American Journal of Transplantation 2009; 9 (Suppl 4): S166–S172
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2009.02908.x

RNA Respiratory Viral Infections in Solid Organ Transplant Recipients

M. G. Ison[a,*], M. G. Michaels[b] and the AST Infectious Diseases Community of Practice

[a] *Divisions of Infectious Diseases & Organ Transplantation, Northwestern University Feinberg School of Medicine, Chicago, IL*
[b] *Departments of Pediatrics and Surgery, Division of Pediatric Infectious Diseases University of Pittsburgh School of Medicine, Pittsburgh, PA*
**Corresponding author: Michael G. Ison, mgison@northwestern.edu*

Key words: Human metapneumovirus, influenza, organ transplantation, parainfluenza virus, rhinovirus, RSV

Introduction and Epidemiology

A wide range of RNA 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), coronavirus, bocavirus and polyomaviruses (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. Symptoms commonly associated with a respiratory viral infection include fevers, nasal congestion, rhinorrhea, watery eyes, cough, sore throat, sputum production, wheezing, shortness of breath and fevers.
3. Transplant recipients often present with mild or atypical symptoms. 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). Fever may be absent in transplant recipients with pneumonia or may be the sole presenting sign or symptom (1,4). As such, any fever or respiratory symptom should prompt the consideration of a respiratory viral infection as the potential cause.
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. In the older studies, initial evidence of or progression to lower tract involvement with viruses occurred frequently, but may in part be due to ascertainment biases as sicker patients were more likely to be seen by physicians and have specimens sent for viral assays (1). Respiratory viral infections are a significant risk factor for subsequent development of fungal and bacterial pneumonia (1). Other infections, such as CMV viremia, may complicate respiratory viral infections as well.
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). Concurrent rejection and graft dysfunction has been documented with other solid organ transplant recipients as well, although at a lower frequency than in lung transplant recipients (1) (III). 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 RNA viral infections and more severe courses and complications (1).
8. All are potential nosocomial pathogens which can be potentially spread by staff or visitor with mild upper respiratory illness.
9. There are few prospective studies of respiratory virus infections in most solid organ transplant populations, with the exception of lung transplant recipients. Most of these studies were retrospective in nature and focused on individuals who were hospitalized with infections (1). In addition, most studies evaluated patients close to the time of transplantation when specimens were more likely to be obtained for diagnosis. This likely leads to an overestimation of the severity and underestimation of the incidence of these infections among transplant recipients.

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[2]	M2 inhibitor[1] Neuraminidase inhibitor[2]
RSV	Contact	RSV Ig, palivizumab	Aerosolized ribavirin[3] ± IgIV RSV-active antibodies[4]
PIV	Contact	None	Aerosolized ribavirin
hMPV	Contact	None	Aerosolized ribavirin ± IgIV
Rhinovirus	Contact	None	None
Coronavirus	Standard precautions except for SARS which requires contact, droplet and airborne precautions	None	None

[1]Amantadine or rimantadine (for susceptible viruses only).
[2]Oseltamivir or zanamivir (for susceptible viruses only).
[3]Oral or IV ribavirin can be used as well, although patients should be monitored for hemolytic anemia; less are available about the efficacy of these formulations in treating RSV than with aerosolized ribavirin.

Diagnosis

Because one cannot clinically distinguish disease caused by any of the RNA 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, virus culture, antigen detection and nucleic acid testing. Serology is generally not clinically useful. In general, all patients with presumed respiratory viral infection should have a nasopharyngeal swab, wash or aspirate performed and sent for rapid antigen testing, if available. Although positive results for the test may be considered diagnostic, negative results do not rule out infection. Rapid antigen testing may only detect a limited number of viruses (i.e. only influenza and/or RSV) and therefore additional testing may be warranted. Negative rapid tests does not rule out infection and should trigger additional testing with polymerase chain reaction (PCR), direct florescent antibody (DFA) or culture, dependent on which is available locally. 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. Testing of a wide range of pathogens is most important among lung transplant recipients.

Rapid antigen detection, using several different techniques, is available for influenza and RSV. Despite their speed, sensitivity may be lower than reported in licensing studies, particularly among immunocompromised patients (10). 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 (11).

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 (standard cultures typically do not detect hMPV, coronaviruses, bocaviruses and polyomaviruses) (1); not all hospitals have access to molecular diagnostics for respiratory viruses, although these are increasingly available through reference laboratories. As with other diagnostic strategies, yields of cultures are dependent on the site of sampling; greatest yield is from BAL and nasal wash (1,10).

Several studies of DFA testing of primary patient specimens have documented sensitivity that approached that of PCR for certain viruses (12,13). DFA testing is limited by lack of reagents for some of the viruses (hMPV, rhinovirus, coronavirus) (14) and appears to be less sensitive than PCR in detecting dual infections (13). Like PCR, though, DFA testing can detect several viruses from a single specimen.

A wide range of PCR-based assays to detect respiratory virus are commercially available and many centers have locally developed assays that detect select viruses. Most of the available assays are able to screen for a wide range of pathogens in tandem and many have been tested in transplant populations (4,9,15,16). 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).

Influenza

Virology and epidemiology

Influenza viruses are orthomyxovirus and are associated with substantial morbidity and mortality worldwide with epidemics during the winter months. Antigenic variability gives this virus a survival advantage allowing for its

continued virulence during yearly epidemics. Few studies have examined the prevalence of influenza virus infection prospectively in organ transplant recipients (1,3,10,17,18). Risk of disease and complications appear to be greatest in pediatric and lung transplant patients with variable levels of severity in other transplant populations (1,3,10,17,18). Transmission occurs through inhalation of infectious droplets or through contact with fomites; some forms of influenza, particularly avian influenza, may be spread through aerosols.

Prevention

Patients with known or suspected influenza should be isolated from other patients using standard and droplet precautions (19,20). There are two types of influenza vaccine currently available: a number of formulations of injectable, killed vaccine and a single inhaled live, attenuated vaccine. The injectable vaccine has been studied in all transplant patients and has been found to be safe and not associated with an increased risk of rejection or adverse outcomes (21). There is potential for replication of the live attenuated vaccine, so its use is contraindicated in highly immune suppressed patients and their close contacts (22). Although responses vary based vaccine year, specific influenza strains, immunosuppressant and recipient type, and while responses in transplant recipients are less robust than those of healthy controls, most recipients do have some benefit. Accordingly, annual trivalent inactivated influenza vaccination is strongly recommended for transplant recipients, their close contacts and caretakers >6 months of age (I) (22). Antiviral chemoprophylaxis can be considered as an alternative or supplement to vaccination (I) (22). Agents active against circulating influenza strains should be used. A randomized, double-blind study of oseltamivir prophylaxis in high-risk transplant recipients found a protective efficacy of 75%; of note, 40% also received vaccination (23).

Treatment

There are two classes of antiviral compounds that are approved for the treatment of influenza: M2 inhibitors (amantadine and rimantadine; Table 2) which are effective against susceptible influenza A strains only, and neuraminidase inhibitors (zanamivir and oseltamivir; Table 3) which are active against susceptible influenza A and B viruses (22). Treatment with these agents in transplant recipients has been studied in case reports and is associated with reduced risk of lower respiratory tract complications (e.g. bronchiolitis, pneumonia), duration of symptoms, mortality and possibly a reduced risk of progression to bronchiolitis obliterans after infection (17) (III). Prospective studies have not been conducted, although a dose ranging study of oseltamivir is underway. There are frequent changes to the recommended management of influenza based on currently circulating strains; treatment decisions should be aligned with current recommendations as outlined by the Centers for Disease Control and Prevention (http://www.cdc.gov/flu/).

Some key caveats about the treatment of influenza in transplant recipients should be recognized. First, patients have prolonged viral replication, even with therapy, such that the approved 5 day duration of therapy may be insufficient to treat transplant recipients (24). Likewise, immunocompromised transplant recipients may benefit from therapy even if they have had symptoms beyond 48 h before presentation. Higher doses of medications or combinations of antivirals may have benefit in transplant recipients (1). Some experts recommend treating all transplant recipients with proven influenza, irrespective of symptom onset, and continue therapy until viral replication has been documented to have ceased; culture or PCR-based methods should be used to monitor patients for shedding (1) (III).

Finally, resistance to available antivirals has complicated the routine management of influenza. In general, nearly

Table 2: Agents used to prevent and treat influenza: M2 inhibitors (22)

		Usual adult dosage[1]		
Drug	Suggested dosage	Prophylaxis	Treatment	Dose adjustment state
Amantadine		100 mg b.i.d.	100 mg b.i.d.	
	5 mg/kg to max of 150 mg in two divided doses			Age 1–9 years
	100 mg q.o.d.			CrCl 30–50 mL/min
	100 mg q.o.d.			CrCl 15—30 mL/min
	100 mg q. week			CrCl 10—15 mL/min
	100 mg q week			CrCl,10 mL/min
	100 mg q.o.d.			Age ≥65 years
Rimantadine		100 mg b.i.d.	100 mg b.i.d.	
	5 mg/kg to max of 150 mg in two divided doses			Age 1–9 years[2]
	100 mg q.o.d.			CrCl,10 mL/min
	100 mg q.o.d.			Severe hepatic dysfunction
	100 mg q.o.d.			Age ≥65 years

[1]Duration of treatment is usually 5 days. Duration of prophylaxis depends of the clinical setting.
[2]Investigational: Not approved for treatment of children by the US Food and Drug Administration and Health Canada.

Table 3: Agents used to prevent and treat influenza: neuraminidase inhibitors (22)[1]

Drug	Dosage for treatment	Dose adjustment	
		State	Dosage
Zanamivir[2]	2 puffs (10 mg) b.i.d.	No dose adjustment needed	
Oseltamivir[3]	75 mg b.i.d.[2]	CrCl <30[4]	75 mg QD
		12 months of age or older	
	C	≤15 kg	30 mg b.i.d. (2.5 mL[5])
	H	16–23 kg	45 mg b.i.d. (3.8 mL[5])
	I	24–40 kg	60 mg b.i.d. (5 mL[5])
	L	>40 kg	75 mg b.i.d. (6.2 mL[5])
	D	<12 months of age[6]	3 mg/kg/dose/bid
	R		
	E		
	N		

[1]Prophylaxis: Adults (normal renal function): Doses as above, but given once daily. Infants and children (normal renal function): Doses as above, but given once daily. Prophylaxis is not recommended for infants <3 months of age.
[2]Zanamivir is indicated for prophylaxis in children ≥5 years old and for treatment in children ≥7 years old.
[3]The dosing of infants less than 1 year of age remains problematic, as data are limited on appropriate dose of oseltamivir in this age group, notably neonates and those with lower body weights. Please consult current dosing recommendations available on the CDC's web site and in any updated package insert for dose adjustments in renal impairment.
[4]No treatment or prophylaxis dosing recommendations are available for patients undergoing renal dialysis.
There are a number of antivirals and antiviral combinations that are currently undergoing investigation and/or are available for by compassionate use. Up to date information on these can be obtained from: http://www.clinicaltrials.gov.
[5]Volume of suspension—dose recommended in normal renal function.
[6]Per Emergency Use Authorization (http://www.cdc.gov/h1n1flu/recommendations.htm#table1).

all influenza A/H3 viruses are resistant to M2 inhibitors and this resistance affects both amantadine and rimantadine equally (25). Many influenza A/H1 viruses have developed resistance to oseltamivir, although currently they retain susceptibility to zanamivir and most are also susceptible to M2 inhibitors (22,26). There are limited data about the use of zanamivir in lung transplant recipients; as with all patients with underlying lung disease, if zanamivir is used, rescue inhalers should be readily available and the first dose should be given in a monitored setting. Recommendations as to the optimal management of influenza are updated based on real-time surveillance of circulating strains and their susceptibility. As such, current dosing recommendations from health authorities should be consulted regularly.

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 2 years of age, virtually all children have experienced a primary infection, although reinfection 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 (1,8,27–32). 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) (19,20). Prophylaxis with the RSV-specific monoclonal antibody (palivizumab) or high titer RSV-IVIG has been shown to be effective for specific groups of high-risk infants and young children (I) (33,34). 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. Despite this, some experts would support the use of immunoprophylaxis for children less than 1 year of age who receive their transplant during the RSV season (III); survey data suggest that antibody-based prophylaxis is commonly used among pediatric transplant centers (35). There are no approved vaccines for treatment 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 (36). Despite its FDA approval, convincing data describing the clinical efficacy of this agent are lacking and a consensus

on the utility of this drug in the treatment of RSV disease does not currently exist. Published data on the treatment of RSV disease in solid organ transplant recipients are very limited. Experience in stem cell transplant populations suggest that the use of aerosolized ribavirin may reduce mortality associated with severe RSV infections, particularly those affecting the lower airways (30,36,37). The combination of aerosolized ribavirin and antibody-based interventions, including IgIV, RSV-Ig and palivizumab appear to have an even greater impact on mortality (1,38). Many experts, therefore, would recommend the use of the combination of aerosolized ribavirin and an antibody preparation for the treatment of severe RSV infections (II-2) (1,28). 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) (28). There are published reports of successful treatment of RSV in lung transplant recipients with oral and IV ribavirin with and without corticosteroids (39,40). Further studies are needed to determine the clinical efficacy of these alternatives because there is a risk of adverse effects, notably hemolytic anemia.

Parainfluenza Virus

Virology and epidemiology

Parainfluenza is a pneumovirus for which there are four 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 whereas 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 (1,5,41). 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 (19,20). 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 as well (30,31,41).

Human Metapneumovirus

hMPV discovered in 2001 is a relatively newly recognized pneumovirus that has clinical pattern similar to RSV and is a significant cause of disease in transplant recipients (42). As with other pneumoviruses, there are no vaccines and prevention is focused on tight infection control measures, including contact precautions (20). Case reports and animal data suggest that ribavirin and IgIV can be considered for the management of severe cases of hMPV but supportive care remains the mainstay of treatment (1,43).

Rhinovirus

Human rhinoviruses (hRV) 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 (44,45). Most of the fatalities are associated with coinfections. 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 (1,8,45,46). Pleconaril which was studied extensively in healthy adults with rhinoviral upper respiratory infections, was well tolerated, and led to faster resolution of symptoms, to more rapid improvement in symptom scores, and to clearance of virus from nasal mucous (47). However, it was not approved for use by the FDA due to safety concerns (47). 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 because 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, involving both inpatients and outpatients, 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 with mild or asymptomatic infection, are needed, particularly in lung transplant recipients in which lower tract infection has been associated with an increased risk of chronic rejection. Prospective studies, using contemporary molecular diagnostic tools, are also needed to define the efficacy and cost of preventative interventions, particularly in high-risk pediatric populations. Finally, prospective therapeutic trials are needed to define the optimal timing, duration and treatment regimen of each of the viruses is needed.

Disclosures

Michaels M.: Grant Support, Sanofi Pasteur, Roche. *Ison M.G.:* Consultant: BioCryst, Adamas, Roche; Lectures Fees, Abbott Molecular, ViraCor; Site PI, ViraCor, BioCryst, Roche.

References

1. Ison MG. Respiratory viral infections in transplant recipients. Antivir Ther 2007; 12(4 Pt B): 627–638.
2. Couch RB, Englund JA, Whimbey E. Respiratory viral infections in immunocompetent and immunocompromised persons. Am J Med 1997; 102(3A): 2–9; discussion 25–26.
3. Lopez-Medrano F, Aguado JM, Lizasoain M et al. Clinical implications of respiratory virus infections in solid organ transplant recipients: A prospective study. Transplantation 2007; 84: 851–856.
4. Peck AJ, Englund JA, Kuypers J et al. Respiratory virus infection among hematopoietic cell transplant recipients: Evidence for asymptomatic parainfluenza virus infection. Blood 2007; 110: 1681–1688.
5. Billings JL, Hertz MI, Savik K, Wendt CH. Respiratory viruses and chronic rejection in lung transplant recipients. J Heart Lung Transplant 2002; 21: 559–566.
6. Ison MG, Gubareva LV, Atmar RL, Treanor J, Hayden FG. Recovery of drug-resistant influenza virus from immunocompromised patients: A case series. J Infect Dis 2006; 193: 760–764.
7. Khalifah AP, Hachem RR, Chakinala MM et al. Respiratory viral infections are a distinct risk for bronchiolitis obliterans syndrome and death. Am J Respir Crit Care Med 2004; 170: 181–187.
8. Kumar D, Erdman D, Keshavjee S et al. Clinical impact of community-acquired respiratory viruses on bronchiolitis obliterans after lung transplant. Am J Transplant 2005; 5: 2031–2036.
9. Milstone AP, Brumble LM, Barnes J et al. A single-season prospective study of respiratory viral infections in lung transplant recipients. Eur Respir J 2006; 28: 131–137.
10. Englund JA. Diagnosis and epidemiology of community-acquired respiratory virus infections in the immunocompromised host. Biol Blood Marrow Transplant 2001; 7(Suppl): 2S–4S.
11. Englund JA, Piedra PA, Jewell A, Patel K, Baxter BB, Whimbey E. Rapid diagnosis of respiratory syncytial virus infections in immunocompromised adults. J Clin Microbiol 1996; 34: 1649–1653.
12. Roghmann M, Ball K, Erdman D, Lovchik J, Anderson LJ, Edelman R. Active surveillance for respiratory virus infections in adults who have undergone bone marrow and peripheral blood stem cell transplantation. Bone Marrow Transplant 2003; 32: 1085–1088.
13. Rovida F, Percivalle E, Zavattoni M et al. Monoclonal antibodies versus reverse transcription-PCR for detection of respiratory viruses in a patient population with respiratory tract infections admitted to hospital. J Med Virol 2005; 75: 336–347.
14. Landry ML, Ferguson D. SimulFluor respiratory screen for rapid detection of multiple respiratory viruses in clinical specimens by immunofluorescence staining. J Clin Microbiol 2000; 38: 708–711.
15. Garbino J, Crespo S, Aubert JD et al. A prospective hospital-based study of the clinical impact of non-severe acute respiratory syndrome (Non-SARS)-related human coronavirus infection. Clin Infect Dis 2006; 43: 1009–1015.
16. Kuypers J, Wright N, Ferrenberg J et al. Comparison of real-time PCR assays with fluorescent-antibody assays for diagnosis of respiratory virus infections in children. J Clin Microbiol 2006; 44: 2382–2388.
17. Ison MG, Sharma A, Shepard JA, Wain JC, Ginns LC. Outcome of influenza infection managed with oseltamivir in lung transplant recipients. J Heart Lung Transplant 2008; 27: 282–288.
18. Vilchez RA, McCurry K, Dauber J et al. Influenza virus infection in adult solid organ transplant recipients. Am J Transplant 2002; 2: 287–291.
19. Raad I, Abbas J, Whimbey E. Infection control of nosocomial respiratory viral disease in the immunocompromised host. Am J Med 1997; 102(3A): 48–52; discussion 53–44.
20. Siegel JD, Rhinehart E, Jackson J, Chiarello L, Committee atHICPA. 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings. Available at: http://www.cdc.gov/ncidod/dhqp/pdf/isolation2007.pdf. Accessed November 5, 2009.
21. Duchini A, Goss JA, Karpen S, Pockros PJ. Vaccinations for adult solid-organ transplant recipients: Current recommendations and protocols. Clin Microbiol Rev 2003; 16: 357–364.
22. Fiore AE, Shay DK, Broder K et al. Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008. MMWR Recomm Rep 2008; 57(RR-7): 1–60.
23. Ison MG, Szakaly P, Shapira M, Kriván G, Nist A, Dutkowski R. Oseltamivir prophylaxis significantly reduces the incidence of seasonal influenza infection in immunocompromised patients. In: XI International Symposium on Respiratory Viral Infections. Bangkok, Thailand, 2009.
24. Nichols WG, Guthrie KA, Corey L, Boeckh M. Influenza infections after hematopoietic stem cell transplantation: Risk factors, mortality, and the effect of antiviral therapy. Clin Infect Dis 2004; 39: 1300–1306.
25. Bright RA, Shay DK, Shu B, Cox NJ, Klimov AI. Adamantane resistance among influenza A viruses isolated early during the 2005–2006 influenza season in the United States. JAMA 2006; 295: 891–894.
26. CDC Issues Interim Recommendations for the Use of Influenza Antiviral Medications in the Setting of Oseltamivir Resistance among Circulating Influenza A (H1N1) Viruses, 2008–09 Influenza Season. Available at: http://www2a.cdc.gov/HAN/ArchiveSys/ViewMsgV.asp?AlertNum=00279. Accessed November 5, 2009.
27. Bellau-Pujol S, Vabret A, Legrand L et al. Development of three multiplex RT-PCR assays for the detection of 12 respiratory RNA viruses. J Virol Methods 2005; 126: 53–63.
28. Flynn JD, Akers WS, Jones M et al. Treatment of respiratory syncytial virus pneumonia in a lung transplant recipient: Case report and review of the literature. Pharmacotherapy 2004; 24: 932–938.

29. Krinzman S, Basgoz N, Kradin R et al. Respiratory syncytial virus-associated infections in adult recipients of solid organ transplants. J Heart Lung Transplant 1998; 17: 202–210.
30. McCurdy LH, Milstone A, Dummer S. Clinical features and outcomes of paramyxoviral infection in lung transplant recipients treated with ribavirin. J Heart Lung Transplant 2003; 22: 745–753.
31. Wendt CH. Community respiratory viruses: Organ transplant recipients. Am J Med 1997; 102(3A): 31–36; discussion 42–33.
32. Blanchard SS, Gerrek M, Siegel C, Czinn SJ. Significant morbidity associated with RSV infection in immunosuppressed children following liver transplantation: Case report and discussion regarding need of routine prophylaxis. Pediatr Transplant 2006; 10: 826–829.
33. Groothuis JR, Simoes EA, Levin MJ et al. Prophylactic administration of respiratory syncytial virus immune globulin to high-risk infants and young children. The Respiratory Syncytial Virus Immune Globulin Study Group. N Engl J Med 1993; 329: 1524–1530.
34. Thomas NJ, Hollenbeak CS, Ceneviva GD, Geskey JM, Young MJ. Palivizumab prophylaxis to prevent respiratory syncytial virus mortality after pediatric bone marrow transplantation: A decision analysis model. J Pediatr Hematol Oncol 2007; 29: 227–232.
35. Michaels MG, Fonseca-Aten M, Green M et al. Respiratory syncytial virus prophylaxis: A survey of pediatric solid organ transplant centers. Pediatr Transplant 2008 (in press).
36. Boeckh M, Englund J, Li Y et al. Randomized controlled multicenter trial of aerosolized ribavirin for respiratory syncytial virus upper respiratory tract infections in hematopoietic cell transplant recipients. Clin Infect Dis 2007; 44: 245–249.
37. Nichols WG, Gooley T, Boeckh M. Community-acquired respiratory syncytial virus and parainfluenza virus infections after hematopoietic stem cell transplantation: The Fred Hutchinson Cancer Research Center experience. Biol Blood Marrow Transplant 2001; 7(Suppl): 11S–15S.
38. Chavez-Bueno S, Mejias A, Merryman RA, Ahmad N, Jafri HS, Ramilo O. Intravenous palivizumab and ribavirin combination for respiratory syncytial virus disease in high-risk pediatric patients. Pediatr Infect Dis J 2007; 26: 1089–1093.
39. Pelaez A, Lyon GM, Force SD et al. Efficacy of oral ribavirin in lung transplant patients with respiratory syncytial virus lower respiratory tract infection. J Heart Lung Transplant 2009; 28: 67–71.
40. Glanville AR, Scott AI, Morton JM et al. Intravenous ribavirin is a safe and cost-effective treatment for respiratory syncytial virus infection after lung transplantation. J Heart Lung Transplant 2005; 24: 2114–2119.
41. Vilchez RA, Dauber J, McCurry K, Iacono A, Kusne S. Parainfluenza virus infection in adult lung transplant recipients: An emergent clinical syndrome with implications on allograft function. Am J Transplant 2003; 3: 116–120.
42. Hopkins P, McNeil K, Kermeen F et al. Human metapneumovirus in lung transplant recipients and comparison to respiratory syncytial virus. Am J Respir Crit Care Med 2008; 178: 876–881.
43. Raza K, Ismailjee SB, Crespo M et al. Successful outcome of human metapneumovirus (hMPV) pneumonia in a lung transplant recipient treated with intravenous ribavirin. J Heart Lung Transplant 2007; 26: 862–864.
44. Ison MG, Hayden FG, Kaiser L, Corey L, Boeckh M. Rhinovirus infections in hematopoietic stem cell transplant recipients with pneumonia. Clin Infect Dis 2003; 36: 1139–1143.
45. Kaiser L, Aubert JD, Pache JC et al. Chronic rhinoviral infection in lung transplant recipients. Am J Respir Crit Care Med 2006; 174: 1392–1399.
46. van Kraaij MG, van Elden LJ, van Loon AM et al. Frequent detection of respiratory viruses in adult recipients of stem cell transplants with the use of real-time polymerase chain reaction, compared with viral culture. Clin Infect Dis 2005; 40: 662–669.
47. Hayden FG, Herrington DT, Coats TL et al. Efficacy and safety of oral pleconaril for treatment of colds due to picornaviruses in adults: results of 2 double-blind, randomized, placebo-controlled trials. Clin Infect Dis 2003; 36: 1523–1532.