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REVIEW ARTICLE

Post-transplant Viral Respiratory Infections in the Older Patient: Epidemiology, Diagnosis, and Management

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Abstract Organ and stem cell transplantation has been one of the greatest advances in modern medicine, and is the primary treatment modality for many end-stage diseases. As our population ages, so do the transplant recipients, and with that comes many new challenges. Respiratory viruses have been a large contributor to the mortality and morbidity of solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) recipients. Respiratory viruses are generally a long-term complication of transplantation and primarily acquired in the community. With the emergence of molecular methods, newer respiratory viruses are being detected. Respiratory viruses appear to cause severe disease in the older transplant population. Influenza vaccine remains the mainstay of prevention in transplant recipients, although immunogenicity of current vaccines is suboptimal. Limited therapies are available for other respiratory viruses. The next decade will likely bring newer antivirals and vaccines to the forefront. Our goal is to provide the most up to date knowledge of respiratory viral infections in our aging transplant population.

Key Points

Given new molecular identification techniques, a greater number of respiratory viruses are being identified.

The older transplant patient has a greater risk of lower respiratory disease from respiratory viruses.

Therapies are limited for the majority of viruses, and prevention is key.

1 Introduction

For many patients with severe and life-threatening conditions such as end-stage organ disease and hematological malignancy, transplantation is a life-saving modality. The shift towards a growing aging population has had a direct impact on this field. During the 1980s, the number of people between the ages of 75 and 79 increased by 28.8%, and those over the age of 85 years increased by 52.4% [1]. Not only has the life expectancy in older individuals increased, but their general health has also improved [1, 2].

The direct impact of the aging population has been seen in the transplant population. The average age of patients on the kidney transplant waiting list has increased. Just within the past decade, we have seen the doubling of registrants aged 50–69 years old. Those aged 70 years or older have also increased more than 5-fold. This is in stark contrast to the declining number of patients younger than the age of 50 who are on the waiting list [3]. This trend is not only seen in kidney transplantation; Su et al. reported the mean age of liver transplant registrants increased from 51.2 to

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55.7 years, and the proportion of registrants aged 60 years or older increased from 19 to 41% [4]. Graft survival data in older individuals, as reported by the United Network for Organ Sharing (UNOS), has also shown that 5-year graft survival is similar in transplant recipients above age 60 years when compared to those aged less than 60 years [1].

Respiratory viral infections (RVIs) are a significant cause of morbidity and mortality in immunocompromised patients. With the increasing numbers of elderly patients being transplanted, this review will highlight the knowledge about transplant [both solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT)] recipients infected with respiratory viruses and make note when there is a specific impact on the aging transplant patient.

2 Epidemiology

The prevalence of RVIs in any given season depends on a combination of factors: the method of exposure, types of circulating viruses, virulence of the virus, and the detection methods used. The majority of respiratory virus transmission occurs via direct contact or air droplets. The incubation periods range between 1 and 10 days; however, for other viruses, such as bocavirus, the incubation period is still unknown [5, 6]. One study noted the incidence of RVIs in the SOT population as 0.91 episodes/patient/year [7]. Drieghe et al. evaluated the epidemiology of respiratory viruses in bronchoalveolar lavage (BAL) specimens from patients with lower respiratory tract disease in a group of immunocompromised adults and found that coronavirus was the most common pathogen found (13.4%), followed by rhinovirus (5.2%), respiratory syncytial virus (RSV) (4.5%), and bocavirus (3.7%) [8]. In general, studies of RVI incidence in the transplant population show that older individuals have a similar incidence of RVI acquisition compared to the younger population. Within the SOT group, lung transplant recipients appear to have the greatest frequency of RVI and of developing lower airway disease. A prospective study in 93 lung transplant recipients from 2003–2006 showed that progression of RVI to involve the lower respiratory tract occurred in 6.2% of the cohort [9]. This may be due to the direct contact of the allograft with the environment, immune dysregulation within the allograft, and potentially a greater degree of immunosuppression after lung transplantation compared to other organ transplant types [10]. Some studies have found a time-dependent association of RVIs with acute rejection and chronic lung allograft dysfunction (CLAD) in the lung transplant population [9, 11, 12]. Fisher et al. found that the risk of CLAD increased $\sim$ 5-fold in the 3 months following an RVI episode [12]. Similarly, a case–control study noted that acute rejection or a $\geq$ 20% decline in the forced expiratory volume occurred in 33.3% of patients with RVI [9].

More specific studies focusing on the epidemiology of community respiratory viruses in allogeneic HSCT patients have shown that rhinovirus and coronaviruses are common, followed by adenovirus and RSV [13, 14]. The fatality rate from viral pneumonia has been reported to be anywhere between 12 and 43% amongst the HSCT population [15–19]. Risk factors for lower respiratory disease in HSCT recipients include older age (greater than 65 years), severe neutropenia, severe lymphopenia, myeloablative conditioning, the presence of graft versus host disease (GVHD) and cytomegalovirus seropositivity [13, 20, 21].

3 Clinical Presentation

Clinical presentation is similar among all RVIs; rhinitis, pharyngitis, malaise, coryza, and cough are common symptoms [7, 13]. The presence of fever is variable and occurs in 13.5–85%, depending on the specific RVI, and cannot be used as a reliable marker [7, 22–26]. Chest radiograph findings in lower respiratory tract infection are nonspecific and can include interstitial disease, consolidation, or small pulmonary nodules [27]. In cases of lower respiratory infection, bacterial superinfection is important to consider.

Respiratory virus positivity in respiratory specimens is generally up to 14 days in most series; however, virus can remain positive for several months despite resolution of symptoms [13, 23, 28]. In one study, corticosteroid dosages greater than 1 mg/kg daily were shown to prolong influenza virus positivity compared to persons treated with lower doses (15 vs 9 days) [17]. The clinical relevance of prolonged shedding is unknown. However, it is seen even with the use of antivirals against influenza and could contribute to the increased risk of resistant viruses [23, 29].

4 Laboratory Diagnosis

All patients with suspected RVI should have a nasopharyngeal swab, wash, or aspirate for diagnosis. BAL specimens can also be used for detection. Viral culture has historically been used, although it can take up to 10 days, leading to delays in diagnosis. In addition, culture methods are not available for all respiratory viruses. Direct fluorescent antibody (DFA) can provide results in a few hours, but reagents are available for only a limited number of viruses, such as influenza A and B; parainfluenza 1, 2, and 3; RSV and adenovirus [6, 30]. DFA also requires the presence of epithelial cells for higher sensitivity and

requires technical expertise to interpret results [31]. Sensitivity of DFA has ranged from 23 to 80% [31, 32]. Rapid antigen detection assays are primarily used for influenza and RSV diagnosis. However, the new gold standard in testing is now multiplex nucleic acid testing (NAT) because of the ability to detect a diverse number of respiratory viruses, with results being available within 12–24 h. Sensitivity of multiplex NAT assays ranges from 72 to 100%, with best sensitivity seen for influenza and lower sensitivities for adenovirus and parainfluenza [33–35].

5 Specific Respiratory Viruses

5.1 Influenza

Influenza virus is a negative-sense, single-stranded RNA orthomyxovirus that circulates primarily in the winter months. The predominant circulating seasonal strains are A/H1N1, influenza A/H3N2, and influenza B [29]. Influenza virus undergoes antigenic drift (small mutations in the genome that lead to changes primarily in hemagglutinin) and shift (larger mutations). Since antibody responses are primarily directed against hemagglutinin, changes in this protein decrease the protective effects of antibodies [36].

In the elderly and transplant communities, influenza is known to cause significant morbidity, mortality, and economic burden [37–40]. The elderly and immunosuppressed are considered to be at high risk for influenza infection and account for the majority of all influenza-related deaths. Using national surveillance data from the USA, Thompson et al. showed that the population aged 85 years or older has a 16-fold greater mortality from influenza compared with persons aged 65–69 years [41]. Vilchez et al. studied a cohort of organ transplant recipients with seasonal influenza and showed that the incidence of influenza was 41.8, 2.8, and 4.3 cases per 1000 person years in lung, liver, and kidney transplant recipients, respectively [42]. A subsequent large multicenter study of SOT recipients with the 2009 pandemic H1N1 influenza strain showed that 16% of patients required admission to the intensive care unit (ICU) [24]. Delayed antiviral treatment begun ≥ 48 h after symptom onset and history of diabetes were both associated with an increased risk of ICU admission. The median age of adults in this cohort was 47 years (range 18–95); however, older age was not associated with negative outcomes. A similar European study of 2009 pandemic influenza in the HSCT population included 286 patients—222 allogeneic and 64 autologous transplant recipients [43]. Almost one-third of patients (32.5%) developed lower respiratory tract disease, including pneumonia in almost half of patients over age 60 years; age and lymphopenia were significant risk factors for severe disease.

Investigators also reported a 6.3% mortality rate for A/H1N1 infection or its complications.

The presentation of influenza in transplant patients can be nonspecific, especially in elderly recipients. Classic symptoms of influenza-like illness (ILI) may be absent in both the elderly and transplant community. ILI criteria are not validated for use in the transplant community; one study showed that the positive predictive value for the definition of ILI in transplant recipients was only 50% and resulted in the overuse of antivirals and missed diagnoses of other respiratory viruses [44].

Lower respiratory tract infections including bacterial superinfection occur in up to one-third of transplant patients with influenza. Other complications seen in transplant recipients are allograft dysfunction, acute rejection, myocarditis, myositis, increased rates of obliterative bronchiolitis in lung transplant recipients, prolonged shedding of influenza virus, and emergence of antiviral resistance [12, 29, 30, 42, 45, 46].

The mainstay of antiviral therapy for influenza in transplant recipients is neuraminidase inhibitors such as oseltamivir, zanamivir, and peramivir [47] (Table 1). Neuraminidase inhibitors prevent the cleavage of sialic acid residues, which are the point of attachment for influenza virions [48]. The standard dosage of oseltamivir in adults is 75 mg twice daily and requires dose adjustment for diminished renal function as well as in pediatric populations. Double-dose oseltamivir has been used in critically ill transplant recipients, although recent evidence in the immune competent population indicates that higher doses have no additional benefit [49, 50]. The typical duration of treatment is 5 days; however, longer durations have been suggested by some experts if symptoms are ongoing. Transplant recipients are known to have prolonged influenza viral shedding; however, expert opinion suggests that antivirals should not be used for asymptomatic patients. Repeated nasopharyngeal sampling may be used to make decisions regarding infection control.

Influenza A/H1N1 viruses, and some influenza A/H5N1 and influenza B viruses, have been able to develop resistance to oseltamivir [51, 52]. Options to treat oseltamivir-resistant viruses include zanamivir and peramivir. Zanamivir is an inhaled medication with a recommended dosage of 10 mg, or two puffs, twice daily for 5 days. Intravenous zanamivir is also available and can be used in critically ill patients in whom oseltamivir resistance is suspected or proven [53–55]. A newer neuraminidase inhibitor, peramivir, is Food and Drug Administration (FDA) approved and has been compared to oseltamivir in a multicenter clinical trial. In this study, patients treated with peramivir had a greater viral load reduction than those given oseltamivir; however, efficacy and tolerability were similar [56, 57]. Peramivir is also an option for influenza virus

Table 1 Therapeutic options and prevention measures for respiratory viruses in transplant recipients

Virus	Treatment[a]	Prevention
Influenza	Neuraminidase inhibitors (oseltamivir or zanamivir or peramivir)	Contact
		Droplet precautions
	M2 inhibitors generally not used due to resistance	Annual vaccination—trivalent or quadrivalent inactivated vaccines
RSV	Supportive care	Contact and droplet precautions
	Ribavirin aerosolized, oral, intravenous formulations	Airborne precautions may be used for emerging viruses
PIV	Supportive care	
	Ribavirin likely not helpful	
Adenovirus	Cidofovir	
	Immune globulin	
Coronaviruses	Supportive care	
hMPV		
Rhinovirus		

hMPV human metapneumovirus, *PIV* parainfluenza virus, *RSV* respiratory syncytial virus

[a]Reduction of immunosuppression is likely beneficial for all respiratory viral infections

resistant to oseltamivir and has been used in cases of oseltamivir resistance in transplant recipients [58].

Although antivirals should be started as early in the illness as possible, they may remain effective even after 48 h of symptoms and can be used at any point during the illness [59, 60]. Oseltamivir chemoprophylaxis has been studied in a randomized trial of transplant recipients and was not found to be effective, likely because of overall low rates of influenza infection [61]. However, chemoprophylaxis can be considered in special settings such as for transplant recipients during an influenza outbreak. Long-term prophylaxis may lead to resistance and should be avoided.

Treatment with M2 inhibitors, such as amantadine, is generally not used in transplant recipients because of widespread resistance, the association with prolonged shedding of virus and increased adverse effects [6, 30]. DAS181, a sialidase fusion protein inhibitor, developed primarily for parainfluenza virus (PIV), also has been shown to have promise in influenza infection [62–64]. Other investigational compounds for influenza include an RNA polymerase inhibitor, favipiravir, and monoclonal antibodies directed against epitopes of the conserved M2 protein [65–67].

5.1.1 Influenza Vaccine

Inactivated influenza vaccine is widely recommended to prevent infection in transplant candidates, recipients, close contacts, and healthcare workers [68]. In recent years, trivalent formulations have been available containing two A and one B strain; however, given the frequent co-

circulation of a second B strain, quadrivalent vaccines have been developed [69–71]. Immunogenicity of influenza vaccine depends on the type of transplant population studied, immunosuppression, and time from transplant. Lung transplant recipients generally have lower immunogenicity than other organ transplant types. Higher doses of mycophenolate mofetil have been shown to inhibit influenza vaccine immunogenicity. Vaccine immunogenicity is lowest in the first 6 months after SOT. Guidelines generally suggest to immunize patients starting at 3 months post-transplant; however, starting as early as 1 month post-transplant has also been suggested [72]. Early post-transplant vaccination may be immunogenic and should especially be considered in pandemics or outbreak situations. For HSCT recipients, influenza vaccine has poor immunogenicity in the first 4–6 months post-transplant, so many centers will delay vaccination until this time. Various types of inactivated influenza vaccines are available: unadjuvanted vaccines, adjuvanted vaccines, and high-dose vaccines. Seroconversion and seroprotection rates from the non-adjuvanted standard dose vaccine range 15–90% in transplant recipients [73–77]. Factors influencing the variability include type of transplant, time from transplant, and immunosuppression as well as the presence of GVHD in allogeneic HSCT. One study investigated the use of a novel high-dose intradermal (ID) and showed the use of mycophenolate mofetil was inversely associated with vaccine response in a dose-dependent manner [78]. Contrary to in the general population, age has not traditionally been a factor that has impacted standard influenza vaccine response in transplant recipients, potentially because the impact of immunosuppressive medication supersedes the

impact of age. Various strategies to improve influenza vaccine response have been studied in the transplant population. Administering two doses of vaccine in the same season appears to have marginal benefit in SOT recipients and no significant benefit in allogeneic HSCT [73, 79]. An MF59-adjuvanted influenza vaccine is also available and has shown promise in the population ≥ 65 years of age [80]. MF59 is an oil-in-water emulsion that works by locally attracting inflammatory cells to the site of injection [81]. A randomized trial of MF59-adjuvanted influenza vaccine in kidney transplants showed that this vaccine had similar immunogenicity to unadjuvanted vaccine. In this study, persons aged ≥ 65 years had significantly diminished vaccine immunogenicity; after this group was excluded from the analysis, a subgroup analysis of patients aged 18–65 years showed that the adjuvanted vaccine performed better than standard vaccine [82]. In adult allogeneic HSCT patients, another randomized control trial using MF59, done by Natori et al., also found that adjuvanted vaccine demonstrated similar immunogenicity to non-adjuvanted vaccine [83]. A high-dose vaccine containing four times the antigen of standard dose vaccine is also authorized for persons aged ≥ 65 years. This vaccine has shown improved immunogenicity in a cohort of HSCT transplant recipients as well as pediatric organ transplant recipients [84, 85]. Trials of high-dose vaccine in adult SOT recipients are underway.

5.2 Respiratory Syncytial Virus (RSV)

RSV is also a leading cause of RVI and can cause severe disease in transplant recipients. In HSCT recipients, the incidence of lower respiratory infection can be up to 55% and mortality up to 33% [14]. Risk factors for progression of infection to the lower respiratory tract include degree of immunosuppression, presence of neutropenia, lymphopenia, and GVHD [6, 86]. Waghmare et al. [86] showed that older age was not associated with RSV mortality in multivariate analysis. In the SOT group, lung transplant recipients are at the greatest risk of lower respiratory tract disease. RSV infection along with other community acquired RVIs is a risk for acute rejection and CLAD in lung transplant recipients [12, 87].

Ribavirin has been the mainstay in treatment for RSV infections and can be given in the aerosolized, oral, and intravenous formulations. A survey done of RSV treatment in 13 US organ transplant centers showed that ribavirin was used at all centers for lung transplant recipients with lower respiratory tract RSV infection [88]. Practice for RSV upper or lower tract infection in non-lung recipients was variable. The nebulized form of ribavirin is given via a small particle aerosol generator (SPAG) unit at dosages of 2 g every 8 h or one dose of 6 g over 18 h. Aerosolized ribavirin is teratogenic and requires a negative pressure room. A small randomized study in HSCT patients with RSV showed a decrease in viral load over time, but no effect on development of pneumonia [89]. Subsequently, retrospective reviews of HSCT recipients infected with RSV demonstrated that ribavirin therapy reduced risk of lower respiratory tract infection and RSV-associated mortality [86, 90]. Oral ribavirin has also been used in small case series of HSCT recipients. Gorcea et al. treated 23 RSV-positive patients with oral ribavirin for a median of 10 days and noted only one RSV-related death [91]. Intravenous immunoglobulin and palivizumab have not been shown to have benefit in the HSCT setting [92]. An immunodeficiency scoring index to determine risk-based ribavirin therapy for HSCT recipients has been suggested [21, 93]. In lung transplant recipients, both aerosolized and oral ribavirin have been used. Burrows et al. reported 56 episodes of RSV in lung transplant recipients treated with an intravenous ribavirin loading (33 mg/kg) dose followed by oral ribavirin (20 mg/kg/day) for a median of 8 days [94]. Although there were no untreated controls, bronchiolitis obliterans developed in 2.6% of patients and anemia worsened in half the patients [94]. A smaller study of 21 lung transplant recipients showed no significant difference in clinical outcomes between those who received oral versus aerosolized ribavirin [95]. More aggressive protocols have been used and include aerosolized ribavirin, methylprednisolone, intravenous immunoglobulin and palivizumab [96]. On the contrary, good outcomes with observation alone have also been seen in lung transplant patients with RSV [97]. Therefore, there is no consensus on whether to treat lung transplant recipients with RSV upper tract infection [88]. Taken together, the data with ribavirin involve retrospective case series, many of which have limited sample sizes and/or are inadequately powered to show differences in therapies. There may also be reporting bias in the literature. Therefore, no firm conclusion can be drawn regarding the effectiveness of ribavirin in treatment of RSV. Newer therapies are under development for RSV. These include an inhaled small interfering RNA (siRNA) that was shown to prevent bronchiolitis obliterans in a randomized trial of lung transplant recipients with RSV [98]. Fusion inhibitors such as GS-5806 and monoclonal antibodies directed against the fusion protein of RSV have shown promise in early trials and may form future therapies in transplant recipients [99]. Multiple RSV vaccine candidates are under development, and these have potential to be studied in transplant populations [100].

5.3 Parainfluenza Virus

PIVs are single-stranded, enveloped RNA viruses of the *Paramyoviridae* family. PIV comprises a group of four

serotypes. Serotypes 1 and 2 tend to occur sporadically in fall and winter months in mild environments. Type 3 occurs all year and is the most common type to cause outbreaks among HSCT and organ transplant recipients [101]. Type 4 is less common, and its epidemiology is under study [29].

Similar to the other respiratory viruses, PIV is associated with severe lower respiratory tract infection in transplant patients. In one study of 200 leukemia and HSCT patients with PIV, mortality for lower respiratory tract infection was 17% [102]. There was a trend to greater PIV pneumonia in those ≥ 65 years ($p = 0.06$) compared to younger patients. A systematic review found that GVHD was a risk factor for the acquisition of PIV infection and lower respiratory infection [103]. Lymphopenia, neutropenia, and steroid use also predicted lower respiratory infection with PIV.

Currently, supportive care is the mainstay in treatment for PIV infection. A few studies have shown that ribavirin is not beneficial in the therapy of PIV in HSCT patients [102, 104]. The experience with ribavirin for PIV infections in organ transplant recipients is limited [105, 106]. Similar to influenza, PIV also binds to sialic acid on host epithelial cells. DAS181, an inhaled sialidase fusion protein inhibitor, has shown promising results for the treatment of PIV in immunocompromised patients [107]. Waghmare et al. used DAS181 to treat PIV disease in four pediatric patients who were immunocompromised. All patients tolerated the drug well, and improvement in both viral loads and symptoms after initiation of therapy was observed [108]. DAS181 may be an option to treat PIV in transplant recipients in the future.

5.4 Adenovirus

Adenovirus produces a wide array of clinical symptoms in transplant patients. It is a non-enveloped, double-stranded DNA virus with 52 immunologically unique serotypes that are then further classified into subgroups A through F [109]. Adenovirus can establish lifelong asymptomatic infection in lymphoid tissue, and it has been suggested that adenovirus disease may occur because of reactivation of latent infection rather than de novo infection. For de novo infection, the incubation period ranges from 2 days to 2 weeks depending on serotype. In the transplant population, the incidence rates range between 3 and 29% in HSCT recipients and between 5 and 10% in SOT recipients [30]. The clinical presentation is nonspecific and includes upper respiratory tract symptoms, conjunctivitis, fever, enteritis, hepatitis, and encephalitis. Mortality rates related to adenovirus pneumonia and hepatitis can be up to 75% [110]. In one prospective study of SOT recipients, adenovirus was found in 7.2% of patients throughout the first year post-

transplant. In this study, older age was not a factor in development of viremia. The majority of patients were asymptomatic, and though some had respiratory or gastrointestinal symptoms, none of the patients had adenovirus-directed therapy and no serious sequelae were observed [111]. In kidney transplant recipients, adenovirus may cause pyelonephritis [110, 112]. In lung transplant recipients, adenovirus is associated with graft loss, death, or progression to obliterative bronchiolitis.

Diagnosis can be made by serology, NAT, culture, polymerase chain reaction (PCR), in situ hybridization, and immunochemistry.

There is no established therapy for adenovirus, although small case series of disseminated adenovirus in SOT recipients have documented successful treatment with the use of cidofovir and adjunctive intravenous immunoglobulin [113, 114]. Reduction of immunosuppression appears to be an important intervention in organ transplant recipients with disseminated disease [115]. In allogeneic HSCT recipients, hemorrhagic cystitis from adenovirus has been shown to improve with intravesicular instillation of cidofovir [116]. Brincidofovir remains an investigational compound with in vitro activity against DNA viruses, including adenovirus, with some case series documenting successful outcomes [117]. Adenovirus-specific T cells are emerging therapies in the future [118].

5.5 Coronaviruses

Due to historically limited diagnostic testing specific to human coronavirus (hCoV), the incidence in transplant recipients has likely been underestimated. However, with the development of NAT, strains such as OC43, 229E, HKU1, NL63, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS) have been seen to affect transplant patients [6]. As with other respiratory viruses, symptoms are non-specific and include fever, myalgia, cough and dyspnea. Characteristic laboratory markers include lymphopenia, thrombocytopenia, and elevated lactate dehydrogenase. Viral pneumonitis may be evident on chest radiograph.

In 2003, a new coronavirus that caused SARS emerged [119]. Common presenting symptoms included fever, chills, headache, malaise, nonproductive cough, and dyspnea [120, 121]. Lower respiratory tract infection was common, and mortality was approximately 15–20% [122]. Lymphopenia, elevated lactate dehydrogenase levels, and elevated creatinine kinase levels were seen in patients afflicted with SARS [120, 121]. Advanced age was a risk factor for an adverse outcome from SARS (odds ratio 1.8 per decade of life) [121]. SARS was distinctly linked to exposure in the healthcare setting. A liver transplant patient who developed SARS was likely exposed at an outpatient

podiatry appointment 5 days prior to his presentation [123]. The patient was treated with intravenous ribavirin, ceftriaxone, and azithromycin, but succumbed to his illness.

MERS-CoV is a relatively new coronavirus that was identified in June 2012 and has had a mortality rate up to 40% in immunocompetent persons [124] (http://www.who.int/mediacentre/factsheets/mers-cov/en/) [125–127]. There have been two microbiologically documented MERS-CoV cases reported in renal transplant recipients [128]. Both patients presented with fatigue and dyspnea as well as fever in one case. One patient was treated with ribavirin and pegylated interferon, but succumbed to disease. The other patient only received supportive care and recovered.

There is no specific targeted therapy for hCoV. Ribavirin has been used as above in the treatment for SARS. Observational studies of intravenous ribavirin treatment for SARS indicated improvement in the majority of patients, although patients had significant toxicity, including hemolysis in 76% of patients [120, 129, 130]. Interferon-alpha was also used as a potential immunomodulatory therapy for SARS, with limited effectiveness [131–133]. Adjunctive corticosteroids showed some benefit in a randomized trial with regard to reducing mortality [131].

5.6 Human Metapneumovirus

Human metapneumovirus (hMPV) is a relatively newer paramyxovirus, closely related to RSV, which can cause both upper and severe lower respiratory tract infection after transplantation [134]. Englund et al. documented the association between hMPV, respiratory failure, and a septic shock-like presentation, with death from acute respiratory failure occurring in HSCT recipients [135]. Progression to lower respiratory tract can occur in up to 60% of HSCT recipients, especially those with lymphopenia and systemic corticosteroids [136]. Older age was not identified as a risk factor for progression in this study. In lung transplant recipients, infections with hMPV have been associated with graft dysfunction [137].

Treatment consists of supportive care and reduction in immunosuppression. The use of ribavirin has also been studied, although the effectiveness is difficult to assess because of lack of controls [134, 138].

5.7 Other Respiratory Viruses

Rhinovirus A, B, and C circulate year-round and are a common cause of upper respiratory tract infection in transplant recipients in various studies. The significance of rhinovirus is currently unclear, although it may be found as a coinfection in many patients. Some reports suggest that lower respiratory tract infection with rhinovirus can occur

in HSCT recipients and has a mortality of up to 41% [139, 140]. Seo et al. showed that 30% of patients with lower respiratory infection from rhinovirus were > 60-years of age [139]. Greater viral loads of rhinovirus tend to correlate with symptoms [141]. Prolonged shedding can occur.

KI and WU polyomaviruses have also recently been discovered and are reported predominantly in the pediatric HSCT population. One study in kidney transplant patients found KI in 14.3, 3.9, and 4.1% of respiratory, plasma, and urine specimens, respectively [142]. Similarly, WU was found in 9.1 and 5.3% of respiratory and plasma specimens, respectively. The clinical consequences of these infections have yet to be defined.

Bocaviruses are parvoviruses that are also noted in several studies of respiratory virus infections in transplant recipients. However, no significant clinical consequences have been reported. Management of these viruses in transplant recipients consists of close observation and supportive therapy [143, 144].

6 Prevention

Nosocomial infections associated with community respiratory viruses can lead to devastating disease in immunocompromised patients. Prevention of transmission includes general infection control measures such as single-room isolation and droplet precautions [145]. Screening and restricting visitors with respiratory symptoms and asking symptomatic hospital staff to avoid immunocompromised patients are precautions that should be adhered to. For more virulent viruses such as pandemic influenza strains, newer coronaviruses with high mortality, fit test N95 masks and negative pressure isolation might be required. If an outbreak occurs on a transplant unit, hospitals may want to consider a temporary hold on performing 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 influenza infections, during an outbreak on a transplant ward, inpatients should be offered chemoprophylaxis if available. Close contacts of transplant patients should be vaccinated.

7 Summary

Due to advances in treatment for end-stage organ diseases and hematologic malignancy, transplantation is being offered to older individuals. Respiratory viruses continue to be an important cause of morbidity and mortality in the

transplant community. Using molecular diagnostics, a wider array of viruses can be detected although specific therapies are not available for most RVIs. Specific data on respiratory viruses in older transplant recipients are lacking. However, large cohort studies show that many respiratory viruses appear to cause severe disease in those with advanced age. Influenza is important to prevent in the older transplant patient, and vaccination is the key to prevention. Standard inactivated influenza vaccines have poor immunogenicity, especially in older transplant patients, and newer vaccination strategies are needed. RSV can cause severe lower respiratory disease, and controversy exists over the effectiveness of different formulations of ribavirin. For other RVIs, supportive care is the primary management. Given the important clinical consequences in the older transplant population, it is important to develop new antivirals and vaccines to prevent morbidity and mortality.

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