# Influenza and other respiratory virus infections in solid organ transplant recipients

O. Manuel[1], F. López-Medrano[2], L. Kaiser[3], T. Welte[4], J. Carratalà[5,6], E. Cordero[7], H. H. Hirsch[8] on behalf of the ESCMID Study Group of Infection in Compromised Hosts (ESGICH)

1) *Infectious Diseases Service and Transplantation Center, University Hospital and University of Lausanne, Lausanne, Switzerland,* 2) *Unit of Infectious Diseases, Hospital Universitario '12 de Octubre', Instituto de Investigación Hospital '12 de Octubre' (i+12), School of Medicine, Universidad Complutense, Madrid, Spain,* 3) *Division of Infectious Diseases and Division of Laboratory Medicine, University of Geneva Hospitals, Geneva, Switzerland,* 4) *Department of Respiratory Medicine, Hannover Medical School, Hannover, Germany,* 5) *Department of Infectious Disease, Hospital Universitari de Bellvitge,* 6) *Insitut d'Investigació Biomèdica de Bellvitge (IDIBELL), L'Hospitalet de Llobregat, University of Barcelona, Barcelona,* 7) *Hospital Universitario Virgen del Rocío, Instituto de Biomedicina de Sevilla, Seville, Spain and* 8) *Transplantation and Clinical Virology, Department of Biomedicine (Haus Petersplatz), University of Basel, Basel, Switzerland*

## Abstract

Community-acquired respiratory viruses (CARVs) are a frequent cause of disease in solid organ transplant (SOT) recipients. Lower respiratory tract infections with CARVs can be associated with significant morbidity and even mortality in this population. This article reviews the clinical manifestations of CARVs infections and summarizes the evidence-based recommendations on the preventive and therapeutic strategies to decrease the burden of these viral infections in SOT recipients.

**Corresponding author:** O. Manuel, Infectious Diseases Service and Transplantation Center, University Hospital and University of Lausanne, MP14/316, CHUV, Lausanne, Switzerland
**E-mail:** oriol.manuel@chuv.ch

## Hot topics

- Community-acquired respiratory viruses (CARVs) are a frequent cause of disease in solid organ transplant (SOT) recipients. Lower respiratory tract infections with CARV can be associated with significant morbidity and even mortality in this population
- The impact of CARV infections on the progression of chronic allograft dysfunction in lung transplant recipients remains controversial
- Among CARVs, influenza infection may particularly present with severe disease in SOT recipients. The main risk factors for severe influenza infection are a shorter time from transplant and the presence of pneumonia
- Nucleic acid amplification testing (NAT) has become the main diagnostic method for detecting CARVs in clinical specimens. NAT is significantly more sensitive than other methods such as direct antigen detection or virus isolation by cell culture
- Infection control measures remain an essential element in decreasing the burden of CARVs in SOT recipients
- The main strategy for preventing influenza is yearly administration of the inactivated influenza vaccine, and it is highly recommended after transplantation. While most studies have shown a reduction in the immunogenicity of influenza vaccine in SOT recipients, some degree of efficacy is expected in this population
- The role of palivizumab or IVIG in preventing respiratory syncytial virus (RSV) infection in SOT recipients has not been established
- The use of antiviral therapy with neuraminidase inhibitors is associated with improved outcomes in SOT recipients, irrespective of the duration of symptoms. Antiviral therapy should be empirically administered to all SOT recipients

with influenza-like symptoms during the influenza season while waiting for microbiological confirmation

- The efficacy of ribavirin (aerosolized or oral) for the treatment of RSV infection in SOT recipients has not been determined

## Introduction

Community-acquired respiratory virus (CARV) infections are a common cause of medical consultations and hospitalizations in solid organ transplant (SOT) recipients [1]. They are caused by a variety of RNA viruses, including influenza A and B, respiratory syncytial virus (RSV), parainfluenza virus (PIV), rhinovirus (hRV), human metapneumovirus (hMPV) and coronavirus. In addition, DNA viruses, such as adenovirus, polyomavirus, and bocavirus, may also be responsible for cases of respiratory tract infection. While the majority of infections due to CARV are restricted to the upper respiratory tract (URT), SOT recipients, due to alterations in cellular and humoral immunity, are at a higher risk of developing progression to the lower respiratory tract (LRT) [2]. CARV LRT infections are associated with significant morbidity in SOT recipients. Specifically in lung transplant recipients, CARV LRT infections may be associated with a higher incidence of chronic lung allograft dysfunction (CLAD), although the literature on this topic is controversial [3]. While all viruses share similar clinical manifestations, influenza viruses appear to be particularly associated with impaired outcomes in SOT recipients [4].

The 2009 influenza A pandemic has led to epidemiological studies assessing the clinical manifestations and outcomes of influenza A infection [5,6], as well as clinical trials on the efficacy of preventive strategies for influenza, including in SOT recipients [7,8]. Also the routine use of molecular methods for detecting other CARVs has increased our knowledge on their epidemiology and their direct and indirect effects on SOT outcomes [9].

Given the updated knowledge on the topic, a panel of European experts in the management of viral infections in transplant patients has developed evidence-based recommendations for the management of CARVs in SOT recipients.

## Epidemiology and Clinical Manifestations of CARV Infections in SOT Recipients

### Influenza viruses

Influenza is an acute, usually self-limiting, febrile illness that occurs every winter season. Infection with influenza virus can occur at any time after transplantation, and it appears to be most severe in the early post-transplant period (<3 months) [10]. The risk of influenza is also related to the type of organ transplant. In a study involving 3569 SOT recipients, the incidence of influenza was 41.8, 4.3 and 2.8 cases/1000 person-years among lung, kidney and liver transplant recipients, respectively [4]. Similarly, studies performed during the pandemic documented that the incidence of influenza A/H1N1 infection was higher in recipients of lungs (30–400 cases per 1000 person-years) than in recipients of other organs, such as the kidney (19–22 cases per 1000 person-years), liver (29 cases per 1000 person-years) or heart (37 cases per 1000 patient-years) [11,12]. Fewer data are available regarding the epidemiology of influenza B virus infection in transplant recipients. Some series have reported that influenza B virus may cause up to one-fourth of the total number of influenza cases [13,14], but it is not known whether influenza B virus infection may be associated with different outcomes in SOT recipients.

The clinical features of influenza in SOT recipients do not considerably differ from those described in the general population. Influenza should be clinically suspected in all SOT recipients presenting with respiratory symptoms such as fever, rhinorrhea, cough and sore throat, with or without myalgias and headaches and dyspnoea during the influenza season [4,15]. However, fever may be missing, and the usually abrupt onset may be delayed in immunocompromised patients [16]. Therefore, a proposal has been made to modify the definitions of influenza-like illness provided by the ECDC to better capture the presentation in immunocompromised patients [17]. Basically, the definition of CARV disease includes: (i) a new onset of symptoms and (ii) at least one of the following four respiratory symptoms (cough, sore throat, shortness of breath and coryza) and (iii) the clinician's judgment that the illness is due to an infection. The occurrence of pneumonia in SOT recipients with influenza infection ranges from 14% to 49%, and bilateral involvement is frequently observed [4–6]. Bacterial, viral or fungal co-infection is relatively common in SOT recipients and reported co-infection frequency ranges from 7% to 29% [5,18]. An increased risk of acute and chronic allograft rejection also has been associated with infection by influenza and other respiratory viruses [4,5,11]. In lung transplant recipients, influenza has been linked to the occurrence of chronic lung allograft dysfunction (CLAD) [12,19], although not consistently in all studies [3]. Other less frequent complications of influenza in SOT recipients include encephalitis, myocarditis and myositis. Influenza in SOT recipients has been associated with high rates of medical complications and even mortality [4–6]. The main risk factors associated with impaired outcomes are the presence of pneumonia and diabetes mellitus, the use of antilymphocyte globulin (<6 months), and delayed antiviral therapy [10].

### Respiratory Syncytial Virus

RSV is one of the more common causes of respiratory tract infection during childhood. The epidemiology and clinical characteristics of RSV infection are incompletely determined in SOT recipients; most studies have included only lung transplant recipients [9,20]. The incidence of RSV infection may range from 2.4% to 15% of all CARV infections occurring in SOT recipients [9,20–22]. Clinical manifestations of RSV infection in SOT recipients include fever, cough and dyspnoea. Ground-glass opacities and lung nodules are common findings on CT scans in cases of LRT disease [23]. Recent data suggest that RSV infection is currently a rare cause of hospitalization and mortality among SOT recipients [9,20]. In lung transplant recipients, RSV LRT disease appears to contribute to the development of CLAD, but it is not associated with acute rejection [3].

### Parainfluenza Virus

Parainfluenza is a paramyxovirus for which four species (PIV-1, -2, -3 and -4) are described. PIV-1 and PIV-2 show a pronounced seasonality in the autumn, whereas PIV-3 is more frequently detected in spring. Incidence of PIV infection in SOT recipients varies between 3.4% and 20% of all CARV infections [9,21,22]. While clinical manifestations of PIV infection in SOT recipients are not different to those seen in other CARV infections, some severe cases of PIV disease have been described, especially in children [24]. A recent study showed a higher incidence of hospitalization in lung transplant recipients with PIV infection (50%) as compared with infection with other CARVs (16.9%) [9].

### Rhinovirus

Human rhinovirus is a picornavirus that is the most frequent cause of the common cold in the general population. In SOT recipients, rhinovirus is the respiratory virus most commonly identified in prospective studies assessing the incidence of CARV infections [9]. Infections with rhinovirus are usually mild and self-limiting, although some cases of severe LRT disease and chronic viral shedding have been described in lung transplant recipients [25]. Rhinovirus appears to be less commonly associated with CLAD than other respiratory viruses.

### Other CARVs

Clinical characteristics of adenovirus, hMPV and coronavirus infections are similar to those seen with other CARVs. The clinical significance of newly discovered viruses such as polyomaviruses (WU and KI virus) or bocavirus in the transplant population has not completely been determined [26].

## Diagnostics of CARV Infections

In 2014, nucleic acid amplification testing (NAT) has become the main diagnostic method for detecting CARVs in clinical specimens. NAT has proved to be significantly more sensitive than other methods such as direct antigen detection or virus isolation by cell culture. This increased sensitivity is also associated with an excellent specificity, particularly when the detection of the amplified product uses a specific probe [27]. At this time NAT are frequently based on the real-time PCR technology and present theoretically the following advantages: they could detect viral load as low as few copies of genome equivalent introduced into the amplification reaction, the analytical specificity approaches 100%, and the technique can provide semi-quantitative results. A challenge for CARV detection is related to the number of different agents that need to be detected, which may encompass 16 or more different viral species, types or subtypes depending on the completeness of the screening and the spectrum of agents targeted [27]. The technical solution adopted (e.g. multiplexing) could impact the performance and possibly decrease the sensitivity.

Rapid influenza diagnostic tests have appropriate specificity, but low sensitivity, so that their performance in the diagnosis of influenza (and particularly in clinical decision-making for antiviral therapy) in the immunocompromised host appears to be suboptimal.

Nasopharyngeal specimens collected with a swab are the most convenient and effective respiratory specimens for the initial screening of viral respiratory viruses; pooled nasopharyngeal and pharyngeal specimens are used by some and could possibly increase the sensitivity along with decreasing variability of results. In cases of LRT disease, bronchoalveolar lavage (BAL) is the preferred specimen for diagnostic testing of CARVs. This is particularly important, as patients with LRT disease may present with a negative test for the nasopharyngeal swab.

Respiratory specimens are not standardized: this limits the ability to provide reproducible quantitative assays although the real-time technology offers the opportunity to semi-quantitatively assess the viral load. Therefore, one should be cautious not to over-interpret quantitative results. Also, the duration of viral shedding using sensitive molecular assays can be significantly longer compared with immunocompetent adults. In immunocompetent adults we expect a rapid viral clearance and nucleic acid detection to be negative within 7–10 days. Prolonged shedding for weeks and months is a common occurrence in highly immunocompromised individuals [16,28]. Particularly for influenza, protocols for establishing the best

frequency for viral testing and appropriate cut-offs for discontinuation of antiviral therapy in SOT recipients have not been described.

## Prevention of CARV Infections (Table 1)

Infection control measures remain an essential element for decreasing the burden of CARVs in SOT recipients. Overall awareness among healthcare personnel and caregivers about the potential deleterious outcomes of CARV infections in SOT recipients and the importance of early detection of infection may have a major impact on the incidence of CARV infections and subsequent complications. More specifically, hand hygiene and adherence to contact and respiratory droplet isolation will help reduce CARV infections in SOT recipients. These infection control measures need to be taken until the patient is sent home or until PCR is negative.

The influenza virus is currently the only CARV that can be prevented with vaccination [29]. The few studies assessing the clinical effectiveness of influenza vaccine in SOT recipients have reported an overall low rate of clinical failures of vaccination (ranging from 1.1% to 3.6% with the use of adjuvanted vaccines during the pandemic), although this is also dependent on the matching between the vaccine and the circulating strains [30,31]. In addition, patients who developed symptomatic influenza infection after vaccination had a 70% reduced risk of subsequent pneumonia [32]. In a large registry of kidney transplant recipients, influenza vaccination during the first year after transplantation was associated with a reduced incidence of graft loss and mortality [33]. However, data on the immunogenicity of influenza vaccination in the transplant population are controversial and most published studies suggest that a reduced humoral immune response is expected in SOT recipients [29,34]. Lung transplant recipients appear to have a poorer response than recipients of other allografts, probably related to the higher degree of immunosuppression needed after lung transplantation and the allogeneic constellation between virus-infected host cells and effector T cells [8]. The use of mycophenolate mofetil and mTOR inhibitors has been related to a weaker response to influenza vaccine in some studies [8,35,36], but not in others [37]. Responses to influenza B virus are usually weaker than those seen with influenza A viruses [38].

Different strategies have been proposed to improve the immunogenicity of influenza vaccine in SOT recipients, including administration of a boosting dose, intradermal vaccination, higher doses of vaccine antigen and the use of adjuvanted vaccines. Adjuvanted vaccines with MF59 or AS03 adjuvants have proven improved efficacy in the elderly [39], and an overall increased immunogenicity in transplant recipients [7,8]. How-

ever, there are not enough data in the transplant population to currently recommend specifically any of these approaches [29]. Household members and healthcare workers in contact with SOT recipients should also receive influenza vaccination. Additional pneumococcal vaccination (and particularly the administration of the 13-valent pneumococcal conjugate vaccine) should be proposed for SOT recipients to potentially reduce the risk for influenza-related complications [40].

Inactivated influenza vaccine is generally well tolerated in SOT recipients. Some reports during the pandemic found an increased rate of *de novo* anti-HLA antibodies after the administration of adjuvanted influenza vaccine, although without clinical significance at 1 year [41]. Subsequent studies have not confirmed these results [38]. Influenza vaccine is usually recommended 3–6 months after transplantation, in order to avoid any temporal relationship between vaccination and acute rejection during the period when the patient is at higher risk of allograft rejection [29]. Some studies have shown an appropriate antibody response and safety profile also if the vaccine is administered during the first weeks post-transplant [35]. Overall, the need for protection against influenza in SOT recipients clearly outweighs the theoretical safety concerns of vaccination.

No vaccine is yet available for RSV. There is very limited experience with the use of immunoprophylaxis with non-specific intravenous immunoglobulin (IVIG), RSV-IVIG or palivizumab (a monoclonal antibody specific for the RSV-F protein) for prevention of RSV infection in SOT recipients. Palivizumab may be considered for children <2 years old during the RSV season [42]. However, the high cost of palivizumab combined with a lack of clear evidence of efficacy in SOT recipients precludes their wide-scale use.

## Treatment of CARV Infections (Table 2)

Upper respiratory tract disease caused by CARVs can be symptomatically treated with analgesics, anti-inflammatory drugs and nasal decongestants. Due to the risk of developing Reye's syndrome, salicylates should be avoided in children and adolescents with influenza-like symptoms. In cases of LRT disease (including pneumonia), bacterial or fungal infection must be ruled out or appropriately treated. Empirical antibiotic therapy should be directed against *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus*.

**Specific antiviral treatment for infection by influenza virus**
Adequate antiviral therapy should be initiated, as soon as possible, in all SOT recipients with suspected influenza infection [4,10]. This recommendation is made irrespective

**TABLE 1. Recommendations on prevention of community-acquired respiratory virus infection**

SOT recipients should avoid close contact with individuals with respiratory tract infections. AII
All SOT recipients and candidates should receive annual seasonal influenza vaccination. AII
Household members and HCWs in contact with SOT recipients should also receive influenza vaccination. AII
Live-attenuated influenza vaccine is not recommended in SOT recipients. DII
In selected patients to whom influenza vaccine cannot be administered, prophylaxis with oseltamivir 75 mg/day for 12 weeks during the influenza season may be proposed. CI
The use of palivizumab for prevention of respiratory syncytial virus infection is not recommended in SOT recipients. CIII

SOT, solid organ transplant; HCW, healthcare workers.

**TABLE 2. Recommendations for treatment of community-acquired respiratory virus infection**

Antiviral therapy with oseltamivir or zanamivir should be administered to solid organ transplant (SOT) recipients with a clinical suspicion of influenza infection, before laboratory confirmation, irrespective of the duration of symptoms. AII
Treatment of influenza with M2 inhibitors (amantadine and rimantadine) is not recommended. DII
In the absence of a concern over drug absorption, a double dose of oseltamivir (i.e. 150 mg BID) is not recommended. CI
The use of intravenous zanamivir or peramivir can be considered in patients not responding to oseltamivir therapy or for whom oral absorption is a concern. BII
In severe cases of low respiratory tract infection with respiratory syncytial virus (RSV) and parainfluenza virus (PIV) infections in SOT recipients, therapy with aerosolized or oral ribavirin may be used. BII
Intravenous immunoglobulin can be combined with antiviral therapy in severe cases of RSV and PIV infection. BIII
There are insufficient data to recommend therapy with ribavirin in lung transplant recipients with non-severe cases of RSV or PIV infection. CIII
The use of ribavirin may be considered in severe cases of hMPV infection. CIII

of the duration of the symptoms and the severity of illness. In any case, antiviral treatment of influenza-like illness should not be delayed by waiting for microbiological confirmation, but rather discontinued when appropriate test results are negative. Early specific antiviral treatment should be especially encouraged in cases of pneumonia. Two classes of antiviral drugs are currently approved for treatment of influenza infection: M2 inhibitors (amantadine and rimantadine), which are active only against influenza A, and neuraminidase inhibitors (oseltamivir and zanamivir). Other drugs under investigation are parenteral zanamivir and peramivir. M2 inhibitors are not currently recommended due to resistance of most circulating influenza A strains and the variable, but at times predominant, circulation of influenza B. Neuraminidase inhibitors are usually well tolerated, with the most common adverse effects being gastrointestinal symptoms. In children, the use of oseltamivir has been associated with neuropsychiatric adverse events. Inhaled zanamivir (two puffs, 10 mg, twice daily) does not require dose adjustment either for hepatic or renal failure. Oral oseltamivir (75 mg twice daily) dose adjustment is not needed in hepatic impairment but doses should be modified in renal insufficiency according to the recommendations included in Table 3. Proven benefits of higher doses of oseltamivir in SOT recipients with severe influenza infection are lacking [43].

If available, intravenous zanamivir or peramivir can be considered in SOT recipients who are severely ill despite oral oseltamivir, in patients in whom oral absorption is a concern, or in those with suspected or confirmed oseltamivir resistance. Duration of antiviral therapy is 5 days in mild cases of influenza, but it can be prolonged in more severe cases with protracted evolution until viral load in the nasopharyngeal swab is undetectable. Pregnancy is not a contraindication for the administration of oseltamivir and pregnant women should be encouraged to receive influenza vaccination.

Development of oseltamivir resistance is promoted by the lack of an efficient immune response, high viral load and prolonged viral shedding, frequently observed in immunocompromised hosts [44]. Resistance should be suspected when prolonged shedding over *c.* 10 days is observed. Resistance is diagnosed by specialized laboratories using genotypic or phenotypic assays. When resistance to oseltamivir develops, strains are generally cross-resistant to peramivir but most of them remain susceptible to zanamivir, and hence parenteral zanamivir (compassionate use) is an option. Transmission of resistant strains has been occasionally described in high-risk hospital wards [45]. Cross-resistance to all available neuraminidase inhibitors has been described and underscores the need for new therapies.

**Specific treatment for infection by other respiratory virus infections**

The use of ribavirin for the treatment of RSV infection is controversial. Nevertheless, some experts consider ribavirin for the treatment of severe forms of LRT disease in SOT recipients [17]. Aerosolized ribavirin can be administered as 2 g for 2 h every 8 h or as 6 g over 18 h/day for 7–10 days. Appropriate precautions should be taken to avoid environ-

**TABLE 3. Oseltamivir doses for adult patients with normal renal function or renal function impairment and for those under renal replacement therapies and other extracorporeal therapies**

|  | Doses for treatment 75 mg first dose in all cases, then: |
| --- | --- |
| GFR >60 mL/min | 75 mg BID |
| GFR 30–60 mL/min | 75 mg BID |
| GFR <30 mL/min | 75 mg OD |
| Haemodialysis | 30–75 mg after haemodialysis session[a] |
| Peritoneal dialysis | 30 mg OD[a] |
| Continuous renal replacement therapy | 75 mg OD |
| Extracorporeal membrane oxygenation | Standard treatment according to renal function |

GFR, glomerular filtration rate; BID, twice daily; OD, once daily; SD, single dose.
[a]Dose administered after the session.
Adapted from [59].

mental teratogenic exposure in pregnant healthcare workers and visitors when aerosolized ribavirin is used. A few reports have reported the use of systemic ribavirin for RSV disease: orally or intravenously as 10–30 mg/kg of body weight in three divided doses [46–50]. Patients treated with systemic ribavirin should be checked for haemolysis, abnormal liver function and kidney failure. Of note, there are few data about the potential impact of the use of ribavirin on the prevention of indirect effects in lung transplant recipients with RSV infection [51].

For the treatment of severe forms of PIV infection, there is marginal experience with the use of ribavirin with or without intravenous immunoglobulin and steroids [52–54]. Ribavirin was used for the treatment of LRT disease caused by coronavirus during the outbreak of severe acute respiratory syndrome (SARS); however, there are no data to recommend ribavirin for the treatment of coronavirus infection in SOT recipients [55]. For the management of severe hMPV infection, supportive care is the main treatment, although anecdotal reports have been published about successful treatment with ribavirin and intravenous immunoglobulin [56–58]. No specific treatment is approved for rhinovirus infection.

## Transparency Declaration

## References

1. Ison MG. Respiratory viral infections in transplant recipients. *Antivir Ther* 2007; 12(4 Pt B): 627–638.
2. Ison MG. Influenza, including the novel H1N1, in organ transplant patients. *Curr Opin Infect Dis* 2010; 23: 365–373.
3. Vu DL, Bridevaux PO, Aubert JD, Soccal PM, Kaiser L. Respiratory viruses in lung transplant recipients: a critical review and pooled analysis of clinical studies. *Am J Transplant* 2011; 11: 1071–1078.
4. Manuel O, Estabrook M, AST Infectious Diseases Community of Practice. RNA respiratory viruses in solid organ transplantation. *Am J Transplant* 2013; 13(suppl 4): 212–219.
5. Cordero E, Perez-Romero P, Moreno A et al. Pandemic influenza A (H1N1) virus infection in solid organ transplant recipients: impact of viral and non-viral co-infection. *Clin Microbiol Infect* 2012; 18: 67–73.
6. Kumar D, Michaels MG, Morris MI et al. Outcomes from pandemic influenza A H1N1 infection in recipients of solid-organ transplants: a multicentre cohort study. *Lancet Infect Dis* 2010; 10: 521–526.
7. Manuel O, Pascual M, Hoschler K et al. Humoral response to the influenza A H1N1/09 monovalent AS03-adjuvanted vaccine in immunocompromised patients. *Clin Infect Dis* 2011; 52: 248–256.
8. Siegrist CA, Ambrosioni J, Bel M et al. Responses of solid organ transplant recipients to the AS03-adjuvanted pandemic influenza vaccine. *Antivir Ther* 2012; 17: 893–903.
9. Bridevaux PO, Aubert JD, Soccal PM et al. Incidence and outcomes of respiratory viral infections in lung transplant recipients: a prospective study. *Thorax* 2014; 69: 32–38.
10. Lopez-Medrano F, Cordero E, Gavalda J et al. Management of influenza infection in solid-organ transplant recipients: consensus statement of the Group for the Study of Infection in Transplant Recipients (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) and the Spanish Network for Research in Infectious Diseases (REIPI). *Enferm Infecc Microbiol Clin* 2013; 31: 526.e1–526.e20.
11. Low CY, Kee T, Chan KP et al. Pandemic (H1N1) 2009 infection in adult solid organ transplant recipients in Singapore. *Transplantation* 2010; 90: 1016–1021.
12. Ng BJ, Glanville AR, Snell G et al. The impact of pandemic influenza A H1N1 2009 on Australian lung transplant recipients. *Am J Transplant* 2011; 11: 568–574.
13. Vilchez R, McCurry K, Dauber J et al. Influenza and parainfluenza respiratory viral infection requiring admission in adult lung transplant recipients. *Transplantation* 2002; 73: 1075–1078.
14. Vilchez RA, McCurry K, Dauber J et al. Influenza virus infection in adult solid organ transplant recipients. *Am J Transplant* 2002; 2: 287–291.
15. 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.
16. Khanna N, Widmer AF, Decker M et al. Respiratory syncytial virus infection in patients with hematological diseases: single-center study and review of the literature. *Clin Infect Dis* 2008; 46: 402–412.
17. Hirsch HH, Martino R, Ward KN, Boeckh M, Einsele H, Ljungman P. Fourth European Conference on Infections in Leukaemia (ECIL-4): guidelines for diagnosis and treatment of human respiratory syncytial virus, parainfluenza virus, metapneumovirus, rhinovirus, and coronavirus. *Clin Infect Dis* 2013; 56: 258–266.
18. Smud A, Nagel CB, Madsen E et al. Pandemic influenza A/H1N1 virus infection in solid organ transplant recipients: a multicenter study. *Transplantation* 2010; 90: 1458–1462.
19. Garantziotis S, Howell DN, McAdams HP, Davis RD, Henshaw NG, Palmer SM. Influenza pneumonia in lung transplant recipients: clinical features and association with bronchiolitis obliterans syndrome. *Chest* 2001; 119: 1277–1280.
20. Uckay I, Gasche-Soccal PM, Kaiser L et al. Low incidence of severe respiratory syncytial virus infections in lung transplant recipients despite the absence of specific therapy. *J Heart Lung Transplant* 2010; 29: 299–305.
21. Gottlieb J, Schulz TF, Welte T et al. Community-acquired respiratory viral infections in lung transplant recipients: a single season cohort study. *Transplantation* 2009; 87: 1530–1537.
22. Kumar D, Husain S, Chen MH et al. A prospective molecular surveillance study evaluating the clinical impact of community-acquired respiratory viruses in lung transplant recipients. *Transplantation* 2010; 89: 1028–1033.
23. Ariza-Heredia EJ, Fishman JE, Cleary T, Smith L, Razonable RR, Abbo L. Clinical and radiological features of respiratory syncytial virus in solid organ transplant recipients: a single-center experience. *Transpl Infect Dis* 2012; 14: 64–71.
24. 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.
25. 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.

26. Babakir-Mina M, Ciccozzi M, Perno CF, Ciotti M. The human polyomaviruses KI and WU: virological background and clinical implications. *APMIS* 2013; 121: 746–754.

27. Buller RS. Molecular detection of respiratory viruses. *Clin Lab Med* 2013; 33: 439–460.

28. Khanna N, Steffen I, Studt JD et al. Outcome of influenza infections in outpatients after allogeneic hematopoietic stem cell transplantation. *Transpl Infect Dis* 2009; 11: 100–105.

29. Kumar D, Blumberg EA, Danziger-Isakov L et al. Influenza vaccination in the organ transplant recipient: review and summary recommendations. *Am J Transplant* 2011; 11: 2020–2030.

30. Cordero E, Aydillo TA, Perez-Ordonez A et al. Deficient long-term response to pandemic vaccine results in an insufficient antibody response to seasonal influenza vaccination in solid organ transplant recipients. *Transplantation* 2012; 93: 847–854.

31. Schuurmans MM, Tini GM, Dalar L, Fretz G, Benden C, Boehler A. Pandemic 2009 H1N1 influenza virus vaccination in lung transplant recipients: coverage, safety and clinical effectiveness in the Zurich cohort. *J Heart Lung Transplant* 2011; 30: 685–690.

32. Perez-Romero P, Aydillo TA, Perez-Ordonez A et al. Reduced incidence of pneumonia in influenza-vaccinated solid organ transplant recipients with influenza disease. *Clin Microbiol Infect* 2012; 18: E533–E540.

33. Hurst FP, Lee JJ, Jindal RM, Agodoa LY, Abbott KC. Outcomes associated with influenza vaccination in the first year after kidney transplantation. *Clin J Am Soc Nephrol* 2011; 6: 1192–1197.

34. Eckerle I, Rosenberger KD, Zwahlen M, Junghanss T. Serologic vaccination response after solid organ transplantation: a systematic review. *PLoS ONE* 2013; 8: e56974.

35. Cordero E, Perez-Ordonez A, Aydillo TA et al. Therapy with m-TOR inhibitors decreases the response to the pandemic influenza A H1N1 vaccine in solid organ transplant recipients. *Am J Transplant* 2011; 11: 2205–2213.

36. Orcurto A, Pascual M, Hoschler K, Aubert V, Meylan P, Manuel O. Impact of anti-T-cell therapy in the immunogenicity of seasonal influenza vaccine in kidney transplant recipients. *Transplantation* 2012; 94: 630–636.

37. Sanchez-Fructuoso AI, Prats D, Naranjo P et al. Influenza virus immunization effectivity in kidney transplant patients subjected to two different triple-drug therapy immunosuppression protocols: mycophenolate versus azathioprine. *Transplantation* 2000; 69: 436–439.

38. Baluch A, Humar A, Eurich D et al. Randomized controlled trial of high-dose intradermal versus standard-dose intramuscular influenza vaccine in organ transplant recipients. *Am J Transplant* 2013; 13: 1026–1033.

39. McElhaney JE, Beran J, Devaster JM et al. AS03-adjuvanted versus non-adjuvanted inactivated trivalent influenza vaccine against seasonal influenza in elderly people: a phase 3 randomised trial. *Lancet Infect Dis* 2013; 13: 485–496.

40. Danziger-Isakov L, Kumar D, AST Infectious Diseases Community of Practice. Vaccination in solid organ transplantation. *Am J Transplant* 2013; 13(suppl 4): 311–317.

41. Katerinis I, Hadaya K, Duquesnoy R et al. De novo anti-HLA antibody after pandemic H1N1 and seasonal influenza immunization in kidney transplant recipients. *Am J Transplant* 2011; 11: 1727–1733.

42. Committee on Infectious Diseases. From the American Academy of Pediatrics: Policy statements—modified recommendations for use of palivizumab for prevention of respiratory syncytial virus infections. *Pediatrics* 2009; 124: 1694–1701.

43. South East Asia Infectious Disease Clinical Research N. Effect of double dose oseltamivir on clinical and virological outcomes in children and adults admitted to hospital with severe influenza: double blind randomised controlled trial. *BMJ* 2013; 346: f3039.

44. Ison MG. Antivirals and resistance: influenza virus. *Curr Opin Virol* 2011 Dec; 1: 563–573.

45. Chen LF, Dailey NJ, Rao AK et al. Cluster of oseltamivir-resistant 2009 pandemic influenza A (H1N1) virus infections on a hospital ward among immunocompromised patients—North Carolina, 2009. *J Infect Dis* 2011; 203: 838–846.

46. Molinos-Quintana A, Perez-de Soto C, Gomez-Rosa M, Perez-Simon JA, Perez-Hurtado JM. Intravenous ribavirin for respiratory syncytial viral infections in pediatric hematopoietic SCT recipients. *Bone Marrow Transplant* 2013; 48: 265–268.

47. 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.

48. Keck M, Mindru C, Kalil AC, Mercer DF, Florescu DF. Respiratory syncytial virus lower respiratory tract infection in a pediatric liver transplant recipient treated with oral ribavirin. *Pediatr Transplant* 2012; 16: E348–E351.

49. Mori T, Nakamura Y, Kato J et al. Oral ribavirin therapy for lower respiratory tract infection of respiratory syncytial virus complicating bronchiolitis obliterans after allogeneic hematopoietic stem cell transplantation. *Int J Hematol* 2011; 93: 132–134.

50. Lehners N, Geis S, Eisenbach C, Neben K, Schnitzler P. Changes in severity of influenza A(H1N1)pdm09 infection from pandemic to first postpandemic season, Germany. *Emerg Infect Dis* 2013; 19: 748–755.

51. Fuehner T, Dierich M, Duesberg C et al. Single-centre experience with oral ribavirin in lung transplant recipients with paramyxovirus infections. *Antivir Ther* 2011; 16: 733–740.

52. Shima T, Yoshimoto G, Nonami A et al. Successful treatment of parainfluenza virus 3 pneumonia with oral ribavirin and methylprednisolone in a bone marrow transplant recipient. *Int J Hematol* 2008; 88: 336–340.

53. Stankova J, Carret AS, Moore D et al. Long-term therapy with aerosolized ribavirin for parainfluenza 3 virus respiratory tract infection in an infant with severe combined immunodeficiency. *Pediatr Transplant* 2007; 11: 209–213.

54. Kalimuddin S, Sessions OM, Hou Y et al. Successful clearance of human parainfluenza virus type 2 viraemia with intravenous ribavirin and immunoglobulin in a patient with acute myocarditis. *J Clin Virol* 2013; 56: 37–40.

55. Wong SS, Yuen KY. The management of coronavirus infections with particular reference to SARS. *J Antimicrob Chemother* 2008; 62: 437–441.

56. 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.

57. Bonney D, Razali H, Turner A, Will A. Successful treatment of human metapneumovirus pneumonia using combination therapy with intravenous ribavirin and immune globulin. *Br J Haematol* 2009; 145: 667–669.

58. Shachor-Meyouhas Y, Ben-Barak A, Kassis I. Treatment with oral ribavirin and IVIG of severe human metapneumovirus pneumonia (HMPV) in immune compromised child. *Pediatr Blood Cancer* 2011; 57: 350–351.

59. Widmer N, Meylan P, Ivanyuk A, Aouri M, Decosterd LA, Buclin T. Oseltamivir in seasonal, avian H5N1 and pandemic 2009 A/H1N1 influenza: pharmacokinetic and pharmacodynamic characteristics. *Clin Pharmacokinet* 2010; 49: 741–765.