J Respir Crit Care Med 2004;170:181.
131. Husain S, Singh N. Bronchiolitis obliterans and lung transplantation: evidence for an infectious etiology. Semin Respir Infect 2002;17:310.
132. Ison MG, Sharma A, Shepard JA, et al. Outcome of influenza infection managed with oseltamivir in lung transplant recipients. J Heart Lung Transplant 2008;27:282.
133. Vu D, Peck AJ, Nichols WG, et al. Safety and tolerability of oseltamivir prophylaxis in hematopoietic stem cell transplant recipients: a retrospective case-control study. Clin Infect Dis 2007;45:187.