REVIEW 10.1111/1469-0691.12595

Influenza and other respiratory virus infections in solid organ transplant recipients

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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.

Keywords: Antiviral therapy, chronic allograft dysfunction, influenza, respiratory syncytial virus, vaccination
Article published online: 17 February 2014
Clin Microbiol Infect 2014; **20** (Suppl. 7): 102–108

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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].