International Journal of Infectious Diseases 62 (2017) 86–93

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Review

Respiratory viruses in transplant recipients: more than just a cold. Clinical syndromes and infection prevention principles

Salma Abbas*, Jillian E. Raybould, Sangeeta Sastry, Oveimar de la Cruz

Division of Infectious Diseases, Virginia Commonwealth University, Richmond, Virginia, USA

ARTICLE INFO

Article history:
Received 6 April 2017
Received in revised form 13 July 2017
Accepted 14 July 2017
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Respiratory viral infections
Transplant recipients
Infection prevention

ABSTRACT

Objectives: The aim of this review is to provide updated information on the clinical spectrum, treatment options, and infection prevention strategies for respiratory viral infections (RVIs) in both solid organ (SOT) and hematopoietic stem cell transplant (HSCT) patients.
Methods: The MEDLINE and PubMed databases were searched for literature regarding the aforementioned aspects of RVIs, with focus on respiratory syncytial virus, adenovirus, influenza virus, parainfluenza virus, human metapneumovirus, and rhinovirus.
Results: Compared to immunocompetent hosts, SOT and HSCT patients are much more likely to experience a prolonged duration of illness, prolonged shedding, and progression of upper respiratory tract disease to pneumonia when infected with respiratory viruses. Adenovirus and respiratory syncytial virus tend to have the highest mortality and risk for disseminated disease, but all the RVIs are associated with higher morbidity and mortality in these patients than in the general population. These viruses are spread via direct contact and aerosolized droplets, and nosocomial spread has been reported.
Conclusions: RVIs are associated with high morbidity and mortality among SOT and HSCT recipients. Management options are currently limited or lack strong clinical evidence. As community and nosocomial spread has been reported for all reviewed RVIs, strict adherence to infection control measures is key to preventing outbreaks.

Contents

* Corresponding author at: Division of Infectious Diseases, Virginia Commonwealth University, VMI Building, Suite 205, PO Box 980049, Richmond, VA 23298, USA.
E-mail address: salma.abbas@vcuhealth.org (S. Abbas).

http://dx.doi.org/10.1016/j.ijid.2017.07.011

Introduction

Respiratory viral infections (RVI) such as those caused by respiratory syncytial virus (RSV), adenovirus (ADV), influenza virus, parainfluenza virus (PIV), human metapneumovirus (hMPV), and rhinoviruses typically cause self-limited upper respiratory tract infections (URTI) in immunocompetent hosts, but are associated with high morbidity and mortality in both bone marrow and solid organ transplant (SOT) recipients. The rates of these infections typically mirror epidemiological prevalence in the community, but the clinical course tends to be more aggressive early post-transplant. Most patients initially develop a URTI, and up to half may develop complicated lower respiratory tract infections (LRTI) (Raad et al., 1997; Lee and Barton, 2007), resulting in a prolonged duration of illness with viral shedding, graft dysfunction, graft loss, and sometimes even bronchiolitis obliterans among lung transplant recipients (LTRs) (Ison, 2009; Lee and Barton, 2007).

These respiratory infections are known to be community-acquired in the general population, but in transplant patients, nosocomial transmission is frequently encountered. In a study performed among bone marrow transplant (BMT) patients, 48% of RVIs were associated with nosocomial transmission (Whimbey et al., 1996).

The Centers for Disease Control and Prevention (CDC) recommend the implementation of specific measures to prevent the spread of RSV, PIV, ADV, and influenza virus infections within healthcare settings (Tablan et al., 2004). Studies suggest that infection control practices vary across institutions throughout the country and unfortunately are not widely implemented. Strict adherence to infection control measures such as hand hygiene and contact precautions, staff education regarding modes of transmission and disease prevention, regular monitoring of healthcare worker practices, and surveillance are key elements in the prevention of outbreaks (Tablan et al., 2004).

This article aims to review the literature on RVIs among transplant recipients, including their management and principles of infection prevention.

Respiratory syncytial virus

RSV is a common infectious complication of transplantation, with an incidence of up to 12% in hematopoietic stem cell transplant (HSCT) patients and 16% in adult LTRs. It has year-round prevalence, with peak incidence from September through April (Hirsch et al., 2013; Renaud and Campbell, 2011). Infections from RSV typically manifest as self-limiting URTIs in immunocompetent adults. However, LRTIs develop in about two-thirds of HSCT recipients (Hattington et al., 1992; Weigt et al., 2011). The progression to an LRTI is commonly observed in patients with an allogeneic stem cell transplant, mismatched donor transplant, graft-versus-host disease, old age, myeloablative therapy, long duration of lymphopenia, and early post-transplant infection (Weigt et al., 2011; Lavergne et al., 2011; Neemann and Freifeld, 2015). RSV infections in this patient population are associated with higher morbidity and mortality when compared to other RVIs.

Although the incidence of these infections typically follows community outbreaks, one study reported that up to two-thirds of RSV infections were hospital-acquired (Whimbey et al., 1995). During an outbreak of RSV infection among BMT recipients, pre-engraftment patients had a higher risk of acquiring RSV infections than engrafted patients (Hattington et al., 1992). If patients developed an infection isolated to the upper respiratory tract, outcomes were generally good, with 100% survival; however, mortality rose to 78% among patients with RSV pneumonia despite treatment with inhaled ribavirin. Prolonged viral shedding (21.7 days) was also associated with a higher rate of mortality (Hattington et al., 1992). In another study, RSV pneumonia was associated with 100% mortality among adult BMT recipients in whom antiviral therapy was started after the onset of respiratory failure.

The LTR population is the best studied group among adult SOT recipients for RSV infections. The overall mortality for RSV infections ranges from 10% to 20% among immunocompromised patients (Weigt et al., 2011). Although mortality is lower in LTRs than in BMT patients, morbidity remains high. According to one study, 72% of LTRs with RSV infections developed graft dysfunction (Hopkins et al., 2008). In terms of long-term sequelae, LRTIs caused by RSV have been associated with the development of reactive airway disease in pediatric patients, airflow decline in HSCT patients, and bronchiolitis obliterans syndrome in LTRs (Weigt et al., 2011).

Transmission

RSV infection is transmitted via droplets and direct skin contact (Jensen et al., 2016). Droplet transmission requires close contact (<1 m) with large-particle virus-containing droplets (>5 μm). While this may occur during sneezing, coughing, and procedures such as bronchoscopy, it is a less common means of nosocomial transmission, because larger particles do not remain suspended in air for a long time (Garner, 1996). Skin contamination, likely of healthcare workers, results in the nosocomial spread of RSV from one patient to another (Raad et al., 1997).

Treatment and prevention

Currently, no vaccines are available for the prevention of RSV infections (Weigt et al., 2011). Early diagnosis of infection and timely institution of antiviral therapy is critical to prevent progression to LRTI and to achieve a favorable outcome (Jones et al., 2000). Although there are no clear recommendations or randomized study data regarding the treatment of RSV, there are early reports of improved outcomes with inhaled ribavirin. However, aerosolized ribavirin is logistically difficult to administer and has teratogenic potential. Dispensing systemic oral and intravenous ribavirin has been effective in some cohort studies, with no available evidence to strongly recommend a specific route of administration (Weigt et al., 2011; Neemann and Freifeld, 2015; Lehners et al., 2013; Gross and Bryson, 2015; Beaird et al., 2016). Several reports describe combining ribavirin with intravenous immunoglobulin (IVIG) or RSV-specific immune globulin

(Neemann and Freifeld, 2015; Whimbey et al., 1995; Beaird et al., 2016). Novel drugs such as ALN-RSV01 are currently under investigation with promising phase 2b results demonstrating a low incidence of RSV-induced bronchiolitis obliterans syndrome in LTRs (Gottlieb et al., 2016).

Intensifying infection prevention practices such as vigilant hand washing, contact precautions, and the use of masks and eye protection while performing procedures are key elements to prevent the nosocomial transmission of RSV (Tablan et al., 2004; Lehners et al., 2013; Hall, 2000; Garcia et al., 1997). In addition, interactions with visitors and other staff members should be reduced by screening visitors for symptoms of respiratory tract infection, employing universal masking in transplant units, prohibiting children <12 years of age from visiting patients admitted to the unit, moving patients with suspected RSV to a private room, and limiting transport while diagnostic testing is underway (Tablan et al., 2004; Hattington et al., 1992; Garcia et al., 1997). According to one study, the incidence density of RSV infections among BMT recipients declined from 1.4 to 0.2 per 1000 patient-days with the implementation of such measures (Raad et al., 1997; Lavergne et al., 2011; Jones et al., 2000; Garcia et al., 1997). Further proposed prevention strategies include the use of palivizumab, a monoclonal antibody approved for RSV prophylaxis among infants born prior to 29 weeks of gestation (American Academy of Pediatrics, 2014). There is no consensus regarding its off-label use for RSV prophylaxis in HSCT and SOT recipients (Gaboli et al., 2014). Although palivizumab is not currently recommended for the prevention of RSV infections among adults, a growing body of evidence suggests that it may represent a safe option for RSV prophylaxis among the pediatric as well as adult HSCT patient population (Weigt et al., 2011; American Academy of Pediatrics, 2014; Recommendations of the Center for International Blood and Marrow Transplant Research (CIBMTR®) et al., 2009; Kassis et al., 2010). Kassis and colleagues used active surveillance successfully to identify patients infected with RSV and instituted necessary infection control measures along with palivizumab prophylaxis for high-risk patients to successfully prevent an outbreak among adult HSCT patients (Kassis et al., 2010).

Adenovirus

ADV can be grouped into seven distinct subgroups (A–G) and 53 serotypes. Serotypes 1–4, 7, and 21 cause disease in humans and each serotype is associated with a specific clinical syndrome (Sandkovsky et al., 2014). The American Society of Transplantation defines ADV infections based on symptoms, detection of virus by PCR or culture, and the presence of tissue invasive disease. The American Society of Transplantation defines asymptomatic infection as the detection of the virus by PCR in blood, urine, stool, or a respiratory specimen in the absence of overt symptoms. ADV disease is defined as the detection of virus in biopsy specimens or cultures in a patient with compatible symptoms. Patients are diagnosed with disseminated disease if two or more organs are involved regardless of the presence of viremia (Florescu and Hoffman, 2013).

In immunocompetent individuals, the spectrum of infections caused by ADV ranges from mild URTI to conjunctivitis and gastrointestinal infections; in immunocompromised patients, pneumonia, hepatitis, hemorrhagic cystitis, colitis, pancreatitis, meningoencephalitis, and disseminated disease may also be seen (Weigt et al., 2011; Sandkovsky et al., 2014). Infections among HSCT and SOT patients are associated with high morbidity and mortality (Sandkovsky et al., 2014).

The incidence of ADV infections ranges from 2.5% to 14% among autologous HSCT recipients and from 5% to 47% among allogeneic HSCT recipients. The incidence is highest during the first 100 days following transplantation. Factors associated with severe disease and poor outcomes include allogeneic transplant, young age, disseminated disease, exposure to T-cell depleting agents, low T-cell counts following transplantation, graft-versus-host disease, ADV viremia, rising serum viral load, total body irradiation, and HLA mismatch (Sandkovsky et al., 2014).

The true incidence of ADV infections among adult SOT recipients is unknown. In SOT patients, most infections occur within the first year of transplantation. ADV infections are more common in pediatric transplant recipients, with an estimated incidence of 10% (Sandkovsky et al., 2014; Florescu and Hoffman, 2013; McGrath et al., 1998). Asymptomatic viremia is common among adult patients and may be observed in 6.5–22.5%, with a low risk of progression to overt disease (Humar et al., 2005; Ison et al., 2009). The degree of immunosuppression, type of transplanted organ (i.e., small intestine), and sero-mismatched organs are factors associated with worse outcomes among SOT patients (Sandkovsky et al., 2014; Ison et al., 2009; Runde et al., 2001). ADV infections may lead to pneumonia, graft loss, and death among SOT patients. In a pediatric study, 50% of LTRs with graft loss were infected with ADV (Bridges et al., 1998). In a retrospective review of 191 adult orthotopic liver transplant patients, seven cases of ADV disease were diagnosed. All patients had pneumonia, three were diagnosed with disseminated disease, and two patients died (McGrath et al., 1998). While infection may be associated with graft failure in heart, kidney, and liver transplant patients, pneumonia is a less common manifestation than in LTRs (Sandkovsky et al., 2014).

In HSCT, manifestations include severe pneumonia and gastrointestinal disease, including hepatitis and colitis. Other complications may involve hemorrhagic cystitis and adenoviral keratoconjunctivitis (Linderman et al., 2010; Robin et al., 2007).

Transmission

ADV is transmitted through direct contact with a patient's surroundings via fomites and infected secretions. Strains associated with gastroenteritis may be spread via fecal–oral route (Ison et al., 2009). ADV may be associated with healthcare-associated infections. In addition, these infections may be acquired from infected donors. The virus may establish latency in the organ and cause overt disease in the period of high intensity immunosuppression following transplantation (Ison et al., 2009).

Treatment and prevention

Supportive care and a reduction in immunosuppression are the cornerstones of management for ADV infections (Sandkovsky et al., 2014). Although there are no US Food and Drug Administration (FDA) approved medications for the treatment of ADV infections, several agents including cidofovir, brincidofovir, ribavirin, and ganciclovir demonstrate in vitro activity against the virus (Ison et al., 2009). Of these, intravenous cidofovir is favored by most studies because it retains activity against all ADV serotypes (Ganapathi et al., 2016).

While support for the use of antiviral agents is based largely on case reports and series, most transplant centers favor the use of intravenous cidofovir for the treatment of severe, progressive, and disseminated disease. Once initiated, treatment should be continued until symptoms have resolved completely and three consecutive specimens obtained 1 week apart from the site of infection test negative for ADV (Florescu and Hoffman, 2013; Ison et al., 2009). Cidofovir may also be used to preemptively treat viremic patients with a clinical syndrome compatible with ADV infection. Antiviral initiation should be weighed carefully given possible medication side effects, namely nephrotoxicity.

Brincidofovir is a cidofovir derivate with a lipid chain that increases its cellular uptake. It has good in vitro activity against ADV. Phase 2 and 3 studies have shown reduced renal and bone marrow toxicity, making this a promising alternative treatment for double-stranded DNA viruses including ADV. The AdVise trial open-label non-randomized study in pediatric and adult HSCT patients week-24 report showed ADV viral load reduction at week 4 (76% of all pediatric patients and 44% of adults), 60-day all-cause mortality of 19% for pediatric patients vs. 43% for adults, and improved mortality with antiviral response in patients with ADV disseminated disease. Gastrointestinal side effects were a common cause of drug discontinuation in this and previous trials (Florescu et al., 2012; Grimley et al., 2016; Anon, 2017).

Prophylaxis is not recommended for ADV infections and there is no vaccine available for the prevention of these infections (Sandkovsky et al., 2014). Proposed strategies for the prevention of ADV outbreaks include cohorting patients, limiting the number of staff and visitors in a patient's room, and excluding infected hospital staff members from the unit (Weigt et al., 2011). Hand washing is unlikely to eradicate the virus from hands of staff members; therefore the implementation of strategies such as contact and droplet precautions for the duration of an infected patient's hospital stay is recommended (Weigt et al., 2011; Ison et al., 2009).

Influenza virus

There are four types of influenza virus: A, B, C, and D. Influenza A and B viruses are responsible for seasonal epidemics of the disease. A typical case in an immunocompetent host is associated with an average of 3 days (range 4–8 days) of systemic symptoms including fever, myalgia, cough, and diarrhea. However, transplant patients may present atypically and therefore be diagnosed later. For example, in HSCT patients, rhinorrhea was the most common symptom occurring in 85% of patients, followed by cough in nearly half of patients; fever was relatively rare occurring in only 30% of patients (Ison, 2013).

The incidence of influenza virus infection in transplant patients is similar to that in the general population. It is estimated to be 0–13% among SOT recipients and 4–5% among HSCT patients (Weigt et al., 2011). Therefore, organ transplant recipients represent a high-risk group for seasonal influenza viral epidemics and may experience worse outcomes compared to the general population (Raad et al., 1997; Weigt et al., 2011; Whimbey et al., 1994).

Influenza infections may occur at any point following transplantation in comparison to immunocompetent individuals, and the vast majority of these may be complicated by superimposed bacterial or fungal pneumonia (Raad et al., 1997; Weigt et al., 2011). In a study performed among HSCT patients, 23% developed LRTIs and the 30-day mortality was 5% (Kmeid et al., 2016). In a multicenter evaluation of pandemic influenza A/2009 H1N1 in HSCT patients, a 30-day mortality of 18.9% was noted (Reid et al., 2013). In HSCT, poor patient outcomes were associated with augmented immunosuppression for graft-versus-host disease, lymphopenia (CD4 $<$ 100 cells/ml), increasing age, and unrelated or mismatched donors (Ison, 2013; Reid et al., 2013).

In SOT patients, severe disease is usually seen early post-transplant during periods of intense immunosuppression, particularly in LTRs (Ison, 2013). Risk factors for severe disease include recent use of high-dose steroids, recent rejection, lymphocyte depletion, and lung transplantation. According to a retrospective single-center study, 39% of all respiratory infections were causedby influenza and 32% of all viral infections were observed among LTRs (Garbino et al., 2004). Overall, SOT patients are at higher risk of progression to pneumonia, respiratory failure requiring mechanical ventilation, secondary bacterial pneumonia, and extrapulmonary complications including pericarditis, myositis, and bronchiolitis obliterans (LTR) (Whimbey et al., 1994). Influenza infections may be associated with a significant decline in FEV1 (forced expiratory volume in 1 second) in LTRs (Garbino et al., 2004).

Transmission

Influenza viruses may be transmitted through the air in the form of aerosols and droplets, or through direct contact with secretions from infected patients or contaminated surroundings (Recommendations of the Center for International Blood and Marrow Transplant Research (CIBMTR®) et al., 2009). Transplant recipients may acquire an influenza viral infection during hospital admissions. According to one study in BMT patients, more than 50% of cases of influenza A infection may be healthcare-associated, with suspected transmission from infected visitors and healthcare workers (Raad et al., 1997; Whimbey et al., 1994). Another study reported an outbreak of the influenza A(H1N1) pandemic strain in a kidney transplant unit in 2009. Twenty-three patients in postoperative care were included in the cohort and received either prophylactic or treatment doses of oseltamivir based on nasopharyngeal swab PCR testing. Six out of the 23 patients had not received seasonal influenza vaccination previously and had poor outcomes: five of the six were diagnosed with influenza A (H1N1) and three of the five developed severe respiratory distress syndrome and eventually died in the intensive care unit. Of the 17 previously vaccinated patients, only one developed a mild symptomatic illness; the others remained asymptomatic (Helanterä et al., 2015).

Immunosuppressed patients receiving $>$1 mg/kg of corticosteroids and allogeneic stem cell transplant recipients may shed the virus for prolonged durations (often more than 2 weeks, but for up to 6 months), thereby increasing the chance of healthcare-associated infections and outbreaks (Weigt et al., 2011; Klimov et al., 1995). Additionally, donor-derived infections are possible, with transmission of the disease occurring through the lung and small intestines recovered from infected donors. The transmission of infection following transplant of other solid organs has not been well-established. It may occur due to biological plausibility, which may lead to delayed allograft function (Weigt et al., 2011).

Treatment and prevention

A retrospective study revealed that HSCT recipients may recover fully from their infection without sequelae if treatment with antivirals is instituted in a timely manner (Suyani et al., 2011). Annual influenza vaccination is the most effective strategy to prevent infection and is currently recommended for all patients, their families, and healthcare personnel (Tablan et al., 2004; Ferguson et al., 2010). The three drugs currently approved by the FDA for use in the USA and approved by the CDC for the treatment of influenza infections include oseltamivir, zanamivir, and peramivir. These drugs have activity against influenza A and B virus, as opposed to the M2 protein inhibitors which are only effective against influenza A. Moreover, the latter have fallen out of favor given the emergence of resistant influenza A viruses (Centers for Disease Control, 2017). Antivirals must be initiated within 48 h of symptom onset for maximum benefit, but should be initiated in this population regardless of the duration of symptoms. Early treatment with oseltamivir may prevent progression to pneumonia in about 70% of the patients and reduce mortality to $<$10% (Ferguson et al., 2010).

Outbreaks have been described in the inpatient and outpatient settings (Apewokin et al., 2014). To prevent an outbreak, prophylactic oseltamivir or M2 inhibitors are recommended for patients in units where influenza cases are diagnosed, regardless of

vaccination status. Prophylaxis may be considered for BMT patients during the first 6 months following transplantation, for patients with a contraindication to the vaccine, and for all unvaccinated healthcare workers and vaccinated personnel in the event of an outbreak attributed to a strain not covered by the seasonal influenza vaccine. If an influenza outbreak is confirmed, antiviral prophylaxis must be continued for at least 2 weeks or until 1 week following the control of an outbreak. In addition, educating staff, intensifying infection control measures such as hand washing, restricting the number of visitors and personnel entering an infected patient's room, cohorting patients with influenza, and implementing droplet precautions for all patients and airborne precautions in the case of suspected pandemic strains are recommended strategies to minimize the transmission of influenza virus within a facility (Tablan et al., 2004; Weigt et al., 2011).

While these measures are instrumental in limiting influenza outbreaks, it is important to note that the vaccine may be ineffective in BMT and SOT recipients during the first few months following transplantation (Engelhard et al., 1993). However, cohort studies and a recent meta-analysis have shown that influenza vaccination seems to confer clinical protection and is mostly safe in SOT and HSCT patients. An observational cohort study of 168 LTRs reported that 88% had received at least one H1N1 vaccination (68% received a second dose) during the 2009 pandemic. H1N1 was documented in only two of 148 vaccinated patients, in contrast to five infections in 20 non-vaccinated LTRs. Minor-to-moderate self-limited side effects occurred in 66%. A Brazilian cohort of 177 HSCT recipients followed for up to 1 year had 43 patients eligible for vaccination 6 months after BMT. Compliance with vaccination was 44.2% (19 patients) and influenza was diagnosed in only two, compared to 12 out of the 24 unvaccinated patients, translating to vaccine efficacy of 80% (Beck et al., 2012; Schuurmans et al., 2011; Machado et al., 2005).

Parainfluenza virus

There are four distinct serotypes of PIV: PIV1, PIV2, PIV3, and PIV4. PIV1 and PIV2 are implicated in community-acquired infections in children, while PIV3 causes healthcare-associated infections. Infections may occur throughout the year, with a peak incidence in summer and spring (Hirsch et al., 2013; Sydnor et al., 2012). Overall, the virus accounts for about 10% of respiratory infections among BMT recipients (Raad et al., 1997) and is usually associated with a low mortality. Patients initially develop URTIs, with progression to pneumonia observed in 23–60% of infected HSCT patients (Weigt et al., 2011; Wendt et al., 1992). Disease progression has primarily been seen in patients who have received an unrelated donor transplant, developed lymphopenia, and had profound immunosuppression, particularly patients on corticosteroids (Wendt et al., 1992). Although mortality is relatively low, URTIs and LRTIs may be fatal. According to one study, up to two-thirds of the patients may develop pneumonia and a third of those patients with severe disease may die (Wendt et al., 1992). A prospective cohort study of LTRs, systematically screened for different respiratory viruses via nasopharyngeal specimens or bronchoalveolar lavage when indicated, found PIV along with RSV, and PIV associated with a three times higher chance of being hospitalized compared to those without viral or bacterial infection (Bridevaux et al., 2014). Of note, co-infection with other respiratory pathogens and respiratory failure are associated with worse outcomes (Bridevaux et al., 2014).

Among SOT recipients, PIV infections have been the most studied. In SOT recipients, the incidence of disease varies across centers, ranging between 5% and 16% (Vilchez et al., 2001). The vast majority of infections are observed 1 year after transplantation, with most patients being asymptomatic. Infection is associated with allograft rejection in 82% of patients and bronchiolitis obliterans in 32% (Vilchez et al., 2001). PIV LRTIs may also be associated with airway decline among allogeneic HSCT patients (Wendt et al., 1992). As is seen in most RVIs in transplant recipients, PIV infection has been associated with prolonged shedding in HSCT patients (Sydnor et al., 2012).

Transmission

Direct contact with patient surroundings and secretions is the main mode of transmission for PIV infections, but spread through droplets may also occur (Raad et al., 1997; Weigt et al., 2011). Nosocomial transmission and outbreaks of PIV infection have been described in inpatient as well as outpatient settings (Sydnor et al., 2012).

Treatment and prevention

At present, there are no FDA licensed drugs or vaccines for the treatment and prevention of PIV infections (Weigt et al., 2011). Reducing immunosuppression, prophylaxis, and preemptive treatment are some of the recommended strategies (Recommendations of the Center for International Blood and Marrow Transplant Research (CIBMTR®) et al., 2009). Drugs such as ribavirin have been used in some studies, but they have failed to impact mortality among patients with respiratory failure (Weigt et al., 2011; Nichols et al., 2001). The administration of aerosolized ribavirin with or without IVIG has been shown to have no effect on mortality in patients requiring mechanical ventilation (Nichols et al., 2001). Neuraminidase inhibitors may be beneficial, but additional studies are required to further characterize this (Weigt et al., 2011). Novel agents such as DAS181 (a recombinant sialidase fusion protein) and BCX2798 (a hemagglutinin-neuraminidase inhibitor) are under investigation and may be effective in treating PIV infection (Salvatore et al., 2016; Shah et al., 2016a). In a small study of 16 HSCT recipients with PIV infections, 56% had a complete clinical response with DAS181 therapy, while 19% died (Salvatore et al., 2016). Larger studies are required to further evaluate its efficacy (Salvatore et al., 2016). The CDC currently recommends contact isolation, hand hygiene, protective gear such as masks and gloves, and universal precautions to prevent outbreaks (Shah et al., 2016a).

Human metapneumovirus

hMPV was first identified as a cause of upper and lower respiratory tract infection in 2001 (Dosanjh, 2015). It is the second most common cause of bronchiolitis among pediatric patients and most cases are identified between December and May (Weigt et al., 2011; Seo et al., 2016). It is increasingly recognized as a cause of respiratory tract infection among organ transplant recipients (Seo et al., 2016). As with the other RVIs, infections with hMPV may progress from URTI to pneumonia and may even be fatal, with mortality rates of up to 50% (Oliveira et al., 2008). The use of systemic corticosteroids, low lymphocyte counts, and respiratory failure are factors associated with the progression of disease to pneumonia (Seo et al., 2016; Oliveira et al., 2008). Studies have reported an incidence of 4–7% among stem cell transplant recipients, with less well defined statistics for SOT, although similar infection rates in LTRs of around 4–7% have been reported (Lee and Barton, 2007; Shah et al., 2016b; Weinberg et al., 2010). LRTIs may develop in 21–40% of infected patients, with reported fatality rates of up to 80% (Shah et al., 2016b). In a study performed among LTRs, hMPV was isolated from 19 of 47 patients with a viral respiratory tract infection. Sixty-three per cent of these patients developed graft dysfunction (Hopkins et al., 2008). These infections may also be complicated by prolonged viral shedding and allograft dysfunction (Dosanjh, 2015).

Table 1
Strategies for the prevention of respiratory viral infections (Centers for Disease Control and Prevention, 2017; Dignan et al., 2016; Lessler et al., 2009).

Type of virus	Incubation period (days)	Mode of transmission	Infection prevention principles	Treatment options
RSV	3–7	Direct or indirect contact; droplet	Standard precautions; contact precautions; droplet precautions	Ribavirin aerosolized, IV, or PO ± IVIG; palivizumab?
ADV	5–9	Direct contact; aerosol; fecal–oral	Standard precautions; contact precautions; droplet precautions	Cidofovir; brincidofovir
Influenza	1–4	Contact; droplet; aerosol	Standard precautions; droplet precautions; airborne with invasive ventilation; seasonal vaccination; post-exposure prophylaxis with oseltamivir	Oseltamivir; zanamivir; peramivir
PIV	2–6	Direct contact; droplet; large particle aerosol	Standard precautions; airborne precautions; droplet precautions	Ribavirin ± IVIG? DAS-181?
hMPV	4–6	Direct contact; droplet; large particle aerosol	Standard precautions; contact precautions	ND
Rhinovirus	1–9	Direct or indirect contact; large or small particle aerosol	Standard precautions; droplet precautions	ND

ADV, adenovirus; hMPV, human metapneumovirus; IV, intravenous; IVIG, intravenous immunoglobulin; ND, no data; PIV, parainfluenza virus; PO, oral; RSV, respiratory syncytial virus.

Transmission

hMPV spreads from person to person through secretions from coughing and sneezing, close contact, and by touching objects or surfaces contaminated with the virus. These infections are most often community-acquired, but may also be healthcare-associated (Lee and Barton, 2007).

Treatment and prevention

There is currently no approved treatment or vaccine for hMPV, thus further studies are required in this area. Ribavirin has in vitro activity against hMPV and has been used with or without IVIG with mixed results (Hirsch et al., 2013; Shah et al., 2016b). A reduction of immunosuppression may be beneficial in infected patients (Weigt et al., 2011). Investigational drugs such as MoAb 338 and Fab DS7 have shown promising results in vitro and may be options for treating and preventing hMPV infections in the near future (Shah et al., 2016b). Given the lack of effective treatment options, infection control measures such as hand hygiene and contact precautions are crucial in preventing outbreaks. Since many infections may be subclinical at the beginning of illness, routine surveillance for patients with respiratory symptoms may be beneficial (Shah et al., 2016b).

Rhinovirus

Rhinovirus is the most common viral infection in humans and the predominant cause of the common cold. It is no surprise that it is also the most commonly isolated virus among transplant recipients with respiratory infections (Weigt et al., 2011). Most infections are limited to the upper respiratory tract, but involvement of the lower respiratory tract is observed among patients with profound immunosuppression (Weigt et al., 2011; Manuel et al., 2014). According to one study, the cumulative incidence among HSCT was found to be 22.3% and viral shedding ranged from 3 weeks to 3 months (Milano et al., 2010). In a prospective study performed among LTRs, 14.7% of patients had rhinovirus identified in respiratory specimens. Three patients in this study had prolonged viral shedding lasting 12 months; all of these patients had allograft dysfunction and two died (Kaiser et al., 2006).

Transmission

Rhinovirus is spread by direct hand-to-hand contact, via autoinoculation of viral particles into the eyes or nares. It is also thought to spread via aerosolized droplets. Although usually a community-acquired infection, rhinovirus has been associated with healthcare-associated transmission following direct contact of healthcare workers and patients with an infected individual (Jacobs et al., 2013).

Treatment and prevention

The CDC currently recommend droplet precautions for patients with rhinovirus infections. In addition, contact precautions may be required for patients with copious respiratory secretions (Siegel et al., 2007). There are currently no vaccines or drugs approved for the treatment of rhinovirus infections. Treatment options are also limited to largely supportive care and a reduction in immunosuppression. In severe cases, IVIG may be used as an adjunct to these measures (Weigt et al., 2011).

Conclusions

Although often thought to be self-limited in a healthy host, RVIs can persist to cause a prolonged duration of illness and progress to cause LRTIs such as pneumonia, graft loss, and even death in transplant patients. They can disseminate to involve other organs and this is most commonly seen with RSV and ADV infections. Transplant patients are at risk of these infections, particularly during periods when immunosuppression is the highest (usually the first 6 months after transplantation). A prolonged duration of illness and viral shedding is also common in this population. As transplant patients are often grouped together in shared hospital units or clinics, nosocomial spread has commonly been observed. Therefore, vigilant hand washing, as well as other standard precautions recommended by the CDC, is urged. Cohorting may be considered along with additional infection control measures, as outlined in Table 1.

Funding

None.

Conflict of interest

None.

References

American Academy of Pediatrics. 2014; Available at: http://pediatrics.aappublications.org/content/134/2/415.full.
Chimerix Announces Final Data from AdVise trial of brincidofovir for the treatment of adenovirus (AdV) infection in allogeneic hematopoietic cell transplant (HCT) recipients at the BMT Tandem Meetings held February 22-6, 2017 in Orlando, FL. Available at: http://ir.chimerix.com/releasedetail.cfm?releaseid=1013907.

Apewokin S, Vyas K, Lester LK, et al. Influenza A Outbreak in an Ambulatory Stem Cell Transplant Center. Open Forum Infect Dis 2014;1(2).
Beaird OE, Freifeld A, Ison MG, et al. Current practices for treatment of respiratory syncytial virus and other non-influenza respiratory viruses in high-risk patient populations: a survey of institutions in the Midwestern Respiratory Virus Collaborative. Transpl Infect Dis 2016;18(2):210–5.
Beck Charles R, McKenzie Bruce C, Hashim Ahmed B, Harris Rebecca C, University of Nottingham Influenza and the ImmunoCompromised (UNIIC) Study Group, Nguyen-Van-Tam Jonathan S. Influenza Vaccination for Immunocompromised Patients: Systematic Review and Meta-analysis by Etiology. J Infect Dis 2012;206(8):1250–9.
Bridevaux PO, Aubert JD, Soccal PM, Mazza-Stalder J, Berutto C, Rochat T, et al. Incidence and outcomes of respiratory viral infections in lung transplant recipients: a prospective study. Thorax 2014;69(January (1)):32–8.
Bridges ND, Spray TL, Collins MH, et al. Adenovirus infection in the lung results in graft failure after lung transplantation. J Thorac Cardiovasc Surg 1998;116 (4):617–23.
Centers for Disease Control and Prevention. Healthcare Infection Control Practices Advisory Committee (HICPAC). 2007 Available at: https://www.cdc.gov/hicpac/2007IP/2007ip_appendA.html..
Centers for Disease Control. Available at: https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm.
Dignan FL, Clark A, Aitken C, et al. BCSH/BSBMT/UK clinical virology network guideline: diagnosis and management of common respiratory viral infections in patients undergoing treatment for haematological malignancies or stem cell transplantation. Br J Hematol 2016;173(3):380–93.
Dosanjh A. Respiratory metapneumoviral infection without co-infection in association with acute and chronic lung allograft dysfunction. J Inflamm Res 2015;8:79–82.
Engelhard D, Nagler A, Hardan I, et al. Antibody response to a two-dose regimen of influenza vaccine in allogeneic T cell-depleted and autologous BMT recipients. Bone Marrow Transplant 1993;11(1):1–5.
Ferguson PE, Jordens CF, Gilroy NM. Patient and family education in HSCT: improving awareness of respiratory virus infection and influenza vaccination. A descriptive study and brief intervention. Bone Marrow Transplant 2010;45 (4):656–61.
Florescu DF, Hoffman JA. Adenovirus in solid organ transplantation. Am J Transplant 2013;(Suppl. 4):206–11.
Florescu DF, Pergam SA, Neely MN, et al. Safety and efficacy of CMX001 as salvage therapy for severe adenovirus infections in immunocompromised patients. Biol Blood Marrow Transplant 2012;18(May (5)):731–8.
Gaboli M, de la Cruz ÒA, de Agüero MI, et al. Use of palivizumab in infants and young children with severe respiratory disease: a Delphi study. Pediatr Pulmonol 2014;49(5):490–502.
Ganapathi L, Arnold A, Jones S, et al. Use of cidofovir in pediatric patients with adenovirus infection. Version 2. F1000Res 2016;5(758).
Garbino J, Gerbase MW, Wunderli W, et al. Respiratory viruses and severe lower respiratory tract complications in hospitalized patients. Chest 2004;125 (3):1033–9.
Garcia R, Raad I, Abi-Said D, et al. Nosocomial respiratory syncytial virus infections: prevention and control in bone marrow transplant patients. Infect Control Hosp Epidemiol 1997;18(6):412–6.
Garner JS. Guideline for isolation precautions in hospitals. The Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol 1996;17 (1):53–80.
Gottlieb J, Zamora MR, Hodges T, et al. ALN-RSV01 for prevention of bronchiolitis obliterans syndrome after respiratory syncytial virus infection in lung transplant recipients. J Heart Lung Transplant 2016;35(2):213–21.
Grimley M, Papanicolaou G, Prasad VK, et al. Treatment of adeno- virus (AdV) infection in allogeneic hematopoietic cell transplant (HCT) patients (pts) with brincidofovir: 24-week interim results from the AdVise trial. ID Week 2016. New Orleans, LA: Infectious Diseases Society of America; abstract. p. 2339.
Gross AE, Bryson ML. Oral Ribavirin for the Treatment of Noninfluenza Respiratory Viral Infections: A Systematic Review. Ann Pharmacother 2015;49(10):1125–35.
Hall CB. Nosocomial respiratory syncytial virus infections: the “Cold War” has not ended. Clin Infect Dis 2000;31(2):590–6.
Hattington RD, Hooton TM, Hackman RC. An outbreak of respiratory syncitial virus in a bone marrow transplant center. J Infect Dis 1992;165:987–93.
Helanterä I, Anttila VJ, Lappalainen M, Lempinen M, Isoniemi H. Outbreak of Influenza A(H1N1) in a Kidney Transplant Unit-Protective Effect of Vaccination. Am J Transplant 2015;15(September (9)):2470–4.
Hirsch HH, Martino R, Ward KN, et al. Fourth European Conference on Infections in Leukaemia (ECIL-4): guidelines for diagnosis and treatment of human respiratory syncytial virus, parainfluenza virus, metapneumovirus, rhinovirus, and coronavirus. Clin Infect Dis 2013;56(2):258–66.
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(8):876–81.
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(10):2555–9.
Ison MG, Green M, AST Infectious Diseases Community of Practice. Adenovirus in solid organ transplant recipients. Am J Transplant 2009;(Suppl. 4):S161–5.
Ison MG. Respiratory syncytial virus and other respiratory viruses in the setting of bone marrow transplantation. Curr Opin Oncol 2009;21(2):171–6.
Ison MG. Influenza prevention and treatment in transplant recipients and immunocompromised hosts. Influenza Other Respir Viruses 2013;7(Suppl. 3):60–6.
Jacobs SE, Lamson DM, George KS, et al. Human Rhinoviruses. Clin Microbiol Rev 2013;26(1):135–66.
Jensen TO, Stelzer-Braid S, Willenborg C, et al. Outbreak of respiratory syncytial virus (RSV) infection in immunocompromised adults on a hematology ward. J Med Virol 2016;88(10):1827–31.
Jones BL, Clark S, Curran ET, et al. Control of an outbreak of respiratory syncytial virus infection in immunocompromised adults. J Hosp Infect 2000;44(1):53–7.
Kaiser L, Aubert JD, Pache JC, et al. Chronic rhinoviral infection in lung transplant recipients. Am J Respir Crit Care Med 2006;174(12):1392–9.
Kassis C, Champlin RE, Hachem RY, et al. Detection and control of a nosocomial respiratory syncytial virus outbreak in a stem cell transplantation unit: the role of palivizumab. Biol Blood Marrow Transplant 2010;16(9):1265–71.
Klimov AI, Rocha E, Hayden FG, et al. Prolonged shedding of amantadine-resistant influenza A viruses by immunodeficient patients: detection by polymerase chain reaction-restriction analysis. J Infect Dis 1995;172(5):1352–5.
Kmeid J, Vanichanan J, Shah DP, et al. Outcomes of Influenza Infections in Hematopoietic Cell Transplant Recipients: Application of an Immunodeficiency Scoring Index. Biol Blood Marrow Transplant 2016;22(3):542–8.
Lavergne V, Ghannoum M, Weiss K, et al. Successful prevention of respiratory syncytial virus nosocomial transmission following an enhanced seasonal infection control program. Bone Marrow Transplant 2011;46(1):137–42.
Lee I, Barton TD. Viral respiratory tract infections in transplant patients: epidemiology, recognition and management. Drugs 2007;67(10):1411–27.
Lehners N, Schnitzler P, Geis S, et al. Risk factors and containment of respiratory syncytial virus outbreak in a hematology and transplant unit. Bone Marrow Transplant 2013;48(12):1548–53.
Lessler J, Reich NG, Brookmeyer R, Perl TM, Nelson KE, Cummings DAT. Incubation periods of acute respiratory viral infections: a systematic review. Lancet Infect Dis 2009;9(5):291–300.
Linderman CA, Leen AM, Boelens JJ. How I treat adenovirus in hematopoietic stem cell transplant recipients. Blood 2010;116(December (25)):5476–85.
Machado CM, Cardoso MR, da Rocha IF, Boas LS, Dulley FL, Pannuti CS. The benefit of influenza vaccination after bone marrow transplantation. Bone Marrow Transplant 2005;36(November (10)):897–900.
Manuel O, López-Medrano F, Keiser L, ESCMID Study Group of Infection in Compromised Hosts (ESGICH). Influenza and other respiratory virus infections in solid organ transplant recipients. Clin Microbiol Infect 2014;20(Suppl. 7):102–8.
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(2):459–62.
Milano F, Campbell AP, Guthrie KA, et al. Human rhinovirus and coronavirus detection among allogeneic hematopoietic stem cell transplantation recipients. Blood 2010;115(10):2088–94.
Neemann K, Freifeld A. Respiratory Syncytial Virus in Hematopoietic Stem Cell Transplantation and Solid-Organ Transplantation. Curr Infect Dis Rep 2015;17 (7):490.
Nichols WG, Corey L, Gooley T, et al. Parainfluenza virus infections after hematopoietic stem cell transplantation: risk factors, response to antiviral therapy, and effect on transplant outcome. Blood 2001;98(3):573–8.
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(4):265–9.
Raad I, Abbas J, Whimbey E. Infection Control of Nosocomial Respiratory Viral Disease in the Immunocompetent Host. Am J Med 1997;102(3A):48–52.
Recommendations of the Center for International Blood and Marrow Transplant Research (CIBMTR®), the National Marrow Donor Program (NMDP), the European Blood and Marrow Transplant Group (EBMT), the American Society of Blood and Marrow Transplantation (ASBMT), the Canadian Blood and Marrow Transplant Group (CBMTG), the Infectious Disease Society of America (IDSA), et al. Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplant Recipients: A Global Perspective. Biol Blood Marrow Transplant 2009;15(10):1143–238.
Reid G, Huprikar S, Patel G, et al. A multicenter evaluation of pandemic influenza A/H1N1 in hematopoietic stem cell transplant recipients. Transpl Infect Dis 2013;15(5):487–92.
Renaud Christian, Campbell Angela P. Changing Epidemiology of Respiratory Viral Infections in Hematopoietic Cell Transplant Recipients and Solid Organ Transplant Recipients. Curr Opin Infect Dis 2011;24(4):333–43.
Robin M, Marque-Juillet S, Scieux C, et al. Disseminated Adenovirus Infections After Allogeneic Hematopoietic Stem Cell Transplantation: Incidence, Risk Factors And Outcomes. Haematologia 2007;92(9):1254–7.
Runde V, Ross S, Trenschel R, Lagemann E, Basu O, Renzing-Köhler K, et al. Adenoviral infection after allogeneic stem cell transplantation (SCT): report on 130 patients from a single SCT unit involved in a prospective multi center surveillance study. Bone Marrow Transplant 2001;28(July (1)):51–7.
Salvatore M, Satlin MJ, Jacobs SE, et al. DAS181 for Treatment of Parainfluenza Virus Infections in Hematopoietic Stem Cell Transplant Recipients at a Single Center. Biol Blood Marrow Transplant 2016;22(5):965–70.
Sandkovsky U, Vargas L, Florescu DF. Adenovirus: current epidemiology and emerging approaches to prevention and treatment. Curr Infect Dis Rep 2014;16 (8):416.

Schuurmans MM, Tini GM, Dalar L, Fretz G, Benden C, Boehler A. Pandemic 2009 H1N1 influenza virus vaccination in lung transplant recipients: coverage, safety and clinical effectiveness in the Zurich cohort. J Heart Lung Transplant 2011;30(June (6)):685–90.
Seo S, Gooley TA, Kuypers JM, et al. Human Metapneumovirus Infections Following Hematopoietic Cell Transplantation: Factors Associated With Disease Progression. Clin Infect Dis 2016;63(2):178–85.
Shah DP, Shah PK, Azzi JM, et al. Parainfluenza virus infections in hematopoietic cell transplant recipients and hematologic malignancy patients: A systematic review. Cancer Lett 2016a;370(2):358–64.
Shah DP, Shah PK, Azzi JM, et al. Human metapneumovirus infections in hematopoietic cell transplant recipients and hematologic malignancy patients: A systematic review. Cancer Lett 2016b;379(1):100–6.
Siegel JD, Rhinehart E, Jackson M, Health Care Infection Control Practices Advisory Committee. 2007 Guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings. Am J Infect Control 2007;35 (10 Suppl. 2):S65–S164.
Suyani E, Aki Z, Guzel O, Altindal S, et al. H1N1 infection in a cohort of hematopoietic stem cell transplant recipients: prompt antiviral therapy might be life saving. Transpl Infect Dis 2011;13(2):208–12.
Sydnor ERM, Greer A, Budd AP, et al. An outbreak of human parainfluenza virus 3 infection in an outpatient hematopoietic stem cell transplantation clinic. Am J Infect Control 2012;40(7):601–5.
Tablan OC, Anderson LJ, Besser R, CDC, Healthcare Infection Control Practices Advisory Committee. Guidelines for preventing health-care–associated pneumonia, 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. MMWR Recomm Rep 2004;53(RR-3):1–36.
Vilchez RA, McCurry K, Dauber J, et al. The epidemiology of parainfluenza virus infection in lung transplant recipients. Clin Infect Dis 2001;33(12):2004–8.
Weigt SS, Gregson AL, Deng JC, et al. Respiratory Viral Infections in Hematopoietic Stem Cell and Solid Organ Transplant Recipients. Semin Respir Crit Care Med 2011;32(4):471–93.
Weinberg A, Lyu DM, Li S, Marquesen J, Zamora MR. Incidence and morbidity of human metapneumovirus and other community-acquired respiratory viruses in lung transplant recipients. Transpl Infect Dis 2010;12(August (4)):330–5.
Wendt CH, Weisdorf DJ, Jordan MC, et al. Parainfluenza virus respiratory infection after bone marrow transplantation. N Engl J Med 1992;326(14):921–6.
Whimbey E, Elting LS, Couch RB, et al. Influenza A virus infections among hospitalized adult bone marrow transplant recipients. Bone Marrow Transplant 1994;13(4):437–40.
Whimbey E, Champlin RE, Englund JA, et al. Combination therapy with aerosolized ribavirin and intravenous immunoglobulin for respiratory syncytial virus disease in adult bone marrow transplant recipients. Bone Marrow Transplant 1995;16(3):393–9.
Whimbey E, Champlin RE, Couch RB, et al. Community respiratory virus infections among hospitalized adult bone marrow transplant recipients. Clin Infect Dis 1996;22(5):778–82.