

# Respiratory Syncytial Virus, Human Metapneumovirus, and Parainfluenza Virus Infections in Lung Transplant Recipients: A Systematic Review of Outcomes and Treatment Strategies

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**Background.** Respiratory syncytial virus (RSV), parainfluenza virus (PIV), and human metapneumovirus (hMPV) are increasingly associated with chronic lung allograft dysfunction (CLAD) in lung transplant recipients (LTR). This systematic review primarily aimed to assess outcomes of RSV/PIV/hMPV infections in LTR and secondarily to assess evidence regarding the efficacy of ribavirin.

**Methods.** Relevant databases were queried and study outcomes extracted using a standardized method and summarized.

**Results.** Nineteen retrospective and 12 prospective studies were included (total 1060 cases). Pooled 30-day mortality was low (0–3%), but CLAD progression 180–360 days postinfection was substantial (pooled incidences 19–24%) and probably associated with severe infection. Ribavirin trended toward effectiveness for CLAD prevention in exploratory meta-analysis (odds ratio [OR] 0.61, [0.27–1.18]), although results were highly variable between studies.

**Conclusions.** RSV/PIV/hMPV infection was followed by a high CLAD incidence. Treatment options, including ribavirin, are limited. There is an urgent need for high-quality studies to provide better treatment options for these infections.

**Keywords.** lung transplantation; paramyxovirus; pneumovirus; ribavirin.

Infections with noninfluenza RNA respiratory viruses such as respiratory syncytial virus (RSV), parainfluenza virus (PIV), and human metapneumovirus (hMPV) have garnered increasing attention over the years because they are increasingly recognized as a significant cause of morbidity and mortality in high-risk patient populations such as immunocompromised individuals, as well as the elderly [1]. This is especially true in lung transplant recipients (LTR) because of the higher risk of severe infection due to underlying immunosuppression, local factors in the transplanted lung as well as their association with long-term outcomes such as chronic lung allograft dysfunction (CLAD) [2, 3].

Acute infection with respiratory viruses in LTR can cause mild upper respiratory tract infection (URTI), but can also lead to lower respiratory tract infection (LRTI) typically presenting with considerable graft dysfunction necessitating hospitalization or even resulting in death. Acute mortality in LTR with RSV, PIV or hMPV has been reported in up to 6–20% of cases in four studies from 2003–2011 [4–7]. Furthermore, symptomatic respiratory viral infections in LTR have been associated with CLAD [8, 9]. CLAD remains the primary factor limiting survival in LTR making prevention paramount. Of note, RSV, PIV, and hMPV may have a stronger association with these deleterious effects than other respiratory viruses [1, 8]. Despite this significant burden, treatment strategies mainly consist of supportive care and steroid augmentation, although antiviral treatment options such as ribavirin (RBV), or antibody-based treatments like palivizumab for RSV or intravenous immunoglobulins (IVIG) are limited. The broad-spectrum nucleoside analogue RBV has shown activity against RSV, PIV, and hMPV in vitro [10, 11]. Although it has been widely used in the setting of solid organ transplantation as well as hematopoietic stem cell transplantation for RSV (to a lesser extent hMPV and PIV), its clinical benefit remains unclear [2]. Furthermore, new antiviral drugs,

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among which interfering RNAs and fusion proteins, in various stages of development are tested to treat these infections [2].

We performed a systematic review with the primary aim to quantify the impact of RSV/PIV/hMPV infections on CLAD development and the secondary aim to assess the current state of evidence regarding RBV efficacy. In addition, alternative antiviral strategies are discussed.

## METHODS

The review protocol was registered in PROSPERO (CRD42016051912, <http://www.crd.york.ac.uk/PROSPERO>). The Preferred Reporting Items for Systematic Review (PRISMA) guidelines were followed in reporting of this review [12].

### Search Strategy and Study Selection

MEDLINE, EMBASE, and PubMed were queried on 20 June 2021 using the following search terms: *lung transplantation*, *paramyxoviridae*, *paramyxovirus*, *pneumovirus*, *respiratory syncytial virus*, *parainfluenza virus*, and *metapneumovirus*. Furthermore, the register of clinical trials (<http://clinicaltrials.gov>) was searched using the same method. References of included papers were reviewed for articles missed with the original search query.

First, the titles and abstracts of search results were screened and thereafter the full texts were independently evaluated for inclusion by A. d. Z. and E. V. Discrepancies were resolved by consensus. Inclusion criteria for final selection were: studies describing lung transplant or heart-lung transplant recipients with laboratory-confirmed infection with RSV, hMPV, or PIV, and adequate reporting of longer-term ( $\geq 90$  days postinfection) and acute ( $\leq 30$ -days) graft outcomes (CLAD, FEV1, death/graft loss).

### Data Extraction

The following was extracted from each included study using a standardized data extraction form: authors, publication date, design, objective, follow-up, patient characteristics, any therapeutic options used (antiviral/supportive), presentation (URTI/LRTI as defined by the authors), FEV1, mortality/graft loss during follow-up, and acute rejection and CLAD incidence (as defined by ISHLT criteria [3]). CLAD incidence 180–360 days postinfection was the primary outcome of interest and data for studies reporting this outcome were independently validated by A. d. Z., E. V., and A. R. Also, 180–365 days were chosen to better distinguish temporary or slow FEV1 recovery from CLAD.

Papers without original data, conference abstracts, studies with duplicate data, and review papers were excluded. To retrieve additional information not described in the included articles. The corresponding authors were contacted.

### Risk of Bias

The mixed methods appraisal tool (MMAT) was used to assess risk of bias of the papers with regards to [1] CLAD incidence

postinfection and (2) antiviral treatment effects on prevention of CLAD development. The MMAT allows simultaneous appraisal of all available literature and has been found to be reliable [13].

### Statistical Analysis

To evaluate heterogeneity and estimate a treatment effect of RBV, available data of studies reporting proportions of CLAD development postinfection in RBV treated and untreated LTR was extracted for an exploratory meta-analysis. A (mixed effect) binomial-normal logistic regression model with maximum likelihood estimation was used to estimate odds ratios, 95% confidence intervals (CI), and study heterogeneity ( $\tau^2$ ). Further elaboration of the analysis are found in [Supplementary Materials](#).

## RESULTS

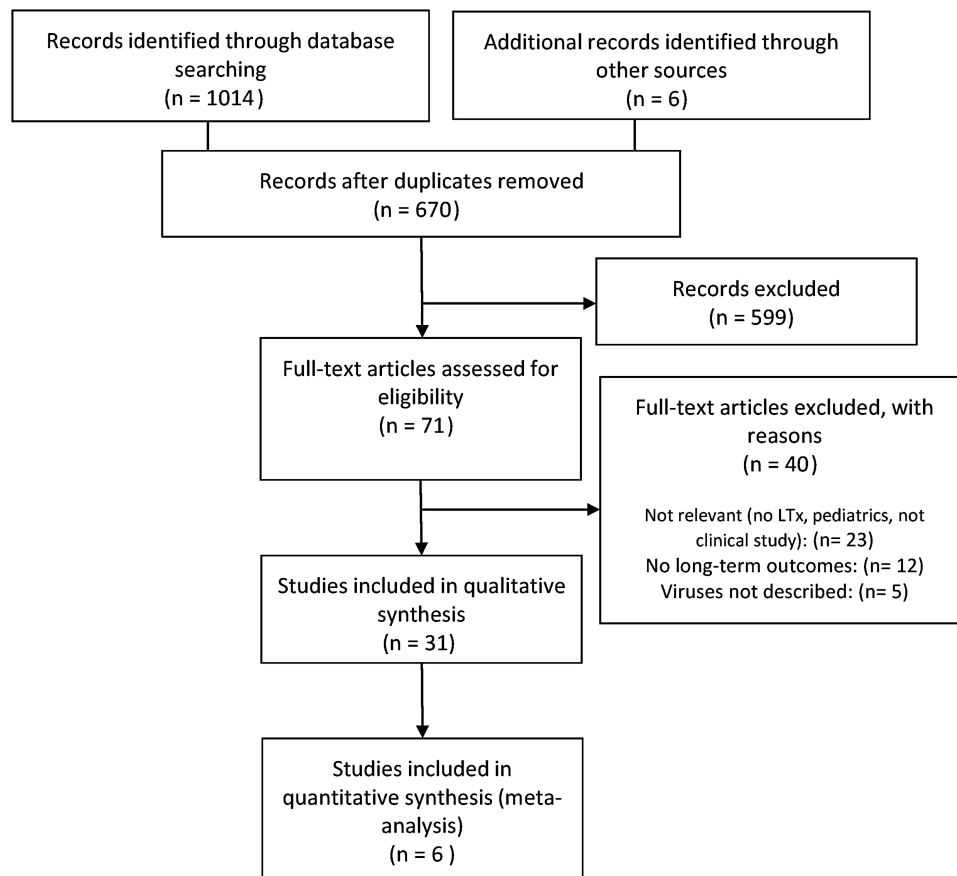
Thirty-one studies were included reporting 1060 cases in total (PRISMA flowchart in [Figure 1](#)).

Eighteen studies reported CLAD incidences after infection ([Table 1](#)), and 11 reported other long-term allograft outcomes ([Table 2](#)). Authors of 3 studies provided additional data after being contacted. Most studies had a retrospective design ( $n = 19$ ). Twelve studies were prospective [4, 7, 14–20], among which 2 randomized controlled trials [19, 20]. Study quality regarding estimation of CLAD incidence and antiviral treatment effects varied and was mostly hampered by lack of a comparator group or analyses lacking control for confounders (MMAT results in [Supplementary Material](#)). Five studies reporting long-term outcomes, but not specifying outcomes for RSV/hMPV/PIV cases individually are reported in [Supplementary Table 4](#).

### Clinical Presentation and Long-Term Graft Outcomes

Thirty-day mortality was mostly low ranging from 0 to 3%, except for 3 smaller studies reporting mortalities of 13%, 14%, and 50%, respectively, in RSV and hMPV cases [5, 21, 22]. Combining all studies reporting 30-day mortality, 1% (9/775 cases) died within 30 days postinfection overall, with 1% for RSV (6/533 cases) and 2% (3/122 cases) for hMPV, respectively. There were no deaths within 30 days reported for PIV. Mortality ranged from 0 to 13% for studies with a follow-up of 180 days to 1 year and up to 47% in a single study with a mean follow-up of 2.9 years [23]. However, these deaths were unlikely attributable to the viral respiratory infection (VRI), although in 2 studies patients died from allograft failure during follow-up, which may have been aggravated by the preceding infection [4, 24].

Prior to 2019 most studies did not differentiate phenotypes of CLAD, but instead used the term bronchiolitis obliterans syndrome, which is the most dominant CLAD phenotype. Overall CLAD incidence postinfection is reported in [Table 1](#). CLAD progression postinfection was substantial with pooled incidences of 19% (58/308 cases from 4 studies) and 24% (53/224



**Figure 1.** Prisma flow chart.

cases from 8 studies) for 180 days and 1 year postinfection, respectively. Only 2 smaller studies reported no new or progressive CLAD during follow-up [6, 16]. Pooled CLAD incidences 180 days and 1 year per virus were: RSV 32/208 (15%) and 13/47 (28%), hMPV 8/65 (12%), and 13/41 (32%), PIV 12/47 (26%) and 30/89 (34%) (Supplementary Tables 3–5).

Four studies compared LTR with an RSV/hMPV/PIV infection to uninfected LTR [14, 16, 18, 23]. A prospective study [14] compared a cohort of LTR with a viral respiratory infection (34 episodes, 25 RSV/hMPV/PIV) to LTR without and found highly symptomatic infection was a risk factor for CLAD development (adjusted hazard ratio [aHR] 4.05 [1.59–10.33]) with an especially high CLAD incidence in case of RSV/hMPV/PIV infection. Likewise, Khalifah et al [23] analyzed 259 LTR, including 21 cases of VRI (15 RSV/hMPV/PIV) and found an association with CLAD, death, and death from CLAD in multivariate models. This trend seemed more pronounced in patients with LRTI and distinct from the risk attributable due to acute rejection. Furthermore, Magnusson et al [18] found that VRI overall in the first year post-transplantation was a risk factor for CLAD development in a multivariate analysis but found no association for RSV or hMPV infection with CLAD in univariate analysis. In contrast, no significant difference was reported in the incidence

of graft dysfunction after one year in a univariate analysis comparing 17 LTR with VRI with 33 uninfected LTR [16]. None of the 9 patients with RSV or PIV developed CLAD. Interestingly, the LRTI incidence (4/17, 24%) was lower compared to most other studies, which may have led to lower allograft dysfunction.

#### Factors Associated With Graft Dysfunction

The impact of infection severity on CLAD was evaluated in five studies, which reported lower CLAD incidence in LTR with mild symptoms compared to more severe symptoms [4, 8, 14, 25, 26]. As stated above, trends toward CLAD development were more pronounced in patients with evidence of LRTI [23]. Similarly, de Zwart et al found severe infection (defined as FEV1 decline of  $\geq 10\%$  during infection compared to preinfection) to be a risk factor for CLAD development (aOR 4.63 [1.66, 12.88]) and worse FEV1 recovery in a retrospective cohort of 139 RSV/hMPV/PIV cases [26]. Permpalung et al studied 84 cases of hMPV and PIV and did not find this association for FEV1 decline at infection in univariate analysis but did find FEV1 decline  $\geq 10\%$  at 90 days postinfection compared to baseline to be associated with CLAD at 1 year in multivariate analysis and new detection of donor specific antibodies in univariate analysis [24]. The effects of new radiographic abnormalities or preexisting CLAD had conflicting

**Table 1. Studies Reporting Incidences of CLAD After RSV/hMPV/PIV Infection**

| Author, year         | Design  | Cases, N                       | Antiviral Treatment  | Other Therapy   | Antiviral Therapy/<br>Cases (%) | New or Progressive CLAD                                      |            |               | Acute Rejection  | Follow-up               |              |
|----------------------|---------|--------------------------------|--|---|---------------------------------|--|------------|---------------|--|-------------------------|--------------|
|                      |         |                                |  |   |                                 | Total, N (%)   | RBV, N (%) | No RBV, N (%) |  |                         |              |
| Pempalung 2021 [24]  | SC, RC  | hMPV: 31<br>PIV: 53            | • RBV 59 cases. Oral (10–30 mg/kg/d 10 d) or inhaled<br>• IVIG (39 cases)  | Mycophenolate dis-continuation  | 59/84 (70)                      | 25/79 (32)   | 17/56 (30) | 8/23 (35)     | 1Y: 94% deaths from graft failure                                    | Acute: 4% 1 Y: 5%       | 1 Y          |
| Testaert, 2020 [30]  | MC, RC  | RSV: 76                        | • Oral or inhaled RBV (19 cases)<br>• Palivizumab or IVIG (6 cases)  | ND  | NR                              | 6/76 (8)   | NR         | NR            | Acute phase: 98%<br>180 d: 95%                                       | 6/76 (8%)               | 90 d         |
| de Zwart, 2020 [26]  | SC, RC  | RSV: 40<br>hMPV: 46<br>PIV: 53 | Oral RBV (60 cases, various doses)<br>Inhaled RBV (11 cases)   | Oral steroids<br>0.5 mg/kg/d  | 71/139 (51)                     | 26/127 (20)  | 8/65 (12)  | 18/62 (29)    | Acute: 100%<br>180 d: 98% unrelated to infection                     | NR                      | 180 d        |
| Gottlieb, 2016 [20]  | MC, RCT | RSV: 77                        | • ALN-RSV01: 0.6 mg/kg/d. (44 randomized cases) + standard care (RBV/IVIG/palivizumab) vs placebo + standard care          | Pulse steroids  | NR                              | • 16/77 (21%)<br>-ALN-RSV 6/44 (14%)<br>-Placebo 10/33 (30%) | NR         | NR            | Acute: 100%<br>180 d: 96% unrelated to infection                     | 6/77 (8%)               | 180 d        |
| Burrows, 2015 [29]   | SC, RC  | RSV: 52                        | RBV (all cases)<br>• Loading: 33 mg/kg IV first 24 h<br>• Maintenance: 20 mg/kg/d oral, mean 10 d                          | Prednisolone<br>(1 mg/kg, max 60 mg/d)  | 52/52 (100)                     | 3/44 (7)   | 3/44 (7)   | N/A           | Acute: 100% 180 d: 96% unrelated to infection                        | NR                      | 1 Y          |
| Li, 2012 [28]        | SC, RC  | RSV: 21                        | RBV (all cases)<br>• Oral (29%): 1200 mg/d, 5–10 d<br>• Inhaled (71%), 3–5 d<br>• IVIG (29%)                               | Methylprednisolone<br>10–15 mg/kg/d (50%)                                       | 21/21 (100)                     | 2/21 (10)  | 2/21 (10)  | N/A           | Acute: 100%  | NR                      | Median 1.5 Y |
| Fuehner, 2011 [7]    | SC, PC  | RSV: 43<br>hMPV: 5<br>PIV: 19  | Oral RBV (all cases) 15–20 mg/kg/d, 14 d   | Oral steroids<br>0.5 mg/kg/d  | 38/67 (57)                      | 11/67 (16)   | 3/38 (8)   | 8/29 (28)     | Acute: 99% 1 hMPV death  | 4/67 (6%) ≥A1 AR        | 180 d        |
| Zamora, 2011 [19]    | MC, RCT | RSV: 24                        | • ALN-RSV01: 0.6 mg/kg/d. (16 cases) + standard care (RBV/IVIG/palivizumab) vs placebo + standard care (8 cases)           | (high dose) steroids  | NR                              | 5/24 (21%)   | NR         | NR            | 24/24 (100%)   | 3/24 (13%)              | 90 d         |
| Glanville, 2005 [15] | SC, PC  | RSV: 18                        | IV RBV (all cases)<br>-Loading: 33 mg/kg/first 24 h<br>-Maintenance: 20 mg/kg/d, median 8 d                                | prednisolone:<br>1 mg/kg/day + taper  | 18/18 (100)                     | 1/18 (6)   | 1/18 (6)   | N/A           | Acute: 100% 180 d: 100%  | NR                      | 1 Y          |
| Pelaez, 2009 [6]     | SC, RC  | RSV: 5                         | Oral RBV (all cases) 15–20 mg/kg/d mean 10 d   | Methylprednisolone<br>10–15 mg/kg/d<br>3 d                                      | 5/5 (100)                       | 0/5 (0)  | 0/5 (0)    | N/A           | Acute: 100% 180 d: 100%  | none                    | 1.5 Y        |
| Hopkins, 2008 [4]    | SC, PC  | RSV: 18<br>hMPV: 19            | IV RBV (LRTI cases)<br>• Loading: 33 mg/kg/first 24 h<br>• Maintenance: 20 mg/kg/d, > 10 d                                 | Methylprednisolone<br>200 mg/d, 3 d,<br>oral predni-<br>sone 1 mg/kg/d<br>taper | 25/37 (68)                      | 5/37 (14)  | 5/25 (20)  | 0/12 (0)      | • Acute: 97% 1 RSV death<br>• 180 d: 95% 1 death from progressive OB | 1 hMPV case grade B2 AR | 180 d        |
| Milstone, 2006 [16]  | SC, PC  | RSV: 8<br>PIV: 1               | Inhaled RBV (2 cases)  | NR  | 2/9 (22)                        | 0/9 (0)  | 0/2 (0)    | 0/7 (0)       | Acute: 100% 180 d: 100%  | none                    | 1 Y          |
| Weinberg 2010 [17]   | SC, PC  | hMPV: 4<br>RSV: 8<br>PIV: 11   | • Inhaled RBV (all cases), 5 d<br>• IVIG (all cases) single dose 0.4g/kg<br>• Palivizumab (RSV only) single dose 7.5 mg/kg | Methylprednisolone<br>10 mg/kg/d (all LRTI)                                     | 23/23 (100)                     | 7/22 (32) <sup>a</sup>                                       | 7/22 (32)  | N/A           | Acute: 100% 180 d: 100%  | Clinical AR <2 m: 14/23 | 1 Y          |

**Table 1. Continued**

| Author, year        | Design | Cases, N                   | Antiviral Treatment   | Other Therapy | Antiviral Therapy/<br>Cases (%) | New or Progressive CLAD |                       |                        | Survival                               | Acute Rejection       | Follow-up  |
|---------------------|--------|----------------------------|---|---------------|---------------------------------|-------------------------|-----------------------|------------------------|--|-----------------------|------------|
|                     |        |                            |   |               |                                 | Total, N (%)            | RBV, N (%)            | No RBV, N (%)          |  |                       |            |
| Uckay, 2010 [25]    | SC, RC | RSV: 10                    | • RBV IV 30 mg/kg/d or oral 1600 mg/d, 7 d<br>• Palivizumab single dose 15 mg/kg IV | NR            | 2/10 (20)                       | 6/10 (60)               | 1/2 (50)              | 5/8 (63)               | Acute: 100%<br>180 d: 100%             | 3/10 (30%) AR         | Mean 45 mo |
| Gottlieb, 2009 [10] | SC, PC | PIV: 12<br>RSV: 7 h MPV: 6 | Oral RBV (5/7 RSV)  | NR            | 5/24 (21)                       | 8/24 (33) <sup>a</sup>  | 1/5 (20)              | 7/19 (37) <sup>a</sup> | Acute: 100%<br>180 d: 100%             | NR                    | 1 Y        |
| Khalifah, 2004 [23] | SC, RC | RSV: 8<br>PIV: 7           | Inhaled RBV (3/7 RSV)   | None          | 3/15 (20%)                      | 8/15 (53%)              | NR                    | NR                     | 53% in follow-up.<br>Causes NR         | 1/15 ≥A1 AR           | Mean 2.9 y |
| Palmer, 1998 [21]   | SC, RC | RSV: 5<br>PIV: 2           | Inhaled RBV (4/5 RSV)   | none          | 4/7 (57)                        | 2/6 (33) <sup>a</sup>   | 2/3 (66) <sup>a</sup> | 0/3 (0) <sup>a</sup>   | Acute: 86%<br>1 RSV death              | NR                    | Mean 2.1 y |
| Vilchez, 2001 [36]  | SC, RC | PIV: 24                    | None  | NR            | 0/24 (0)                        | 7/22 (32) <sup>a</sup>  | NA                    | 7/22 (32) <sup>a</sup> | 1 Y: 92%<br>Infection not direct cause | 18/22 AR at infection | 1 y        |

Abbreviations: AR, acute rejection; CLAD, chronic lung allograft dysfunction, hMPV, human metapneumovirus; IVIG, intravenous immunoglobulin; NA, not applicable; NR, not reported; PC, prospective cohort; PIV, parainfluenza virus; RBV, ribavirin; RC, retrospective cohort; RCT, randomized controlled trials; RSV, respiratory syncytial virus; SC, single center.  
<sup>a</sup>Incidence at 1-year follow-up.

**Table 2. Studies Reporting Other Long-Term Graft Function Endpoints**

| Author, year          | Design    | Cases, N                                     | Antiviral Treatment  | Other Therapy                 | Antiviral Therapy, cases (%) | Outcomes  | Survival   | Acute Rejection | Follow-up    |
|-----------------------|-----------|--|--|-------------------------------|------------------------------|---|--|-----------------|--------------|
| Permpalung, 2019 [37] | SC, RC    | RSV: 85                                      | • Oral RBV (56 cases): 15–20 mg/kg/d in 3 doses 5–10 d<br>• Inhaled RBV (29 cases): 6 g daily, 5 d | NR                            | 85/85 (100)                  | • 90 d FEV1 decline from baseline: ≥5%: 24/76 cases ≥10%: 11/76 cases   | 87% at end of follow-up, all unrelated to RSV              | NR              | 1 y          |
| Magnusson, 2018 [18]  | SC, PC    | RSV: 10<br>hMPV: 5<br>PIV: 4<br>Other: 103   | None   | NR                            | 0/19 (0)                     | Any CARV infection associated with CLAD in multivariate analysis. No association for RSV or hMPV with CLAD in univariate analysis   | NR   | NR              | 5 y          |
| Garcia, 2019 [38]     | MC (2) RC | RSV: 14<br>PIV: 8<br>hMPV: 4                 | Oral RBV: 400–600 mg 2–3/d, 7–10 d   | NR                            | 26/26 (100)                  | 180 d no significant mean FEV1 decline postinfection compared to preinfection for all PMV   | • 180 d: no deaths reported                                | NR              | 180 d        |
| Allyn, 2016 [8]       | SC, PC    | RSV: 24<br>PIV: 42<br>hMPV: 20<br>Other: 196 | NR   | NR                            | NR                           | • Total virus group: viral pneumonia associated with CLAD (aHR 3.94 [1.97–790]) and graft loss (aHR 2.78 [1.55–5.00])<br>• PIV increased risk of CLAD (HR 2.18 [1.34–3.56]), no effect on graft loss. | Total virus group: graft loss hastened by viral pneumonia. | NR              | Median 3.0 y |
| Niggi, 2016 [39]      | SC, RC    | hMPV: 15                                     | Oral RBV First 48 hr: 1600 mg/d Then: 400 mg/d Mean 29 d   | Doubling maintenance steroids | 12/15 (80)                   | 90 d mean FEV1 returned to preinfection value   | • Acute: 100%<br>• 90 d: 100%                              | NR              | 90 d         |
| Bridevaux, 2014 [40]  | SC, PC    | RSV: 11<br>hMPV: 8<br>PIV: 6                 | NR   | NR                            | NR                           | FEV1 dropped at infection, but returned to preinfection values during recovery.   | Acute: 100%  | None            | 720 d        |

**Table 2. Continued**

| Author, year      | Design | Cases, N                  | Antiviral Treatment  | Other Therapy  | Antiviral Therapy, cases (%) | Outcomes   | Survival  | Acute Rejection                                | Follow-up    |
|-------------------|--------|---------------------------|--|--|------------------------------|--|---|--|--------------|
| Shahda, 2011 [22] | SC, RC | hMPV: 4                   | None   | Supportive care  | 0/4                          | 2/4 worsened lung function, 2/4 died   | Acute: 2/4 (50%)  | 2/4  | NR           |
| Kumar, 2010 [41]  | SC, PC | RSV: 2<br>PIV: 15 hMPV: 4 | NR   | NR   | NR                           | >20% FEV1 decline or biopsy proven AR ≤ 3 mo.<br>PIV: 4/15<br>RSV: 1/2<br>hMPV: 1/4  | NR for RSV/hMPV/PIV   | See outcomes                                   | 90 d         |
| Liu, 2010 [27]    | SC, RC | RSV: 23 PIV 1–3: 7        | <ul style="list-style-type: none"> <li>Inhaled RBV (RSV only), 5 d</li> <li>Palivizumab (RSV only) 15 mg/kg IV</li> <li>IVIg (all) Single dose 0.5 g/kg</li> </ul> | Methylprednisolone 500 mg/d<br><br>1 patient high-dose pulsed steroids for rejection | 30/30 (100)                  | <ul style="list-style-type: none"> <li>180 d FEV1 significantly lower in patients with preexisting CLAD and significantly lower compared to baseline.</li> <li>Patients without prior CLAD: mean % of baseline: 105%</li> <li>Patients with prior CLAD: mean % of baseline: 90%</li> </ul> | <ul style="list-style-type: none"> <li>Acute: 100%</li> <li>180 d: 96% unrelated to infection</li> </ul>      | 1 AR at presentation, 3 AR in follow-up low-up | 180 d        |
| McCurdy, 2003 [5] | SC, RC | RSV: 12 PIV: 5            | Inhaled RBV (all patients), median 5 d   |  | 17/17 (100)                  | <ul style="list-style-type: none"> <li>90 d: full FEV1 recovery in 10/13 (77%)</li> <li>3/13 persistent decline of 12%–35%</li> </ul>  | <ul style="list-style-type: none"> <li>Acute 13/15 (87%), 2 RSV deaths</li> <li>180 d: 13/15 (87%)</li> </ul> | 1 AR at presentation                           | Median 343 d |
| Wendt, 1995 [42]  | SC, RC | RSV: 9<br>PIV: 10         | Inhaled RBV (14/19), median 5 d  |  | 14/19 (74)                   | 1/14 vs 1/5 cases no return to baseline FEV1 for RBV treated vs not treated respectively   | <ul style="list-style-type: none"> <li>Acute: 1 RSV death</li> </ul>  |  | 90 d         |

Abbreviations: aHR, adjusted hazard ratio; AR, acute rejection; CLAD, chronic lung allograft dysfunction; hMPV, human metapneumovirus; IVIG, intravenous immunoglobulin; NA, not applicable; NR, not reported; PC, prospective cohort; PIV, parainfluenza virus; RBV, ribavirin; RC, retrospective cohort; RCT, randomized controlled trials; RSV, respiratory syncytial virus; SC, single center.

results with two studies reporting worse recovery and CLAD [8, 27], whereas others found no association with these factors [4, 26]. Other factors associated with increased CLAD incidence postinfection in multivariate models were acute rejection [8, 14, 18, 23] and longer time since transplantation [7].

**Treatment**

Fourteen studies reported temporarily increased steroid therapy during infection, albeit with large variation in doses (Tables 1 and 2). Two studies reported no alteration in immunosuppressive regimen during infection [21, 23].

Antiviral treatment strategies for the included studies are reported in Tables 1 and 2 and consisted mainly of RBV with or without IVIG for RSV, hMPV, or PIV (23 studies) and/or palivizumab for RSV (6 studies). Data on effectiveness of RBV were mostly available from studies not specifically designed or powered to find an association, and outcomes were conflicting (Tables 1 and 2).

Only 1 prospective study compared LTRs with either PIV, RSV, or hMPV treated with oral RBV (n = 38) to LTRs not treated with RBV due to contra indications (n = 29) [7]. There were no baseline differences in time since transplantation, age, transplantation type, or immunosuppressive regimen between the groups. New onset CLAD at 6 months developed in 5% of the RBV group versus 24% of the non-RBV group (P = .02). Graft function recovered within 30 days in 84% of patients treated with RBV and 59% of the non-RBV group (P = .02). Four other studies found similar incidences of graft dysfunction of 6–12% after systemic or aerosolized RBV [15, 26, 28, 29].

de Zwart et al found a positive association of RBV for FEV1 6 months postinfection (+13.2% [7.79, 18.67]) and CLAD incidence (aOR 0.24 [0.10–0.59]) in multivariate analysis of 139 cases (71 received RBV) [26]. Conversely, Permpalung et al did not find a protective effect of RBV therapy on CLAD development in their retrospective cohort of 84 LTR with hMPV or PIV (aHR 1.60 [0.36, 7.05] P = .54, and .31 [0.06, 1.71] P = .18, for PIV and hMPV respectively) [24].

Seven studies reporting CLAD in RBV treated and untreated cases were included for exploratory meta-analysis into RBV effect (Table 3). No significant overall effect of RBV was detected (OR 0.61 [0.27–1.18], P = .16,  $\tau^2 = 0.24$ ); however, studies showed considerable heterogeneity in effect estimates (Figure 2). Furthermore, an additional analysis was performed including only the studies which reported proportions of suspected LRTI for the treatment groups and used the difference between these proportions as a covariate in the same model. This resulted in a similar overall effect estimate for RBV (OR 0.57 [0.24–1.30] P = .16) as well as an indeterminate association of the difference in treatment ratio with CLAD (OR 0.33 [0.10–0.99], P = .05,  $\tau^2 = 0.30$ ) with the latter coefficient suggesting a lower CLAD incidence if LRTI was more common in RBV treated patients compared to RBV untreated patients.

**Table 3. Studies Reporting on Incidence of New or Progressive CLAD in Ribavirin Treated and Untreated Cases**

| Author, year          | LRTI Suspected                           | New or Progressive CLAD |               |
|-----------------------|--|-------------------------|---------------|
|                       |  | RBV Treated, N (%)      | No RBV, N (%) |
| Permpalung, 2021 [24] | RBV: 29/56 (52%)<br>non-RBV: 13/23 (56%) | 17/56 (30)              | 8/23 (35)     |
| De Zwart, 2020 [26]   | RBV: 55/65 (84%)<br>non-RBV: 29/62 (47%) | 8/65 (12)               | 18/62 (29)    |
| Fuehner, 2011 [7]     | RBV: 20/38 (52%)<br>non-RBV: 15/29 (53%) | 3/38 (8)                | 8/29 (28)     |
| Hopkins, 2008 [4]     | RBV: 25/25 (100%)<br>non-RBV: 0%         | 5/25 (20)               | 0/12 (0)      |
| Gottlieb, 2009 [14]   | Overall 76%                              | 1/5 (20)                | 7/19 (37)     |
| Palmer, 1998 [21]     | RBV: 3/3 (100%)<br>non-RBV: NR/3         | 2/3 (66)                | 0/3 (0)       |
| Milstone, 2006 [16]   | RBV: 2/2 (100%)<br>non-RBV: 1/7 (14%)    | 0/2 (0)                 | 0/7 (0)       |
|                       |  | Pooled incidence        |               |
|                       |  | 19/138 (14)             | 33/132 (25)   |

Abbreviations: CLAD, chronic lung allograft syndrome; LRTI, lower respiratory tract infection; RBV, ribavirin.

**Other Antivirals**

We focused our main analysis on RBV because this is the most widely used antiviral for RSV/hMPV/PIV infections; however 10 studies reported on other antivirals [17, 19, 20, 24, 25, 27, 28, 30]. Two sequential phase-2 randomized controlled trials (RCTs) studied the interfering RNA ALN-RSV01, which targets RSV. The first study (ALN-RSV01 n = 8, placebo n = 16) was designed to determine safety of the drug with graft function and viral parameters as secondary explorative endpoints and found significantly lower symptom scores and CLAD incidence in the ALN-RSV01 group compared to placebo [19]. No significant effect was observed on viral clearance. The second study (ALN-RSV01 n = 44, placebo n = 33) found the primary endpoint of incidence of new or progressive CLAD at 180 days to be lower in the ALN-RSV01 group with a treatment effect of 55% in the intention to treat population (P = .058) and 65% for the per protocol population (P = .025) [20]. No effects on viral clearance, symptom score,

duration of hospitalization, acute rejection, survival, or FEV1 return to >80% of preinfection value were detected. RBV and increased steroids were permitted at physician preference and were balanced between the groups (78% of patients received RBV). Although not powered for this, the study found no modifying effects of RBV on outcomes in a multivariate analysis.

Unfortunately, data on palivizumab and IVIG use were too fragmented in the included studies to meaningfully analyze.

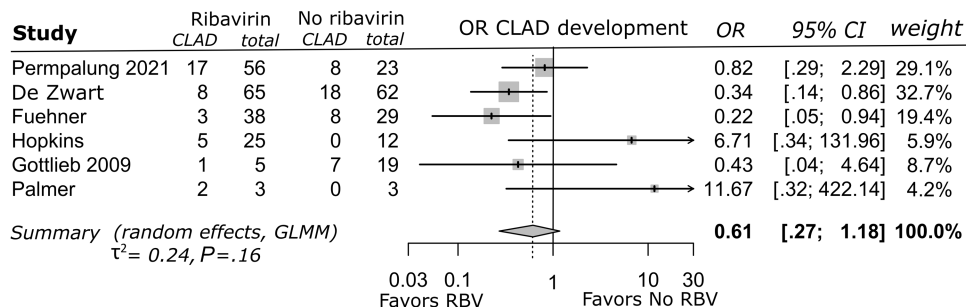
Finally, 2 case-reports studying inhaled DAS181 (a sialidase fusion protein) for PIV3 described beneficial outcomes, with no larger studies available [31, 32].

**DISCUSSION**

In this systematic review we aimed to gather all available data on RSV/hMPV/PIV infections in LTR to estimate associations with long-term morbidity and evaluate treatment strategies.

We found an overall low incidence of 30-day mortality for RSV/hMPV/PIV infections in LTR of 0–1%.

Although direct virus-attributed long-term mortality was mostly low (with some marked exceptions), the high pooled CLAD incidence of 19–24% 180 days to 1 year postinfection is of concern. Of the few studies comparing LTR with a VRI to LTR without, most found an association with VRI and the development of CLAD, which is in concordance with earlier studies [14, 18, 23]. Fisher et al showed that VRI were independently associated with CLAD development (aHR 1.9 [1.1–3.5]) in a retrospective study of 250 LTR [33]. Likewise, Peghin et al identified viral LRTI to be independently associated with CLAD development (aHR 3.00 [1.52–5.91]), but found no association in case of URTI or asymptomatic infection [9]. Finally, Allyn et al described that viral pneumonia (defined as symptomatic infection with a chest infiltrate on X-ray without clear explanation) was associated with CLAD and graft loss, whereas no associations for asymptomatic or symptomatic patients without infiltrates was found [8]. This underlines the importance of the initial severity of infection



**Figure 2.** Forest plot of odds ratio for CLAD according to ribavirin treatment. Summary odds ratio is from the random effects generalized linear mixed effect model ( $\tau^2 = 0.24$ ). Abbreviations: CI, confidence interval; CLAD, chronic lung allograft dysfunction; GLMM: generalized linear mixed effect model; OR: odds ratio; RBV, ribavirin.

when studying an association with subsequent allograft dysfunction and may explain the relatively favorable outcomes of patients with a mild infection [4, 16, 25]. Although risk factors for CLAD development were mostly non-consistent across studies, more clinically severe infection [8, 9, 14, 26] and failure of early recovery of FEV1 [24] may be of predictive value for CLAD development and may help clinicians identify LTR at risk.

The precise pathological mechanisms through which these infections relate to CLAD are unknown but may involve alveolar damage through the CXCR3 ligand pathway, which has been linked to decreased FEV1 postinfection [34], or exosome induction which may result in CLAD [35]. It is plausible these mechanisms are aggravated in patients showing severe infection, leading to adverse outcomes. Yet it is unclear to what extent mildly symptomatic patients exhibit these mechanisms.

Although most of the included studies used some modality of RBV with or without IVIG combined with temporary steroid augmentation, the efficacy of this treatment strategy was unclear. High-quality evidence in the form of randomized trials regarding RBV treatment is lacking, limiting assessment of its true effectiveness. RBV treatment showed promising results in smaller studies but conflicting results between the larger studies using multivariate analysis methods. In the exploratory meta-analysis RBV was overall not significantly associated with a reduction in CLAD. However, because of the relatively small studies with heterogeneous effect estimates and lack of adequate controlling for confounders (including differing virus species and variability in steroid use), firm conclusions about RBV efficacy cannot be made. Furthermore, the found heterogeneity could probably be partially explained by the difference in treatment ratios of LRTI, as patients with LRTI (compared to URTI) likely have a higher propensity to receive RBV thereby confounding effect estimates. To explore this phenomenon, we performed an additional analysis concerning the association of difference in suspected LRTI rates between treatment groups with CLAD. Although subjected to the same limitations as the primary analysis, it raises the question as to whether starting RBV may be beneficial in more severe cases compared with milder cases.

Potential future vaccines are currently being developed and tested for RSV [2], hMPV, and PIV (Trial Registration NCT04144348). Several developmental antivirals have been tested for RSV and PIV, although 3 RSV compounds (ALN-RSV01, presatovir/GS-5806, lumicitabine/ALS-008112), were discontinued or have no registered follow-up studies planned for this population [2].

This review has some limitations. First, the inability to abstract individual patient data from some of the studies despite contacting authors, limits their inclusion in the meta-analysis. Nonstandardized definitions of LRTI as well as different respiratory viruses across studies probably rendered the results more

heterogeneous. Although RSV/hMPV/PIV are all in vitro susceptible to RBV, sensitivity and clinical efficacy may differ per specific virus, with least evidence available for PIV [2]. Indeed, treatment outcomes varied between the viruses as well within types of virus in the included studies, with most evidence concerning RSV and hMPV. One study found no interaction of treatment with specific viruses indicating this did not influence the association of RBV and CLAD [26], although another found no association for RBV and CLAD when analyzing hMPV and PIV separately [24]. We could not assess the effect of RBV per specific virus due to sample size restrictions, but the overall results may have been influenced by different susceptibility to RBV.

In summary, we report a comprehensive oversight of the impact, risk factors and treatment strategy for RSV/hMPV/PIV infections in LTR. RBV was frequently offered, with or without additional therapy. Data were too variable and included study quality was insufficient for formal statements about RBV efficacy. Physicians should individually weigh potential benefits, harm and costs before starting RBV (combined with corticosteroids and/or IVIG and/or palivizumab in case of RSV) for RSV and hMPV (to a lesser extent PIV) in LTR for prevention of CLAD. Such treatment is preferably evaluated under study conditions while awaiting better antiviral options or more evidence from well-designed trials on RBV effectiveness.

#### Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

#### Notes

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