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Viral Respiratory Tract Infections in Transplant Patients

Epidemiology, Recognition and Management

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Contents

Abstract

Viral respiratory tract infections (RTIs) are common causes of mild illness in immunocompetent children and adults, with occasional significant morbidity or mortality in the very young, very old or infirm. However, recipients of solid organ transplants (SOT) or haematopoietic stem cell transplants (HSCT) are at markedly increased risk for significant morbidity or mortality from these infections. The infections are generally acquired by transmission of large respiratory droplets and can be nosocomial in origin with many documented outbreaks on specialised transplant units. Typically, the infections begin as upper RTIs, with cough or rhinorrhoea predominating. Many will resolve at this stage, but more immunocompromised patients, typically closer in time to their SOT or HSCT, may develop progressive infection to lower RTI or pneumonia. The most common RTI pathogens are influenza viruses, parainfluenza viruses and respiratory syncytial viruses. Newer polymerase chain reaction-based diagnostic strategies are more sensitive than previous assays, and allow rapid and accurate diagnoses of these infections. These newer assays may also detect emerging pathogens of significance, one of which is human metapneumovirus. While diagnostic techniques have advanced significantly in the past decade, well established and effective specific treatments for these infections remain elusive. The epidemiology, clinical presentation, diagnosis and treatment of the common viral RTIs in SOT or HSCT recipients are reviewed, and recommendations presented based on a thorough review of recent literature.

Respiratory viruses are common causes of mild, self-limited, upper respiratory tract infections (URTIs) in immunocompetent individuals. They vary in their seasonality and frequency, and tend to infect children more often than adults. While symptomatic disease may persist for days to weeks in healthy outpatients, significant morbidity or mortality is uncommon.

In immunocompromised patients, including haematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT) recipients, respiratory viruses may be either community acquired or hospital acquired. They are associated with longer periods of infection, increased progression to lower respiratory tract infections (LRTIs), as well as higher mortality rates.[1,2] Incidence rates have ranged from 11–65% in surveillance studies of HSCT recipients to 4–27% in retrospective studies of HSCT recipients and 8–21% in lung transplant recipients with symptomatic disease.[3-13] A surveillance study of hospitalised patients with leukaemia and hospitalised or clinic patients with recent HSCT at the MD Anderson Cancer Center reported that >60% of patients had progression of viral URTIs to pneumonia.[2] Mortality rates associated with respiratory viruses have varied in the literature. Earlier case series of hospitalised HSCT or SOT recipients with LRTIs reported high mortality rates (≥50%).[8] More recent studies of HSCT recipients with URTIs, including those treated as outpatients, reported low-

er mortality rates of 2–18%.[4,11,12] In addition to increased disease severity, certain viral infections – including those caused by influenza virus A and B, parainfluenza virus (PIV) and adenovirus – have also been associated with an increased risk for rejection in SOT recipients.[13-15]

Early diagnosis of respiratory viruses in immunocompromised patients is crucial to the consideration of therapies and to efforts to limit the spread of disease among patient populations. Several testing options are available. A combination of direct (DFA) or indirect (IFA) fluorescent antibody testing with viral culture has been the standard used at many institutions. However, in recent years, polymerase chain reaction (PCR) has gained popularity, given its increased sensitivity and fast processing time, and is being used more often in the diagnosis of respiratory syncytial virus (RSV), influenza A and B, PIV and adenovirus.[6] Serological assays are not routinely helpful in detecting acute infection. Of note, bacterial or fungal infection is often found as a co-pathogen along with viral infections, and this may be more common with PIV.[16,17]

Treatment and prevention of respiratory tract infections can vary depending on the pathogen. In 2000, the Centers for Disease Control and Prevention, Infectious Disease Society of America and the American Society of Blood and Marrow Transplantation established guidelines for preventing opportunistic infections in HSCT recipients.[18] General preventative guidelines include instituting infection-control measures such as appropriate hand hygiene, early isolation of patients with suspected respiratory tract infections and avoidance of sick contacts. These measures aim to limit the exposure of HSCT recipients to viral infections. Other preventative measures include vaccination or antiviral prophylaxis. Treatment options are limited but should be considered when available.

This article reviews the current literature on respiratory tract infections in HSCT and SOT recipients, starting with the most commonly reported respiratory viruses including RSV, PIV, influenza A and B, and adenovirus, and concluding with less reported or newly recognised viral infections including rhinovirus, coronavirus, herpesviruses excluding cytomegalovirus (CMV), and human metapneumovirus (table I provides a synopsis of the key points).

1. Respiratory Syncytial Virus

1.1 Epidemiology

RSV is a single-stranded RNA virus and a member of the paramyxovirus family. The seasonality of RSV outbreaks varies according to latitude. In temperate areas, RSV occurs seasonally from winter to early spring. In tropical and subtropical areas, there is less seasonal variation, and RSV outbreaks in the tropics may be associated with the rainy season.[19] RSV is a common cause of community-acquired respiratory tract infections with a tendency to infect children more often than adults. Almost all children have had primary infection by the age of 2 years, with more severe disease seen in higher risk groups, including very-low-birth-weight infants, as well as children with bronchopulmonary dysplasia, congenital heart disease and immune deficiencies.[20] RSV is highly contagious and reinfection can occur at any point later in life as a result of incomplete immunity.

RSV is an important pathogen in immunocompromised patients, with many observational studies finding that it is the most commonly identified viral RTI in HSCT and SOT recipients. Studies have shown a cumulative incidence ranging across 3.5–8.8% in allogenic HSCT recipients,[21-23] 0.4–1.5% in autologous HSCT recipients,[22,23] and 3.4–10% in paediatric liver and adult lung transplant recipients.[24,25]

Although RSV is often considered a community-acquired infection, nosocomial transmission is also common. Hospital-acquired infection may occur for

Table I. Summary of common respiratory tract viruses in transplant patients

Incidence	Diagnosis	Treatment	Prognosis	Prevention
Respiratory syncytial virus				
Most commonly identified viral RTI in HSCT and SOT recipients 0.4–1.5% in autologous HSCT recipients 3.5–8.8% in allogenic HSCT recipients 3.4–10% in paediatric liver and adult lung transplant recipients	PCR may be more sensitive than traditionally used fluorescent antibody testing (DFA/IFA) and viral culture	Available and sometimes recommended; not conclusively beneficial Consider ribavirin (aerosolised or intravenous) with or without palivizumab RSV IVIg is no longer available	Increased mortality in patients with progression to LRTIs	Infection control methods (hand hygiene, droplet and contact isolation for patients with known or suspected RSV) No available vaccine
Parainfluenza virus				
Second most commonly identified viral RTI in transplant patients 7.1% in HSCT recipients (similar incidence in autologous and allogenic HSCT recipients) 1.6–11.9% in lung transplant recipients	PCR may be more sensitive than traditionally used fluorescent antibody testing (DFA/IFA) and viral culture	Available but not routinely recommended because of limited benefit Consider ribavirin (aerosolised or intravenous)	Mortality rates 0–73% in patients with progression to LRTIs Bacterial or fungal co-infection can occur May be associated with bronchiolitis obliterans and allograft rejection in lung transplant recipients	Infection control measures (hand hygiene, droplet and contact isolation for patients with known or suspected PIV) Formalin-inactivated PIV vaccine is available but has not been shown to prevent infection Studies with intranasal PIV vaccine in immunocompetent patients are underway
Influenza virus				
2.8 cases/1000 person-years in liver transplant recipients 41.8 cases/1000 person-years in lung transplant recipients	PCR, viral culture, and fluorescent antibody tests (DFA/IFA)	Widely available and routinely recommended Neuraminidase inhibitors (oseltamivir and zanamivir) are preferred Adamantanes (amantadine and rimantadine) should *not* be used, because of increasing resistance	Generally low rates of significant morbidity or mortality in transplant recipients Bacterial superinfections, disseminated infection, and graft rejection possible	Infection control measures (hand hygiene, droplet and contact isolation for patients with known or suspected influenza) Inactivated vaccine routinely recommended, although efficacy unpredictable Consider prophylactic neuraminidase inhibitors in transplant patients not eligible for inactivated vaccine (e.g. HSCT patients <6 months post-transplant) Live attenuated intranasal vaccine is not currently recommended for transplant recipients
Adenovirus				
Less common than other well-known viral RTIs Occurs more often in HSCT recipients than SOT recipients	PCR, viral culture and fluorescent antibody tests (DFA/IFA)	Available but may not always be necessary or recommended Consider cidofovir	Cumulative mortality of 56% in HSCT recipients (many with disseminated disease) May be associated with acute or chronic rejection in lung transplant recipients	Infection control measures (hand hygiene, droplet and contact isolation for patients with known or suspected adenovirus) No available vaccine

DFA = direct fluorescent antibody; **HSCT** = haematopoietic stem cell transplant; **IFA** = indirect fluorescent antibody; **IVIg** = intravenous immunoglobulin; **LRTI** = lower respiratory tract infection; **PCR** = polymerase chain reaction; **PIV** = parainfluenza virus; **RSV** = respiratory syncytial virus; **RTI** = respiratory tract infection; **SOT** = solid organ transplant.

several reasons. HSCT and SOT recipients with RSV infection may have difficulty clearing the virus because of their immunosuppressed states, and therefore have prolonged periods of shedding.[26,27] These patients should be isolated but are often placed in close proximity to each other on dedicated wards. Therefore, they have opportunities to infect multiple other immunocompromised patients through environmental contamination or by infecting staff members who are then exposed to other patients. Taylor and colleagues[26] reported that during the 1995–6 season, there were ten cases of RSV at an HSCT unit in Bristol, UK. Of the nine RSV specimens that could be amplified, restriction enzyme analysis demonstrated that eight sequences were identical – the patients had become infected with the same strain of virus. This strain also differed from those found in patients hospitalised from the community, suggesting that RSV had been nosocomially acquired within this HSCT unit. In addition, during an RSV season, 15–20% of healthcare providers may shed RSV, with this figure increasing to 50% during community outbreaks.[28] Because of these factors, nosocomial transmission may be responsible for approximately 50% of all cases.[29-31]

1.2 Clinical Manifestations

RSV typically begins as a URTI, with a majority of patients experiencing cough. Other symptoms may be present, including fever, rhinorrhoea, sinus congestion and wheezing. Prognosis in transplant recipients has been associated with disease severity, with those developing LRTIs experiencing worse outcomes. Early series described mortality rates of 30–80% in patients progressing to pneumonia, with perhaps 60% progressing to pneumonia.[32] However, more recent studies have reported lower mortality rates. A study by Machado and colleagues[33] found that during the 2001–2 season, 55.5% of HSCT patients with RSV developed LRTIs, and only one of those patients died (6.6%).

In patients with haematological malignancies or HSCT recipients with RSV infection, progression to LRTIs may be associated with increased age and lack of RSV treatment.[34] In HSCT recipients, prognosis is also associated with timing of the disease in relation to the transplantation. Patients infected pre-engraftment or ≤1 month post-transplant tend to have higher complications rates of pneumonia and death.[35] Peck and colleagues[36] performed a retrospective study following 37 HSCT candidates who were diagnosed with RSV URTIs pre-transplantation (n = 31) or early during their conditioning regimen (n = 6). The six patients diagnosed early in their conditioning regimen all had symptoms prior to treatment but had delayed virological confirmation. Of the 34 patients who had their HSCT delayed, only one progressed to proven RSV pneumonia, compared with two of three patients in the group who did not delay HSCT. Given their findings, the authors recommended that physicians should strongly consider delaying transplantation in those patients with RSV infection and perhaps also in those patients with URTI symptoms (even prior to virological confirmation).

1.3 Diagnosis

RSV antibody titres tend to be low in adults, particularly those who are immunosuppressed. Therefore, a combination of fluorescent antibody testing (DFA and IFA) with viral culture has traditionally been used to make the diagnosis of RSV. Processing time varies between these two tests; results from fluorescent antibody tests are available within hours to days in contrast to viral culture in cell lines such as human epithelial (Hep-2), human lung fibroblast (WI-38 or MRC-5) or rhesus monkey kidney cells, which may take up to several weeks.[37]

Over the past few years, PCR has become more commonly used. PCR can identify RSV in patients

with lower viral levels, and therefore may be more sensitive than traditionally used viral cultures. Van Elden and colleagues[38] compared the TaqMan® PCR versus viral culture or shell vial culture in diagnosing RSV in HSCT recipients. TaqMan® [1] PCR was positive for RSV in 13 samples. Conventional culture detected only four of these cases, while none were detected using shell vial culture. A study by Weinberg and colleagues[39] found that multiplex PCR was more sensitive in detecting respiratory tract infections, particularly RSV B and PIV 1, in lung transplant recipients compared with viral culture, enzyme immunoassays and rapid shell vial detection tests. PCR was also associated with the fastest processing time of 6–8 hours. Other rapid detection tests include enzyme-linked immunosorbent assay and immunofluorescence.

1.4 Treatment

Antiviral treatment for RSV is controversial, with conflicting study results found in the literature. Ribavirin, a guanosine analogue, is the main antiviral agent that has been studied in immunocompromised patients, particularly HSCT recipients.

Although it can be given orally, intravenously or via inhalation, only aerosolised ribavirin is approved by the US FDA for the treatment of RSV. Aerosolised ribavirin is difficult to administer. It requires a small particle nebuliser machine, which may not be available at some institutions. Adverse effects – including psychological distress for the patient due to isolation during treatments, rash, headache and conjunctivitis – may occur in anyone exposed to aerosolised ribavirin. There is also concern that ribavirin may be teratogenic, and that patients, visitors and staff may be at risk from aerosolised ribavirin. Animal studies have noted an increase in skeletal malformations in pregnant rats and hamsters treated with ribavirin.[40,41] There are insufficient data in humans, with only case reports in the literature of pregnant women who were treated with ribavirin in the latter half of their pregnancy and did not experience adverse fetal outcomes.[42] However, given this concern, pregnant women should try to avoid entering a patient's room during treatment with the aerosolised product.

Although there are no definitive trials evaluating the therapeutic role of ribavirin in immunocompromised patients with RSV, trials of various doses and treatment durations have been reported in the literature. In HSCT recipients with RSV pneumonia or LRTI, aerosolised ribavirin alone has not shown significant benefit, with mortality rates as high as 70% reported in the literature.[43] Boeckh and colleagues designed a randomised multicentre trial to study the effects of aerosolised ribavirin in HSCT recipients with RSV URTIs.[44] The authors reported that patients randomised to receive aerosolised ribavirin had a nonsignificant decrease in the rate of progression to pneumonia (one of nine patients in the ribavirin group vs two of five patients in the control group; $p = 0.51$) and lower 10-day viral loads (0.75 log10 copies/mL reduction versus 1.26 log10 copies/mL increase; $p = 0.07$) compared with patients receiving best supportive care. Although the findings are intriguing, it is difficult to make further conclusions given that the study was insufficiently powered as a result of slow patient accrual. In a phase 1 study by Lewinsohn and colleagues,[32] intravenous ribavirin had similar efficacy to aerosolised ribavirin. However, it was also associated with adverse effects, including haemolysis, significant enough to require drug cessation in two of ten patients. In contrast, Glanville and colleagues reported that lung transplant recipients with RSV who were treated with a combination of intravenous ribavirin and corticosteroids had excellent prognoses (0% mortality) and only experienced mild adverse effect profiles.[45]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Combination treatment with ribavirin and RSV intravenous immunoglobulin (IVIg) has yielded potentially encouraging results (mortality rates of 14–42%), particularly if given earlier in the course of respiratory illness.[46,47] In a study by Ghosh and colleagues,[46] aerosolised ribavirin and RSV IVIg were administered to 14 bone marrow transplant (BMT) recipients with RSV URTIs. Four patients (29%) developed pneumonia and two died. RSV IVIg has subsequently been discontinued worldwide and replaced by the monoclonal antibody formulation palivizumab. Two phase 1 studies by Boeckh and colleagues[48] reported long half-lives (10.7–22.4 days), mild adverse-effect profiles, and high survival rates in HSCT recipients treated with aerosolised ribavirin and palivizumab. An abstract from Zamora and colleagues[49] found that combination treatment with aerosolised ribavirin and either RSV IVIg or palivizumab and IVIg decreased rates of acute rejection, bronchiolitis obliterans and mortality in lung transplant recipients with pneumonia.

Given the available information, the Swedish Consensus Group proposed that aerosolised ribavirin and RSV IVIg be considered in allogenic HSCT or SOT recipients with >1 episode of rejection with mild or moderate RSV pneumonia.[50] The American Society of Transplantation (AST) guidelines state that "for patients with upper respiratory tract disease and the presence of risk factors and for those organ transplant recipients with lower respiratory tract disease the use of aerosolised ribavirin in combination with RSV immune globulin or palivizumab should be considered".[51]

1.5 Prevention

Infection control methods are crucial in the prevention of respiratory viral infections including RSV. Because RSV is transmitted via aerosolised droplets or fomites, hand hygiene is an important and effective preventive measure. Many hospitals offer alcohol-based hand-washing products to facilitate this process. Another important intervention involves quickly implementing droplet and contact isolation measures when RSV infection is first suspected, particularly given the potential for a 24- to 48-hour delay before confirmation of infection through diagnostic testing. Raad and colleagues[30] reported that instituting isolation precautions decreased the rates of RSV in a HSCT ward by 81%. There is no currently available RSV vaccination.

2. Parainfluenza Virus

2.1 Epidemiology

PIV, like RSV, is a single-stranded RNA virus and a member of the paramyxovirus family. However, PIV has four different serotypes that vary in prevalence, seasonality and clinical disease. PIV1 and 2 are common causes of childhood croup, resulting in outbreaks during autumn (fall) and winter. PIV3, which is more often associated with adult disease, is found year-round with an increased incidence during spring and summer. PIV4 is the least commonly isolated serotype and has not as been well characterised.

There are a limited number of studies evaluating PIV infections in transplant recipients. Nichols and colleagues[16] reported that 7.1% of HSCT recipients acquired PIV infection (90% PIV3, 6% PIV1 and 4% PIV2) at the Fred Hutchinson Cancer Research Center over a 9-year period. Unlike RSV, the rates of PIV infection were similar between autologous and allogenic HSCT recipients. Studies have also reported that 1.6–11.9% of lung transplant recipients become infected with PIV (63% PIV3, 29% PIV1 and 8% PIV2).[52,53]

A study by Nichols and colleagues reported during the 1998–9 season, 93 HSCT recipients at the Fred Hutchinson Cancer Research Center acquired PIV.[54] Approximately 71% cases occurred in patients seen in outpatient clinics. An increased number of cases were identified at this hospital during

September and October, suggesting an outbreak, even though there was no increase in PIV infections in the community. Molecular analysis demonstrated that many of the isolates were related and fell into distinctive clusters, suggesting that many of the PIV cases occurred via nosocomial transmission in the outpatient setting.

2.2 Clinical Manifestations

PIV is a common cause of community-acquired respiratory illness in children, and progresses to LRTIs 15% of the time.[52] In immunocompetent adults, who have often developed incomplete immunity, infections are restricted to the upper respiratory tract and tend to be mild.

Over the past several years, studies have demonstrated that PIV is associated with significant morbidity and mortality in transplant recipients. In immunocompromised patients, PIV may initially present as a URTI, with 70% of patients having a cough.[52] Other symptoms – including rhinorrhoea, wheezing, coryza and fever – are less common. Approximately one-third of HSCT recipients with PIV then progress to LRTIs, and of those who do, the literature cites a mortality rate in the range of 0–73%.[3,8,11,14,16,17,55] Corticosteroid administration for graft-versus-host disease is believed to be a risk factor for pneumonia.[16] In lung transplant recipients, 10–66% of PIV infections involve the lower respiratory tract.[52]

PIV infection predisposes transplant recipients to co-infection with other bacterial or fungal pathogens. Studies have reported that 50% of HSCT recipients with PIV have superimposed bacterial or fungal pneumonias.[16,17] PIV has also been associated with higher rates of bronchiolitis obliterans and allograft rejection in lung transplant recipients.[52]

2.3 Diagnosis

Diagnostic methods for PIV are similar to those for RSV and include fluorescent antibody tests (DFA or IFA), viral culture using primary monkey kidney tissue and PCR. Because adults tend to shed low titres of PIV, there has been an emphasis on finding more sensitive detection methods, namely PCR. A study by Weinberg and colleagues[39] found that PCR was in fact more sensitive in detecting PIV serotype 1.

2.4 Treatment

Although *in vitro* studies have shown that ribavirin has activity against PIV, clinical studies have yielded mixed results. Smaller studies in HSCT recipients seemed to suggest that aerosolised and intravenous ribavirin resulted in decreased mortality rates compared with historical controls.[12,56] Larger series using ribavirin with or without IVIg, however, have not shown the same efficacy.[16,17] Nichols and colleagues[16] also reported that ribavirin did not affect the duration of viral shedding. After reviewing the available information, the AST guidelines state that "because no other therapeutic options are currently available, consideration can be given to the use of aerosolised ribavirin for high-risk patients with PIV-associated severe lower tract disease".[51] Careful attention to diagnosis and treatment of bacterial or fungal co-infections is also important.

2.5 Prevention

As with RSV, infection control measures are important in preventing the spread of PIV among transplant recipients. Because inoculation occurs through direct contact with fomites or other infected objects, proper hand hygiene is again essential. Contact and droplet precautions should also be instituted early when viral infection is first suspected. It is important to note that immunocompromised patients may have prolonged shedding durations, as demonstrated by one report in which two HSCT recipients shed PIV for >100 days.[17]

A formalin-inactivated PIV vaccination is available. While this vaccination results in antibody response, it has not been shown to prevent infection.[57] Studies are currently underway to evaluate the efficacy of intranasal PIV vaccination in immunocompetent patients.

3. Influenza

3.1 Epidemiology

Influenza virus is a single-stranded, negative sense RNA virus and a member of the orthomyxovirus family. There are three types – influenza A, B and C – based on antigenic differences. Influenza is highly infectious, spreads through respiratory droplets, and epidemics typically occur during winter months resulting in significant morbidity and mortality. Machado and colleagues[58] reported that 12% of influenza cases occurred during summer months in a tropical climate, although given the known potential for prolonged shedding and the limited ability to detect other viruses in their study, it is not completely clear that these represented true incident cases of influenza. Within a single influenza season, most cases will be of the same (major) strain, although other (minor) strains may also cause disease. However, antigenic changes in the virus, vaccine contents and population vaccine penetration, and antiviral use and resistance, lead to different circulating influenza strains each year. Several articles have noted infections in transplant patients with either influenza A or B,[58-60] but it is unclear in these small series whether there are substantive differences in clinical presentation or outcomes. Although influenza is commonly considered a community-acquired respiratory illness, nosocomial spread also occurs. Hospitalised HSCT or SOT recipients may become infected soon after transplantation, resulting in severe disease and worse prognosis.

The incidence of influenza in SOT recipients varies, depending on the type of transplantation. A study conducted over a 10-year period reported that there was anywhere from 2.8 cases of influenza/1000 person-years in liver transplant recipients to 41.8 cases/1000 person-years in lung transplant recipients.[15] Viral shedding occurs for 5–10 days in immunocompetent patients, with longer durations of shedding occasionally noted in immunocompromised patients. Nichols and colleagues[61] reported that the mean duration of influenza virus shedding in allogenic HSCT recipients was 7 days (range 2–37 days) and that patients who did not receive treatment shed for longer periods (average 11 days). Other case reports have noted shedding of influenza virus for >1 year,[62] but more research is needed to determine the frequency and significance of prolonged shedding in transplant recipients.

3.2 Clinical Manifestations

Most patients infected with influenza develop typical symptoms such as fever, headache and myalgias. These symptoms may be less common in some transplant patient populations,[62] although few papers report a methodical gathering of detailed symptoms prospectively. Some patients from whom influenza virus is recovered are asymptomatic (e.g. lung transplant patients undergoing routine bronchoscopy), but the significance of this finding is unclear. In general, influenza should be suspected in any patient who presents with a constellation of fever, rhinorrhoea, cough, malaise, myalgias and/or headache during the winter season. Progression from URTI to pneumonia is rare in immunocompetent patients, and may be underestimated in immunocompromised patients.[63] Certain complications are more common in BMT or SOT recipients. These include bacterial superinfection, CNS involvement, myocarditis, and graft dysfunction or rejection.[15,25,64]

3.3 Diagnosis

Nasopharyngeal and throat specimens, bronchoalveolar lavage and endotracheal aspirates can be used in the diagnosis of influenza. The gold standard is viral culture, which has a processing time of 3–7 days. Other tests including fluorescent antibody techniques (DFA or IFA) are also available. Because viral load is highest during the first few days of illness and then quickly decreases afterwards, diagnosis is easier earlier on in the course of illness. PCR testing is available and becoming more commonly used at most institutions for diagnosing respiratory viruses, including influenza A and B.

3.4 Treatment

Two classes of antiviral medications exist for prevention and treatment of influenza infections: M2 inhibitors or adamantanes (amantadine and rimantadine), which have activity against influenza A, and neuraminidase inhibitors (oseltamivir and zanamivir), which have activity against both influenza A and B. Over the past several years, there has been a worldwide increase in adamantane-resistant influenza A virus. In the US, up to 92% of influenza A (H3N2) virus was adamantane resistant, resulting in guideline changes.[65] In 2006, the Advisory Committee on Immunisation Practices stated that amantadine and rimantadine should not be used for treatment or chemoprophylaxis of influenza A in the US.[65]

Oseltamivir and zanamivir are the two neuraminidase inhibitors that are currently available for treatment. Oseltamivir, which is administered orally, and zanamivir, which is inhaled, are able to shorten the duration of illness by 1 day in immunocompetent patients when given within 48 hours of symptom development. Although there is a paucity of data in transplant recipients, most experts including the AST recommend treating HSCT and SOT recipients with influenza using the same dose and duration as is prescribed for immunocompetent individuals.[51] Although infrequent, resistance to oseltamivir has been reported in the literature. Machado and colleagues[58] have reported a systematic approach using oseltamivir to treat early influenza infection in BMT recipients. Progression to pneumonia was observed in 5% of patients, similar to other series, although notable for the fact that many patients in this series were at especially high risk in the early post-BMT period, and therefore not vaccinated.

Ribavirin is another antiviral agent that has been mentioned in the literature. Small studies have shown *in vitro* activity against influenza and anecdotal reports suggest possible activity in immunocompetent patients.[51] Some experts suggest adding aerosolised ribavirin to neuraminidase inhibitor therapy in transplant recipients with severe influenza infection.[51]

3.5 Prevention

Careful hand hygiene, avoidance of sick contacts and yearly vaccination are the main preventative measures against influenza. Transplant recipients, close contacts and healthcare workers should all receive the standard inactivated vaccination intramuscularly; the live attenuated intranasal vaccine is not recommended in this patient population. Transplant recipients may develop weaker antibody responses to vaccination compared with immunocompetent individuals.[66] The frequency of protective responses has ranged widely from 15–100% in varied transplant populations,[67-70] and probably also depends both on individual factors (e.g. type and intensity of immunosuppression, time from transplant) and vaccine factors (e.g. immunogenicity of the particular vaccine strains, correlation of the vaccine strain with epidemic strain). Given that many patients will achieve protective antibody responses and that the annual variability in response rates is not predictable, yearly vaccination should be en-

couraged. Currently, there are no recommendations to monitor vaccine titres. It is also unclear whether there is a role for higher dose or repeated vaccinations in HSCT or SOT recipients to increase protective immunity.

Preventative antiviral medications may be considered in those patients who do not respond or have not had a chance to respond to vaccination, and in those who are unable to receive the vaccination. It is unclear whether such a strategy should be employed during the full course of an influenza season or in a post-exposure manner.

3.6 Pandemic Influenza

Influenza has resulted in three 20th century pandemics, in 1918, 1957 and 1968; the highest mortality was associated with the 1918 Spanish flu pandemic which resulted in 40 million deaths.[71] Currently, there is concern that avian influenza (H5N1) could progress to become the next pandemic. The first case of avian influenza was reported in 1997 during a poultry outbreak in Hong Kong and was followed by 18 human cases.[72] The incidence appeared to decrease until 2003 when it was re-identified with cases reported from Azerbaijan, Cambodia, China, Djibouti, Egypt, Indonesia, Iraq, Laos, Nigeria, Thailand, Turkey and Vietnam.[73] Most human cases have occurred via bird-to-human transmission, although there is speculation that there may have been limited human-to-human transmission. Human cases of avian influenza have been associated with high mortality rates (54%), particularly in younger patients who are able to mount significant immunological responses.[74]

To date, there have not been any cases of avian influenza in transplant recipients. However, given the heightened concern, experts have extrapolated the information known about other respiratory viruses in transplant recipients to address the implications of possible pandemic influenza in this population. On the patient level, it is possible that transplant recipients may be more susceptible to pandemic influenza, given their immunocompromised state as well as their frequent exposure to the healthcare system. Once infected, transplant patients may be prone to more severe disease with higher rates of complications. These patients may also have difficulty clearing the virus and could become 'super-spreaders', as was the concern with severe acute respiratory syndrome (SARS).[71,75] Pandemic influenza would also be likely to affect transplant centres. Similar to the SARS outbreak, pandemic influenza may lead to closing of transplant centres for periods of time, and prompt consideration for at least a temporary revision of transplantation guidelines (e.g. donor and recipient screening).

Avian influenza is inherently resistant to adamantanes. Neuraminidase inhibitors have been used in patients with H5N1 avian influenza and have demonstrated some efficacy when started early. However, there are oseltamivir-resistant viruses that have been identified in patients who did not improve with treatment.[76] No vaccinations are currently available.

4. Adenovirus

4.1 Epidemiology

Adenovirus may be acquired by person-to-person transmission as a primary RTI. However, some adenovirus disease in immunocompromised patients may represent reactivation of latent infection. In addition, adenovirus infection can produce a variety of clinical syndromes in addition to respiratory tract illness, and these patterns of illness may vary by host, transplant type and adenovirus serotype.[77]

Adenovirus infections account for 0–21% of viral RTIs in recent large case series,[3-5,8-10,78,79] and are more common in children.[80] While adenovirus is the least commonly reported of the common respiratory viruses, most of these series tested patients with

symptomatic URTI – the true incidence of adenovirus infection would probably be higher if patients with other clinical manifestations were tested and included.

4.2 Clinical Manifestations

Patients with adenovirus infection after HSCT and SOT recipients may be asymptomatic, develop symptomatic RTI or develop disseminated disease. Of note, dissemination does not require progressive RTI. Unlike other viral RTIs, cases of fatal adenovirus infection are reported in patients with adenovirus isolated only from the upper respiratory tract, without radiographic evidence of pneumonia or positive testing from lower respiratory tract samples.[11,81] In these patients, mortality may result from involvement of the digestive system, kidneys or CNS. Outcomes from adenovirus RTI after HSCT have been poor, with a cumulative mortality of 56% (30 of 54 cases).[8,9,11,81] One-third of these deaths occurred in patients with adenovirus URTI without evidence of pneumonia.

Fewer cases of adenovirus infection have been reported in SOT recipients. McGrath and colleagues performed the largest review of adenovirus infection in adult liver transplant recipients, and showed an overall incidence of 5.8%.[82] Several longitudinal studies have reviewed the potential significance of adenovirus infection in lung transplant patients, demonstrating a 1–3% incidence.[83] It is hypothesised that adenovirus and other RTIs may predispose to acute or chronic rejection in lung transplant recipients, but the data to support this hypothesis are inconclusive at present.

4.3 Diagnosis

Adenovirus infection may be diagnosed by DFA, but the test is insensitive, missing up to 50% of cases. While emerging PCR assays may provide easier and faster diagnosis, viral culture remains the gold standard for identification of adenovirus infection.

4.4 Treatment

High mortality rates from adenovirus infection in the early post-transplant period have prompted consideration for early and aggressive treatment of documented adenovirus infections in HSCT and SOT recipients. Unfortunately, the role of currently available therapeutics is not clear. Neither ribavirin nor ganciclovir has demonstrated significant efficacy, and neither agent is recommended.[77] Anecdotal reports suggest efficacy of cidofovir, but because of the significant risk of nephrotoxicity, this agent should be used with caution in transplant recipients who are at increased risk for renal impairment. Finally, two recent articles have questioned the need for treatment in all patients with documented adenovirus infections, making watchful waiting a reasonable option for minimally symptomatic patients.[6,84]

5. Miscellaneous Respiratory Viruses

5.1 Rhinovirus

Only a few studies have addressed the potential role of rhinoviruses – ubiquitous common cold pathogens – as respiratory pathogens in SOT and HSCT recipients, but in aggregate they suggest that rhinovirus infection may be underdiagnosed. Four recent studies[5,6,81,85] of prospective active surveillance with newer diagnostic techniques noted rhinovirus infection in their cohorts, and in two,[6,85] rhinovirus was the most common isolate. Recent longitudinal studies of HSCT recipients with symptomatic RTI identified rhinovirus in 27% of clinical isolates.[10,55] Progression to LRTI was observed in 17% of cases and two deaths from rhinovirus pneumonia were noted. Children may be particularly susceptible to rhinovirus, as one series noted 18%

mortality in post-BMT patients with rhinovirus.[86] These patients underwent BMT for primary immunodeficiencies and therefore may represent a uniquely susceptible population. Many older DFA or IFA panels did not include rhinovirus in routine testing, so as newer diagnostic technologies (i.e. PCR) become more widely used, the true epidemiology and impact of rhinovirus infections in HSCT or SOT recipients will become clearer. At present, there is no specific antiviral therapy available for the treatment of rhinovirus infections.

5.2 Coronavirus

Coronaviruses, like rhinoviruses, are frequent causes of benign URTIs occurring in annual wintertime community outbreaks. No systematic study of their possible role in LRTIs in HSCT or SOT recipients has been undertaken, but recent experience with SARS coronaviruses, the causative agent of SARS, is noteworthy. A study of tissue obtained at autopsy from a liver transplant recipient revealed extremely high numbers of viral copies,[87] suggesting both a reason for the fatal course as well as the possible role of immunosuppressed patients as 'superspreaders' of this and other epidemics.[75] With the more widespread availability of PCR diagnostics for coronaviruses, more research is needed to clarify the frequency and incidence of these infections in transplant recipients.

5.3 Herpesviruses

Nearly all viruses in the herpesvirus family have been reported as occasional causes of pneumonia in HSCT and SOT recipients. Cytomegalovirus (CMV) is perhaps the most important post-transplant pathogen and an occasional cause of respiratory infection, but its pathophysiology, epidemiology and treatment are beyond the scope of this review. Herpes simplex virus type 1 (HSV-1) and varicella zoster virus (VZV) are both rarely reported but potential pulmonary pathogens.[85] In the era of routine antiviral prophylaxis, these are especially rare pathogens in the first several post-transplant months. VZV may occur at any time post-transplant and dormant virus is ubiquitous in the population. Since most cases of VZV pneumonia in HSCT or SOT recipients are preceded by the characteristic vesicular skin rash,[88] and since VZV pneumonia is very rare, it is presumed that prompt antiviral therapy with aciclovir can halt the progression of reactivation disease to pneumonia. Patients with antecedent herpes zoster followed by pneumonia should also be empirically treated for bacterial superinfection, given the high rates of superinfection and the aggressive nature of some of the more common pathogens like *Staphylococcus aureus*.

The roles of human herpesvirus 6 (HHV)-6 and HHV-7 as pulmonary pathogens remain poorly understood.[89-91] While active replication with either virus may be detected in some transplant recipients (particularly HSCT patients), no consistent pattern of pulmonary disease has been associated with either virus. Proposed associations include pneumonia or bronchiolitis obliterans with or without organising pneumonia.[92] No commonly accepted treatments are available for either virus, though some agents with activity against other herpesviruses (e.g. ganciclovir, cidofovir) have some *in vitro* activity against these viruses.

5.4 Human Metapneumovirus

The newly recognised pathogen human metapneumovirus (hMPV) was first recovered in 2001 from a cohort of Dutch children with RTIs.[93] In the short time since this report, a number of important surveys have demonstrated both the commonness and potential significance of this pathogen in transplant patients. Three studies examining the frequency of hMPV recovery from stored bronchoalveolar lavage specimens documented a positivity rate of 3–9% among transplant recipients with symptomatic RTI; while this rate may seem low, it is compara-

ble to the observed rates for RSV, PIV and influenza.[94-96] Although it is difficult to calculate an accurate frequency of progression to pneumonia or death, these outcomes have been observed.[96] Furthermore, studies demonstrate that cases are clustered in epidemic fashion – whether these are community-based epidemics or nosocomial epidemics has not been firmly established, although some contribution of both is possible.[93] Debiaggi and colleagues[97] have published data which question the pathogenic role of hMPV in HSCT recipients, as many of their patients had detectable hMPV in nasal specimens without clinical disease. This highlights the need for further research in this area. No treatment is yet proposed for hMPV infection, and diagnosis is likely to be difficult because hMPV is not part of even many newer PCR-based panels for the diagnosis of viral infections. Regional laboratory experts should be consulted regarding the availability, feasibility and expense of routine or intermittent testing for this emerging pathogen.

6. Conclusion

Viral respiratory tract infections are commonly found in HSCT and SOT recipients. RSV, PIV, influenza A and B, and adenovirus are most often reported in the literature, with less information available regarding rhinovirus, coronavirus, herpesviruses and hMPV. Progression from URTI to LRTI occurs more often in immunocompromised patients, and once this occurs, is associated with higher complication and mortality rates. Early treatment is limited but should be considered when available. Preventative measures including vaccination, antiviral prophylaxis and appropriate infection control measures are also essential in decreasing morbidity and mortality associated with RTIs in transplant recipients.

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