



HAL
open science

Incidence, management and outcome of respiratory syncytial virus infection in adult lung transplant recipients: a 9-year retrospective multicentre study

Hugo Testaert, Margaux Bouet, Florent Valour, Anne Gigandon, Marie-Edith Lafon, François Philit, Agathe Sénéchal, Jean-Sébastien Casalegno, Elodie Blanchard, Jérôme Le Pavec, et al.

► To cite this version:

Hugo Testaert, Margaux Bouet, Florent Valour, Anne Gigandon, Marie-Edith Lafon, et al.. Incidence, management and outcome of respiratory syncytial virus infection in adult lung transplant recipients: a 9-year retrospective multicentre study. *Clinical Microbiology and Infection*, 2021, 27 (6), pp.897-903. 10.1016/j.cmi.2020.07.050 . hal-04532474

HAL Id: hal-04532474

<https://hal.science/hal-04532474v1>

Submitted on 22 Jul 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

1 **Incidence, management and outcome of respiratory syncytial virus infection in adult**
2 **lung transplant recipients: a nine-year retrospective multicenter study**

3
4 **Authors:**

5 Hugo Testaert^{1,2}, Margaux Bouet³, Florent Valour^{1,4}, Anne Gigandon⁵, Marie-Edith Lafon⁶,
6 François Philit⁷, Agathe Sénéchal⁷, Jean-Sébastien Casalegno^{1,8}, Elodie Blanchard³, Jérôme
7 Le Pavec^{9,10,11}, Florence Ader^{1,4,#}

8
9 **Affiliations:**

10 ¹Centre International de Recherche en Infectiologie (CIRI), Inserm 1111, Université Claude
11 Bernard Lyon 1, CNRS, UMR5308, Ecole Normale Supérieure de Lyon, Univ Lyon, F-
12 69007, Lyon, France.

13 ²Service de Pneumologie, Centre Hospitalier Régional et Universitaire de Caen, F-14033,
14 Caen, France.

15 ³Service des Maladies respiratoires, Hôpital Haut-Levêque, Centre Hospitalier Universitaire
16 de Bordeaux, F-33604 Pessac, France.

17 ⁴Département des Maladies infectieuses et tropicales, Hospices Civils de Lyon, F-69004,
18 Lyon, France.

19 ⁵Laboratoire de Microbiologie, Hôpital Marie Lannelongue, F-92350, Le Plessis-Robinson,
20 France.

21 ⁶Laboratoire de Virologie, Centre Hospitalier Universitaire de Bordeaux, F-33000 Bordeaux,
22 France.

23 ⁷Département de Pneumologie et de Transplantation pulmonaire, Hospices Civils de Lyon, F-
24 69500, Bron, France.

25 ⁸Institut des Agents Infectieux, Hospices Civils de Lyon, F-69004, Lyon, France.

26 ⁹Service de Chirurgie Thoracique, Vasculaire et Transplantation Cardio-pulmonaire, Hôpital
27 Marie Lannelongue, Le Plessis-Robinson, France.

28 ¹⁰Université Paris-Sud, Faculté de Médecine, Université Paris-Saclay, Le Kremlin Bicêtre,
29 France.

30 ¹¹UMR_S 999, Université Paris-Sud, INSERM, Hôpital Marie Lannelongue, Le Plessis-
31 Robinson, France.

32

33 **#Corresponding author:** Florence Ader, M.D., Ph.D. Département des Maladies infectieuses
34 et tropicales, Hôpital de la Croix-Rousse, Hospices Civils de Lyon, Lyon, France. ☎: +33
35 (0)472 071 560; 📠: +33 (0)472 072 441; 📧: florence.ader@chu-lyon.fr

36

37 **Keywords:** respiratory syncytial virus; lung transplantation; ribavirin; azithromycin; graft
38 rejection; bronchiolitis obliterans syndrome; chronic lung allograft dysfunction.

39

40 **Text:** 2498

41

42 **Short title:** Respiratory syncytial virus infection in lung transplantation

43 **ABSTRACT**

44 **Objectives.** To analyze functional outcome parameters according to antimicrobial treatments
45 after respiratory syncytial virus (RSV)-confirmed infection in adult lung transplant recipients.

46 **Methods.** A 9-year retrospective multicenter cohort study (2011-2019) included adult lung
47 transplant recipients with RSV-confirmed infection. The first endpoint determined new
48 allograft dysfunction (acute graft rejection, chronic lung allograft dysfunction [CLAD]) 3
49 months after infection. Then, baseline and 3-months post-infection forced expiratory volume
50 in 1-second (FEV1) values were compared according to antimicrobial treatments. Univariate
51 logistic regression analysis was used.

52 **Results.** RSV infection was confirmed in 77/424 lung transplant recipients (estimated
53 incidence of 0.025 per patient/year, 95% [confidence interval] CI [0.018;0.036]). At 3
54 months, 22 (28.8%) recipients developed allograft dysfunction: 10 (13%) possible CLAD, 6
55 (7.9%) acute rejection and 6 (7.9%) CLAD. Recipients with the lowest pre-infection FEV1
56 had a greater risk of developing pneumonia (1.5 [IQR, 1.1-1.9] *versus* 2.2 [1.5-2.4] L/s;
57 $P=0.003$) and a higher odds of receiving antibiotics (1.6 [IQR, 1.3-2.3] *vs* 2.3 [1.9-2.5] L/s;
58 $P=0.017$; Odd ratio [OR] 0.52 95%CI [0.27;0.99]). In comparison with
59 tracheobronchitis/bronchiolitis, VRS-induced pneumonia led more frequently to
60 hospitalization (22 [91.7%] *vs* 29 [58.0%]; $P=0.003$) and ICU admission (8 [33.3%] *vs* 0
61 [0%]; $P<10^{-3}$). For ribavirin-treated recipients (n=19, 24.7%) and azithromycin prophylaxis
62 (n=39, 50.6%), 3-month FEV1 values were not different from untreated recipients. The
63 overall mortality was 2.5% at 1 month, 5.3% at 6 months, unrelated to RSV.

64 **Conclusions.** At 3 months after RSV-confirmed infection, 22 (28.8%) recipients had new
65 allograft dysfunction. Ribavirin treatment and azithromycin prophylaxis did not prevent
66 FEV1 decline.

67

68 **INTRODUCTION**

69 Lung transplantation is the only effective treatment for patients with end-stage lung disease
70 associated with a rather poor median recipient survival of 5.8 years [1,2]. Post-transplant lung
71 allograft failure is the major cause of fatal outcome [3]. The range of pathological processes
72 in the allograft that lead to a durable deterioration of lung function beyond three months post-
73 transplant is now termed chronic lung allograft dysfunction (CLAD). This includes a
74 spectrum of manifestations ranging from bronchiolitis obliterans syndrome (BOS) to
75 restrictive allograft syndrome (RAS) defined by a decline in measurable forced expiratory
76 volume in 1-second (FEV1) from the reference baseline value [4]. Annual incidence of BOS
77 is estimated to be 9% and affects more than 50% of lung transplant recipients who survive
78 beyond 5 years [5]. Approximately 75% of recipients who develop BOS die from respiratory
79 failure within five years after diagnosis [5].

80 Community-acquired respiratory virus infections are associated with the development of
81 CLAD [6-12]. In a recent retrospective cohort of 250 lung transplant recipients, community-
82 acquired respiratory virus infections were independently associated with CLAD (adjusted
83 hazard ratio, HR [95% CI] 1.9 [1.1–3.5], $P=0.03$) [6]. Another observational cohort study
84 that prospectively followed 563 recipients with 245 CARV infection episodes found that viral
85 pneumonia independently increased the risk of CLAD (HR 3.94 95%CI [1.97, 7.90], $P< 0.01$)
86 [7].

87 Among the genus *Pneumovirus*, respiratory syncytial virus (RSV) is responsible for
88 bronchiolitis in infants but is known to be relatively infrequent after lung transplantation
89 [13,14]. There are discrepancies regarding the outcome of lung transplant graft after RSV
90 infection. Studies have reported insignificant negative impact on FEV1 after RSV-confirmed
91 infection in comparison with baseline FEV1 [15-17]. Nonetheless, severe complications are
92 described such as enhancement of allograft failure and the development of BOS [18,19]. A

93 study has reported 13 BOS onset or progression, among which five (38%) recipients had RSV
94 infection within 6 months prior to BOS [19]. Case-fatality rate due to RSV infection in the
95 lung transplant setting has been reported to range from 10 to 20% [18,19]. Ribavirin therapy
96 for RSV infection is controversial and its toxicity is a concern. Recent guidelines have
97 recommended oral or aerosolized ribavirin with adjunctive corticosteroids and intravenous
98 immunoglobulins in RSV-infected lung transplant recipients (weak to moderate evidence)
99 [20].

100 To gain further insights into RSV infection in the lung transplant setting, the outcome of
101 recipients who developed RSV-confirmed infection was investigated with regards to the
102 development of CLAD according to antimicrobial strategies.

103 **PATIENTS AND METHODS**

104 *Study design and patient population.* A retrospective, multicenter cohort study was
105 conducted among adult (≥ 18 year-old) lung transplant recipients transplanted for end-stage
106 lung disease at three French tertiary-care university hospitals (Paris, Hôpital Marie
107 Lannelongue; Lyon, Centre Hospitalier Lyon-Est; Bordeaux, Hôpital Haut-Levêque) between
108 January 2011 and July 2019. Case recipients eligible for inclusion were those who had RSV
109 positive polymerase chain reaction (PCR) or immunofluorescence assay results from a least
110 one respiratory tract sample [21]. For further details on microbiological diagnosis assessment,
111 refer to supplemental digital content. Sampling for detection of respiratory viral infections
112 was only performed in symptomatic recipients, as no standardized routine screening was
113 active during the study period. When administrated, ribavirin was delivered either by aerosol
114 or oral route. Pre-existing azithromycin prophylaxis was systematically investigated in the
115 form of 250 mg capsule formulation taken three times a week started at least a month before
116 RSV-confirmed infection.

117 Upper and lower respiratory tract infections were defined according to the International
118 Society for Heart & Lung Transplantation (ISHLT) criteria [21]. RSV-confirmed infections
119 were classified as non- or poorly symptomatic, tracheobronchitis/bronchiolitis, or pneumonia.
120 The following patient characteristics were collected: demographics; underlying pulmonary
121 diseases; comorbidities; pulmonary function testing; respiratory bacterial co-infection(s);
122 immunologic status; clinical and radiologic features; immunosuppressive treatment and dose
123 of corticosteroid therapy; initiation and duration of anti-infectious treatment regimen;
124 outcome. Because of the retrospective observational nature of the study, the need for
125 informed consent was waived by the ethics committee of the Lyon teaching hospitals (*Comité*
126 *d’Ethique, Hospices Civils de Lyon*, approval number 19-117).

127 **Definitions of lung allograft dysfunction.** Acute rejection was defined as a biopsy of lung
128 tissue demonstrating injuries as defined by the ISHLT guidelines [22]. BOS was defined as a
129 substantial and persistent decline ($\geq 20\%$) in measurable forced expiratory volume in 1-
130 second (FEV1) from the reference baseline value, associated with airflow obstruction marker.
131 The baseline value was computed as the mean of the best two post-operative FEV1
132 measurements taken more than 3 weeks apart [4]. The latest pre-infection FEV1 was the last
133 measurement recorded within 3 months prior to RSV infection. Possible CLAD was defined
134 as a 10 to 20% FEV1 decline from baseline (formerly stage BOS 0-p). Definite CLAD was
135 defined as an irreversible $\geq 20\%$ decline in FEV1 at 3 months and beyond compared to the
136 reference baseline value [3,4].

137 **Endpoints.** The primary endpoint was to determine new occurrences of lung allograft
138 dysfunction three months after RSV-confirmed infection as well as factors associated with the
139 use of ribavirin and the co-prescription of antibiotics and their influence on FEV1. Secondary
140 endpoints were: the assessment of annual incidence and seasonal distribution RSV-confirmed
141 infection among the lung transplant population; clinical presentations and factors associated

142 with RSV tracheobronchitis/bronchiolitis or pneumonia; the need for hospitalization or
143 intensive care unit (ICU) admission; and the overall outcome.

144 **Statistical analysis.** Descriptive data were used to estimate the frequencies of the study
145 variables, expressed as count (percentage, %) for dichotomous variables and as medians
146 (interquartile range [IQR]) for continuous values. The number of missing values was
147 excluded from the denominator. Non-parametric statistical methods Fisher's exact test, χ^2
148 test, and Mann-Whitney U test were used to compare groups, where appropriate. Evolution
149 over time of dichotomous and continuous variables was assessed using the McNemar and
150 Wilcoxon matched-pairs signed rank tests, respectively. Determinants of the main study
151 endpoints were determined using a univariate logistic regression, expressed as odds ratios
152 (OR) with 95% confidence intervals (95%CI). The incidence of hospitalization due to RSV-
153 confirmed infection was estimated per patient/year within the temporal window of three full
154 years after transplantation for patients transplanted after 2011. A value of $P < 0.05$ was
155 considered significant. All analyses were performed using SPSS software version 24.0 (SPSS,
156 Chicago, IL).

157 **RESULTS**

158 ***Epidemiology of RSV-confirmed infection and characteristics of lung transplant recipients*** 159 ***with RSV-confirmed infection***

160 From 2011 to 2019, the cohort of lung transplant recipients in the three centers increased from
161 381 to 805 patients for a total of 424 new procedures. Among them, 77 recipients developed
162 an RSV-confirmed infection requiring 57 (74%) hospitalizations. Monthly distribution of
163 RSV infection cases in lung transplant recipients peaked in January (Figure S1 of
164 supplementary material). The overall incidence of RSV-confirmed infection was estimated at
165 0.025 per patient/year [95%CI 0.018;0.036] and that of RSV-related hospitalization at 0.020
166 per patient/year [95%CI 0.013;0.029]. Incidence of RSV-related hospitalization did not

167 significantly differ between the first (0.025 per patient/year, [95%CI 0.015;0.041]) and
168 second year (0.014 per patient/year, [95%CI 0.007;0.028]) following transplantation. RSV-
169 confirmed infection incidence drastically dropped to 0.002 per patient/year [95%CI
170 0.001;0.008] in the third year after lung transplantation.

171 Median age at infection was 45.1 years [IQR, 34-53.9] and the sex ratio M/F was 0.83 (Table
172 1). Median time from lung transplantation to RSV-confirmed infection was 28.7 months
173 [IQR, 10.3-62.8]. Of note, in addition to their rejection therapy, 39/77 (50.6%) recipients
174 received azithromycin prophylaxis. Although RSV was the only infectious agent identified in
175 a majority of cases (54.5%, n=42/77), this was significantly more frequently the case in
176 tracheobronchitis/bronchiolitis (62.0%, n=31/50) than in pneumonia (37.5%, n=9/24;
177 $P=0.048$). The proportion of recipients hospitalized was significantly higher in the pneumonia
178 subset (22/24 [91.7%] *versus* 29/50 [58.0%]; $P=0.003$), which accounted for all ICU
179 admissions ~~and~~ for mechanical ventilation supports (8/24 [33.3%] *vs* 0/50 [0%]; $P<10^{-3}$)
180 (Table 2). The median follow-up time was 37 months [IQR, 19-65]. The overall mortality was
181 2.5% (n=2/76) at 30 days and 5.3% (n=4/76) at 6 months post RSV-confirmed infection, and
182 none of these deaths were directly attributable to RSV.

183 ***Lung allograft dysfunction after RSV-confirmed infection***

184 Recipients who developed pneumonia had significantly lower FEV1 values compared to
185 recipients who developed RSV tracheobronchitis/bronchiolitis at baseline (1.8 [IQR, 1.4-2.2]
186 L/s *vs* 2.4 [IQR, 1.8-2.6]; $P=0.021$) and at the latest pre-RSV measurements (1.5 [IQR, 1.1-
187 1.9] *vs* 2.2 [1.5-2.4]; $P=0.003$, Table 2). Prior to RSV-confirmed infection, 46/76 (60.5%)
188 acute rejections and 13/77 (16.9%) CLAD were documented. Three months after RSV-
189 confirmed infection, 6/76 (7.9%) new acute rejections and 6/76 (7.9%) CLAD (5 BOS and 1
190 RAS) were recorded but none of them were among the previously documented CLAD (Table
191 2). Of note, 10/77 (13.0%) additional recipients qualified for possible CLAD. The association

192 between RSV-confirmed infection and CLAD was addressed by comparing different values
193 of FEV1 over time. When comparing the FEV1 baseline values (2.3 [IQR, 1.6-2.6] L/s) to the
194 FEV1 values measured 3 months post-RSV infection (2.0 [IQR, 1.5-2.5]), the latter were
195 significantly lower ($P < .0001$; Figure 1A) corresponding to a median net loss of 7.3% [IQR, -
196 0.9--20.4]. No significant difference was found when comparing the latest pre-RSV infection
197 FEV1 value (2.0 [IQR, 1.4-2.4]) to the FEV1 value measured at 3 months post-RSV infection
198 (-0.6% [IQR, -5.2-+9.1], $P=0.56$; Figure 1A). In summary, at 3 months after RSV-confirmed
199 infection, 22 (28.5%) recipients had some degree of new lung dysfunction classified as
200 possible CLAD (13%), acute rejection (7.9%, $n=6/76$), and CLAD (7.9%).

201 ***Antimicrobial treatments during RSV-confirmed infection***

202 At 3 months post-infection, the FEV1 values of ribavirin-treated and -untreated recipients
203 were not different (2.2 [1.7-2.4] vs 1.9 [1.4-2.5] L/s; $P=0.34$; Figure 1B). Ribavirin
204 administration did not influence short-term outcomes such as hospital length of stay (9.5
205 [IQR, 7-10] vs 7 [3-14.5] days; $P=0.139$); and ICU admission for mechanical ventilation
206 requirement (2/19 [10.5%] vs 6/58 [10.3%]; $P=1.000$). Recipients with respiratory bacterial
207 co-infection were significantly less likely to receive ribavirin (4/19 [21.1%] vs 31/58 [53.4%];
208 OR 0.23, 95%CI [0.07;0.78], $P=0.019$) and more likely to receive antibiotics (31/52 [59.6%]
209 vs 4/25 [16.0%]; OR 7.75, 95%CI [2.3;25.8], $P=0.001$). Recipients having the lowest FEV1
210 values before RSV-confirmed infection were more likely to receive antibiotics (1.6 [IQR, 1.3-
211 2.3] vs 2.3 [1.9-2.5] L/s; OR 0.52, 95%CI [0.27;0.99], $P=0.045$; Table 3). Three-month FEV1
212 values were significantly lower in antibiotic treated recipients than in the untreated ones (1.7
213 [IQR, 1.3-2.4] vs 2.2 [1.9-2.8] L/s; $P=0.013$; Figure 1B), with no significant difference
214 regarding their loss compare to baseline (-8.6% [IQR, -21.0--2.9] vs -4.4% [IQR, -12.8-+0.9];
215 $P=1.000$). In recipients receiving azithromycin for BOS prevention, 3-month FEV1 values
216 were not different in azithromycin-treated (2.0 [IQR, 1.4-2.4] L/s) and -untreated (2.0 [1.5-

217 2.7] L/s) recipients in comparison to baseline ($P=0.37$; Figure 1C). Azithromycin prophylaxis
218 was associated with significantly less bacterial co-infections ($n=14/39$ [35.9%] vs $21/38$
219 [55.3%]; $P=0.023$).

220 **DISCUSSION**

221 In a cohort of 77 lung transplant recipients with RSV-confirmed infection, nearly 30% of
222 recipients developed some degree of new lung allograft dysfunction at 3 months post-RSV
223 infection, including 7.9% of acute rejections and 7.9% of CLAD. Curative ribavirin and
224 preventive azithromycin did not influence functional outcome parameters. It appears that the
225 poorer the functional status at baseline, the greater the risk of developing pneumonia, and the
226 higher the association with antibiotic co-prescription.

227 The present study confirms the low incidence of RSV infection after lung transplantation
228 (0.025 per patient/year [95%CI 0.018;0.036]) in the era of widely available PCR testing.
229 Interestingly, most cases occurred during the second year or beyond, certainly reflecting
230 higher protection measures applied to and by recipients during the first year after
231 transplantation.

232 There is concern that community-acquired respiratory virus infections can trigger local
233 alloimmune responses and result in a durable negative impact on lung function [23]. Recent
234 studies suggest that the inflammatory infiltrates noted on biopsy specimens during acute
235 rejection are mostly antiviral response effectors in the process of clearing the infection [17].
236 Accordingly, studies have suggested the lack of impact of RSV infection on FEV1 after lung
237 transplantation; of note, all recipients received anti-inflammatory corticosteroids and/or
238 immunoglobulins in addition of ribavirin treatment. In our study, nearly half of recipients
239 received steroid therapy at the time of infection and 5/77 recipients received
240 immunoglobulins. Although we observed a decline in 3-month FEV1 compared to baseline,
241 we consider difficult to draw definite conclusion with regards to the raw negative impact of

242 RSV. Most recipients of our study developed RSV infection rather late (median of 28 months
243 post-transplant) implying that FEV1 might have considerably changed in the interval.
244 Although biased by numerous missing values and temporal heterogeneity, this is suggested by
245 the lack of difference between the latest pre-infection and the 3-month FEV1 values. Thus, we
246 strongly subscribe to the necessity of monitoring FEV1 at least every 6 months [3], or more
247 frequently in case of progressive FEV1 decline. This is of particular importance when
248 considering that recipients with the poorest lung function have higher odds of developing
249 pneumonia, ICU admission and ventilation support.

250 Prophylactic azithromycin has been demonstrated to significantly reduce the overall
251 prevalence of BOS in a randomized clinical trial [4,24]. In the pediatric setting, two studies,
252 which included a total of 281 participants, compared azithromycin with placebo in children <
253 2 years diagnosed with RSV bronchiolitis. Both studies found no significant difference for
254 length of hospital stay, duration of oxygen requirement, and readmission [25,26].

255 Bacterial co-infections is highlighted herein and has been described previously. A nested
256 case-control analysis performed in a lung transplant recipient cohort (n=98) monitored for
257 respiratory virus infections (n=10 RSV infections), showed that *Pseudomonas aeruginosa*
258 was significantly associated with lower respiratory tract infections (HR [95%CI] 8.54
259 [1.54;47.4], $P < 0.01$) [27]. Another retrospective study that documented 89 RSV-confirmed
260 pneumonia across various adult settings found 27 bacterial super-infections with
261 *Streptococcus pneumonia* (9.3%), *Haemophilus influenza*, *Staphylococcus aureus*, *P.*
262 *aeruginosa*, and *Moraxella catarrhalis* [28]. The authors concluded that no major
263 epidemiological difference was observed compared to post-influenza pneumonia.

264 The present study has limitations. Data should be interpreted with caution because of the
265 retrospective nature of the study and the absence of a control group. It is possible that the
266 collected data misestimate true RSV-related morbidity and mortality, particularly among

267 recipients who did not seek medical attention for minor respiratory symptoms. A quantitative
268 PCR assay follow-up could have been of more value for detecting RSV in respiratory
269 specimens and evaluating the efficacy of antiviral therapy. There were no definite criteria for
270 prescribing ribavirin, initiated at the discretion of physicians, thus resulting in analyzing
271 outcome parameters in a non-controlled manner. Weak consistency in antimicrobial treatment
272 decision-making likely reflects differences among physician management strategies.
273 Treatment duration and outcome criteria were not standardized, which prevented a more
274 precise assessment of treatment efficacy. Finally, to avoid over-interpreting the current data,
275 no multivariable model analysis was performed due to the lack of a RSV-uninfected control
276 cohort comparator, as well as insufficient power.

277 At 3 months after RSV-confirmed infection, 28.8% of new allograft dysfunction was
278 observed in a retrospective cohort of 77 lung transplant recipients with a proportion of 7.9%
279 acute rejections and 7.9% CLAD. Recipients with the lowest FEV1 at baseline were at higher
280 risk of developing pneumonia and more likely to receive antibiotics. Ribavirin curative
281 treatment and azithromycin prophylaxis did not prevent FEV1 decline after RSV-confirmed
282 infection.

283 **AUTHORSHIP STATEMENTS**

284 HT contributed to study conception and design, acquisition of the data, interpretation of the
285 data, drafted the manuscript and approved the final version; MB contributed to acquisition of
286 the data and approved the final version; FV and JSC carried out the statistical analysis,
287 participated in the revision of the manuscript for important intellectual content, and approved
288 the final version; JSC, AG, MEL provided RSV case list as members of the virology
289 laboratories. They participated in the revision of the manuscript for important intellectual
290 content, and approved the final version; FP, AS, EB, JLP substantially contributed to
291 acquisition of the data, revision of the manuscript for important intellectual content, and

292 approved the final version; FA is the project initiator, contributed to study conception and
293 design, drafted the manuscript, and approved the final version. All authors read and approved
294 the final manuscript.

295 **ACKNOWLEDGMENTS**

296 The authors gratefully acknowledge V er ena Landel and Pr Jean-Fran ois Mornex for helpful
297 insights.

298 **COMPETING INTERESTS**

299 The authors have no relevant affiliations or financial involvement with any organization or
300 entity with a financial interest or financial conflict with the subject matter or materials
301 discussed in the manuscript. Production of this manuscript did not require writing assistance.

302 **FUNDING**

303 No external funding was received for this study.

304 **REFERENCES**

- 305 [1] Opelz G, D ohler B, Ruhstroth A, et al. The collaborative transplant study registry.
306 *Transplant Rev Orlando Fla* 2013;27:43-5.
- 307 [2] Chambers DC, Yusen RD, Cherikh WS, et al. The Registry of the International Society for
308 Heart and Lung Transplantation: thirty-fourth adult lung and heart-lung transplantation report-
309 2017; focus theme: allograft ischemic time. *J Heart Lung Transplant* 2017;36:1047-59.
- 310 [3] Verleden GM, Glanville AR, Lease ED, et al. Chronic lung allograft dysfunction:
311 definition, diagnostic criteria, and approaches to treatment-A consensus report from the
312 Pulmonary Council of the ISHLT. *J Heart Lung Transplant* 2019;38:493-503.
- 313 [4] Meyer KC, Raghu G, Verleden GM, et al. An international ISHLT/ATS/ERS clinical
314 practice guideline: diagnosis and management of bronchiolitis obliterans syndrome. *Eur*
315 *Respir J* 2014;44:1479-1503.

- 316 [5] Finlen Copeland CA, Snyder LD, Zaas DW, et al. Survival after bronchiolitis obliterans
317 syndrome among bilateral lung transplant recipients. *Am J Respir Crit Care Med*
318 2010;182:784-89.
- 319 [6] Fisher CE, Preiksaitis CM, Lease ED, et al. Symptomatic respiratory virus infection and
320 chronic lung allograft dysfunction. *Clin Infect Dis* 2016;62:313-19.
- 321 [7] Allyn PR, Duffy EL, Humphries RM, et al. Graft loss and CLAD-onset is hastened by
322 viral pneumonia after lung transplantation. *Transplantation* 2016;100:2424-31.
- 323 [8] Magnusson J, Westin J, Andersson L-M, et al. The impact of viral respiratory tract
324 infections on long-term morbidity and mortality following lung transplantation: a
325 retrospective cohort study using a multiplex PCR panel. *Transplantation* 2013;95:383-88.
- 326 [9] Gottlieb J, Schulz TF, Welte T, et al. Community-acquired respiratory viral infections in
327 lung transplant recipients: a single season cohort study. *Transplantation* 2009;87:1530-37.
- 328 [10] Milstone AP, Brumble LM, Barnes J, et al. A single-season prospective study of
329 respiratory viral infections in lung transplant recipients. *Eur Respir J* 2006;28:131-37.
- 330 [11] Khalifah AP, Hachem RR, Chakinala MM, et al. Respiratory viral infections are a
331 distinct risk for bronchiolitis obliterans syndrome and death. *Am J Respir Crit Care Med*
332 2004;170:181-87.
- 333 [12] Billings JL, Hertz MI, Savik K, et al. Respiratory viruses and chronic rejection in lung
334 transplant recipients. *J Heart Lung Transplant* 2002;21:559-66.
- 335 [13] Griffiths C, Drews SJ, Marchant DJ. 2017. Respiratory syncytial virus: infection,
336 detection, and new options for prevention and treatment. *Clin Microbiol Rev* 30:277-319.
- 337 [14] Uckay I, Gasche-Soccal PM, Kaiser L, et al. Low incidence of severe respiratory
338 syncytial virus infections in lung transplant recipients despite the absence of specific therapy.
339 *J Heart Lung Transplant* 2010;29:299-305.

- 340 [15] Liu V, Dhillon GS, Weill D. A multi-drug regimen for respiratory syncytial virus and
341 parainfluenza virus infections in adult lung and heart-lung transplant recipients. *Transpl Infect*
342 *Dis* 2010;12:38-44.
- 343 [16] Fuehner T, Dierich M, Duesberg C, DeWall C, Welte T, Haverich A, et al. Single-centre
344 experience with oral ribavirin in lung transplant recipients with paramyxovirus infections.
345 *Antivir Ther.* 2011;16:733-40.
- 346 [17] Bridevaux P-O, Aubert J-D, Soccac PM, Mazza-Stalder J, Berutto C, Rochat T, et al.
347 Incidence and outcomes of respiratory viral infections in lung transplant recipients: a
348 prospective study. *Thorax* 2014;69:32-8.
- 349 [18] McCurdy LH, Milstone A, Dummer S. Clinical features and outcomes of paramyxoviral
350 infection in lung transplant recipients treated with ribavirin. *J Heart Lung Transplant*
351 2003;22:745-53.
- 352 [19] Hopkins P, McNeil K, Kermeen F, et al. Human metapneumovirus in lung transplant
353 recipients and comparison to respiratory syncytial virus. *Am J Respir Crit Care Med*
354 2008;178:876-81.
- 355 [20] Manuel O, Estabrook M, American Society of Transplantation Infectious Diseases
356 Community of Practice. RNA respiratory viral infections in solid organ transplant recipients:
357 Guidelines from the American Society of Transplantation Infectious Diseases Community of
358 Practice. *Clin Transplantation* 2019;e13511.
- 359 [21] Husain S, Mooney ML, Danziger-Isakov L, et al. A 2010 working formulation for the
360 standardization of definitions of infections in cardiothoracic transplant recipients. *J Heart*
361 *Lung Transplant* 2011;30:361-74.
- 362 [22] Stewart S, Fishbein MC, Snell GI, et al. Revision of the 1996 working formulation for
363 the standardization of nomenclature in the diagnosis of lung rejection. *J Heart Lung*
364 *Transplant* 2007;26:1229-42.

- 365 [23] Cainelli F, Vento S. Infections and solid organ transplant rejection: a cause-and-effect
366 relationship? *Lancet Infect Dis* 2002;2:539-49.
- 367 [24] Corris PA, Ryan VA, Small T. et al. A randomised controlled trial of azithromycin
368 therapy in bronchiolitis obliterans syndrome (BOS) post lung
369 transplantation. *Thorax* 2015;70: 442-50.
- 370 [25] Pinto LA, Pitrez PM, Luisi F, et al. Azithromycin therapy in hospitalized infants with
371 acute bronchiolitis is not associated with better clinical outcomes: a randomized, double-
372 blinded, and placebo-controlled clinical trial. *J Pediatr* 2012;161:1104-08.
- 373 [26] McCallum GB, Morris PS, Chatfield MD, et al. A single dose of azithromycin does not
374 improve clinical outcomes of children hospitalised with bronchiolitis: a randomised, placebo-
375 controlled trial. *PloS One* 2013;8:e74316.
- 376 [27] Peghin M, Hirsch HH, Len Ó, et al. Epidemiology and immediate indirect effects of
377 respiratory viruses in lung transplant recipients: A 5-Year Prospective Study. *Am J Transplant*
378 2017;17:1304-12.
- 379 [28] Jeannoël M, Lina G, Rasigade JP, et al. Microorganisms associated with respiratory
380 syncytial virus pneumonia in the adult population. *Eur J Clin Microbiol Infect. Dis*
381 2019;38:157-60.

383 Table 1. Lung transplant recipient characteristics

n=77	
Demographics	
age, years, median [IQR]	45.1 [34-53.9]
male, n (%)	35 (45.5)
Pulmonary and transplant-related characteristics, n (%)	
<i>Underlying pulmonary diseases</i>	
interstitial lung disease	21 (27.3)
pulmonary hypertension	19 (24.7)
COPD/emphysema	16 (20.8)
cystic fibrosis	15 (19.5)
others	6 (7.8)
<i>Type of lung transplantation</i>	
double-lung	53 (68.8)
single-lung	16 (20.8)
cardiothoracic	8 (10.4)
<i>Immunomodulatory therapies within the previous year</i>	
biotherapies (anti-CD20, anti-TNF- α)	3 (3.9)
azithromycin	39 (50.6)
<i>Immunosuppressive drug regimen</i>	
tacrolimus or everolimus and MMF	58 (75.3)
^a high-dose CST therapy	35 (45.5)
^b maintenance CST therapy	36 (46.8)
Post-transplant complications, n (%)	
chronic renal failure (GFR < 40 mL/min)	12 (15.6)
any cardiac disease requiring specific treatment	14 (18.2)
diabetes mellitus	10 (13)
Time from transplantation to RSV infection,	28.7 [10.3-62.8]
months, median [IQR]	
Infection type, n (%)	
tracheobronchitis/bronchiolitis	50 (65)
pneumonia	24 (31.2)
non-symptomatic or poorly symptomatic URTI	3 (3.8)
RSV-related hospitalization	57 (70.1)
length of hospital stay, days	7 (4-13)
ICU admission, n (%)	9 (11.7)
length of ICU stay, days	7 (6.5-12)
mechanical ventilation, n (%)	8 (10.4)
vasoactive drug requirement, n (%)	3 (3.9)
^c Neutropenia	1 (1.4)
^d Lymphocytopenia	27 (38)
Antiviral treatment, n (%)	
^e ribavirin	19 (24.7)
palivizumab infusion	3 (3.9)
IVIg infusion	2 (2.6)
Overall mortality (6 months), n (%)	4 (5.3)
death within 30 days after RSV infection	2 (2.5)
RSV-related death	0

384 ^aHigh dose corticosteroid therapy ≥ 1 mg/kg > 21 days or ≥ 10 mg/day > 3 months.385 ^bMaintenance corticosteroid therapy < 10 mg/day.

386 ^cNeutropenia was defined as polymorphonuclear neutrophils < 0.5 G/L at inclusion.

387 Information available for only 71 recipients.

388 ^dLymphocytopenia was defined as absolute lymphocyte count < 1 G/L at inclusion.

389 Information available for only 71 recipients.

390 ^eAdministered for at least 48 hours.

391 Abbreviations: COPD, chronic obstructive pulmonary disease; CST, corticosteroid; GFR,

392 glomerular filtration rate; ICU, intensive care unit; IQR, interquartile range; IS,

393 immunosuppressive; IVIG, intravenous immunoglobulins; MMF, mycophenolate mofetil;

394 RSV, respiratory syncytial virus; TNF, tumor necrosis factor; URTI, upper respiratory tract

395 infection.

396

397 **Table 2. Characteristics of recipients according to respiratory syncytial virus-confirmed**
 398 **infection type**

	Tracheobronchitis n=50	Pneumonia n=24	P-value
Demographics			
age at transplantation, years, median [IQR]	40.8 (30.5-52.7)	47.7 (41.1-56.6)	0.076
CST therapy, n (%)			
[#] high-dose	25 (50)	8 (33.3)	0.17
[§] maintenance	22 (44)	13 (54.2)	0.41
Time since transplantation, months, median [IQR]	24.5 [11.9-55.6]	41.1 [8.6-94.7]	0.48
RSV as only documentation, n (%)	31 (62)	9 (37.5)	0.048
Respiratory bacterial co-infection at RSV-confirmed infection, n (%)	21 (42)	13 (54.2)	0.32
Non-fermenting Gram negative bacteria	11 (50)	6 (46.2)	0.82
Respiratory fungal co-infection at RSV-confirmed infection, n (%)	13 (26)	5 (20.8)	0.62
Respiratory viral co-infection at RSV-confirmed infection, n (%)	6 (12)	4 (16.7)	0.72
C-reactive protein at RSV infection, mg/L, n (%)			
< 50	19 (42.2)	11 (47.8)	0.66
50-100	2 (4.4)	5 (21.7)	0.039
> 100	4 (8.9)	5 (21.7)	0.25
RSV-related hospitalization	29 (58)	22 (91.7)	0.003
ICU admission	0	8 (33.3)	< 0.0003
Antiviral therapy, n (%)			
ribavirin	11 (22)	8 (33.3)	0.29
palivizumab or IVIG infusions	2 (4)	4 (16.7)	0.08
Antibiotic treatment during RSV infection	31 (62)	20 (83.3)	0.1
FEV1, L/sec, median [IQR]			
[*] baseline value (2 best values)	2.4 [1.8-2.6]	1.8 [1.4-2.2]	0.021
latest pre-RSV infection value	2.2 [1.5-2.4]	1.5 [1.1-1.9]	0.003
at RSV infection	1.9 [1.5-2.3]	1.2 [1-1.6]	0.023
at 3 months post-RSV infection	2.2 [1.6-2.7]	1.7 [1.3-1.9]	0.015
FEV1 loss vs. baseline values, % [IQR]	-5.8 [-15-0]	-15.9 [-26.7- -6.4]	0.2
FEV1 loss vs. latest value, % [IQR]	0 [-0.1- -0.1]	0 [0- -0.1]	0.95
New or worsening graft dysfunction at 3 months			
acute rejection	5 (10)	1 (4.2)	0.65
CLAD compared to baseline FEV1	5 (10)	1 (4.3)	0.31
CLAD compared to pre-infection FEV1	3 (7.5)	0 (0)	0.5

399 [#]High dose corticosteroid therapy ≥ 1 mg/kg > 21 days

400 [§]Maintenance corticosteroid therapy < 10 mg/day

401 ^{*}Baseline value is defined by the mean of the best two post-operative FEV1 measurements

402 taken more than three weeks apart.

403 Abbreviations: CLAD, chronic lung allograft dysfunction; CMV, cytomegalovirus; CST,
404 corticosteroid; FEV1, forced expiratory volume in 1-second; ICU, intensive care unit; IQR,
405 interquartile range; IVIG, intravenous immunoglobulins; RSV, respiratory syncytial virus.

406 **Table 3. Comparison of treated and untreated recipients**

n, %	Ribavirin-treated (n=19)/ untreated (n= 58)	OR [95% CI]	<i>P-value</i>	Antibiotic therapy (n= 52)/ no antibiotic therapy (n=25)	OR [95% CI]	<i>P-value</i>
Latest pre-infection FEV1, L/sec, median [IQR]	2.1 [1.7-2.3]/1.9 [1.4-2.5]	1.08 [0.55-2.13]	0.5	1.6 [1.3-2.3]/2.3 [1.9-2.5]	0.52 [0.27-0.99]	0.045
RSV as only documentation	14 (73.7)/28 (48.3)	3 [0.95-9.4]	0.06	23 (44.2)/19 (76)	0.25 [0.08-0.73]	0.011
Respiratory bacterial co- infection at RSV-confirmed infection	4 (21.1)/31 (53.4)	0.23 [0.07-0.78]	0.019	31 (59.6)/4 (16)	7.75 [2.3-25.8]	0.001
Ribavirin treatment	/	/	/	9 (17.3)/10 (40)	0.31 [0.11-0.92]	0.035
Antibiotic treatment upon RSV-confirmed infection	9 (47.4)/43 (74.1)	0.31 [0.1-0.82]	0.035	/	/	/
Type of RSV-confirmed infection						
Tracheobronchitis/bronchiolitis	11 (57.9)/39 (67.2)	0.67 [0.23-1.9]	0.46	31 (59.6)/19 (76)	0.46 [0.16-1.36]	0.16
Pneumonia	8 (42.1)/16 (27.6)	1.9 [0.65-5.6]	0.24	20 (38.5)/4 (16)	3.28 [0.98-10.9]	0.054

407

408 Abbreviations: FEV1, forced expiratory volume in 1-second; IQR, interquartile range; RSV, respiratory syncytial virus.

409 **FIGURES LEGENDS**

410 **Figure 1. Panel A: values of forced expiratory volume in 1-second before and 3 months**
411 **after respiratory syncytial virus-confirmed infection. Panel B: values of forced**
412 **expiratory volume in 1-second before and 3 months after respiratory syncytial virus-**
413 **confirmed infection according to ribavirin or antibiotic treatment. Panel C: changes**
414 **over time of forced expiratory volume in 1-second values according to long-term**
415 **azithromycin prophylaxis.**

416 Abbreviations: AZM, azithromycin; FEV1, forced expiratory volume in 1-second; RSV,
417 respiratory syncytial virus.

418

