Review

Antiviral therapies for respiratory viral infections in lung transplant patients

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Because the lung is in constant contact with the environment, infections with respiratory viruses are a common and potentially serious complication of lung transplantation. Infection can cause direct effects, typically manifested as respiratory symptoms and changes in pulmonary function, and indirect effects, such as an enhanced risk of developing chronic allograft rejection. Infections with all of the identified respiratory viruses have been associated with infection in lung transplant recipients. Specific antiviral options have been studied for influenza and respiratory syncytial virus, and investigational agents are in development for other respiratory viruses. This paper will review the epidemiology and management strategies of respiratory viral infections in lung transplant recipients.

Epidemiology and significance of respiratory viral infections in lung transplantation

Advances in surgical technique, immunosuppression and antimicrobial prophylaxis has transformed lung transplantation into an important therapy for end-stage lung disease with 1-, 5- and 10-year unadjusted survival rates of 83%, 54% and 29%, respectively [1]. Early mortality is typically associated with graft failure and non-cytomegalovirus infections, whereas later mortality results from chronic allograft rejection followed closely by a wide range of infectious complications, including cytomegalovirus, bacterial and fungal infections [2]. Community respiratory viruses – including influenza, respiratory syncytial virus, human metapneumovirus, parainfluenza virus and rhinovirus – are a common cause of infections in lung transplant recipients, and most available data suggest that respiratory virus infections significantly increase the risk of chronic allograft rejection or bronchiolitis obliterans [3–5].

This review will report on the current understanding of the epidemiology and importance of respiratory viral infections in lung transplant recipients. Additionally, it will consider the available and investigational antivirals that have been or could be utilized by infected lung transplant recipients. To collect up-to-date literature on this topic, a PubMed search was conducted for ‘lung transplantation’ and each of the viruses or antivirals reviewed; the references of identified articles were also checked for information relevant to this review.

While our understanding of the epidemiology and significance of community respiratory viruses in lung transplantation has improved over time, gaps still exist [6]. Available studies are heterogeneous in their source population (all lung transplant recipients versus those admitted with pneumonia), monitoring strategy, diagnostic techniques utilized (culture versus antigen detection versus PCR) and site of sampling (nasal versus nasopharyngeal versus bronchoalveolar lavage) [6]. Consequently, there are wide ranges in the reported incidences of the identified viruses (Table 1) [6]. Most studies utilizing molecular diagnostic techniques, however, have documented that rhinoviruses are the most common cause of infections followed by parainfluenza viruses (PIV), respiratory syncytial virus (RSV), influenza and coronaviruses [5–10]. The incidence of respiratory viral infections appears to increase steadily over time since transplant, without a peak post-transplant [5]. The incidence of viral infections appears to parallel the incidence of respiratory viruses in the community in which the recipient lives [11]. Importantly, nosocomial infections have also been identified in lung transplant recipients; therefore, diligence with isolation practices is needed. Furthermore, incidence appears to be higher, especially for adenovirus, among paediatric transplant recipients as compared to adult recipients [9,10].

Diagnosis of respiratory viruses in the lung transplant population can be accomplished by direct
Table 1. Prevalence of respiratory viral infections

<table>
<thead>
<tr>
<th>Virus</th>
<th>Minimum, %</th>
<th>Maximum, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus</td>
<td>0</td>
<td>5.6</td>
</tr>
<tr>
<td>Coronavirus</td>
<td>0</td>
<td>26.9</td>
</tr>
<tr>
<td>Influenza</td>
<td>1.6</td>
<td>25</td>
</tr>
<tr>
<td>Human metapneumovirus</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Parainfluenza virus</td>
<td>5.6</td>
<td>35.3</td>
</tr>
<tr>
<td>Respiratory syncitial virus</td>
<td>2.4</td>
<td>22.2</td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>8.8</td>
<td>55.5</td>
</tr>
</tbody>
</table>

Data from [6]. *Most patients were symptomatic at the time of diagnosis.

Outcomes of infection are strongly associated with site of involvement, net state of immune suppression, and availability and use of antiviral agents. Patients who are more heavily immune suppressed at the time the infection is acquired, who have lower tract involvement and who fail to receive timely antiviral therapy are more likely to develop chronic rejection or bronchiolitis obliterans, and death, following a respiratory viral infection; risk of developing chronic rejection appears to be highest for PIV [3,6,14,15,17,18]. Overall, mortality has ranged from 0–25% [6]. Biopsy-confirmed acute rejection that is at least mild (A2) has been diagnosed in 5.9–47.6% of patients with respiratory viral infections in available studies, although a causal association with the onset of respiratory viral infections is more challenging to assess [6,19]. The reduction in pulmonary function and increases in lymphocytic infiltration that are frequently noted during the acute infection likely represents host responses to the infection instead of rejection. In four studies with robust data, one study demonstrated a strong association between respiratory viral infection and acute rejection (OR 7, 95% CI 1.88, 26.1) [15], whereas the other three studies did not (ORs 0.9, 2.0 and 0.5 and 95% CIs 0.35, 2.13, 0.11, 36.3 and 0.26, 0.96, respectively) [3,17,18]. Nevertheless, transplant pulmonologists frequently treat patients with clinically obvious respiratory viral infections with systemic corticosteroids for possible rejection in addition to antibacterial and, when available, antiviral agents. The need for corticosteroids in this situation has not been studied prospectively in controlled trials.

A far clearer association exists between respiratory viral infection and chronic rejection; the latter generally has been documented by biopsy-proven obliteratorive bronchiolitis or clinically by a sustained FEV1 decline of ≥20% (bronchiolitis obliterans syndrome [BOS]). The rate of chronic rejection following documented respiratory viral infections has ranged from 5.4% to 62.5% [3,6,15,17,20–27]. Careful review of studies with more complete data suggests that the pooled prevalence rates of chronic rejection, or BOS, are 18% in patients with documented respiratory viral infection infections and 11.6% in those without [6]. Available data suggests that the incidence of post-respiratory viral infection BOS is greater in patients with lower tract involvement that those with disease limited to the upper tract [3,4].
Management options for selected respiratory viral infections in lung transplantation

Influenza

**Prevention**

In addition to non-pharmaceutical interventions to reduce risk of exposure, prevention of influenza in lung transplant patients can be accomplished through specific immunization and/or the use of antivirals. Influenza vaccination is currently recommended by the Advisory Committee on Immunization Practices, the American Society for Transplantation Infectious Diseases Community of Practice, and the International Society for Heart and Lung Transplantation for all lung transplant recipients and their close contacts [13,28–30]. Unfortunately, influenza vaccination may not be effective in providing protective immunity early post-transplant, particularly if lymphocyte-depleting antibodies or rituximab are utilized [13,29,31]. Antiviral prophylaxis is an attractive alternative or addition to vaccination if there is a contraindication to vaccination, if vaccine is unavailable (as was the case early in the 2009 influenza A/H1N1 pandemic) or if influenza vaccine responses are predicted to be poor [13,29]. Studies of neuraminidase inhibitors in non-immunocompromised patients have clearly demonstrated significant protective efficacy when used for short-term prophylaxis and similar effects would be predicted in immunocompromised patients [32]. One randomized, blinded, placebo-controlled study of seasonal prophylaxis with oseltamivir 75 mg once daily in stem cell, kidney and liver transplant recipients found that oseltamivir was safe, well tolerated, and resulted in fewer PCR- (2.1% versus 8.4%) or culture- (0.4% versus 3.1%) proven cases of influenza [33]. Although no studies have been conducted in lung transplant recipients, the results in healthy patients and the single study in transplant patients suggests that such an intervention can be considered in lung transplant recipients and is recommended by current guidelines [13,29]. If oseltamivir prophylaxis is utilized, the patients should be told to immediately inform the transplant team if they develop any symptoms compatible with influenza. In such patients, screening for influenza is recommended and use of alternative antiviral therapies active against oseltamivir-resistant variants (that is, zanamivir) may be considered.

**Therapy**

Two classes of antivirals are currently available to treat influenza – M2 inhibitors (amantadine and rimantadine) and neuraminidase inhibitors (NAIs; oseltamivir, zanamivir, laninamivir [in Japan only] and peramivir [in Japan and South Korea only]). Widespread resistance among all circulating strains of influenza currently precludes the use of M2 inhibitors; monitoring changes in susceptibility patterns are essential to inform the medical community about the optimal use of these agents [30,34].

NAIs are active against most influenza A and B viruses, but resistance may emerge limiting the efficacy of individual or all NAIs, particularly in immuno-compromised hosts. Resistance to NAIs can occur secondary to mutations in the neuraminidase or haemagglutinin gene, or both [35]. The specific mutation determines which antivirals the specific virus is resistant to and the degree of cross-resistance [35]. Oseltamivir resistance due to the H275Y mutation, that confers large increases in the 50% inhibitory concentration (IC50) to oseltamivir and to a lesser extent to peramivir [35], is only occurring sporadically at present, although widespread circulation during the 2008–2009 influenza season was a problem [14]. Different NAI resistance mutations may occur, especially if antivirals other than oseltamivir are used, and with different subtypes of influenza viruses. Resistance should be considered and tested for in any patient who develops influenza after recent exposure to NAIs, used as either treatment or prophylaxis, or if there is failure to improve clinically despite 5–7 days of antiviral therapy [35]. When testing for resistance, either phenotypic assays or assays that can genotypically detect a wide range of mutations (that is, not just the H275Y mutation) should be considered to detect all potentially significant mutations, including those that may compensate for changes in enzyme function [35].

There have been no prospective studies of the optimal timing, dose or duration of antivirals for influenza in lung transplant recipients [14,28]. A number of studies have retrospectively analysed outcomes in lung transplant patients given antivirals, but none of these studies included robust serial quantitative assessments of viral replication and few studies had qualitative ones [7,8,15,16,36]. In general, antiviral therapy appears to reduce the risk of developing viral pneumonia (0% versus 2.5%) and of death (0% versus 2.5%) if started early. While delayed initiation of therapy is associated with a higher frequency of progression to pneumonia and death in most studies [7,8,15,36], there appears to be benefit in these patients even if symptoms have been ongoing for >48 h. In one retrospective study, oseltamivir was associated with a reduced risk of BOS as compared to historical controls [16]. In another study, during the pandemic, the effect of antiviral therapy on development of BOS was less clear, although may have been lower than predicted based on the proportion of patients with lower tract involvement [8]. Of note, most of the patients affected were previously vaccinated and most of the patients had symptoms ≥48 h before starting antiviral therapy, typically oseltamivir.

Consequently, all lung transplant patients with suspected influenza should be initiated on antiviral therapy
empirically, irrespective of duration of symptoms, and therapy should not await the results of diagnostic studies. Furthermore, since patients with lower tract involvement may have negative nasal swab testing, even by RT-PCR, therapy should continue until influenza has been ruled out in both the upper and lower airway. In general, oseltamivir has been well tolerated. Viral detection may be prolonged and, as a result, longer courses than the usual 5 day course are required in lung transplant recipients, but studies are needed to determine the optimal dose and duration of therapy [8,37]. Likewise, the role of combination antiviral therapy needs further study in lung transplant patients. Most experts recommend treating until cessation of detectable replication is confirmed [13,28,29].

Zanamivir has been studied in patients with underlying lung disease but has not been well studied in lung transplant recipients [32]. Exacerbation of underlying airway disease and bronchospasm may occur with the use of inhaled zanamivir. If inhaled zanamivir therapy is considered in a lung transplant recipient, the first dose should be monitored and bronchodilators should be readily available with any dose [32]. Although intravenous zanamivir is being studied for the treatment of severe influenza, such studies typically exclude lung transplant patients. It is available for compassionate use for lung transplant patients who cannot tolerate other formulations of antivirals and in those with proven or probable resistance to oseltamivir.

Respiratory syncytial virus
RSV is a major cause of respiratory viral infections in lung transplant patients, particularly children [9]. No vaccine is currently available against RSV, although several candidates are under investigation [38]. As a result, diligent infection control practices and the use of prophylactic antibody infusions are the only options for prophylaxis. Palivizumab, an RSV monoclonal antibody, is associated with reduced RSV hospitalizations in high-risk children [39]. Although it has not been specifically studied in lung transplant patients, antibody-based prophylaxis, typically with palivizumab, is commonly used in paediatric lung transplant programmes in the US [39].

There are currently few studies of antiviral therapy in managing RSV infection in lung transplant recipients. Traditionally, aerosolized ribavirin has been advocated for treatment, particularly pneumonia [40–43], but prospective studies of ribavirin, in any formulation, have not been conducted in lung transplant patients with RSV infection. One retrospective study of aerosolized ribavirin in lung transplant recipients suggested that it may have reduced mortality, although about a third of treated patients with lower tract disease still died [43]. A more recent study of aerosolized ribavirin, palivizumab, and corticosteroids found the combination therapy to be safe and effective with low mortality rate (4%) [9].

Given this result and data suggesting that combinations of ribavirin plus antibodies have been demonstrated to improve outcomes compared to ribavirin alone for the management of RSV in stem cell transplant patients, such combinations should be considered in lung transplant patients with severe RSV or significant immune compromise [44]. Further studies are needed to determine if routine immunoglobulin intravenous (IgIV), RSV hyperimmune globulin (available for compassionate use; ADMA Biologics, Inc., Hackensack, NJ, USA), or palivizumab is superior for this indication.

Major drawbacks of aerosolized ribavirin include cost, intolerance and bronchospasm in the treated patients, and risk to the caretakers exposed to ribavirin in the environment [45]. As a result, several groups have looked at alternative delivery methods in lung transplant recipients [41,45,46]. Intravenous ribavirin (33 mg/kg on day 1 and 20 mg/kg/day thereafter in three divided doses) in addition to oral prednisolone (1 mg/kg) were given until repeat nasopharyngeal swab were negative for RSV by immunofluorescent antibody to 18 RSV-infected lung transplant recipients in one retrospective experience [46]. No patients died and all returned to near baseline pulmonary function testing. Treatment (median of 8 days) was well tolerated except for mild haemolytic anaemia in several of the patients [46]. Another group used oral ribavirin (15–20 mg/kg in three divided doses for a total of 10 days) combined with steroids in five infected lung transplant patients and found that the combination was well tolerated, effective and less costly than inhaled ribavirin [45]. However, these uncontrolled retrospective reports have outcomes similar to groups that have not used specific antiviral therapy [47]; therefore, prospective randomized studies are clearly needed.

A novel small interfering RNA preparation specific for the viral N protein of RSV, ALN-RSV01, is under investigation as a potential therapy for RSV infections and has been specifically studied in lung transplant patients [48]. It is currently in Phase II studies in lung transplant recipients but not available for compassionate use. ALN-RSV01 administered by inhalation has been generally well-tolerated without perturbations in lung function in studies to date [49]. In a prospective study, 16 lung recipients with RSV received ALN-RSV01 (0.6 mg/kg aerosolized) and 8 received placebo with randomization stratified by ribavirin use [48]. Symptoms scores were lower in patients who received active therapy, and the incidence of new or progressive BOS at 90 days was significantly reduced in the ALN-RSV01 population (6.3% versus 50%; P=0.027), despite the finding that there were no significant differences in the mean daily viral load (P=0.236), the rate
of viral clearance, or in the duration of viral shedding between treatment groups [48].

Other community respiratory viruses

Paramyxoviruses

A number of cases, some severe, of human metapneumovirus (hMPV) [5,7,17,21,25,50] and PIV [7,24,26,43] infections have been described in lung transplant recipients. There are currently no proven preventative strategies other than infection control to prevent hMPV or PIV in this population, and no prospective studies have examined therapeutic interventions for these virus infections in lung transplant recipients. Intravenous ribavirin has been used in a few cases of severe hMPV infection in lung transplant patients with successful outcomes; the dose of ribavirin in one case report was 33 mg/kg intravenous on day 1, followed by 16 mg/kg intravenous daily on days 2–5 and then 8 mg/kg intravenous daily on day 6–15 [51,52]. IgIV was not used in either case, although IgIV has been used in other populations because in vitro activity has been demonstrated against hMPV [53].

Ribavirin has been used in a few cases of severe PIV infection in lung transplant patients with successful outcomes [43,54]. For PIV infections, ribavirin was delivered as an aerosol (20 mg/ml) for 16–24 h a day for 3–7 days in one study and over 8 h for 15 days in the other. No IgIV was used in either study.

A novel recombinant sialidase fusion protein (DAS181 or FluDase) has in vitro and in vivo activity against PIV and has been shown clinical efficacy in a few stem cell transplant patients with PIV [55,56]. DAS181 is currently under investigation for treatment of influenza, but it is available for compassionate use in patients with severe PIV infection.

Picornaviruses

Prolonged shedding, sometimes in the absence of symptoms, has been recently documented with many respiratory viral infections in lung transplant recipients, particularly rhinovirus [57]. In one study, rhinoviral infections were documented in bronchoalveolar lavage specimens of 10 recipients, and 3 presented with a persistent infection [57]. A more recent study identified two additional persistent infections among lung transplant recipients [58]. Sequencing of all serial viruses from these five individuals (three had HRV-A species [HRV-A64, -A24 and -A9] and two had HRV-B species [HRV-B3 and -B27]) demonstrated evolution of these viruses over time, suggesting that one potential mechanism for their persistence is immune evasion. The clinical effect of this prolonged shedding warrants further study. There are no controlled trials of IgIV or interferon for rhinovirus in lung transplant patients, therefore they cannot be recommended for treatment.

An investigational capsid-binding anti-picornavirus agent, BTA798, is undergoing clinical development for rhinovirus infections, but it is not currently being studied in lung transplant recipients (John Lambert, Biota Holdings, Ltd, Notting Hill, Victoria, Australia, personal communication); it may be available for compassionate use for selected cases.

Adenoviruses

Adenoviruses can also cause clinically significant infections in lung transplant recipients. Low-level adenoviraemia occurs in approximately 22.5% of lung transplant patients during the first year post-transplant, but such episodes are self-limited and do not appear to trigger acute rejection or a decline in pulmonary function [59]. When clinically significant adenovirus infection occurs, pneumonia and disseminated infections are associated with poor outcomes [60,61]. Although ribavirin has been demonstrated to have in vitro activity against some adenoviruses, it clinical effectiveness has been unclear [60,61]. Cidofovir (which can be dosed at 5 mg/kg per week for 2 weeks then every other week or 1 mg/kg three times a week) appears to be associated with improved outcomes in lung transplant patients [62]. CMX001 is a lipid ester of cidofovir that is orally bioavailable, associated with less bone marrow suppression and nephrotoxicity, and appears to be more active against adenoviruses than cidofovir [63]. CMX001 is undergoing clinical studies for adenovirus and is available for treatment of serious adenovirus infections for compassionate use.

Data on other respiratory viruses (for example, human coronaviruses) in lung transplant recipients is limited to epidemiological studies (Table 1), and therapeutic interventions are either of unproven value, because of the lack of controlled trials, or lacking for the other respiratory viruses [57,64–67]. Recently, the respiratory polyomaviruses WU and KI have been detected in both symptomatic and asymptomatic lung transplant recipients [64,65]. In these studies, WU virus was found in 12.3–29% and KI virus in 9.2–25% of lung transplant recipients, although there were no significant associations with a specific clinical and/or histopathological pattern in these individuals [64,65]. No antivirals have been studied for the respiratory polyomaviruses in lung transplant patients.

Respiratory viruses and organ donation

The incidence of donor-derived respiratory virus transmission is unknown [68,69]. Nevertheless, lung transplantation presents a unique risk for transmitting respiratory viruses of donor origin because the lung is exposed to the environment and may be the primary
site of infection by these pathogens. At least two confirmed transmissions of influenza of donor-origin have been documented in the literature [70,71]. As a result of the risk of transmission, current guidelines recommend against the use of donors with recognized influenza infection for lung transplantation [13,29,72]. If a donor with a documented recent influenza infection is used for lung transplantation, it is recommended that the recipients are treated with active anti-influenza agents at full therapeutic doses [13,29,72]. Donors with documented pneumonia secondary to other respiratory viruses likely should be precluded from lung donation as well since there are no clearly documented treatments for many of the other respiratory viruses. Likewise, lung candidates with documented respiratory viral infection involving the lower airway should likely be deferred from transplantation until they have cleared the virus [13,29,72].

Disclosure statement

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References


