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Special Article

RNA Respiratory Viruses in Solid Organ Transplantation

O. Manuel[a,*], M. Estabrook[b] and the AST Infectious Diseases Community of Practice

[a] *Infectious Diseases Service and Transplantation Center, University Hospital and University of Lausanne, Lausanne, Switzerland*
[b] *Division of Pediatric Infectious Diseases, Washington University School of Medicine, St. Louis, MO*
* *Corresponding author: Oriol Manuel, oriol.manuel@chuv.ch*

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Abbreviations: BAL, bronchoalveolar lavage; hMPV, human metapneumovirus; IgIV, intravenous immunoglobulin; LAIV, live-attenuated influenza vaccine; PIV, parainfluenza virus; RSV, respiratory syncytial virus; SOT, solid organ transplant.

Introduction and Epidemiology

A wide range of respiratory viruses have been identified as causes of significant morbidity and mortality among transplant recipients, including: influenza, respiratory syncytial virus (RSV), parainfluenza virus (PIV), rhinovirus, human metapneumovirus (hMPV), and coronavirus (1) (Table 1). Several features are common among all of these viruses in the transplant population:

1. The seasonality of respiratory viral infections among transplant recipients usually follows that of the general population (2,3).
2. The viruses all cause a range of disease, from mild congestion and rhinorrhea to more severe tracheobronchitis, bronchiolitis and pneumonia. No one virus is exclusively associated with one clinical syndrome (i.e. influenza-like illness, croup, etc.). As such, diagnostic strategies should initially be broad, attempting to screen for all recognized viruses (3,4) with particular emphasis on ones that might be amenable to therapy.
3. Transplant recipients often present with mild or atypical symptoms and fever may be absent. Lung transplant recipients, for example, may initially only have subjective symptoms of shortness of breath or subtle changes in pulmonary function testing without more typical symptoms (5).
4. Viral shedding is usually prolonged among transplant recipients. Prolonged shedding is seen even with the use of antivirals and therefore may contribute to the increased risk of resistant variant emergence (1,6).
5. Transplant recipients are at higher risk of infectious complications compared to immunocompetent hosts. Respiratory viral infections are a significant risk factor for subsequent development of fungal and bacterial pneumonia (1).
6. Respiratory viral infections appear to be a risk factor for both acute and chronic rejection with the greatest risk in lung transplant recipients (5,7–9) (II-2), although data on this topic in the literature are conflicting (10). The pathogenesis of the link between respiratory viral infections and rejection is not clearly understood.
7. All pediatric solid organ and lung transplant recipients appear to have the greatest risk of both respiratory viral infections and more severe courses and complications (1).
8. All are potential nosocomial pathogens that can be potentially spread by staff or visitor with mild upper respiratory illness.

Diagnosis

Since one cannot clinically distinguish disease caused by any of the respiratory viruses, diagnosis using broad ranging techniques should be considered particularly in the early period after transplantation or augmented immunosuppression and during respiratory viral season. Diagnosis can be achieved by combinations of serology, viral culture, antigen detection, and nucleic acid testing. In general, all patients with presumed respiratory viral infection should have a nasopharyngeal swab, wash, or aspirate performed and sent for testing. If upper tract samples fail to document the cause of the respiratory illness or if there is clinical or radiologic evidence of lower tract involvement, bronchoalveolar lavage (BAL) should be considered and sent for the range of available tests. Testing of a wide range of pathogens is most important among lung transplant recipients.

Serology is not useful for diagnosis of acute infection, but can be used for epidemiological studies in case of influenza, although some SOT recipients might not respond and antibody can wane quickly, even after infection. Rapid antigen detection is available for influenza and RSV and has the advantage of rapid result testing (within 15′). For influenza, rapid antigen detection testing has high specificity but variable sensitivity (20–70%) as compared to other assays, making them less useful in SOT recipients (11). Some

Table 1: Common respiratory virus infections in solid organ transplant recipients

Virus	Isolation recommendations	Prophylactic interventions	Therapeutic alternatives
Influenza	Contact and droplet	Annual Injectable Vaccine Neuraminidase inhibitor[1]	Neuraminidase Inhibitor[1] M2 Inhibitor[2]
RSV	Contact	Palivizumab	Aerosolized ribavirin[3] ± Antibody-based treatment[4] ± Corticosteroids
PIV	Contact	None	Aerosolized ribavirin[3] ± IgIV
hMPV	Contact	None	Aerosolized ribavirin[3] ± IgIV
Rhinovirus	Droplet contact added if copious secretions or close contact	None	None
Coronavirus	Standard precautions except for SARS, which requires contact, droplet, and airborne precautions	None	None

[1] Oseltamivir or zanamivir.
[2] Amantadine or rimantadine. Currently not recommended due to high rate of antiviral resistance.
[3] Oral or IV ribavirin can be used as well, although patients should be monitored for hemolytic anemia; less data are available about the efficacy of these formulations in treating RSV than with aerosolized ribavirin.
[4] IgIV, palivizumab, RSV-Ig (no longer produced but may still be available in some locations).

commercial assays can distinguish between influenza A and B, but some others cannot. In the case of RSV, one study documented a sensitivity with one rapid test method of 15% for nasal wash specimens among immunocompromised patients; sensitivity is improved to 89% when BAL is used (12). Several studies of direct fluorescent antibody (DFA) testing of primary patient specimens have documented sensitivity that approached that of PCR for certain viruses (13,14). DFA testing is limited by lack of reagents for some of the viruses (hMPV, rhinovirus, coronavirus) (15). Although viral cultures previously were considered the preferred diagnostic tests, molecular tests tend to provide higher yields and can detect a wider range of viruses in a more timely fashion (1). For influenza, viral culture has the advantage of allowing the identification of the influenza strain and to test antiviral susceptibility (11).

A wide range of PCR-based assays to detect respiratory viruses are commercially available and many centers have locally developed assays that detect select viruses. Nucleic acid amplification assays appear to be the most sensitive diagnostic tools available and most allow for simultaneous detection of a broad range of respiratory pathogens from a single sample and is therefore preferred testing method for immunocompromised patients (1). Multiplex PCR assays provide the advantage of identification of viruses not routinely found by conventional methods, including rhinovirus and hMPV (16–19). Commercially available multiplex assays differ in sensitivity and specificity for different viruses most notably adenovirus (16,20–22). New assays are being developed to address these limitations (23,24) but the clinician should be aware of the performance characteristics of the assay used. For influenza, PCR can distinguish among viral subtypes and can quantify viral load, making them useful for the monitoring of viral shedding. Recently, rapid PCR-based assays allow rapid results (within 3–4 hours), although their sensitivity may vary among virus types (25).

Influenza Virus

Epidemiology and risk factors

Influenza virus is an orthomyxovirus associated with significant morbidity and mortality during the winter season. Three main viral strains are associated with human infection, namely influenza A/H1N1, influenza A/H3N2, and influenza B. In 2009 a new strain of influenza A/H1N1, coming from reassortant animal and human viruses, caused a global pandemic (26). In the last influenza seasons, the pandemic influenza A/H1N1 virus replaced prior seasonal influenza A/H1N1 virus.

Recent studies performed during the pandemic have greatly increased our knowledge of the epidemiology of influenza infection in the transplant population (27–32). The risk of complications appears to be higher in SOT recipients as compared to the general population, particularly the incidence of pneumonia (up to 22%–49% in transplant recipients). Allograft dysfunction and acute rejection have been observed after severe cases of influenza (28). Most studies have observed an excess of influenza-associated morbidity and mortality in SOT recipients as compared to the general population. Rates of reported severe influenza varied between 16 and 20%, and attributable mortality was estimated to be 4%–8% (27–32). Ascertainment biases towards inclusion of patients with more severe disease may overestimate the severity of influenza in SOT recipients.

Risk factors for severe influenza in SOT recipients include use the antilymphocyte globulins, diabetes mellitus, pneumonia, bacterial and fungal co-infection, and early infection (<3 months) after transplantation (27,28). Use of early antiviral therapy has been consistently associated with a reduced rate of influenza-associated complications (admission to ICU, use of invasive ventilation, and death) (27–31).

Prevention/prophylaxis

Patients with known or suspected influenza infection should be isolated from other patients with standard and droplet precautions. Influenza vaccination is an important measure to prevent influenza infection (33). Two types of influenza vaccine exist, the inactivated influenza vaccine and intranasal live-attenuated influenza vaccine (LAIV). LAIV is contra-indicated in SOT recipients and close contacts, due to a potential risk of dissemination of the vaccine strain. One dose of the seasonal intramuscular trivalent influenza vaccine is the standard of care in adults, and two doses 4 weeks apart is recommended for naïve children <9 years of age (33). Immunogenicity of influenza vaccine is variable in SOT recipients, depending on the type of organ, immunosuppressive regimen used, and composition of the vaccine (34). However, there is increasing data reporting on the beneficial effects of influenza vaccination in SOT recipients. In lung transplant recipients, vaccination with adjuvanted influenza A H1N1/09 vaccine was associated with a reduced incidence of subsequent influenza infection (1.3% vs. 25% in unvaccinated patients) (35). Influenza vaccination was also associated with a lower risk of graft loss and death in kidney transplant recipients (36). Even if vaccinated patients develop influenza, a reduction in the severity of the disease as compared to unvaccinated patients has been observed (37). Influenza vaccine is therefore recommended for all SOT recipients and household members (33) (Table 2).

Influenza vaccine is well tolerated in SOT recipients, and adverse events to vaccination are usually mild and short lived. Recently, a study described the development of low-level anti-HLA antibodies in kidney transplant recipients who received multiple doses of adjuvanted influenza vaccine in one season. There was no proven association between vaccination, the development of the *de novo* antibodies, and graft rejection. Further studies are required to clarify this potential association (38). The optimal timing for vaccination after transplant has not been established. It is generally recommended to vaccinate at least 3 months post transplantation (33), although in this early period post transplant is when the risk of influenza-associated complications is higher (28). Antiviral prophylaxis with oseltamivir may be an alternative to influenza vaccination in case of contra-indication or expected nonresponse to the vaccine. A randomized controlled trial in transplant recipients found an efficacy of ~80% of prophylaxis (39).

Table 2: Summary recommendations for treatment and prevention of influenza in solid organ transplant recipients

Recommendations	Grading
• Transplant recipients should receive antiviral therapy with a neuraminidase inhibitor (either oseltamivir or zanamivir) when influenza is suspected.	II-2
• Although early (<48h) administration of antivirals is associated with better outcome, all symptomatic patients should receive antiviral therapy, irrespective of symptom onset.	III
• Duration of antiviral therapy should be at least 5 days. Antiviral therapy may be prolonged in case of persistent viral shedding.	III
• Double dosing of oseltamivir may be considered in severe cases or in case of insufficient response to therapy.	III
• IV drugs (peramivir or zanamivir) can be also used in selected cases (intubated patients, concerns with oral absorption).	III
• Patients with influenza infection need to be isolated with standard and droplet measures.	II-2
• Trivalent inactivated influenza vaccine should be administered to SOT recipients and household members.	II-2
• In patients whom influenza vaccine is contraindicated or may have insufficient response (e.g. therapy for acute rejection, early after transplantation), antiviral prophylaxis with oseltamivir 75 mg OD for a duration of 12 weeks starting at the beginning of the influenza season may be proposed.	I

Treatment

Two families of drugs are approved for the treatment of influenza, namely M2 inhibitors and neuraminidase inhibitors (11). M2 inhibitors (amantadine and rimantadine) are not active against influenza B, and because of the high incidence of antiviral resistance to influenza A/H1N1 and A/H3N2, theses drugs are no longer recommended for treatment of influenza (11). Neuraminidase inhibitors include oral oseltamivir, and inhaled zanamivir (Table 3). An intravenous form of oseltamivir and zanamivir is also available as investigational drug, but not currently approved. Intravenous peramivir, another neuraminidase inhibitor, is approved for its use in South Korea and Japan. None of these drugs has been specifically tested in prospective trials in SOT recipients for the therapy of influenza. Studies performed during the influenza A/H1N1 pandemic showed that early treatment with oseltamivir was associated with decreased mortality, admission at the ICU and complicated outcomes in SOT recipients (27–31). Less data are available for zanamivir, but it appears to be equally effective. Therapy with neuraminidase inhibitors may be associated with reduced incidence of allograft dysfunction in lung transplant recipients (31,40). Given the beneficial effect of early administration of antiviral drugs, oseltamivir or zanamivir therapy should be started empirically in all patients with symptoms compatible with influenza, before microbiological confirmation.

Transplant recipients are known to have prolonged viral replication, so it is generally recommended to extend the duration of therapy beyond the approved 5 days period. Monitoring of viral replication in naso-pharyngeal swabs by PCR may be used to guide duration of antiviral therapy (41). Although early (<48h) administration of antivirals is associated with better outcome, patients may still benefit from

Table 3: Recommended dosage of neuraminidase inhibitors for treatment of influenza[1]

		Adjustment for renal failure in adults		Children (≥1 year old)	
Drug	Adults	Renal function	Dose	Weight	Dose
Oseltamivir	75 mg BID	CrCl ≥ 30 mL/min	75 mg BID	≤15 kg	30 mg BID
		CrCl < 30 mL/min	75 mg OD	16–23 kg	45 mg BID
		Hemodialysis/CAPD	30–75 mg after dialysis	24–40 kg	60 mg BID
		CRRT	75 mg BID	>40 kg	75 mg BID
				Infants (<1 year old)	
				3 mg/kg/dose BID	
Zanamivir	10 mg (2 inhalations) BID	No adjustment required		Zanamivir approved for treatment and prophylaxis of persons ≥5 years, same dose than adults	

BID = twice daily; CAPD = continuous ambulatory peritoneal dialysis; CRRT = continuous renal replacement therapy; OD = once daily.
[1]Resistance patterns may change and affect recommended antiviral strategies; consult your national health authority regularly for updated recommendations.

therapy irrespective of the duration of symptoms. In severe cases, double dosing (i.e. 150 mg of oseltamivir twice a day for normal kidney function) is recommended by some experts, with some anecdotal cases of positive outcomes in SOT recipients reported in the literature (42). Importantly, pharmacokinetic studies have not observed a clinically relevant interaction between oseltamivir and immunosuppressive drugs (tacrolimus, cyclosporine, and mycophenolate) (43). The use of peramivir or IV zanamivir can be considered in cases of life-threatening infection or concerns with oral absorption, although experience with these drugs in SOT recipients is lacking (44,45).

As mentioned, the use of M2 inhibitors for treatment of influenza is no longer recommended due to the high rate of resistance to these drugs (>95%). Rates of oseltamivir resistance were high for prepandemic influenza A/H1N1 virus, but antiviral resistance has been only occasionally described for the new influenza A/H1N1 strain (46). Immunosuppression and exposure to oseltamivir are risk factors for development of antiviral resistance (47). Most resistance in H1N1 viruses in patients exposed to oseltamivir is caused by the H275Y mutation, which results in increase IC50 for peramivir but retains activity of zanamivir (46). Resistance to neuraminidase inhibitors is uncommon in influenza A/H3N2 and influenza B viruses. Most commercially available resistance assays only detect H275Y and other mutations may occur, particularly when agents other than oseltamivir are used or influenza A/H3N2 or B are being treated. As resistance patterns may change and affect recommended antiviral strategies, it is important to regularly consult the national health authority for updated recommendations.

Respiratory Syncytial Virus

Virology and epidemiology

RSV is a paramyxovirus in the genus pneumovirus that causes seasonal annual epidemics worldwide; year round disease is seen in some tropical locations. By two years of age, virtually all children have experienced a primary infection although re-infection can occur throughout life. Risk factors for more severe disease after organ transplantation include infection in children under a year of age or with underlying lung disease (1,9). Early acquisition of RSV after transplantation or after augmented immunosuppression has been associated with increased severity of disease in some but not all studies (1,8,48–53). Transmission occurs through inhalation of infectious droplets or through contact with fomites.

Prevention

Patients with known or suspected RSV should be isolated from other patients using standard contact precautions (II-2) (54,55). Prophylaxis with the RSV-specific monoclonal antibody (palivizumab) or high titer RSV-IgIV has been shown to be effective for specific groups of high-risk infants and young children (I) (56,57). However, no studies have been conducted to evaluate their use in the transplant setting and the cost of the weight adjusted dosing of these products in adults would be extremely high. Palivizumab is recommended for children less than two years of age with chronic lung disease or with cyanotic or complicated congenital heart disease during the RSV season (58) (III), however, guidelines regarding use of this agent in older children and adults do not exist. Survey data suggest that antibody-based prophylaxis is commonly used among pediatric transplant centers (59,60). There are no approved vaccines for prevention of RSV.

Treatment

Given the limited data on treatment of RSV, supportive care is recommended (II-2) and reduction of immune suppression should be considered, particularly in those with severe disease. The role of specific antiviral treatment is controversial. Ribavirin has been shown to have *in vitro* activity against RSV and the aerosolized form of this drug has been approved for the treatment of lower respiratory tract disease due to RSV in certain at-risk populations (61). Despite its FDA approval, convincing data describing the clinical efficacy of this agent are lacking and a consensus on the treatment of RSV disease does not

currently exist (60,62). Published data on the treatment of RSV disease in SOT recipients are limited and most of the data pertains to lung transplant recipients. Experience in stem cell transplant populations suggests that the use of aerosolized ribavirin may reduce mortality associated with severe RSV infections, particularly those affecting the lower airways (51,61,63). The combination of aerosolized ribavirin and antibody-based interventions, including IgIV, RSV-Ig, and palivizumab appeared to have an even greater impact on mortality (1,64,65). Many experts, therefore, would recommend the use of the combination of ribavirin and an antibody preparation with or without corticosteroids for the treatment of severe RSV infections (II-2) (1,49,65). Based upon published experience from pediatric organ transplant recipients, patients without risk factors for severe disease and with only upper respiratory infections are unlikely to benefit from aerosolized ribavirin (II-2) (49). There are also published reports of successful treatment of RSV in lung transplant recipients with oral and IV ribavirin with and without corticosteroids (66–68). Further studies are needed to determine the clinical efficacy of these alternatives since there is a risk of adverse effects, notably hemolytic anemia.

Parainfluenza Virus

Virology and epidemiology

Parainfluenza is a pneumovirus for which there are 4 types that commonly cause disease in humans (types 1–4). PIV types 1 and 2 tend to circulate sporadically in fall and winter months in temperate areas while type 3 occurs year round; type 4 is least commonly isolated and its epidemiology is still being defined (1). Transmission occurs via person-to-person spread by direct contact with infectious secretions or fomites. Disease can be serious, particularly in pediatric transplant recipients and lung transplant recipients of any age (1,5,69). Although all respiratory viruses are associated with an increased risk of progression to obliterative bronchiolitis in lung transplant recipients, the association appears to be clearest and strongest with PIV lower tract disease (5,7,8).

Prevention

Patients with known or suspected PIV should be isolated from other patients using standard contact precautions (54,55). There are no approved vaccines nor are there recognized preventative antiviral agents.

Treatment

Although the use of IgIV and ribavirin are not associated with benefit in the management of PIV infections in stem cell transplant recipients, ribavirin has *in vitro* activity and has been used to treat lung transplant recipients with lower tract disease; some experts also consider the use of IgIV and corticosteroids as well (51,52,65,69).

Human Metapneumovirus

Human metapneumovirus discovered in 2001 is an RNA paramyxovirus that has a clinical pattern similar to RSV and is a significant cause of disease in transplant recipients (70). As with other pneumoviruses, there are no vaccines and prevention is focused on tight infection control measures, including contact precautions (55). Case reports and animal data suggest that ribavirin with or without immunoglobulin can be considered for the management of severe cases of hMPV (1,70–72) but supportive care remains the mainstay of treatment.

Rhinovirus

Human rhinoviruses are members of the *Picornaviridae* family and are the most common cause of colds in adults and children. They have been recognized to cause clinically significant disease in some transplant recipients with fatal cases described (73,74). Most of the fatalities are associated with co-infections. Prolonged shedding with minimal symptoms has been described, particularly in lung transplant recipients. The clinical importance of this prolonged shedding has not been fully defined, although could potentially pose a threat of nosocomial transmission (1,8,74,75). Currently, there are no approved preventive or therapeutic interventions.

Other Respiratory Viruses

With the use of molecular diagnostics, a wider range of respiratory viruses have been isolated. Many of these viruses, such as newly recognized variants of coronavirus (HKU1, NL63), the polyomaviruses (WU, KI viruses), and bocavirus have not been widely studied in transplant recipients and so their clinical impact has not been fully assessed (1). Severe and sometimes fatal cases of all of these viruses in immunocompromised patients have been recognized, so they should be considered in the differential diagnosis of patients presenting with severe lower tract disease. The newer agents are more challenging to diagnose since they are not included in the routine, clinically available diagnostic tests. In addition, optimal management of these agents has not been defined.

Future Studies

Although respiratory viruses are increasingly recognized as causes of morbidity and mortality in transplant recipients, there is still much to be learned about the impact of these viruses. Prospective studies using molecular diagnostics are needed to understand the true epidemiology and clinical spectrum of respiratory viral diseases. In particular, studies of the long-term consequences of infection, even when mild or asymptomatic, are needed. This is

particularly important in lung transplant recipients in whom lower tract infection has been associated with an increased risk of chronic rejection and bronchiolitis obliterans syndrome. Prospective studies, using contemporary molecular diagnostic tools including metagenomics, are also needed to define the efficacy and cost of preventative interventions, particularly in high risk pediatric populations and lung transplant recipients. Novel therapeutic agents are also under development (76) and may be useful in the SOT population. Prospective trials are needed to define the optimal timing, duration, and treatment regimen for each of the viruses.

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