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Low incidence of severe respiratory syncytial virus infections in lung transplant recipients despite the absence of specific therapy

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BACKGROUND: Respiratory syncytial virus (RSV) infections in lung transplant recipients (LTRs) have been associated with significant morbidity and mortality. Immunoglobulins, ribavirin, and palivizumab are suggested treatments for both pre-emptive and therapeutic purposes. However, in the absence of randomized, placebo-controlled trials, efficacy is controversial and there is toxicity as well as cost concerns.
METHODS: We retrospectively reviewed cases of lower respiratory tract RSV infections in adult LTRs. Diagnosis was based on clinical history, combined with a positive polymerase chain reaction (PCR) and/or viral cultures of bronchoalveolar lavage (BAL) specimens.
RESULTS: Ten symptomatic patients were identified (7 men and 3 women, age range 28 to 64 years). All were hospitalized for community-acquired respiratory tract infections. Two patients had a concomitant acute Grade A3 graft rejection, and 1 patient had a concomitant bacterial pneumonia. Eight patients did not receive a specific anti-RSV treatment because of clinical stability and/or improvement at the time of RSV diagnosis. Only 2 patients (1 with Grade A3 allograft rejection and 1 requiring mechanical ventilation) received ribavirin and palivizumab. All patients recovered without complications and with no persistent RSV infection. However, bronchiolitis obliterans (BOS) staging worsened in 6 patients during the mean follow-up of 45 months.
CONCLUSIONS: Our data suggest that mild RSV infections in LTRs might evolve favorably in the absence of specific anti-viral therapy. However, this observation needs confirmation in a large clinical trial specifically investigating the development of BOS in untreated vs treated patients.
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Respiratory syncytial virus (RSV) has been described as a pathogen responsible for severe respiratory tract infections in solid-organ transplant recipients.[1] Lung transplant recipients (LTRs) are the most frequently infected transplant patients.[1–3] RSV infections in LTRs have been associated with mortality rates of 10% to 20%.[1,3–7] Immunoglobulins, ribavirin, and palivizumab have been suggested both for therapeutic and pre-emptive approaches to RSV infections in LTRs. However,

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Table 1 Clinical Characteristics of 10 Cases of RSV Infection in Lung Transplant Recipients

	Case 1	Case 2	Case 3	Case 4	Case 5
Gender	Female	Male	Female	Male	Male
Indication for transplantation	α_1-anti-trypsin deficiency	Cystic fibrosis	Lymphangioleiomyomatosis	COPD	COPD
Type of transplantation	Double	Double	Double	Heart–lung	Double
Age at diagnosis (years)	54	28	48	62	58
Time after lung transplantation (months)	36	6	6	54	48
Clinical symptoms at hospitalization	Rhinitis, cough	Rhinitis, cough, fever	Rhinitis, cough	Rhinitis, cough, dyspnea, fever, rigors, myalgia, wheezing	Rhinitis, progressive dyspnea
Period/month	February	January	March	December	March
RSV detection	PCR in BAL	PCR in BAL	PCR and viral culture in BAL	Viral culture in BAL	Viral culture in BAL
Specific anti-RSV treatment	No	No	Ribavirin, palivizumab	No	No
Mechanical ventilation	No	No	No	No	No
Concomitant pathology	10^5 CFU/ml of *S aureus* and *S marcescens*	No	Acute Grade A3 allograft rejection	No	Acute Grade A1 allograft rejection
Chest radiology	Normal	Normal	Normal	Ground-glass opacities	Normal
Immediate outcome	Recovery	Recovery	Recovery	Recovery	Recovery
Long-term outcome	Alive at 40 months	Died of bacterial infection after 35 months	Died of chronic rejection after 22 months	Alive at 54 months	Died of chronic rejection after 39 months

AML, acute myeloid leukemia; BAL, bronchoalveolar lavage; CFU, colony forming units; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; MRSA, methicillin-resistant *Staphylococcus aureus*; PCR, polymerase chain reaction; RSV, respiratory syncytial virus.

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no placebo-controlled trial has clearly established their indication and efficacy in this population. Moreover, their widespread use is limited by concerns of toxicity (mainly nephrotoxicity) and elevated costs. Recommendations are few, often controversial, and have been established primarily for bone marrow transplant (BMT) recipients.[4,8–17] Little has been published on the treatment of RSV infection in solid-organ transplant recipients.[5,6,18] Official recommendations specifically for the management of RSV in transplant patients are available only in a few countries, such as the United States,[4] Sweden,[19] and Switzerland.[20] In Switzerland, pre-emptive therapy in cases of low-grade immunosuppression, prophylaxis in severe immunosuppression, and combined treatment with immunoglobulin (Ig), ribavirin, and palivizumab in cases of proven infection have been suggested for both BMT recipients and LTRs.[20]

To get a better overview on the clinical evolution of RSV infections in LTRs we retrospectively searched our virology reports and identified 10 adult LTRs with proven lower respiratory tract RSV infection.[11] Herein we describe their clinical evolution according to treatment.

Methods

Setting

The study was conducted at the Hôpitaux Universitaires de Genève (HUG) and Centre Hospitalier Universitaire Vaudois (CHUV), Switzerland. Both hospitals belong to the "Centre Universitaire Romand de Transplantation," which performed 194 LTRs since 1993. Both hospitals use similar immunosuppressive regimens with initial anti–interleukin-2R induction, and long-term triple associations, including either cyclosporine (trough target levels between 150 and 200 μg/liter), tacrolimus (trough target levels between 10 and 15 μg/liter), or everolimus (trough target levels between 3 and 15 μg/liter), with mycophenolate mofetil (2×1 g/day) and low-dose prednisone (5 to 25 mg/day).

Case findings and virologic diagnosis

Since 2003, all LTRs have been followed in a prospective cohort study ($n = 77$). We identified all cases of lower respiratory tract infection due to RSV in LTRs from 2003 to

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Case 6	Case 7	Case 8	Case 9	Case 10
Female	Male	Male	Male	Male
Idiopathic pulmonary fibrosis	α_1-anti-trypsin deficiency	Pulmonary hypertension	COPD	Bronchioalveolar carcinoma
Single	Double	Double	Single	Double
62	64	58	63	47
144	48	12	72	0.5
Rhinitis, cough, sputum, orthopnea	Dyspnea, cough	Cough	Rhinitis, cough, pharyngitis	Cough
March	December	April	April	April
Viral culture in BAL	Viral culture in BAL	PCR in BAL	PCR in BAL	PCR in BAL
Ribavirin, palivizumab	No	No	No	No
Yes (17 days)	No	No	No	No
Asymptomatic CMV replication	Acute Grade A3 allograft rejection	Lymphocytic alveolitis	No	Symptomatic CMV disease
Interstitial infiltrate	Pre-existing right pleural effusion	Interstitial infiltrate	Normal	Normal
Recovery	Recovery	Recovery	Recovery	Recovery
Died of AML and MRSA pneumonia after 8 months	Alive at 54 months	Alive at 74 months	Alive at 75 months	Alive at 50 months

March 2006 in patients hospitalized for respiratory tract infection who underwent bronchoalveolar lavage (BAL, $n = 343$) assessment. All BAL fluid specimens[21,22] were processed in a standardized manner, according to local[21,22] and international guidelines.[15,23,24] Specimens for histology were sampled and standard microbiologic techniques were employed to test for the presence of aerobic and anaerobic bacteria, mycobacteria, fungi, and *Pneumocystis jiroveci* in respiratory secretions. Before 2006, all viral pathogens were detected by culture. Since 2006, an in-house[22] real-time reverse-transcription polymerase chain reaction (PCR)[23] in BAL fluid specimens was used to detect the presence of influenza A and B, RSV A and B, parainfluenza virus 1 and 3, human rhinovirus, enterovirus, coronaviruses OC43, NL63, and 229E and HKU1, and human metapneumovirus,[22] whereas cytomegalovirus, adenovirus, herpes simplex virus, *Legionella* sp, *Mycoplasma* sp, and *Chlamydia* sp continued to be detected by culture and/or regular specific PCRs. Patient charts of identified cases were retrospectively reviewed for symptoms, treatments, and clinical evolution. No serologic investigations were performed.

Table 2 FEV_1 Before and After RSV Infection in Lung Transplant Recipients

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Best FEV_1 before RSV infection	3.72	4.39	2.29	3.07	5.11	2.72	2.52	3.77	2.43	2.49
FEV_1 1 month before RSV infection	3.21	4.19	2.29	2.62	4.0	1.09	1.68	3.66	2.17	2.49
FEV_1 at RSV infection	3.31	3.79	2.16	1.36	4.0	1.04	0.93	3.59	2.28	NA
FEV_1 change (%) at RSV infection	+3%	−10%	−6%	−42%	0%	−5%	−41%	−2%	+5%	NA
FEV_1 1 month after RSV infection	3.46	4.24	2.41	2.71	3.8	1.0	1.38	3.26	NA	2.9
Best FEV_1 after RSV infection	3.68	4.24	3.33	2.76	3.8	1.0	1.75	3.26	2.09	3.39
BOS stage before RSV infection	0	0	0	0p	1	2	2	0	0	0
BOS stage after RSV infection (last available)	0p	1	3	0p	3	2	2	1	1	0
Number of acute rejection episodes after RSV infection	0	3	3	0	6	0	4	1	1	0

Table 3 Selected Publications With References, Reporting Lower Respiratory Tract Infections Due to RSV in Lung Transplant Recipients (All Patients Symptomatic)

Study (year)	*n*	Study design	Radiologic abnormalities	RSV detection
Data from Allen et al[43] (1986)	1	Retrospective	No	BAL culture
Data from Doud et al[44] (1992)	1	Retrospective	Yes	BAL culture
Data from Murris-Espin et al[45] (1993)	2	Retrospective	2/2	FA
Data from Wendt et al[46] (1995)	9	Retrospective	At least 5/9	6 BAL cultures, 2 throat cultures, 1 sputum culture, 3 EIA
Data from Krinzman et al[18] (1998)	4	Retrospective	2/4	BAL culture antigen, EIA
Data from Palmer et al[6] (1998)	5	Retrospective	NA, at least 1 chest radiography normal	BAL culture FA
Data from McCurdy et al[5] (2003)	14	Retrospective	At least 12/14	11 BAL culture, 6 EIA, 1 PCR
Data from Khalifah et al[28] (2004)	4	Retrospective	4/4	FA, BAL culture
Data from Glanville et al[8] (2005)	18	Prospective	NA	18 FA, 14 cultures
Data from Milstone et al[1] (2006)	8	Prospective	Maximal 6/8	5 PCR, 1 EIA, 1 culture, 7 serology
Data from Pelaez et al[37] (2009)	10	Prospective	NA	10 cultures
Present article	10	Retrospective	3/10	3 PCR, 2 BAL cultures
Summary	86	9 retrospective, 2 prospective	35/54 (65%)	Mostly BAL culture

BAL, bronchoalveolar lavage; CMV, cytomegalovirus; EBV, Epstein-Barr virus; EIA, enzyme immunoassay test; FA, direct fluorescent antibody test; NA, not available; PCR, polymerase chain reaction; RSV, respiratory syncytial virus.

[a]Number of RSV episodes.

[b]Besides reduction of immunosuppression and supportive care.

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Results

The 77 LTRs in our cohort witnessed a total of 68 viral respiratory tract infections between November 2003 and March 2006, including 10 episodes with respiratory secretions positive for RSV in 10 patients (7 men and 3 women, age range 28 to 64 years). Thus, RSV accounted for 14.7% of these viral respiratory infections. Diagnosis of RSV was established by viral culture in 4 patients, by PCR in 5 cases, and by both techniques in 1 patient. No other concomitant viral pathogens were found. In addition, in 1 LTR, RSV was detected by PCR during an annual control in the absence of any respiratory symptoms. This patient was excluded from analysis. None of our patients had a secondary respiratory specimen positive for RSV in later time periods.

The clinical characteristics of the 10 cases are presented in detail in Table 1. All patients were symptomatic for community-acquired respiratory tract infection at the time of their positive respiratory tract specimen. All episodes occurred during the winter and early spring, without any epidemiologic inter-case link. Seven episodes occurred at least 1 year after transplantation, 2 occurred at 6 months, and 1 occurred at 15 days (range 15 to 144 days post-transplantation). Three patients had a concomitant biopsy-proven allograft rejection[25]: Patients 3 and 7 had acute Grade A3 rejection and were treated with anti-thymocyte globulins and intravenous methylprednisolone, respectively, and Patient 5 had acute Grade A1 rejection that did not require specific anti-rejection therapy. Two patients had concomitant infection requiring specific therapy: Patient 1 had a bacterial pneumonia, and Patient 10 had a symptomatic cytomegalovirus (CMV) disease. Patient 6 was treated for an asymptomatic concomitant low-grade re-activation of CMV replication. A new infiltrate on the chest X-ray was noted for 3 patients (Patients 4, 6, and 8). Individual evolution data for forced expiratory volume in 1 second (FEV_1) are shown in Table 2. Compared with 1 month prior to RSV infection, the FEV_1 changes ranged from +5% to −42%, with only 2 patients having a >10% FEV_1 reduction (Patients 4 and 7). Four patients never recovered their pre–RSV infection FEV_1 value (Patient 5: −5%; Patient 6: −8.3%; Patient 8: −10.9%; and Patient 9: −3.7%).

All patients recovered from their RSV infection. Eight of the 10 patients already had clinical improvement at the time of RSV diagnosis. In 2 of these patients the immunosuppression had been temporarily reduced; however, no patient was given specific RSV treatment. Strikingly, this group included 7 patients who concomitantly received methylprednisolone for a rejection episode and had an FEV_1 reduction of 41%; Patient 4 also had a transient FEV_1 reduction of 42%. Two patients were treated with ribavirin for 7 days (orally with 1,600 mg/day or intravenously with 10 mg/kg 3 times daily) concomitant with intravenous palivizumab (a single dose of 15 mg/kg) (Table 1), including Patient 3, who required anti-thymocyte globulins for non-responding con-

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Concomitant pathology	RSV treatment[b]	Mechanical ventilation	Outcome
No	Steroids	No	Recovery
No	Aerosolized ribavirin	No	Recovery
No	Aerosolized ribavirin 2/2	No	Recovery 2/2
1 EBV-related lymphproliferative disorder, 1 pneumonia due to *Pseudomonas aeruginosa*, 2 CMV in BAL	Aerosolized ribavirin 8/9, 1 untreated	At least 1/9	Recovery 8/9, death 1/9
1 bacterial sepsis?	Aerosolized ribavirin 3/4, 1 untreated	NA	Recovery 3/4, death 1/4
1 *Pseudomonas aeruginosa* and *Aspergillus* pneumonia	Aerosolized ribavirin 4/5, 1 untreated	2/5	Recovery 4/5, death 1/5
1 *Haemophilus influenzae* pneumonia, 1 *Aspergillus*?, 1 acute rejection, 2 parainfluenza	Aerosolized ribavirin 14/14	At least 2/14	Recovery 12/14, death 2/14
NA	NA	NA	Death 4/4
No	Intravenous ribavirin with steroids 18/18	No	Recovery 18/18
No	NA	NA	Recovery at least 7/8
No	10 oral ribavirin	NA	Recovery 10/10
1 bacterial pneumonia, 1 asymptomatic CMV replication 1 CMV disease, 3 acute rejections	2 ribavirin and palivizumab, 8 untreated	1/10	Recovery 10/10
	49 aerosolized ribavirin, 2 intravenous ribavirin, 1 peroral ribavirin, 2 palivizumab, 13 untreated	6/62 (10%)	Recovery 76/86 (88%), death 10/80 (13%)

comitant allograft rejection, and Patient 6, who had clinically severe disease requiring mechanical ventilation (pre-RSV $FEV_1 = 1.09$). Prior to RSV infection, 6 patients had bronchiolitis obliterans syndrome (BOS) Stage 0, whereas 2 patients (Patients 6 and 7) had a BOS Stage 2 (Table 2). Post-RSV worsening of the BOS staging occurred in 6 patients (Patients 1, 2, 3, 5, 8 and 9), compared with the overall incidence of BOS (independently of RSV infection) in our LTR cohort of 33.5%. Post–RSV infection acute rejection episodes occurred in 6 patients (Table 2). Four patients had ≥3 rejection episodes, including Patients 2, 3, and 5, who had a worsened BOS stage.

Discussion

The detection of RSV by PCR in respiratory secretions is highly sensitive and specific,[24] and is currently considered the best available test for the diagnosis of respiratory tract infections in adult lung transplant recipients.[15,20,21,23] It has been implemented in many lung transplant centers and may increase the number of patients diagnosed with RSV infections. Therefore, guidelines are needed to help clinicians decide whether all LTRs with documented RSV require specific treatment. Herein we have reported 10 cases of proven community-acquired lower respiratory tract RSV infections in adult lung transplant recipients. Surprisingly, as a result of delayed diagnosis, 8 of them had already improved clinically before the diagnosis of RSV infection was made. These patients therefore recovered without receiving specific anti-RSV therapy. In only 2 of these cases was the immunosuppression temporarily reduced. In 1 patient a new ground-glass opacity on computed tomography scan[18,26,27] (for which no other cause than RSV was found) cleared spontaneously. As previously described in BMT recipients,[8,10] RSV can also be recovered from the lung of asymptomatic lung transplant recipients.[28] Indeed, an eleventh, asymptomatic patient not included in this case description had a positive RSV PCR in an annual control BAL assessment. He remained clinically stable without any treatment. This case illustrates a possible detection bias in our study. Clearly, patients with asymptomatic RSV infections would not seek medical advice, so the true incidence of

respiratory tract infections due to RSV in LTRs could be higher.

Our observation of a high number of RSV-infected LTRs spontaneously evolving favorably contrasts with previous reports supporting early specific anti-RSV therapy (especially aerosolized ribavirin),[5,6,18] and raises critical questions regarding the more aggressive therapeutic approaches recommended.[20] According to our review of the 86 previously published cases of RSV infections among adult LTRs, our patients were not less immunosuppressed than those described elsewhere (Table 3). Previous studies suggested that severe RSV infections may occur early after transplantation when the immune response is most compromised.[6] However, a more recent study reported only 24% of infections during the first 3 months post-transplantation.[5] In our cohort, only 1 patient developed an RSV infection during the first 3 months post-transplantation. He evolved favorably without any specific therapy. Clearly, further studies are needed to determine whether time after transplantation impacts on the severity of disease and necessity of treatment.

Both RSV infections and acute rejection episodes have been suggested to be risk factors for the development of BOS.[7,8,29,30] It has also been suggested that RSV infections may trigger acute rejection.[3,18,29] Strikingly, we observed post-RSV infection worsening of BOS stage in 60% of patients, during a mean follow-up time of 45 months. Interestingly, half of these patients also experienced ≥3 post-RSV acute rejection episodes. Because of the small number of cases, and confounding rejection episodes, it remains difficult to ascertain the potential responsibility of RSV infections in the development and/or worsening of BOS in our cohort. However, this warrants further investigation in large LTR cohorts. A possible causality between mild RSV infections that *per se* evolve favorably without specific treatment and BOS would potentially have major diagnostic and therapeutic implications. Indeed, such an association would support screening for RSV in LTRs, even those with mild symptoms. Moreover, one would have to establish in controlled trials whether specific anti-RSV treatment could prevent BOS worsening in such conditions.

One should not forget both the increased costs and potential adverse effects associated with specific RSV therapy. Immunoglobulins,[31,32] ribavirin,[33] and pavilizumab[34,35] may all have significant adverse effects. In some studies the incidence of serious adverse effects of ribavirin was high, with hemolytic anemia occurring in 61% of treated patients.[36] In our study, none of the 2 patients treated with ribavirin developed serious adverse effects. Likewise, Pelaez et al reported only 1 episode of mild reversible anemia among LTRs treated with oral ribavirin for RSV.[37] They further suggested that oral ribavirin might be as efficient—but 20-fold less expensive—than nebulized ribavirin. Cost-effectiveness analyses for pavilizumab for the treatment of RSV infections in adults are missing. Such studies are presently available only for prophylaxis in infants,[38,39] who require much smaller doses than adults.[40]

In conclusion, our observations support that LTRs without severe disease due to RSV, and without particularly enhanced immunosuppression (eg, anti-thymocyte globulins), do not necessarily require specific anti-viral treatment. This contrasts with previous reports and expert opinions,[41–46] which favor early specific anti-RSV treatment in LTRs. However, most of these earlier studies were retrospective, included small numbers of patients, assessed several different respiratory viruses, and contained incomplete clinical information. Finally, many recommendations were derived from BMT recipients,[4,8–17] who represent a clinically distinct patient population. We therefore suggest that LTRs positive for RSV at least 3 months after transplantation, with only minor clinical symptoms, may be observed carefully with a transient reduction of immunosuppression, and that a specific anti-RSV treatment be initiated only in cases of clinical deterioration. However, a randomized clinical trial is warranted to determine whether this less aggressive, step-by-step approach is safe, and does not expose LTRs to an increased risk of BOS development.

Disclosure Statement

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