Community-Acquired Respiratory Viruses

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Abstract

The incidence of community-acquired respiratory viruses (CARVs) is ~15 cases per 100 patient-years after lung transplantation (LTx). Paramyxoviruses account for almost 50% of the cases of CARV infection in LTx. Most patients will be symptomatic with a mean decline of 15 to 20% in forced expiratory volume in 1 second. The attributable death rate is low in recent years 15 to 25% CARV infected LTx patients will develop chronic lung allograft dysfunction within a year after CARV infection. This risk seems to be increased in comparison to the noninfected LTx recipient.

Detection rate of CARV dependent on clinical awareness, sampling, and diagnostic method with nucleic acid testing by polymerase chain reaction in bronchoalveolar lavage is the gold standard after LTx.

There is no approved treatment for paramyxoviruses, most centers use ribavirin by various routes. Toxicity of systemic ribavirin is of concern and some patients will have contraindication to this treatment modality. Treatment may reduce the risk to develop chronic lung allograft dysfunction and respiratory failure. Agents under development are inhibiting viral attachment and use silencing mechanisms of viral replication.

Keywords

- lung transplantation
- community-acquired respiratory viruses
- ribavirin
- bronchiolitis obliterns syndrome

The respiratory tract is a major entry through which viruses initiate infection. The respiratory tract can be divided anatomically into the upper respiratory tract and the lower respiratory tract divided by the lymphoid tissue of Waldeyer's ring. Community-acquired respiratory viruses (CARVs) are highly developed and ubiquitous pathogens which can cause infection of both the upper and lower respiratory tract.[1] Infection with these viruses usually results in a mild, self-limited disease in the nonimmunocompromised adult. Some CARV may result in respiratory failure even with fatal outcome (e.g., Middle East respiratory syndrome coronavirus, corona virus associated severe acute respiratory syndrome).

CARVs have been increasingly recognized as common pathogens after lung transplantation (LTx).[2] CARV are a diverse group of viruses including the paramyxoviridae: respiratory syncytial virus (RSV), parainfluenza virus (PV), human metapneumovirus (hMPV); the orthomyxoviridae: influenza A and B (flu); the picornaviridae: rhinovirus (RV) and enterovirus; the coronaviridae: coronavirus (CoV); and the adenoviridae: adenovirus (AV) (see ►**Table 1**).

Most viruses will cause local infection in the respiratory tract first with secondary dissemination to other sites in the body, while other viruses typically remain limited to the respiratory tract and induce tissue injury locally.

Pathomechanism of CARV Infection

Various defense mechanisms have evolved in the respiratory tract to prevent and control infection. Advances in the pathomechanisms involved in CARV infection has been made recently.[3] Excessive inflammation associated with severe infection can be controlled by blocking costimulatory signals, without altering immune-mediated virus clearance. Recent studies suggest that the activation of effector T cells in virus-infected lungs is generated by inflammatory cells locally. This modification of the immune response in the infected epithelium may lead to virus clearance and will regulate acute inflammation, and possibly immunological memory. Resolution of respiratory virus infection requires not only the elimination of the

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Table 1 Overview of community-acquired respiratory virus

	RSV	Parainfluenza (PV)	Influenza	Adeno-virus	hMPV	Corona	Rhino	Bocavirus
Season	Winter-Spring	Summer-Fall	Winter	All year	Winter-Spring	Winter	Fall-Spring	Fall-Winter
URTI	Rhinitis, pharyngitis	Croup, laryngitis	Pharyngitis, rhinorrhea	Rhinitis, pharyngi-tis	Rhinitis	Croup, laryngitis	Rhinitis	Otitis
LRTI	Bronchiolitis, CAP	Bronchiolitis, CAP	Tracheo-bronchitis, CAP	CAP (rare)	Tra-cheo-bron-chitis, bronch-iolitis, CAP	Bronchio-litis, CAP		Bronchitis
Frequency in LTx studies ($n = 456$ patients)	19%	23%	12%	3%	8%	9%	26%	$< 1\%$
Rapid antigen testing	+	(+)[a]	+	+	−	−	−	−
Cultures	+	+	+		(+)	(+)	(+)	(+)
ELISA	+		++	++				−
Antigen (IFT)	++	+	++	++	+	(+)		−
PCR	+	+	+	+	+	+	+	+

Abbreviations: CAP, community-acquired pneumonia; ELISA, enzyme-linked immunosorbent assay; hMPV, human metapneumovirus; IFT, immunofluorescence testing; LRTI, lower respiratory tract infection; PCR, polymerase chain reaction; PV, parainfluenza virus; RSV, respiratory syncytial virus; URTI, upper respiratory tract infection.
[a]PV 1, 2, 3.

virus but also the repair and regeneration of normal lung structures and restoration of normal pulmonary function. Cells and molecules regulate processes such as epithelial cell to mesenchymal cell transitions, as well as the transformation of fibroblasts and fibrocytes into myofibroblasts. Dysregulation of these processes in response to lung inflammation is associated with progressive pulmonary injury and lung fibrosis.

In LTx recipients, CARV infection may cause inflammatory processes mediated by both innate and adaptive immune responses that result in injury to airway epithelial cells and subepithelial structures leading to obliteration of small airways. Apart from direct sequelae, CARV may promote immunologically mediated lung injury resulting in the development of acute rejection (AR). A clinical term for chronic lung allograft dysfunction (CLAD) is bronchiolitis obliterans syndrome (BOS). The clinical picture is an irreversible decline in forced expiratory volume in 1 second (FEV_1).[4] Histopathologically obliteration of terminal bronchioli by fibromyxomatous tissue is recognized.[5] BOS is the most important prognosis limiting factor following LTx, and remains the major impediment to long-term graft and patient survival after LTx.[6]

On average, it affects every second recipient after 5 years.[6] The annual incidence of BOS after LTx is ~9%. BOS is a progressive disease and 75% of BOS patients die from respiratory failure with a 5-year survival in affected patients of 26%.[7]

Clinical Picture

In LTx recipients, symptoms of CARV infections may resemble those of other clinical problems like other causes of infection (bacterial or fungal), acute rejection, and drug toxicities. Bacteria (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*) also cause community outbreaks, share similar clinical features, and may present diagnostic difficulties.[8] In contrast to the nonimmunosuppressed host, CARV infection usually leads to more severe illness in the lung transplanted recipient with a higher incidence of respiratory failure. In a recent clinical trial with 77 RSV-infected LTx patients, median decline in FEV_1 compared with the preinfection level was 13%.[9] Seventy-four percent of these patients had symptoms of a lower respiratory tract infection and 10% a significant infiltrate on chest X-ray. In a retrospective single-center study over a 13-year time span, 38% of 138 LTx patients presenting with CARV infection (41% coxsackie and RV, 16% PV, 14% CoV, 10% RSV, 8% hMPV, 6% flu) demonstrated a pulmonary infiltrate and 22% were asymptomatic.[10]

Acute consequences of RSV infection include bronchiolitis, pneumonia, and respiratory failure. Permanent long-term effects following LTx include the development of new or progressive chronic allograft dysfunction that manifest clinically as BOS.[4,5] Rhinoviral infection can be persistent in lung transplant recipients with graft dysfunction.[11]

No temporal association was observed between CARV infection and AR.[12,13]

Epidemiology in Lung Transplantation

Cumulative infection rates of CARV in lung transplant recipients in earlier retrospective single-center studies of 5 to 7 years ranged from 5 to 13%.[14–17] Retrospective studies did not test for viruses newly recognized as important pathogens for BOS, especially hMPV. Therefore, apart from methodological issues, BOS incidence may not be exactly estimated from these studies.

There are several published prospective studies using polymerase chain reaction (PCR) techniques of CARV in LTx involving between 50 and 388 patients during surveillance periods of 6 to 24 months.[12,18–21] Symptoms of respiratory tract infection (RTI) were frequent 50 to 64% in screened patients but incidence of CARV was variable between 7.8 and 34%. The different incidences can be explained by different methodology and inclusion criteria. In the Swiss study, only patients who underwent bronchoscopy were studied, making it difficult to calculate the true incidence of respiratory viral infections and comparing it with uninfected patients.[22] In a Canadian study, only stable patients were included and screened for CARV and matched with uninfected patients, which excluded an estimation of the true incidence of CARV during the observation period.[18] In a U.S. study, LTx recipients were contacted weekly by telephone and screened for symptoms.[19] Symptoms of RTI were, therefore, more frequent. Serology identified most of the CARV in this study and hMPV was not investigated.

PVs were the dominant pathogens in a German surveillance study using PCR testing in upper respiratory samples and antigen testing in sample from the lower respiratory tract followed by RSV (13–22% in other prospective studies).[21] In the German surveillance study, an annual incidence of 25% in CARV-positive recipients was described, which is higher than 6 to 12% in other prospective studies using PCR techniques.[18,19] In summary, prospective studies have described an incidence of 15 to 50 cases per 100 patient-years (►**Table 2**). Infected LTx recipients in early studies presented with respiratory failure. Interestingly, in retrospective studies[2,3,5] the BOS incidence in CARV-positive lung transplant recipients was much more common after 1 year than in the prospective studies (32–42% versus 6–16%).[6,10,11] Several surveillance and retrospective studies confirmed an association of CARV infection (as well other CARV) with the onset of BOS. These studies are heterogeneous and have limitations in design, case selection, and diagnostic procedures. This association was identified mainly for paramyxoviruses, and the association with influenza and AV is less well documented. According to the published literature, the incidence of BOS was 6 to 40% in LTx recipients infected with CARV during the following 12 months.[15,17,18,21,23] Patients may present with onset of CLAD immediately with CARV infection or later after an initial recovery of FEV_1 after the viral infection.

Diagnosis

There is a lack of information on the potential role of viruses that are difficult to grow, such as RV, human CoV, enteroviruses, and hMPV. Some of them have recently been recognized as important pathogens in LTx.[12,23,24] Virus isolation is still the gold standard for the laboratory detection of respiratory viruses. However, virus isolation in cell cultures is slow and not always technically successful. Therefore, this method is no longer used in the transplant setting where rapid workup is crucial. Rapid antigen detection tests or antibodies for immunofluorescence testing (IFT) are not available for all CARV. The detection of viral antigens is reported to be less sensitive and less specific than cell cultures but allows rapid detection. Nucleic acid amplification tests for CARV by PCR are rapid and sensitive. They are commercially available in single or multiplex format. The significance of virus detection by PCRs in asymptomatic patients is unknown[15] and virus detection by PCR may not reflect active infection. Serology plays no role in detecting CARV infection after LTx.

Upper respiratory sampling by naso–oropharyngeal swab (NOS) are useful in combination with PCR techniques avoiding the need for bronchoscopy. Special swabs samples should be used.[21] Mouth rinses are an acceptable alternative. In LTx recipients, bronchoalveolar lavage (BAL) is a widespread diagnostic tool. Given the broad spectrum of other possible diagnosis in a LTx patient with symptoms of upper respiratory tract infection (URTI) or lower respiratory tract infection (LRTI), bronchoscopy with BAL is advised in most circumstances. BAL was most sensitive do detect CARV in surveillance studies.[21] In a recent randomized controlled trial (RCT), 6% of all RSV infections were detected by PCR.[9]

Therapy of CARV Infection

The potential incidence of BOS after untreated CARV infections and the threat of respiratory failure in infected LTx recipients illustrate the need for effective treatment of CARV infections. Unfortunately, respiratory viruses are a hard target for various reasons. Most of the time the virus spends in the host and will be inside the host cell. The virus is protected from the host immune system as well as from available circulating enzymes. There are a limited number of potential drug targets since viruses use the host biochemical mechanisms to multiply. Viruses multiply very quickly, so antiviral drugs will often have little effect by the time symptoms appear. In addition, resistance to commonly used antivirals develops early.

Theoretically, viruses can be targeted by inhibiting the stage of viral attachment, internalization, fusion and uncoating, replication, assembly, and release. Unfortunately, except the neuraminidase inhibitors for influenza, no registered drugs are available for most the treatment of CARV infections in adults. Treatment strategy may be symptomatic in most cases. It usually consists of steroids, oxygen, and antibiotics in case of concomitant bacterial infection.

Ribavirin is known since 1972 and is registered for use in chronic hepatitis C virus infection. Ribavirin, a purine

Table 2 Surveillance studies on CARV infection after lung transplantation

Study	*N* (CARV infected, total, %)	Incidence per 100 patient-years	PCR technique used	Period	CARV types	BOS incidence at 1 y in infected patients
Palmer et al 1998[17]	10/122 = 8	1.6	–	58 mo, retrospective	50% RSV, 20% PV, 30% AV	40%
Khalifah et al 2004[15]	21/259 = 8	9.2	–	48 mo, retrospective	38% RSV, 33% PV, 19% flu, 10% AV	42%
Garbino et al 2004[31]	18/57= 32	16	10+	12 mo, retrospective	22% RSV, 6% PV, 11% flu, 6% AV, 56% RV	n.a.
Kumar et al 2005[16]	37/100 = 37	50	10+	36 mo, prospective	16% RSV, 11% PV, 3% hMPV, 14% flu, 22% CoV, 35% RV	12%
Gerna et al 2006[14]	29/75 = 39	13	5+	36 mo, retrospective	7% RSV, 7% PV, 14% hMPV, 18% flu, 7% CoV, 18% RV	n.a.
Milstone et al 2006[19]	17/50 = 34	68	7+	6 mo, prospective	47% RSV, 6% PV, 56% flu	6%
Weinberg et al 2010[23]	n.a./60	n.a.	10+	12 mo, prospective	12% RSV, 17% PV, 6% hMPV, 12% flu, 3% RV	25%
Gottlieb et al 2009[21]	30/388 = 8	15	12+	6 mo, prospective	21% RSV, 35% PV, 17% hMPV, 3% flu, 14% CoV, 9% RV	25%
Hopkins et al 2008[24]	47/89 = 53	15	8+	42 mo, prospective	29% RSV, 21% PV, 30% hMPV, 16% flu, 3% AV	n.a.
Kumar et al 2010[18]	48/93 = 52	18.5	19+	36 mo prospective	3% RSV, 21% PV, 5% hMPV, 5% flu, 14% CoV, 57% RV	21%
Bridevaux et al 2014[12]	68/112 = 61	52	17+	33 mo, prospective	60% Picornavirus, 14% flu, 5% PV, 3% hMPV, 9% CoV, 6% RSV	n.a.
Magnusson et al 2013[32]	14/39 = 36	36	15+	24 mo, retrospective	10% flu, 14% PV, 32% RV, 5% hMPV, 28% CoV, 8% RSV	8%

Abbreviations: BOS, bronchiolitis obliterans syndrome; CARV, community-acquired respiratory virus; CoV, coronavirus; flu, influenza; hMPV, human metapneumovirus; PCR, polymerase chain reaction; PV, parainfluenza virus; RSV, respiratory syncytial virus; RV, rhinovirus.

nucleoside analogue with efficacy against many RNA viruses, including RSV, hMPV, and PV, represents a viable treatment option for PV infection. Ribavirin has been shown to have in vitro activity against RSV and the aerosolized form has been approved for the treatment of lower respiratory tract disease due to RSV in certain at-risk populations. Data for intravenous use of ribavirin remain limited in LTx recipients.[25] Drawbacks with inhaled ribavirin include difficulties in administration, requiring continuous inhalation, along with associated risks of bronchoconstriction and respiratory distress, which may necessitate discontinuation. In addition, aerosolized ribavirin is considered to be potentially hazardous and teratogenic to the environment including health care workers as well as being excessively expensive. Considering these limitations, widespread acceptance of the nebulized administration is missing. Several centers use oral ribavirin as an off-label alternative treatment in paramyxovirus infections in LTx.[26] A retrospective study demonstrates no significant differences in 6-month outcomes between oral and inhaled ribavirin therapy for RSV infection after LTx.[27]

In a recent multicenter trial involving 77 RSV-infected patients from 33 sites in Australia, Austria, Germany, France, Canada, and the United States, inhaled ribavirin was used in 24% infected individuals, oral ribavirin in 16%, intravenous ribavirin in 11%, intravenous immunoglobulin (IVIG) in 5%, pulsed steroids in 38%, and palivizumab in 6%.[9]

The optimal duration of ribavirin therapy is unknown, although treatment orally for 14 days led to virus elimination in 89% of patients in a retrospective study.[28] Of particular note, ribavirin was contraindicated in 42% of PV-infected recipients in this study and was terminated early in another quarter of cases due to adverse effects. Twice-weekly monitoring of blood cell counts (risk of hemolytic anemia) and renal function is mandatory while under ribavirin therapy. Compared with other patient populations treated with

ribavirin, more frequent discontinuation due to toxicity was necessary in the LTx population. The most likely explanation for this remains combined toxicity of ribavirin and that inherent to the maintenance medication required after LTx.

Distinction must be made between the short- and long-term effects of treatment with ribavirin. Prior studies have focused on short-term effects of ribavirin treatment, such as survival of the acute phase or shorter hospital length of stay, and found no beneficial effect. Retrospective single-center studies suggest that LTx patients treated with ribavirin have a better pulmonary function 6 months after paramyxovirus infection and have found that oral ribavirin reduces the number of complicated courses of paramyxovirus infection and reduces the long-term risk of BOS %. Recovery of pulmonary function postinfection was significantly better in ribavirin-treated patients ($n = 38$) than in patients treated with supportive care ($n = 29$) in a retrospective study. Patients treated with oral ribavirin had a lower incidence of BOS (5% of the ribavirin group versus 24% of the non-ribavirin group [$p = 0.02$]) within 6 months.[28] The latter subgroup was treated with supportive care in this study and had contraindications for ribavirin (e.g., advanced kidney disease, anemia).

All ribavirin studies in LTx lack a randomized placebo-controlled design, which makes them unsuitable to make evidence-based recommendations. There is clearly the need for a RCT to determine the efficacy of oral ribavirin. Since unnecessary treatment with drugs should always be avoided and ribavirin has some unfavorable side effects, a firm conclusion is needed about the clinical benefits of this treatment. Oral ribavirin seems to be a promising and inexpensive therapy which may have a significant impact on long-term morbidity and mortality of lung transplant recipients.

Anecdotal cases have reported the off-label use of pavilizumab and IVIG in RSV-infected LTx recipients. Several agents have been studied against influenza including DAS181 (Fludase) and nitazoxanide, but no data are published for LTx patients.

RNA interference is a natural biological process whereby small interfering RNAs (siRNAs) can direct sequence-specific degradation of mRNA, leading to reduced expression of the corresponding protein. ALN-RSV01 is a siRNA targeting the RSV nucleocapsid messenger RNA, preventing the formation of the nucleocapsid protein and thereby reducing viral replication. Intranasal ALN-RSV01 administration significantly inhibited the rate of RSV infection in a phase 2 experimental infection study in healthy adults.[29] In a pivotal study in 24 RSV-infected LTX patients, nebulized ALN-RSV01 treatment proved to be safe and well-tolerated and incidence of new or progressive BOS was decreased at day 90 in patients treated with ALN-RSV01 compared with placebo.[29] The efficacy of ALN-RSV01 administration in addition to standard of care on preventing new or progressive BOS in RSV-infected LTx patients was evaluated in this large randomized, double-blind, placebo-controlled trial. In this phase 2b, trial subjects were randomized to receive aerosolized ALN-RSV01 or placebo daily for 5 days.[9] ALN-RSV01 was found to be safe and well tolerated. At day 180 in ALN-RSV01-treated patients ($n = 44$) compared with placebo ($n = 33$), there was a trend toward a decrease in new or progressive BOS (13.6% vs. 30.3%, $p = 0.058$), which was significant in the per-protocol cohort ($p = 0.025$). Treatment effect was enhanced when ALN-RSV01 was started < 5 days from symptom onset, and the effect was independent from ribavirin treatment.

Presatovir (GS-5806) is an oral RSV fusion inhibitor with potent and selective anti-RSV activity in vitro. A phase 2a, randomized, double-blind, placebo-controlled study was conducted to evaluate the safety, tolerability, and efficacy of presatovir in healthy adult volunteers infected with an RSV challenge virus.[30] Treatment with presatovir resulted in lower mean area under the curve (AUC) viral load from initial dose through end of quarantine. Viral load was assessed twice daily using nasal washes and in total symptom score during the entire quarantine period. Results from a phase 2b, RCT evaluating the effect of GS-5806 in LTx recipients with RSV infection (NCT02534350) are expected soon.

There are several unmet needs in the development of effective therapies for CARV. One is a wider treatment window. Most agents are reported to be less effective if the patient presents more than 48 hours of symptom onset. Therapies should be cost-effective and reduce the threat of resistance by continuous antigenic drifting and antigenic shifting of viruses.

Alternative formulations (e.g., intravenous drugs) for hospitalized patients should be available as well as drugs for severely ill, hospitalized patients, and for pediatric patients.

Prevention of CARV infection is of utmost importance in LTx. Annual influenza vaccination is strongly recommended for all lung transplant recipients including all their household members. Wearing face masks, avoiding contact with infected persons, and skin disinfection are usually recommended as preventive measures in LTx recipients, although they were not systematically evaluated in this high-risk cohort.

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