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RNA respiratory viral infections in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

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Abstract

These updated guidelines from the Infectious Diseases Community of Practice of the American Society of Transplantation review the diagnosis, prevention, and management of RNA respiratory viral infections in the pre- and post-transplant period. Viruses reviewed include influenza, respiratory syncytial virus (RSV), parainfluenza, rhinovirus, human metapneumovirus (hMPV), and coronavirus. Diagnosis is by nucleic acid testing due to improved sensitivity, specificity, broad range of detection of viral pathogens, automatization, and turnaround time. Respiratory viral infections may be associated with acute rejection and chronic lung allograft dysfunction in lung transplant recipients. The cornerstone of influenza prevention is annual vaccination and in some cases antiviral prophylaxis. Treatment with neuraminidase inhibitors and other antivirals is reviewed. Prevention of RSV is limited to prophylaxis with palivizumab in select children. Therapy of RSV upper or lower tract disease is controversial but may include oral or aerosolized ribavirin in some populations. There are no approved vaccines or licensed antivirals for parainfluenza, rhinovirus, hMPV, and coronavirus. Potential management strategies for these viruses are given. Future studies should include prospective trials using contemporary molecular diagnostics to understand the true epidemiology, clinical spectrum, and long-term consequences of respiratory viruses as well as to define preventative and therapeutic measures.

KEYWORDS

antibiotic prophylaxis, antibiotic: antiviral, guidelines, infection and infectious agents, viral: influenza

1 | 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 (Table 1).[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 (ie, influenza-like illness, croup, etc). As such, diagnostic strategies should initially be broad, attempting to screen

TABLE 1 Common respiratory virus infections in solid organ transplant recipients

Virus	Isolation recommendations	Prophylactic interventions	Therapeutic alternatives
Influenza	Contact & Droplet	Annual inactivated injectable vaccine Neuraminidase Inhibitor[a]	Neuraminidase inhibitor[a]
RSV	Contact	Palivizumab	Aerosolized or oral ribavirin[b] ± Antibody-based treatment[c] ± Corticosteroids
PIV	Contact	None	Aerosolized or oral ribavirin[b] ± IVIG
hMPV	Contact	None	Aerosolized or oral ribavirin[b] ± IVIG
Rhinovirus	Droplet Contact added if copious secretions or close contact	None	None
Coronavirus	Standard precautions except for MERS-CoV which requires Contact, Droplet, and Airborne precautions	None	None

[a]Oseltamivir or zanamivir.
[b]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.
[c]IVIG, palivizumab, RSV-Ig (no longer produced but may still be available in some locations).

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.[1,6,7]
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.[1,8]
6. Respiratory viral infections appear to be a risk factor for both acute and chronic rejection with the greatest risk in lung transplant recipients,[5,9-11] although data on this topic in the literature are conflicting.[12,13] The pathogenesis of the link between respiratory viral infections and rejection is not clearly understood.
7. Pediatric solid organ and lung transplant recipients appear to have the greatest risk of both respiratory viral infections and more severe courses and complications[14] but a recent retrospective observational cohort of 1096 pediatric solid organ transplant recipients found that all-cause death after respiratory viral infection was rare (4%) and no definitive attributable death occurred.[15]
8. All are potential nosocomial pathogens which can be spread by staff or visitors with mild upper respiratory illness or who are asymptomatic. Nosocomial transmission of influenza in transplant wards has been associated with significant mortality/morbidity early after transplant.[7,16]

2 | 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, particularly among lung transplant recipients. 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 should be considered and sent for the range of available tests.

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 are therefore the preferred diagnostic testing method for immunocompromised patients.[14] Multiplex PCR assays provide the advantage of identification of viruses not routinely found by conventional methods, including rhinovirus and hMPV,[17-20] although multiplexing can affect the sensitivity of the assay. Commercially available multiplex assays differ in sensitivity and specificity for different viruses most notably adenovirus,[17,21-23] and the clinician should be aware of the performance characteristics of the assay used. For influenza, PCR assays can distinguish among viral subtypes and can quantify viral load. Although not available at all centers, rapid PCR-based assays allow rapid results (within 3-4 hours), particularly for influenza and RSV, although their sensitivity may vary among virus types.[24,25]

Rapid antigen detection is available for influenza and RSV and has the advantage of rapid result testing (within 15'), but suboptimal

sensitivity (between 50% and 60%) and low predictive value.[26,27] Several studies of direct fluorescent antibody (DFA) testing of primary patient specimens have documented sensitivity that approached that of PCR for certain viruses.[28,29] DFA testing is limited by lack of reagents for some of the viruses (rhinovirus, coronavirus).[30] Serology is not useful for diagnosis of acute infection, but can be used for epidemiological studies in cases of influenza, although some SOT recipients might not respond and antibody can wane quickly, even after infection. Finally, although viral cultures previously were considered the preferred diagnostic tests, they are not currently used in routine clinical practice.

3 | SUMMARY RECOMMENDATIONS FOR DIAGNOSIS OF RNA RESPIRATORY VIRAL INFECTIONS IN SOLID ORGAN TRANSPLANT RECIPIENTS

- All patients with presumed respiratory viral infection should have a nasopharyngeal swab, wash, or aspirate performed and sent for testing (strong, very low).
- In case of diagnostic uncertainty, especially with clinical or radiologic evidence of lower tract involvement, bronchoalveolar lavage should be sent for the range of available tests (strong, very low).

4 | INFLUENZA VIRUS

4.1 | Epidemiology and risk factors

Influenza virus is an orthomyxovirus associated with significant morbidity and mortality during the winter season in both immunocompetent and immunocompromised patients. 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[31] and subsequently replaced prior seasonal influenza A/H1N1 virus. Also, two different strains of influenza B virus (Yamagata and Victoria) had jointly circulated during last influenza seasons.

Clinical presentation of influenza in transplant recipients is similar to that of the general population, with fever (60% of patients), cough (85%), and rhinorrhea (45%) being the most common symptoms reported in a recent large cohort.[7] However, the risk of complications of influenza 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).[7,32-35] Allograft dysfunction and acute rejection have been observed after severe cases of influenza.[32] 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 admission at the ICU and attributable mortality were estimated to be 11%-16% and 3%-8%, respectively.[7,32-35] Ascertainment biases toward inclusion of patients with more severe disease may however overestimate the severity of influenza in SOT recipients.

Risk factors for severe influenza in SOT recipients include use of antilymphocyte globulins, diabetes mellitus, pneumonia, bacterial and fungal co-infection, and early infection (<3 months) after transplantation.[32,33] Nosocomial acquisition of influenza has been described as a risk factor for admission to ICU.[7,16] Use of influenza vaccination and early antiviral therapy has been consistently associated with a reduced rate of influenza-associated complications (pneumonia, admission to ICU, use of invasive ventilation, and death)[7,16,32,33] (see below).

4.2 | Prevention/Prophylaxis

Patients with known or suspected influenza should be isolated from other patients with standard and droplet precautions. Influenza vaccination is the key measure to prevent influenza.[36] Two types of influenza vaccines exist, the inactivated influenza vaccine and intranasal live-attenuated influenza vaccine (LAIV). LAIV is contraindicated in SOT recipients and close contacts, due to a potential risk of dissemination of the vaccine strain. One dose of the seasonal intramuscular trivalent or quadrivalent influenza vaccine is the standard of care in adults, and two doses 4 weeks apart are recommended for naïve children <9 years of age.[36] Immunogenicity of influenza vaccine is variable in SOT recipients, depending on the type of organ, immunosuppressive regimen used, and composition of the vaccine.[37] However, there are 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).[38] Influenza vaccination was also associated with a lower risk of graft loss and death in kidney transplant recipients.[39] Even if vaccinated patients develop influenza, a reduction in the severity of the disease and in viral load in the nasopharyngeal swab as compared to unvaccinated patients has been observed.[7,40] Previous vaccination has been associated with a lower risk for pneumonia and ICU stay in a large cohort of SOT and hematopoietic stem cell transplant (HSCT) recipients.[7] Influenza vaccine is therefore highly recommended for all SOT recipients and household members.[36] Influenza vaccine is well tolerated in SOT recipients, and adverse events to vaccination are usually mild and short lived.[41] Recent randomized controlled trials found increased immunogenicity in SOT recipients using a high-dose vaccine or a booster strategy using two doses of the standard dose vaccine 5 weeks apart.[42,43] These approaches can be particularly used in case of an expected lower response to the vaccine due to enhanced immunosuppression. The reader is referred to the American Society of Transplantation Vaccine Guidelines in this series for a detailed discussion of influenza vaccines.

Antiviral prophylaxis with oseltamivir may be an alternative to influenza vaccination in cases of contra-indication or expected diminished response to the vaccine. A randomized controlled trial in transplant recipients found that prophylaxis had ~80% efficacy.[44] In case of a close contact with a patient with documented influenza, SOT recipients may receive postexposure prophylaxis with a

TABLE 2 Recommended dosage of neuraminidase inhibitors for treatment of influenza

		Adjustment for renal failure in adults		Children (≥1 y 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 y old)	
				3 mg/kg/dose BID	
Zanamivir	10 mg (2 x 5 mg inhalations) BID	No adjustment required		Zanamivir approved for treatment of persons ≥ 7 y, same dose as adults	

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

oseltamivir,[45] particularly in case of high risk for complications (nosocomial influenza early after transplant,[16] lung transplant recipients, or during therapy of rejection).

5 | SUMMARY RECOMMENDATIONS FOR PREVENTION OF INFLUENZA IN SOLID ORGAN TRANSPLANT RECIPIENTS

- Patients with influenza infection in a healthcare setting need to be isolated with standard and droplet measures (Strong, moderate).
- Inactivated influenza vaccine should be administered to all SOT recipients and household members (strong, high).
- In patients whom influenza vaccine is contraindicated or may have insufficient response (eg, therapy for acute rejection, early after transplantation), antiviral prophylaxis with oseltamivir 75 mg once daily for a duration of 12 weeks (renally adjusted if needed) starting at the beginning of the influenza season may be proposed (weak, high).
- In SOT recipients that are close contacts of a patient with documented influenza (in particular in cases of nosocomial influenza and in patients with enhanced immunosuppression), we suggest administering postexposure prophylaxis with oseltamivir (strong, low).

5.1 | Treatment

Two families of drugs are approved for the treatment of influenza, namely M2 inhibitors and neuraminidase inhibitors.[46] 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, these drugs are no longer recommended for treatment of influenza.[46] Neuraminidase inhibitors include oral oseltamivir, inhaled zanamivir, and intravenous peramivir (Table 2). Laninamivir is a long-acting inhaled neuraminidase inhibitor that is approved in Japan for prophylaxis and treatment of influenza.[47] An intravenous form of zanamivir is available in Europe as investigational drug, but not currently approved. None of these drugs has been specifically tested in prospective trials in SOT recipients for the therapy of influenza. Most studies have shown that early treatment with oseltamivir is associated with decreased mortality, admission to the ICU and complicated outcomes in SOT recipients.[7,33-35,48,49] Less data are available for inhaled zanamivir, but it appears to be equally effective. Experience with IV zanamivir in SOT recipients is limited.[50] Intravenous peramivir is approved for use as a single dose, but repeated doses and/or step down with oral oseltamivir may be necessary for SOT recipients.[51] Therapy with neuraminidase inhibitors may be associated with reduced incidence of allograft dysfunction in lung transplant recipients.[35,52] 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. Baloxavir is a single-dose FDA-approved therapy for influenza with a novel mechanism of action, the inhibition of cap-dependent endonuclease. Baloxavir has shown efficacy in treating uncomplicated influenza in healthy subjects; however, data for its use in transplant recipients are lacking.[53]

Transplant recipients are known to have prolonged viral replication. The decision to continue antiviral therapy beyond the standard treatment course generally depends on whether the patient has persistent clinical symptoms. Monitoring of viral replication in nasopharyngeal swabs by PCR can help to guide infection control practices although should generally not be used to guide duration of antiviral therapy.[54] Although early (<48 hour) administration of antivirals is associated with better outcomes, patients may still benefit from therapy irrespective of the duration of symptoms. In severe cases, double dosing (ie, 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.[55] However, a large randomized controlled trial did not find a benefit of using high-dose oseltamivir for influenza in the general population.[56] Importantly, pharmacokinetic studies have not observed a clinically relevant interaction between oseltamivir and immunosuppressive drugs (tacrolimus, cyclosporine, and mycophenolate).[57] The use of the intravenous drugs peramivir or zanamivir

can be considered in cases of life-threatening infection or concerns with oral absorption, although, as mentioned, experience with these drugs in SOT recipients is lacking.[50,51]

The use of amantadine and rimantadine 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 pre-pandemic influenza A/H1N1 virus, but antiviral resistance has been only occasionally described for the new influenza A/H1N1 strain.[58] Immunosuppression and exposure to oseltamivir are risk factors for development of antiviral resistance.[59] Most resistance in A/H1N1 viruses in patients exposed to oseltamivir is caused by the H275Y mutation, which results in an increased IC50 for peramivir, but retains zanamivir activity,[58] and most commercially available resistance assays only detect H275Y; other mutations may occur, particularly when agents other than oseltamivir are used or influenza A/H3N2 or B are being treated. Resistance to neuraminidase inhibitors is uncommon in influenza A/H3N2 and influenza B viruses. Testing for antiviral resistance is indicated in cases of persistent clinical symptoms and/or viral shedding despite appropriate antiviral therapy. As resistance patterns may change and affect recommended antiviral strategies, it is important to regularly consult the national health authority for updated recommendations.

6 | SUMMARY RECOMMENDATIONS FOR TREATMENT OF INFLUENZA IN SOLID ORGAN TRANSPLANT RECIPIENTS

- Transplant recipients should receive antiviral therapy with a neuraminidase inhibitor (either oseltamivir or inhaled zanamivir) when influenza is suspected (strong, moderate).
- Although early (<48 hours) administration of antivirals is associated with better outcomes, all symptomatic patients should receive antiviral therapy, irrespective of duration of symptom onset (strong, low).
- Duration of antiviral therapy should be at least 5 days. Antiviral therapy may be prolonged in cases of persistent clinical symptoms (weak, low).
- Double dosing of oseltamivir may be considered in severe cases or in cases of insufficient response to therapy (weak, low).
- IV drugs (peramivir or zanamivir) can be also used in selected cases (intubated patients, concerns with oral absorption) (weak, low).
- Resistance testing should be considered when clinical symptoms and/or viral shedding are present despite antiviral therapy.

7 | RESPIRATORY SYNCYTIAL VIRUS

7.1 | 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.[60] By 2 years of age, virtually all children have experienced a primary infection; re-infection can occur throughout life. Risk factors for more severe disease after organ transplantation include lung transplantation, infection in children under a year of age or with underlying lung disease.[61] Early acquisition of RSV after transplantation or after augmented immunosuppression has been associated with increased severity of disease in some but not all studies.[62-67] Transmission occurs through contact with contaminated secretions, including exposure to large-particle droplets and fomites.

7.2 | Prevention

Patients with known or suspected RSV should be isolated from other patients using standard contact precautions.[68] Prophylaxis with the RSV-specific humanized monoclonal antibody palivizumab has been shown to be effective for high-risk infants and children <24 months with specific underlying conditions[69-72] and updated recommendations regarding its use were published by the American Academy of Pediatrics in 2014.[73] No specific recommendations were given for immunocompromised individuals except that children younger than 24 months who will be profoundly immunocompromised during the RSV season may be considered for prophylaxis. Survey data suggest that antibody-based prophylaxis is commonly used among pediatric transplant centers.[74,75] However, no studies have been conducted to evaluate its use in the solid organ transplant setting, and the cost in adults is significant. There are no approved vaccines for prevention of RSV, although various vaccine formulations are under development.

7.3 | Treatment

Ribavirin is a nucleoside analog with activity against RSV and the aerosolized form is currently the only FDA-approved drug for treatment of lower respiratory tract disease in certain high-risk populations.[61] Oral and IV preparations are also available. Use of corticosteroids and immunomodulators including immunoglobulin (IVIG), RSV-IVIG (no longer available), and palivizumab has been investigated as adjunctive therapy. Consensus on the treatment of RSV in solid organ transplant recipients remains unsettled, however, as there are no randomized, placebo-controlled trials in this population. Wide variations in approach have been reported.[75] Lung and heart-lung recipients are usually treated for both upper or lower respiratory tract infection. Some non-lung recipients with lower respiratory infection may also be treated, but those with upper respiratory infection are generally not treated.[75]

A comprehensive review of the management of RSV infection in adult HSCT recipients showed that for patients treated with ribavirin, regardless of form or duration of therapy or the addition of an immunomodulator (palivizumab, IVIG, or RSV-IVIG), the rate of progression from upper respiratory to lower respiratory infection was much lower than in patients who did not receive any form of RSV therapy. Mortality rate was also lower in treated patients with lower respiratory infection.[77] It also reported a trend toward a better outcome in progression to lower respiratory infection and death among patients treated with aerosolized ribavirin and an immunomodulator than those treated with aerosolized ribavirin alone.[77] Published studies in symptomatic lung transplant recipients have

reported improved outcome in those treated for RSV as summarized in a recent review.[61] These include IV ribavirin plus corticosteroids,[78] oral ribavirin plus corticosteroids,[79] oral or IV ribavirin,[80,81] and a regimen of inhaled ribavirin plus methylprednisolone, IVIG, and palivizumab.[82] Aerosolized ribavirin is cumbersome and expensive to administer and there is increasing evidence, although only in observational studies, of the efficacy of oral ribavirin in immunocompromised adults[83] and lung transplant recipients.[79-81] Oral ribavirin can be considered especially in areas where aerosolized ribavirin is not available. Most patients also received corticosteroids and some received IVIG as well. Importantly, oral ribavirin is associated with significant toxicity including hemolytic anemia, leucopenia, and neuropsychological symptoms, and its use is contraindicated during pregnancy. Large, multicenter, placebo-controlled trials are needed to determine the efficacy and safety of these alternative treatments including oral ribavirin in solid organ transplant recipients. Presatovir (formerly GS-5806) is a novel, orally administered RSV fusion inhibitor that is under investigation for the treatment of RSV.[84]

8 | SUMMARY RECOMMENDATIONS FOR DIAGNOSIS, TREATMENT, AND PREVENTION OF RSV IN SOLID ORGAN TRANSPLANT RECIPIENTS

- Patients with known or suspected RSV should be isolated from other patients using standard and contact precautions (strong, moderate).
- Prophylaxis with palivizumab may be considered for children <24 months of age who are profoundly immunocompromised during the RSV season (strong, low)
- Treatment with aerosolized or oral ribavirin is recommended for lung transplant recipients with upper or lower respiratory tract infection (weak, moderate)
- Addition of corticosteroids and IVIG to ribavirin can be considered for lung transplant recipients with upper or lower respiratory tract infection (weak, low)
- Treatment with aerosolized or oral ribavirin of non-lung solid organ recipients with lower respiratory tract disease can be considered (weak, low)

9 | PARAINFLUENZA VIRUS

9.1 | Virology and epidemiology

Parainfluenza is a pneumovirus for which there are four serotypes 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.[14] 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.[5,14,85] 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.[5,9,10]

9.2 | Prevention

Patients with known or suspected PIV should be isolated from other patients using standard and contact precautions.[68,86] There are no approved vaccines nor are there recognized preventative antiviral agents.

9.3 | Treatment

Although the use of IVIG and ribavirin is not associated with benefit in the management of PIV infections in stem cell transplant recipients, ribavirin has in vitro activity and the inhaled form has been used to treat lung transplant recipients with lower tract disease; some experts also consider the use of IVIG and corticosteroids as well.[66,67,82,85] Inhaled DAS181 is a recombinant fusion protein that is undergoing investigation for treatment of PIV lower respiratory tract infection.[87]

10 | SUMMARY RECOMMENDATIONS FOR DIAGNOSIS AND TREATMENT OF PIV IN SOLID ORGAN TRANSPLANT RECIPIENTS

- Treatment of lung transplant recipients with PIV lower tract infection with ribavirin can be considered (weak, very low).
- Adjunctive therapies to ribavirin, including IVIG and corticosteroids may be considered in lung transplant recipients (weak, very low)

11 | 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.[88-90] As with other pneumoviruses, there are no vaccines and prevention is focused on tight infection control measures, including contact precautions.[68] Case reports and animal data suggest that ribavirin with or without immunoglobulin can be considered for the management of severe cases of hMPV[14,88,91,92] but supportive care remains the mainstay of treatment.

12 | SUMMARY RECOMMENDATIONS FOR DIAGNOSIS AND TREATMENT OF HUMAN METAPNEUMOVIRUS IN SOLID ORGAN TRANSPLANT RECIPIENTS

- Treatment of lung transplant recipients with human metapneumovirus lower tract infection with ribavirin ± IVIG and corticosteroids can be considered (weak, very low)

13 | RHINOVIRUS

Human rhinoviruses (hRV) are members of the *Picornaviridae* family and are the most common cause of upper respiratory infection in adults and children. They have been recognized to cause clinically significant disease in some transplant recipients with fatal cases described.[93,94] 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.[10,14,94,95] Currently, there are no approved preventive or therapeutic interventions.

14 | 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.[14] 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 respiratory tract disease. Newly identified viruses are more challenging to diagnose since they are not included in the routine, clinically available diagnostic tests. In addition, optimal management of these pathogens has not been defined.

15 | 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[61] and may be useful in the SOT population. Small molecule drugs including oral RSV entry inhibitor Presatovir (GS-5806) are under investigation.[84,96,97] Inhaled DAS181 is a recombinant fusion protein that has shown promise in inhibiting PIV replication.[87] In addition, adoptive T-cell therapy including the generation of PIV specific[98] and hMPV[99] T-cells in healthy donors is an emerging therapeutic modality. Prospective trials are needed to define the optimal timing, duration, and treatment regimen for each of the viruses.

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CONFLICT OF INTEREST

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