Respiratory syncytial virus and human metapneumovirus after allogeneic hematopoietic stem cell transplantation: Impact of the immunodeficiency scoring index, viral load, and ribavirin treatment on the outcomes

Mobil Akhmedov | Verena Wais | Elisa Sala | Adela Neagoie | Thanh Mai Nguyen | Andrea Gantner | Stephanie von Harsdorf | Florian Kuchenbauer | Axel Schubert | Detlef Michel | Hartmut Döhner | Donald Bunjes

1Department of Internal Medicine III, University Hospital of Ulm, Ulm, Germany
2Department of Virology, University Hospital of Ulm, Ulm, Germany

Correspondence
Donald Bunjes, Department of Internal Medicine III, University Hospital of Ulm, 89081, Albert-Einstein-Allee 23, Ulm, Germany.
Email: donald.bunjes@uniklinik-ulm.de

Abstract

Introduction: Respiratory viral infections are a major cause of morbidity and mortality among stem cell transplant recipients. While there is a substantial amount of information on prognostic factors and response to ribavirin therapy is available for RSV infections, this information is largely lacking for hMPV.

Patients and methods: In total, 71 patients were included in this study: 47 patients with RSV and 24 with hMPV. Forty-one patients presented as an upper respiratory tract infection (URTI) and 30 as a primary lower respiratory tract infection (LRTI). Patients were stratified as per ISI criteria into low-, moderate-, and high-risk groups. Twenty-two patients in the URTI cohort received treatment with ribavirin (mainly oral), and 19 patients received no antiviral therapy. The decision for antiviral treatment was at the discretion of the attending physician. All 30 patients with primary LRTI and 10 patients with secondary LRTI were treated with ribavirin, 95% with the intravenous formulation. 45% of these patients received additional treatment with intravenous immunoglobulins. The viral load was assessed indirectly by using the CT value of the RT-PCR.

Results: In the cohort, as whole 11.5% suffered a virus-associated death, 5% in the URTI group, and 20% in the LRTI group. Sixty-day mortality was significantly higher in the ISI high-risk group (log-rank \( P = .05 \)). Mortality was independent of the type of virus (\( P = .817 \)). Respiratory failure with an indication for mechanical ventilation developed in 11.5%, this risk was independent of the type of virus. Progression from URTI to LRTI was observed in 24% of cases with a significantly higher risk (75%) in the ISI high group (log-rank \( P = .001 \)). In the ISI high-risk group, treatment with ribavirin significantly reduced the risk of progression (log-rank \( P < .001 \)). Neither the type of virus nor the viral load in the nasopharyngeal swab impacted the risk of progression (\( P = .529 \) and \( P = .141 \), respectively). The detection of co-pathogens in the BAL fluid was borderline significant for mortality (\( P = .07 \)).
Conclusions: We could detect no differences between RSV and hMPV with respect to progression to LRTI, risk of respiratory failure or need for mechanical ventilation and virus-associated death. The ISI index is of predictive value in hMPV patients with a high ISI score and treatment with oral ribavirin has an equivalent protective effect in RSV and hMPV patients. Treatment of LRTI with intravenous ribavirin results in a similar outcome in RSV- and hMPV-infected patients. We could not detect any benefit of adjunctive treatment with immunoglobulins in both primary and secondary LRTI. No role of viral load as an independent prognostic marker could be detected either for progression to LRTI or death.

KEYWORDS
allogeneic hematopoietic stem cell transplantation, human metapneumovirus, ISI, respiratory syncytial virus, ribavirin

1 | INTRODUCTION

Respiratory syncytial virus (RSV) and human metapneumovirus (hMPV) are Pneumoviridae family RNA viruses that are a common causes of seasonal mild, self-limited upper respiratory tract infection (URTI) in immunocompetent children and nonelderly adults. However, in allogeneic hematopoietic stem cell transplant (allo-HCT) recipients these infections can lead to serious complications including lower respiratory tract infection (LRTI) and death. Multiple risk factors such as lymphopenia, neutropenia, older age, mismatched (MMUD) or matched unrelated donor (MUD), and infection within 1 months after stem cell transplantation or pre-engraftment have been identified to be associated with a higher risk of progression to LRTI and higher mortality rate among allo-HCT recipients infected with RSV.1,3 In order to predict the risk of progression to LRTI and death among RSV-infected allo-HCT recipients and thus identify high-risk patients who could potentially benefit from ribavirin-based therapy, the immunodeficiency scoring index (ISI) was recently introduced.6 Steroid use prior to URTI diagnosis, lymphopenia, and the onset of viral infection before day 30 after stem cell transplant were associated with higher progression to hMPV LRTI5 but the ISI has so far not been evaluated in hMPV infections.

Despite a lack of randomized, controlled trials and uncertainty about the optimum formulation (inhaled, oral or intravenous), ribavirin alone or in combination with intravenous immunoglobulin (IVIg) is the mainstay of therapy of RSV infections in immunocompromised patients.6 It reduces the risk of progression to LRTI and appears to improve outcome if used early.7 Its therapeutic role in hMPV is poorly defined, no significant protective effect of ribavirin in preventing hMPV mortality could be observed in a recent review.8 In view of the virological and clinical similarities between RSV and hMPV, we decided to compare RSV and hMPV with respect to outcome, predictive factors for outcome and response to ribavirin therapy in a cohort of 71 patients with RSV or hMPV infection after allogeneic stem cell transplantation.

2 | PATIENTS AND METHODS

This retrospective study included 71 adult patients diagnosed with RSV and hMPV respiratory tract infections who underwent allogeneic stem cell transplantation at Ulm University Hospital between 2005 and 2018. Detailed patient characteristics are given in Table 1. URTI was defined as a positive RSV or hMPV PCR test from a nasopharyngeal swab with symptoms of upper respiratory tract infection and no pulmonary infiltrates on chest radiograph or CT scan. A probable/presumptive LRTI was defined as per European Conference on Infections in Leukemia (ECIL-8) recommendation update as symptoms of lower respiratory tract infection, pulmonary infiltrates seen on chest radiograph or CT scan and a positive RSV or hMPV PCR or immunofluorescent assay test from bronchoalveolar lavage. A possible LRTI was defined as symptoms of lower respiratory tract infection with pulmonary infiltrates seen on chest radiograph or CT and a positive RSV or hMPV PCR test from the nasopharyngeal swab in the absence of BAL samples. Viral load in the nasopharyngeal swab or BAL was indirectly measured by the real-time polymerase chain reaction (RT-PCR, DiagCORE Respiratory Panel 2, Qiagen) cycle threshold (CT) level. A CT value below the median was defined as a high viral load.

Patients were stratified as per ISI criteria 4—three points for each of: ANC < 500/µl, ALC < 200/µl; two points for age > 40 years; and one point for each: acute or chronic graft-vs-host disease, corticosteroids use within 30 days of infection, viral infection within 30 days after transplant or pre-engraftment—into low (2 points in total), moderate (3-6 points), and high (7-12 points) risk groups.

Patients with URTI received treatment with ribavirin or no treatment. The decision to treat was at the discretion of the attending physician. Treatment consisted of either oral ribavirin (Rebetol®) at a dose of 400 mg TID or QID (n = 20), intravenous ribavirin (n = 1) or with a combination of intravenous ribavirin (Virazole®) 10 mg/kg TID and intravenous immunoglobulin (Pentaglobin®) 5 mL/kg for 3 days (n = 1). Nineteen patients in the URTI cohort received
no antiviral therapy. Before 2011, patients with primary lower respiratory tract viral infection were treated either with intravenous (Virazole®) 10 mg/kg TID (n = 10) or oral (Rebetol®) 400 mg TID or QID (n = 2) ribavirin in monotherapy, after 2011—with a combination of intravenous ribavirin (Virazole®) 10 mg/kg TID and intravenous immunoglobulin (Pentaglobin®) 5 mL/kg for 3 days. (n = 18). Patients who progressed to LRTI from URTI stage (secondary LRTI) received treatment with either oral ribavirin (Rebetol®) at a dose of 400 mg QID (n = 1), intravenous ribavirin (n = 1) or with a combination of intravenous ribavirin (Virazole®) 10 mg/ kg TID and intravenous immunoglobulin (Pentaglobin®) 5 mL/kg for 3 days (n = 8).

Statistical analysis was performed using SPSS version 23.0 (IBM). Categorical variables were analyzed using Pearson’s chi-square test or Fisher’s exact test for small groups. Time to event analysis was performed using the Kaplan-Meier method, and the log-rank test was used to compare risk groups. A Cox proportional hazards regression model was used to estimate the significance of the variables type of virus, viral load, risk group and treatment for the outcome variables progression, death due to viral infection, need for mechanical ventilation and survival. Virus-associated mortality was defined as persistent or progressive RSV or hMPV infection and respiratory failure at the time of death. P < .05 was considered statistically significant.

### RESULTS

Thirty-eight patients were studied. Eight patients (11.5%) died due to their viral infection: 6 (55%) in high-, 2 (14%) in moderate-, 0 in low-risk groups (Tables 2 and 3). The mean time from infection till death was 34 days. No difference in mortality could be detected between RSV and hMPV (P = .814). Eight patients (11.5%) developed severe respiratory failure requiring mechanical ventilation 4 of whom declined treatment. Sixty-day overall survival was significantly lower in the ISI high-risk group (54.5%) compared with low- (90.9%) and moderate-risk (79.6%) patients with a log-rank p-value of 0.05 (Figure 1).

Of the 41 patients with URTI at presentation, 24 had RSV and 17 hMPV identified as the causal pathogen. Ten patients (24%) experienced progression to LRTI (Table 2), 21% in the RSV group and 29% in the hMPV group. The median time to progression was 9.5 days (range 5-42). We evaluated the impact of the virus type, viral load at diagnosis, ISI score and treatment with ribavirin on the risk of progression to LRTI. The type of virus had no significant impact (P = .529). Viral load at presentation as measured by the CT value of RT-PCR performed on the nasopharyngeal swab was available for 38 of the 41 patients (93%). Viral load at diagnosis had no independent prognostic value for the risk of progression (HR = 2.63; 95% CI: 0.68-10.2; P = .142). The ISI score classified 7 patients as low-risk, 30 patients as moderate-risk, and 4 patients as high-risk. The risk of progression in the high-risk group (75%) was significantly higher (P = .001) than in the low- (14%) or moderate-risk (20%) groups. Treatment with ribavirin

### TABLE 1 Patient characteristics in the URTI and LRTI cohorts

| Variable                                      | URTI cohort | LRTI cohort |
|-----------------------------------------------|-------------|-------------|
| N                                             | 41          | 30          |
| Median age, years                             | 53 (range 22-68) | 55.5 (range 20-70) |
| Median time to infection after transplantation, days | 287 (range 5-1495) | 178 (range 5-1740) |
| Gender, n (%)                                 |             |             |
| Male                                          | 36 (65.9)   | 19 (63.3)   |
| Female                                        | 14 (24.1)   | 11 (36.7)   |
| Diagnosis, n (%)                              |             |             |
| AML                                           | 15 (36.6)   | 15 (50)     |
| ALL                                           | 4 (9.8)     | 2 (6.7)     |
| MDS                                           | 8 (18.9)    | 3 (10)      |
| CLL                                           | -           | 2 (6.7)     |
| CML                                           | 3 (7.3)     | 5 (16.7)    |
| MF                                            | 2 (4.9)     | -           |
| NHL                                           | 7 (17)      | 2 (6.6)     |
| MM                                            | 2 (4.9)     | 1 (3.3)     |
| MA conditioning, n (%)                        | 30 (73)     | 16 (53.3)   |
| Donor type, n (%)                             |             |             |
| MRD                                           | 11 (26.8)   | 9 (30)      |
| MUD                                           | 26 (63.4)   | 16 (53.3)   |
| MMUD                                          | 3 (7.3)     | 3 (10)      |
| Haploidentical                                | 1 (2.4)     | 2 (6.7)     |
| Graft Source, n (%)                           |             |             |
| PBSC                                          | 40 (97.6)   | 30 (100)    |
| BM                                            | 1 (2.4)     | -           |
| Virus type, n (%)                             |             |             |
| RSV                                           | 24 (58.5)   | 23 (76.7)   |
| MPV                                           | 17 (41.5)   | 7 (23.3)    |
| Median viral load, RT-PCR CT level            | 31.5 (range 22-40) | 28.5 (range 18-37) |
| ISI Risk Group, n (%)                         |             |             |
| Low                                           | 7 (17.1)    | 4 (13.3)    |
| Moderate                                      | 30 (73.2)   | 19 (63.3)   |
| High                                          | 4 (9.8)     | 7 (23.3)    |
| Treatment, n (%)                              |             |             |
| Ribavirin oral                                | 20 (48.8)   | 2 (6.7)     |
| Ribavirin iv                                  | 1 (2.4)     | 10 (33.3)   |
| Ribavirin iv ± IVlg                            | 1 (2.4)     | 18 (60.0)   |
| None                                          | 19 (46.4)   | -           |

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BM, bone marrow; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; MF, myelofibrosis; MM, multiple myeloma; MMUD, mismatched unrelated donor; MRD, matched related donor; MUD, matched unrelated donor; NHL, non-Hodgkin lymphoma; PBSC, peripheral blood stem cells.
had a significant effect on the risk of progression only in the high-risk patients (P < .001; Figure 2). Overall 2 patients (5%) with an URTI at presentation died of respiratory failure after progression to LRTI.

Thirty patients presented with a primary LRTI (77% RSV, 23% hMPV) and 10 further patients developed secondary LRTI from URTI (50% RSV, 50% hMPV). All patients were treated with ribavirin predominantly intravenously (n = 38) and orally in 2 patients. Eighteen patients received additional treatment with high-dose intravenous immunoglobulins. We investigated the impact of the type of virus, viral load in the BAL fluid, the ISI score, additional treatment with immunoglobulins and the presence of co-pathogens on mortality. The mortality rate of 20% was identical in both primary and secondary LRTI, and there were no significant differences between RSV and hMPV (P = .507). Viral loads in the BAL fluid were available for 18 patients (60%) and had no impact on survival. With respect to the ISI score, we observed a trend toward higher mortality in the high-risk group but this was not statistically significant (P = .160; Figure 3). Additional treatment with intravenous immunoglobulins had no impact on survival (P = .507). Co-pathogens were frequently identified in the BAL fluid (45%) in both RSV (45.4%) and hMPV (41.7%) patients. The most common co-pathogens were aspergillus (61.1%) and influenza B. The detection of a co-pathogen was of borderline significance for survival (P = .07).

Ribavirin treatment was associated with hemolytic anemia and had to be stopped in 18% and 13% of patients in URTI and LRTI cohorts, respectively. There was no significantly different rate of ribavirin-induced side effects between oral (20%) and intravenous (12.5%) formulations (P = .466).

**4 | DISCUSSION**

Respiratory viral infections are a major cause of morbidity and mortality among hematopoietic stem cell transplant recipients. Here, we present a single-center, 14-year experience of RSV and hMPV infections. The aims of the study were to compare RSV and hMPV, to evaluate treatment, and to identify prognostic factors. In view of the latter, several attempts have been made to better define high-risk HCT recipients with respiratory viral infections requiring early intervention. In a report by Khanna et al, severe immunodeficiency as per Basel Immunodeficiency Grades was associated with higher mortality in RSV-infected patients. Both the Basel score and the
ISI were also investigated in HCT recipients with influenza, parainfluenza, hMPV, and other respiratory viral infections\textsuperscript{10-15} and were found to have similar predictive power based on direct comparison of the two approaches.\textsuperscript{12,15,16}

In the current study, the overall outcome of the entire cohort of patients (virus-related mortality 11.5%, need for mechanical ventilation 11.5%) is in line with the results of multiple reviews and studies.\textsuperscript{7,8} There were no significant differences in any of the outcome measures between RSV and hMPV. The ISI proved to be a powerful predictor of survival with patients in the high-risk group having a statistically significant higher risk of death within 60 days of diagnosis. Similar results have been previously reported for RSV but this has not so far been documented for hMPV.\textsuperscript{17}

With respect to URTI, our study confirms the previously reported favorable outcome (virus-related mortality 5%). We observed a progression to LRTI rate of 24% which is in the range documented in previous reports. Two factors had a statistically significant impact on the risk of progression, assignment to the ISI high-risk group and treatment with ribavirin in the ISI high-risk group. The type of virus had no impact. We had hypothesized that the viral load at presentation indirectly measured by the RT-PCR cycle threshold level might prove to be of prognostic value but this was not the case. The value of the ISI score for predicting the risk of progression has been previously reported for RSV as well as for influenza and coronavirus but not for hMPV.\textsuperscript{10,18-20} The ability of ribavirin to reduce the risk of progression in RSV URTI has been reported previously but similar data for hMPV have not been presented. We are not aware of any reports evaluating the role of the viral load at diagnosis for URTI.

The virus-related death rate of 20% in both primary and secondary LRTI is consistent with previous reports.\textsuperscript{7-8,12,15,21} We observed no difference in mortality between RSV and hMPV LRTI similar to the data presented in the only published report directly comparing these 2 infections by Renaud et al.\textsuperscript{17} We were unable to confirm the prognostic impact of the ISI score for LRTI although there was a trend toward higher mortality in the high-risk group. This may simply be due to the sample size. Viral load in the BAL fluid at diagnosis had

**FIGURE 2** Progression to LRTI in URTI cohort. ISI could predict progression to LRTI rate in the entire URTI cohort (left diagram) and after adjustment to antiviral therapy (right diagram). AVT—antiviral therapy

**FIGURE 3** Mortality rate in LRTI cohort. The trend of increasing mortality from low- to moderate- and to high-risk patients with primary LRTI did not meet statistical significance.
no predictive value. Similar results have been previously reported for a variety of respiratory viruses which is in marked contrast to other viruses such as CMV and HSV. Similar to Renaud et al, we observed a high incidence of co-pathogens (45%) with no difference between RSV and hMPV patients. The most common co-pathogens were molds (aspergillus) and viruses (HHV6, influenza B). The presence of a co-pathogen was associated with a higher mortality (33.3% vs 9.1%) but this was of borderline significance (P = .07). This suggests that a comprehensive screening for respiratory co-pathogens is mandatory and is likely to have an impact on therapy and prognosis.

Treatment with ribavirin is a well-established therapeutic modality for RSV infections although there are no randomized clinical trials available to prove its therapeutic efficacy. Ribavirin regardless of its form has been demonstrated to reduce the risk of progression from URTI to LRTI in several studies, and there is also some evidence that the outcome of LRTI might be improved with early treatment. No convincing data are available for ribavirin treatment for hMPV in the same settings. More recently data have emerged suggesting that the oral formulation is as effective as the aerosolized formulation for patients with RSV. 50% of our patients with RSV and hMPV URTI were treated with oral ribavirin, and this significantly reduced the risk of progression in the ISI high-risk group irrespective of the virus type. Although we do recognize relatively small number of hMPV cases included, this provides some indirect evidence for the efficacy of ribavirin in hMPV URTI. Since all our patients with LRTI were treated with intravenous ribavirin, we have no untreated control group. The outcome data can therefore provide only indirect evidence for efficacy of the ribavirin and its intravenous formulation. The data for intravenous ribavirin in the literature are very limited. The rate of virus-related deaths of 20% in a substantial cohort of 40 patients is in line with reports on aerosolized and oral formulations. Given that the risk of virus-related death was identical for RSV and hMPV one can suggest that if there are differences in efficacy for the 2 viruses they are unlikely to be large. By pure chance, approximately 50% of our cohort of LRTI patients were treated with additional high-dose immunoglobulins. We found no evidence of any additional benefit of this adjunctive therapy on survival of patients presented with primary and secondary LRTI (P = .507). This is consistent with most previously published data and reviews showing no or a marginal benefit for conventional immunoglobulins, high-titer anti-RSV immunoglobulins or specific anti-RSV antibodies. The same is likely to be true for hMPV. Nonetheless, in order to make definitive statements the role of adjunctive therapy in the treatment of both RSV and hMPV infections should be further investigated in prospective trial setting.

We are fully aware of the substantial limitations of our study. It is retrospective, covers a period of 15 years, and the size of the cohort is limited especially regarding the number of hMPV patients. This limits our ability to make definitive statements about several aspects of hMPV infections.

In summary, our study provides supportive evidence for extending the recently proposed aggressive diagnostic algorithm aimed at the early identification of patients with LRTI and the identification of co-pathogens for RSV from RSV to hMPV. We were able to confirm the prognostic role of the ISI in RSV and hMPV URTI and provided indirect evidence for efficacy of the ribavirin in both respiratory viral infections: While all patients with RSV or hMPV LRTI should be treated with intravenous or oral ribavirin, antiviral therapy could be limited for the ISI high-risk group patients at URTI stage. No role of viral load as an independent prognostic marker could be detected either for progression to LRTI or death. At present, adjunctive therapy with immunoglobulins is of uncertain benefit and should be further investigated.

CONFLICT OF INTEREST
The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS
MA, VW, HD, and DB contributed to conception and design of the study; MA, VW, ES, AN, TN, AG, SH, FK, AS, and DM contributed to acquisition and analysis of data; MA, VW, and DB contributed to interpretation of data; MA drafted the manuscript; VW, HD, and DB critically revised the manuscript; all authors approved the final version of the manuscript.

ORCID
Mobil Akhmedov https://orcid.org/0000-0002-9646-690X

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How to cite this article: Akhmedov M, Wais V, Sala E, et al. Respiratory syncytial virus and human metapneumovirus after allogeneic hematopoietic stem cell transplantation: Impact of the immunodeficiency scoring index, viral load, and ribavirin treatment on the outcomes. *Transpl Infect Dis.* 2020;22:e13276. [https://doi.org/10.1111/tid.13276](https://doi.org/10.1111/tid.13276)