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Review

Respiratory Viral Infections in Lung Transplant Recipients: Implications for Long Term Outcomes and Emerging Therapies

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Abstract

Lung transplant recipients are at greater risk of respiratory viral infections as compared to other solid organ transplant recipients due to constant exposure of the allograft to the external environment. There are no standardized methods for surveillance, prevention, or treatment of these infections despite their association with increased morbidity and mortality. Various studies have linked respiratory viral infections with acute cellular rejection and chronic allograft dysfunction, and emerging data indicates a role in antibody mediated rejection. This paper will review the prevalence and impact of community acquired respiratory viruses in lung transplant recipients, review the evidence linking these viral infections to long term graft dysfunction and rejection, describe existing strategies for surveillance and prevention, and list the currently available, and promising investigational therapies.

Keywords
Respiratory viral infections; lung transplant; implications; emerging therapies

1. Introduction

Despite advancements in lung transplantation, five-year survival for lung transplant recipients remains lower than other solid organ transplant recipients. Chronic lung allograft dysfunction in the form of bronchiolitis obliterans (BOS) is the most common reason for graft failure and death after the first year of transplant [1]. Long term graft and patient survival are limited due to both acute and chronic allograft rejection. This is believed partly to be due to the constant exposure of the graft to the external environment, which places patients at risk for inhalation of potentially harmful environmental agents, including community-acquired respiratory viruses (CARVs).

The CARVs include rhinovirus, bocavirus, coronavirus, respiratory syncytial virus (RSV), adenovirus, parainfluenza viruses (PIV), influenza A and B, and human metapneumovirus (hMPV). Symptomatic infections with most of these viruses can cause immune mediated deleterious effects on lung function [2, 3], leading to the development of acute cellular rejection, antibody mediated rejection, and chronic lung allograft dysfunction (CLAD). Despite this clinical impact, among transplant centers there are no standardized guidelines for surveillance or treatment of these infections.

In this paper, we will review the prevalence and impact of community acquired respiratory viruses in lung transplant recipients, review the evidence linking these viral infections to long term graft dysfunction and rejection, describe existing strategies for surveillance and prevention, and list the currently available and promising investigational therapies.

2. Epidemiology

Symptomatic respiratory viral infections are extremely common after lung transplantation, with estimations of 25-60% of lung transplant recipients infected at some point after transplant [4-9]. Though some studies have reported increased CARVs within the first year of transplant [8, 10] others have reported that patients are affected at similar rates regardless of time post-transplant [5]. There has not been sufficient data to suggest that higher immunosuppression plays a role. Rhinovirus and PIV occur throughout the year while the other CARVs have a seasonal appearance typically in the winter and spring [11, 12]. The most common CARVs are the picornaviruses (coxsackievirus, rhinovirus and other enteroviruses) [4, 5, 11]. Viruses can enter the distal airway by aspiration of upper airway secretions or by direct inhalation from the environment. Viral tropism also impacts location and extension of infection. Infections range from asymptomatic carriage to acute bronchiolitis, pneumonia, and respiratory failure. The clinical presentation varies depending on symptomatic involvement of upper versus lower respiratory system but can also manifest solely as a decline in pulmonary function testing without overt symptoms.

3. Detection

Multiplex, polymerase chain reaction (PCR) methods are currently the preferred test of choice due to simultaneous identification of multiple viruses, rapid results and higher sensitivity compared to direct fluorescent antibody testing and viral culture [12, 13]. Specimens are obtained by nasopharyngeal swab or bronchoalveolar lavage (BAL), depending on the patient's clinical presentation and ability to ascertain the etiology of the patient's symptoms or PFT decline on nasopharyngeal swab alone versus need for invasive sampling. While surveillance bronchoscopy is commonly performed after lung transplant, the time interval and microbiology and cytological studies performed vary among transplant centers. Furthermore, some centers perform bronchoscopy only if clinically indicated while others may screen for viral infections via nasopharyngeal swab. In a study analyzing over four thousand respiratory samples, Allyn and colleagues found that when compared to other symptomatic and asymptomatic viral infections, viral pneumonia alone increased the risk of CLAD and graft loss [4]. This might suggest that screening detection methods should not be pursued in asymptomatic patients. In contrast, a smaller study by Kumar and colleagues reported that the incidence of CLAD following respiratory viral infections was similar in both symptomatic and asymptomatic patients [12]. These results suggest that screening for viral infections could confer a benefit, possibly in the early post-transplant period when the graft is most vulnerable. Since nasopharyngeal swabs facilitate non-invasive respiratory sampling, a standardized approach would be helpful to guide if and how often to screen. Such an approach would require assessment of the cost of routine testing and opportunity to make a clinically meaningful intervention.

4. Acute Rejection, CLAD, and AMR

A decline in spirometry due to symptomatic lower respiratory tract viral infection that does not progress to chronic graft dysfunction is expected to recover within one to three months [8, 14-18]. These transient decreases in lung function are not necessarily related to acute cellular rejection, but when acute rejection is identified in conjunction with a respiratory viral infection, time to recovery of baseline lung function can be prolonged [18].

The pathogenesis of acute cellular rejection (ACR) involves a T cell driven process characterized by mononuclear cell infiltrates around small vessels and/or airways [19]. Respiratory viral infections can trigger ACR through upregulation of cytokines that lead to T cell activation; however, the link between respiratory viral infections and ACR has not been definitively established. There are several studies that have reported an association between CARVs and acute rejection [2, 12, 20-22]. Among these studies, all of the CARVs were associated with acute rejection. Vilchez and colleagues reported pathologic evidence of acute rejection in 82% of patients with PIV infection who underwent transbronchial biopsies [22]. Other studies, including a recent systematic review, have reported absence of an association [5, 18, 23-26]. It is significant to note that in the studies that reported an association with ACR, there was a higher number of hMPV infections compared to those that did not. One possibility for the heterogeneous findings is the difference in diagnostic methods used among various studies. As mentioned previously, current methods include molecular diagnostic approaches in the form of PCR which increases the sensitivity of diagnosing respiratory viral infections.

Despite improvements in immunosuppressive regimens and reduction in acute cellular rejection, the incidence of CLAD has remain unchanged. The risk for chronic rejection due to respiratory viral infections could partially explain this, as evidenced by many studies [26-29]. Table 1 lists the most relevant studies linking respiratory viral infections to allograft dysfunction.

Lung function is not impacted equally by all the CARVs. Some viral pathogens invoke severe and irreversible long-term graft dysfunction as a result of chronic rejection. Depending on the type of virus, the rate of BOS development after CARV infection has been estimated to range from 32-50% [30]. The time between infection and bronchiolitis obliterans can range between 1 and 14 months [22, 31-34]. The Paramyxoviridae family of viruses (which includes RSV, PIV, and hMPV), influenza, and adenovirus can display high virulence in immunocompetent patients, but particularly in lung transplant patients they have been shown to cause acute respiratory failure, BOS, CLAD development, and sometimes death more than the other CARVs [8, 20, 33, 35-38]. Acute mortality from RSV in lung transplant recipients has been reported to be 10-20% [8, 20, 34], while the development of CLAD after RSV infection has been estimated to be as high as 38% [20]. Recently Magnusson et al. reported that coronavirus infections that occurred in the first year of lung transplantation were associated with an increased risk for CLAD development [39].

The link between respiratory viral infections and antibody mediated rejection (AMR) is new and emerging. There is no agreed upon histologic definition of AMR, but the pathogenesis involves preformed or de novo circulating antibodies that contribute to both acute and chronic rejection. The International Society for Heart and Lung Transplantation released a consensus report [40] defining and staging AMR that includes deposition of complement product C4d on the capillary endothelium which has been shown to be a surrogate marker for AMR in other solid organ transplants [41-44]. Immune stimulation by infections can contribute to antibody formation in susceptible patients. In a retrospective analysis, patients who developed RSV infection within 180 days after lung transplant had significantly higher rates of new human leukocyte antigen [45] and new donor specific antibody (DSA) detection [46]. In a separate study 38% of patients developed de novo DSAs after CARV infection which included PIV, RSV, adenovirus, influenza A and B, hMPV, and picornavirus. 11% developed new de novo DSAs after infection, most of which were class II DSAs [47]. Pulmonary AMR is a developing area with many unknowns, but with the recent release of consensus statements on the definition and management [48], it is likely that additional studies will arise to help identify the triggers and mediators of antibody development.

Table 1 Publications documenting an association of community acquired respiratory viral infections and allograft dysfunction.

Publication	Study design/# Patients	Specimen of CARV diagnosis	Type of graft dysfunction	Findings/Comments
Magnusson et al, 2018 [39]	Retrospective analysis of 98 patients in first year post transplant	BAL and NP swab	CLAD unspecified	RVI during first year associated with long term CLAD
Allyn et al, 2016 [4]	Prospective analysis of 563 LTR over 13	BAL, sputum culture, NP swab	CLAD unspecified	Viral pneumonia alone increased the risk of CLAD

	years			
Fisher et al. 2016 [27]	Retrospective analysis of 250 patients	Nasal swabs, washes, sputum, or BAL	CLAD unspecified	20% of patients diagnosed with CLAD at median time of 95 wks post-transplant
Bridevaux et al, 2014 [5]	Prospective analysis of 112 LTR over 3 years; 903 encounters	NP swab and BAL	Transient reduction in spirometry	Infections associated with transient loss of lung function and high CI levels; acute rejection not associated with RVI
Magnusson et al, 2013 [29]	Retrospective analysis of 39 LTR	BAL	BOS	Patients with one or more viral infections in first year after transplant developed BOS faster than those without viral infections
Sayah et al, 2013 [26]	Retrospective analysis of 59 LTR over 2 years	BAL, sputum culture, NP swab	Allograft dysfunction defined as reduction in spirometry	Non-rhinovirus CARV were associated with allograft dysfunction 1-2.5 months after infection
Kumar et al, 2010 [12]	Prospective analysis of 98 LTR over 3 years	BAL	BOS	BOS diagnosed within 62.5% of patients within 1 year after RVI
Gottlieb et al, 2009 [28]	Prospective cohort study of 300 LTR	NP swabs, OP swabs, sputum culture, BAL	BOS	One-year incidence of BOS was 25% in CARV-positive versus 9% in CARV-negative patients. Higher risk in patients with paramyxovirus infection
Khalifah et al. 2004 [49]	Retrospective analysis of 228 LTR over 5 years	BAL, bronchial washing, tracheal aspirate, sputum culture, NP swab	BOS	Patients with CARV had increased risk of BOS, death, and death from BOS
Billings et al, 2002 [31]	Retrospective analysis of 219 LTR	BAL, NP swab, sputum culture, viral culture,	BOS	BOS found only in patients with lower respiratory tract infection
Bridges et al, 1998 [32]	Prospective case series of 16 LTR	Lung biopsy tissue, BAL, tracheal aspirate, hilar lymph nodes	BOS	Adenovirus infections associated with graft failure, BOS, and death

RVI: respiratory viral infection; LTR: lung transplant recipients; BAL: bronchoalveolar lavage; NP: nasopharyngeal; PCR: polymerase chain reaction; CI: calcineurin inhibitor.

5. Prevention, Infection Control, and Treatment

There is considerable variability among transplant centers in regard to surveillance and treatment strategies. Education and prevention, on the other hand, are strategies that can be applied by all to protect allograft function given the mounting evidence that CARVs play a role in CLAD development. Education should be provided to patients, family members, caregivers, and healthcare professionals on infection-avoidance behavior and the protective effects of community immunity through vaccination conferred to the immunocompromised patient. Exposure prevention should not be underestimated; avoiding or limiting contact with sick individuals and good hand hygiene are important measures that can be practiced by everyone. Specifically, presenteism, which occurs when healthcare workers go to work despite having a medical illness, is a public health hazard in regard to disease transmission and extension. Healthcare work culture, expectations, and the demands of patient care are factors contributing to this problem.

Once considered or confirmed as a diagnosis, infection control is a vital practice to prevent further transmission and avoid outbreaks. The employment of droplet and contact precautions both during waiting times for test results as well as after confirmed diagnosis are methods for containing infection [50, 51]. In cases of outbreaks, other strategies include limiting patient visitors, screening visitors for symptoms of respiratory tract infections, limiting patient transport while diagnostic testing is in process, and moving patients to private rooms.

Primary prophylaxis and vaccinations are the two strategies studied for influenza. Primary prophylaxis can be useful in cases where vaccination is not tolerable or is unavailable. Ison and colleagues evaluated primary prophylaxis with oseltamivir in stem cell, liver, and kidney transplant recipients and found a significant reduction in PCR positive (2.1% versus 8.4%) or culture positive (0.4% versus 3.1%) samples for influenza [52]. Some challenges to adopting this method of prevention include patient concerns regarding pill burden and drug side effects, as well as cost as it relates to insurance coverage for a season long prescription. A separate recent study demonstrated improved influenza vaccine immunogenicity by administering a booster vaccine 4-6 weeks after the initial vaccination in solid organ transplant recipients. After receiving this second dose, recipients had increased seroconversion rates to H1N1 (53.8% versus 37.6%), influenza A (48.1% versus 32.3%), and influenza B (90.7% versus 75%) [53]. In a separate study evaluating high dose versus standard dose flu vaccine administered to solid organ transplant patients, patient who received the high dose demonstrated significantly better immunogenicity, with seroconversions to H1N1, influenza A, and influenza B of 40.5% versus 20.5%, 57.1% versus 32.5%, and 58.3% versus 41.6%, respectively [54]. The benefit of influenza vaccination remains significant even if transplant patients become infected. A recent prospective study evaluating influenza in solid organ transplant recipients, patients who received influenza vaccine in the same season has lower risk of pneumonia and intensive care unit admissions and patients treated with antiviral therapy within 48 hours had better outcomes [55]. Unfortunately, there are no approved vaccinations for the other CARVs. Palivizumab is a monoclonal antibody that is approved for use only in high risk infants for RSV prevention but has rarely been used in thoracic lung transplant recipients with RSV [56].

Similar to the management of non-influenza viral infections in immunocompetent patients, the mainstay of treatment in solid organ transplant recipients is supportive care; however, there is some supportive data showing that treatment of paramyxoviruses results in less risk of BOS or

reduced BOS severity. Table 2 lists the existing studies and outcomes of treatment in regard to graft function, not mortality. Most of the studies have looked at outcomes in RSV treatment, with smaller numbers of studies evaluating treatment of hMPV and PIV infections. Below are the emerging or investigational treatments for some of the respiratory viral infections.

Table 2 Publications evaluating effect of antiviral therapy and graft function.

Publication	Patients	Treatment	Outcome
Trang et al, 2018 [57]	Single center retrospective cohort study of 46 patients with RSV	Aerosolized (N=26)compared to oral ribavirin (N=20)	No difference in clinical outcome between the two group
Gottlieb et al, 2016 [35]	Phase 2b randomized double blind placebo-controlled trail in patients with RSV	ALN-RSV01 (N=44) compared to placebo (N=33)	Patients treated with ALN-RSV01 trended toward a decrease in new of progressive BOS (13.6% vs 30.3%); treatment enhanced when used <5days from symptoms onset
Burrows et al, 2015 [14]	Retrospective analysis of 52 patients with RSV	Oral ribavirin	New onset BOS in one patient
Schuurmans et al, 2014 [38]	Single season retrospective observational study of 173 patients with 22 infections	Oseltamivir	Advanced BOS stage occurred in 3 patients at 6 month follow up
Li et al, 2012 [58]	Retrospective analysis of 21 patients with RSV	Oral ribavirin (N=6) compared to inhaled ribavirin (N=15)	No clinical difference between the groups; 2 patients in the inhaled group developed new onset or progression BOS at 6 months follow up
Fuehner et al, 2011 [15]	Retrospective analysis of 67 patients with paramyxovirus infection	Oral ribavirin (N=38) compared to supportive care and corticosteroids (N=29)	Patients treated ribavirin had greater graft function recovery (84% vs 59%) and less onset of BOS within 6 months (5% vs 24%)
Ng et al, 2011 [37]	Observational study of 24 patients infected with H1N1	Oseltamivir in 23 patients	BOS in 6 patients (32%)
Liu et al, 2010 [56]	25 patients infected with either RSV or PIV	Inhaled ribavirin, methylpred, and IVIG for PIV infections; palivizumab added for RSV patients	Patients without BOS at baseline recovered their in FEV1; patients with BOS at time of infection had a greater decline in FEV1 at time of infection and remained lower on follow up
Pelaez et al, 2009 [59]	5 patients	Oral ribavirin with IV corticosteroids	FEV1 returned to baseline after treatment and there were no deaths

Glanville et al, 2005 [16]	18 patients with RSV	Intravenous ribavirin and oral prednisolone until repeat swabs were negative	All patients experienced a decline in FEV1 at time of infection that recovered within 3 months; 1 patient developed BOS
McCurdy et al, 2003 [8]	Retrospective analysis of 15 patients with RSV or parainfluenza virus	Aerosolized ribavirin	2 patients (13%) died and 3 (20%) patients had a decline in FEV1 that did not return to baseline and was not consistent with BOS

IVIG: intravenous immunoglobulin; BOS: bronchiolitis obliterans syndrome.

6. RSV

Treatment strategies vary among centers in regard to treating lower versus upper respiratory tract RSV infections, the route and dose of antiviral agent, and adjunct therapies such as steroids or intravenous immunoglobulin (IVIG) [60]. Many studies have shown benefit of ribavirin in both inhaled and oral route [15, 58, 59], though inhaled ribavirin is significantly more expensive and poses teratogenic risk to pregnant caregivers, and therefore may influence trends in practice. A recent retrospective study and review showed that oral ribavirin was a safe and cost-effective alternative to inhaled ribavirin without any difference in clinical outcomes [57].

Ongoing investigational therapies for RSV include RNA interference drugs and fusion inhibitors [61]. A recent promising phase 2b study evaluating the impact of drug ALN-RSV01, an interfering RNA, demonstrated reduced incidence of BOS in lung transplant patients after RSV infection [35]. Other investigational drugs that inhibit viral replication and viral entry into cells have been shown in healthy adults inoculated with RSV to result in more rapid RSV clearance and greater reduction in viral load [62, 63]. Presatovir is a promising fusion inhibitor that demonstrated a reduction in viral load in HCT patients. In the hopes of finding the same results in lung transplant patients, Gottlieb and colleagues conducted a double-blind randomized trial in 77 patients and unfortunately did not see any reduction in viral load, clinical improvement, or change in lung function [35].

7. Parainfluenza

Experimental therapies to treat parainfluenza virus have been underway, though nothing has yet been approved for use. These have included host-directed therapies as opposed to a pathogen-targeted approach. In a single arm clinical trial in HCT patients, use of a sialidase protein that inhibits viral attachment to host cells improved the clinical outcome either completely or partially in 13 out of 16 patients [64].

8. Influenza

Neuraminidase inhibitors (oseltamivir, zanamivir, peramivir) have been proven to be effective at decreasing flu severity and duration of symptoms [65, 66]. This year a new flu antiviral medicine, baloxavir, was approved by FDA. Unlike the neuraminidase inhibitors, baloxavir interferes with RNA transcription, thereby inhibiting viral replication. In the phase III trial baloxavir was not only associated with faster recovery and reduced risk of complications in high risk patients, but it was

also superior to oseltamivir in reducing duration of viral replication and in resolving influenza B illness [67, 68]. Potential limitations include development of influenza virus variants with reduced susceptibility after a single dose [69, 70], thereby making it difficult to determine if viral detection after treatment is due to viral shedding or persistent infection. Studies looking at adjunct therapy with other antivirals have not shown any clinical benefit [71]. A phase 3 study is underway to evaluate immune plasma as a treatment for influenza. In the results published from the open label phase 2 trial, patients who were hospitalized with severe infection had a trend toward improved respiratory status and overall mortality [72].

9. Adenovirus

In lung transplant recipients, adenovirus found in the lung has been shown to cause graft failure and even death [32, 49]. Less is known about adenovirus viremia; however, one study suggests that viremia in lung transplant recipients is more common than initially thought, but that in low levels does not contribute to lung allograft dysfunction [73]. The limited data on antiviral therapy for adenovirus comes from hematopoietic cell transplant (HCT) recipients. Cidofovir is used off-label, with some benefit shown in case series and not from controlled studies. High peripheral blood viral loads correlate with disseminated infections and can be used to clinically to assess response to therapy [74, 75]. Nephrotoxicity is a common complication that often limits use. Brincidofovir is a derivative of cidofovir without the associated myelotoxicity or nephrotoxic effects. There have been two clinical trials looking at brincidofovir in allogeneic HCT patients which have demonstrated improved survival in patients who sustained a virologic response, including those who were highly immunosuppressed with CD4 counts less than 50 cells/µl [76, 77]. There are ongoing trials evaluating the use of adenovirus-specific cytotoxic T-lymphocytes.

10. Conclusions

Respiratory viral infections after lung transplantation are common and have been linked to graft dysfunction through acute cellular rejection, CLAD, and more recently antibody mediated rejection. Through these mechanisms they contribute to significant morbidity and mortality in lung transplant recipients, thereby limiting long-term survival. Though generally limited in treatment, there are emerging therapies that are promising to decrease the incidence of BOS after infection. Further investigation and randomized trials are needed to determine the pathogenesis and optimal treatment for respiratory viral infections so that lung transplant centers can achieve an effective standardized approach in management of CARVs.

Author Contributions

Conception and design: All authors (SK, CH, RC, DvD, LJL) contributed to conceptualization and article design.

Administrative support: N/A.

Provision of study materials or patients: N/A

Collection and assembly of data: SK primarily performed pertinent literature searches for data compilation.

Data analysis and interpretation: N/A.

Manuscript writing: All authors (SK, CH, RC, DvD, LJL) were responsible for writing and editing of the manuscript.

Final approval of manuscript: All authors (SK, CH, RC, DvD, LJL) gave final approval of manuscript prior to submission.

Competing Interests

The authors have declared that no competing interests exist.

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