ADDITIONAL DATA

Materials and Methods

We conducted a web-based survey of lung transplant centers from northern Europe. Our survey was registered as an assessment of clinical practice and approved by Research & Development in St-Thomas' Hospital, London (approval no. 6404). The questionnaire was developed in French by EL, MP, GT, HM and OB. It was translated into English by MP, PM and GA and sent to all LTx centers in France, the United Kingdom, The Netherlands, and the Scandinavian transplant network and to 1high-volume center from each of Belgium and Germany. A total of 26 centers of Northern Europe were contacted between April and December 2015, among 42 active centers for LTx in these 8 countries (62%). The percentage of contacted centers among active centers were as follows: 11contacted/11active centers in France, 4 /6 centers in United Kingdom, 3/3 in The Netherlands, 2/15 in Germany, 2/3 in Belgium, 2/2 in Sweden, 1/1 in Norway, and 1/1 in Finland. France was over-represented and Germany under-represented, although the responding center in Germany were a high-volume lung Tx center. We acknowledge that the lack of total coverage of the survey in Northern Europe and its heterogeneous coverage among the 8 countries may have introduced a bias in our survey. Nevertheless, 62% of all active centers in these countries of Northern Europe were contacted, and 80% of the contacted centers responded. Hence, this survey still allowed to catch an instant picture of current practices from a majority of LTx centers in Northern Europe.

French centers received a French version of the questionnaire and other centers received an English version. A majority of French centers ultimately used the English version online questionnaire to answer the questions.

For each LTx center, a chest physician with an interest in managing viral infections was contacted by email and encouraged to respond to the questionnaire online. The email included an introduction statement and link to the online survey. With no reply, 2 other emails were sent to the physician. No further contact was made if the clinician did not reply. A total of 21 of 26 centers (80%) responded, including 11 in France, 4 in United Kingdom, 2 in The Netherlands and 1 each in Germany, Sweden, Norway and Belgium.

The questionnaire collected the identity of the responding physician of each center. Physicians were asked to reply to 7 questions on their center's diagnostic approach and to 18 questions on their center's therapeutic approach regarding the management of respiratory viral infections. Questions were answered by scales (from 0 to 10) or multiple choice or single responses. To reflect local medical practice, the definition of respiratory tract infection and its severity were left to the clinician's discretion. The full questionnaire is available as an online supplement (See appendix 1). https://docs.google.com/forms/d/1S3CIhjCdsSOYb1IdZzW7-yj2CMs43ndd3uUVwm2p6IY/viewform Data are expressed as number (%) and mean (SD) if normally distributed and as median (interquartile range [IQR]) if not. Multiple comparisons involved the Friedman test with Dunn's correction. Analysis was performed with Prism v6 (GraphPad). $P<0.05$ was considered statistically significant.

Additional Results

Therapeutic approach

Route and type of antiviral treatment are shown in Table S1. The decision to initiate ribavirin treatment depended on the detected virus: 80% for RSV, 38% for PIV, and 33% for hMPV.

Cidofovir was used only for adenovirus infections by a few centers (n=3, 14%). Ribavirin treatment varied between centers in terms of duration (10 days, IQR 7.5-12 days) and route of administration, with most centers giving oral ribavirin (42.8%), at a median dose of 1200 mg/day (IQR 1200). Ribavirin treatment was stopped at a fixed time (n=8 centers, 47%) or according to symptoms (n=5 centers, 28%), viral clearance (n=2 centers, 11%) or multiple criteria (n=3, 17%). Use of additional therapies varied considerably among centers. Daily doses of steroids were increased in 7 (43%) centers to a median dose of 0.75 mg/kg/day (IQR 0.5–0.875), for a median duration of 10 days (95% confidence interval 7–14) for RSV, PIV, and hMPV infections but in only 6 (29%) centers for coronavirus, rhinovirus and bocavirus infection. Finally, 5 (24%) centers also administered intravenous immunoglobulins for RSV infection.

The most expected benefit from the use of ribavirin was preventing BOS, graded as a median of 5 (IQR 1–7) (0: not effective at all, to 10: very effective) by physicians (Table 2, see manuscript). This grade represents the median score for each expected benefit. Other expected benefits were a decrease in the intensity of symptoms and their duration and the prevention of acute respiratory failure, graded as a median of 4 [2–6], 3 [1–6] and 3 [2–6], respectively.

The perceived effectiveness of ribavirin depending on each virus is shown in Figure S1. Its effectiveness in RSV infection was considered similar to that in PIV and hMPV ($p=0.05$, $p=0.17$) but higher than that in adenovirus, coronavirus and bocavirus infections ($p=0.03$, $p=0.0008$, $p<0.0001$, respectively) (Figure S1).

Additional discussion

In our survey, the highest perceived risk after CARV infection was indeed an increased incidence of subsequent CLAD (grade 7/10). A well-designed prospective study(1) and another retrospective cohort of 250 LTx patients(2) found a close relation between viral

infections and CLAD. It should be noticed that this previous randomized study(1) needed a large population to be screened before inclusion, emphasizing the difficulties to perform such studies.

Table S1: Route and type of antiviral treatment by lung transplantation centers in terms of the virus (n=21).

Treatment	RSV	PIV	hMPV	Adenovirus	Other
Nebulized ribavirin	6 (28.5%)	1 (4.8%)	1 (4.8%)	0 (0%)	0 (0%)
IV ribavirin	1 (4.8%)	1 (4.8%)	1 (4.8%)	1 (4.8%)	0 (0%)
Oral ribavirin	9 (42.8%)	6 (28.5%)	5 (23.8%)	2 (9.5%)	0 (0%)
Oral and IV ribavirin	1 (4.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Cidofovir	0 (0%)	0 (0%)	0 (0%)	3 (14.3%)	0 (0%)
Centers initiating antiviral treatment	17 (80.9%)	8 (38.1%)	7 (33.4%)	6 (28.6%)	0 (0%)

RSV: respiratory syncytial virus; PIV: para-influenzae virus; hMPV: human metapneumovirus; IV: intravenous

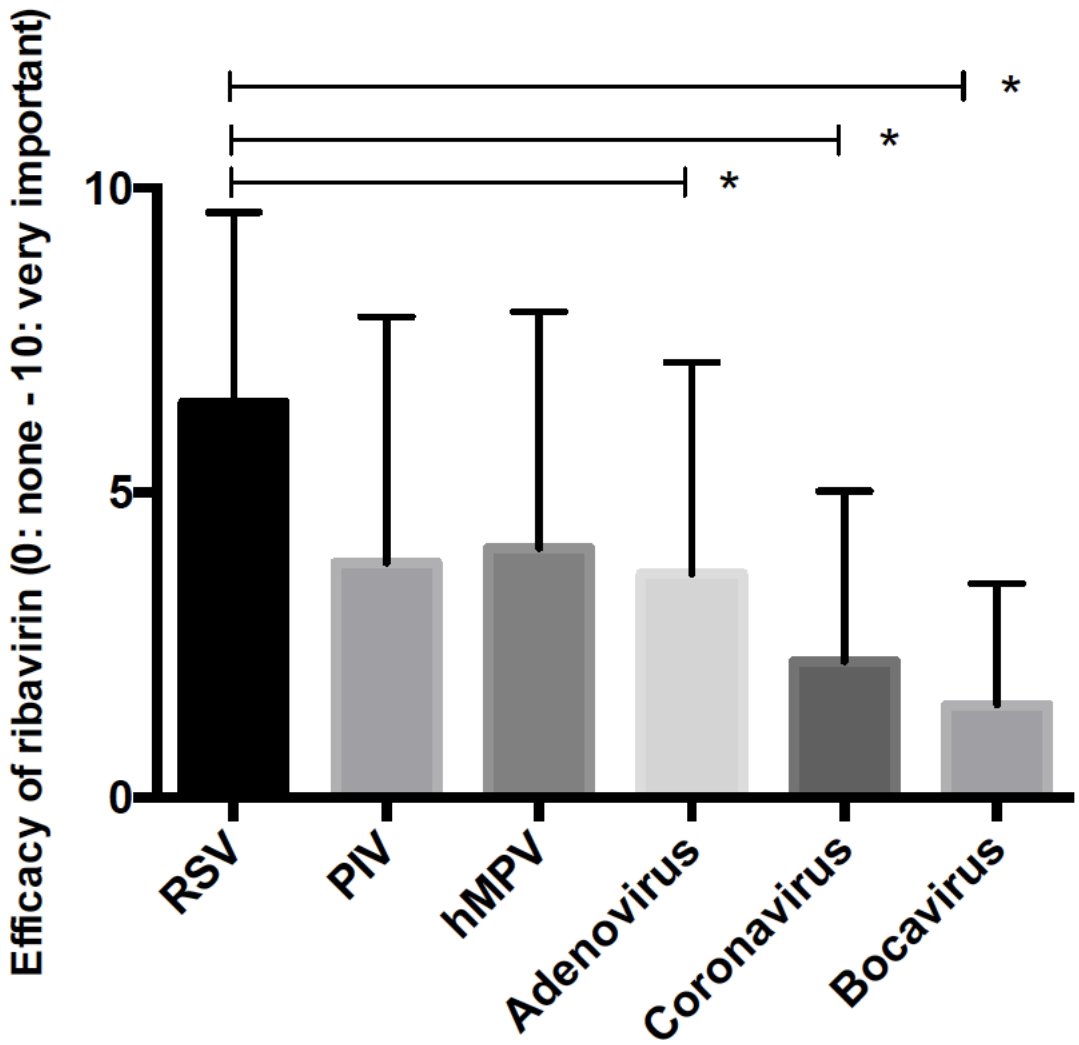

Figure S1: Physicians' perception of ribavirin's efficacy depending on each virus (RSV: respiratory syncytial virus; PIV: para-influenzae virus; hMPV: human metapneumovirus). Ribavirin was considered more effective for RSV than adenovirus ($p = 0.03$), coronavirus ($p=0.0008$) and bocavirus ($p<0.0001$) (Friedman test). Data are mean (SD).

REFERENCES

1. Gottlieb J, Zamora MR, Hodges T, et al. LN-RSV01 for prevention of bronchiolitis obliterans syndrome after respiratory syncytial virus infection in lung transplant recipients. *J Heart Lung Transplant.* 2016;35(2):213-221.
2. Khalifah AP, Hachem RR, Chakinala MM, et al. Respiratory viral infections are a distinct risk for bronchiolitis obliterans syndrome and death. *Am J Respir Crit Care Med.* 2004;170(2):181-187.