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Treatment stratification of respiratory syncytial virus infection in allogeneic stem cell transplantation

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S U M M A R Y

Background: Due to paucity of evidence to guide management of allogeneic haematopoietic stem cell transplantation (allo-HSCT) patients with respiratory syncytial virus (RSV) infections national and international guidelines make disparate recommendations.
Methods: The outcomes of allo-HSCT recipients with RSV infection between 2015 and 2017 were assessed using the following treatment stratification; upper respiratory tract infections (URTI) being actively monitored and lower respiratory tract infections (LRTI) treated with short courses of oral ribavirin combined with intravenous immunoglobulin (IVIG, 2 g/kg).
Results: During the study period 49 RSV episodes were diagnosed (47% URTI and 53% LRTI). All patients with URTI recovered without pharmacological intervention. Progression from URTI to LRTI occurred in 15%. Treatment with oral ribavirin given until significant symptomatic improvement (median 7 days [3–12]) and IVIG for LRTI was generally well tolerated. RSV-attributable mortality was low (2%).
Conclusions: In this cohort study, we demonstrate that active monitoring of allo-HSCT patients with RSV in the absence of LRTI was only associated with progression to LRTI in 15% of our patients and therefore appears to be a safe approach. Short course oral ribavirin in combination with IVIG was effective and well-tolerated for LRTI making it a practical alternative to aerosolised ribavirin. This approach was beneficial in reducing hospitalisation, saving nursing times and by using oral as opposed to nebulised ribavirin.

Introduction

Allogeneic haematopoietic stem cell transplantation (allo-HSCT) remains the only curative treatment for many haematological conditions.[1] Despite gradually improving outcomes over time the success of the procedure is hindered by infectious complications that along with graft-versus-host disease (GVHD) remain the main cause of non-relapse morbidity and mortality.[2,3]

Respiratory syncytial virus (RSV) is a single-stranded RNA virus of the Pneumovirus subfamily of Paramyxoviridae.[4] RSV outbreaks show seasonality, with one peak per year between November and January in the UK.[5] RSV-induced respiratory infection typically affects young children, the elderly, patients with chronic medical conditions and those that are immunocompromised.[6–9] Patients with immunodeficiency are especially vulnerable and early reports from the 1990s documented very high mortality up to 80% in HSCT patients with RSV pneumonia.[10,11]

Evidence to guide the management of immunocompromised patients with RSV infection is limited due to the lack of randomised controlled trials (RCT).[7] Retrospective studies suggest that treatment with the antiviral agent ribavirin can prevent the progression from upper (URTI) to lower respiratory tract infection

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(LRTI) and furthermore favourably influence survival.[12–15] Ribavirin is available in aerosolised, oral and intravenous formulations in the UK. The administration of aerosolised ribavirin proves to be challenging for many reasons, including practicality around the need for patient isolation, adverse effects such as claustrophobia and bronchospasm, treatment cost, and presumed teratogenicity leading to safety concerns for health-care staff and visitors of childbearing potential.[16–18] For these reasons oral ribavirin has been increasingly used in the clinical practice as a substitute for the inhaled formulation.[17,19,20] However, there remains a relative lack of data to support the use of oral ribavirin with or without intravenous immunoglobulin and in this study we explore both the effectiveness and the indication for this treatment combination.

The aim of this study was to assess the outcomes of allo-HSCT patients with RSV infection who were managed in accordance with a restrictive treatment policy (described below) over a two-year period. Data were collected on RSV-related mortality, overall survival, rate of URTI transformation to LRTI, disease morbidity and treatment safety.

Patients and methods

Patients

All consecutive PCR-confirmed RSV infections diagnosed in adult allo-HSCT recipients between November 2015 and December 2017 at our institution were included. All patients signed informed consent at the time of transplant and agreed that their anonymised clinical data can be used for audit and research purposes. Patients with RSV infection were identified from microbiology databases, treatment details were extracted from an electronic prescribing system. Clinical and laboratory data were collected from electronic patient records. Data were analysed retrospectively.

Asymptomatic patients were not routinely screened, testing was only carried out in individuals presenting with symptoms suggestive of possible RSV infection. Disease onset was calculated from the day of RSV detection. A new episode was defined as recurrence of a new RSV infection following complete symptomatic resolution and/or a negative microbiology result since the previous episode.

Microbiology testing

Samples for microbiology investigations included throat swabs and specimens from bronchoalveolar lavage (BAL). Testing for Influenza A, B and RSV was performed using the Cepheid geneXpert polymerase chain reaction (PCR) test (Cepheid Inc., Sunnyvale, CA, USA) and results were reported within 24 h of sampling. Samples negative by the Cepheid assay were examined by multiplex real-time PCR Fast Track Diagnostics (FTD) respiratory pathogens 21 primer kit (Fast Track Diagnostics Ltd, Sliema, Malta).

Definitions

URTI was defined as new onset of upper respiratory tract/coryzal symptoms with presence of RSV detected on a throat swab. Patients with RSV infection routinely underwent chest X-ray (CXR) investigation, and chest computed tomography (CT) imaging was performed if there was significant clinical concern that the patient had a LRTI. LRTI was defined according to the Fourth European Conference on Infections in Leukaemia (ECIL-4) criteria[7] as clinical (pathological sputum production, hypoxia and/or auscultatory chest signs) and/or radiological evidence of pulmonary involvement in the presence of RSV identified from a throat swab or BAL specimen. Infections were considered nosocomial if symptoms developed during hospitalisation, more than 5 days after admission.

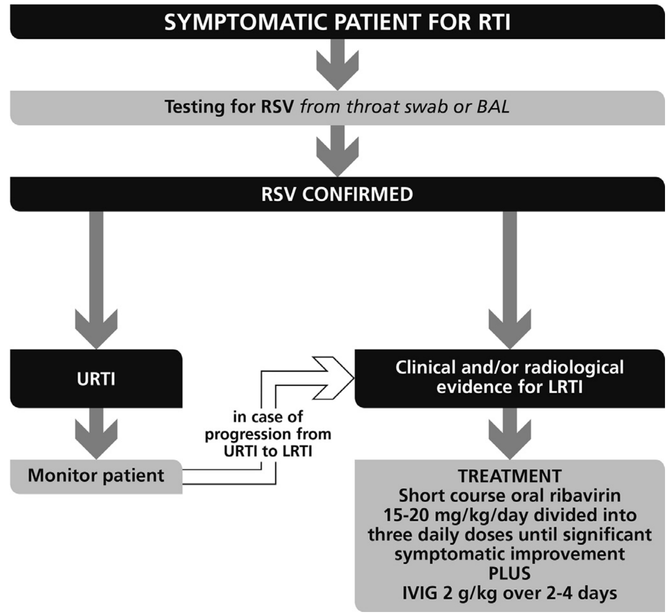

Fig. 1. Proposed treatment algorithm.
Abbreviations: BAL = bronchoalveolar lavage, IVIG = intravenous immunoglobulin, LRTI = lower respiratory tract infection, RSV = respiratory syncytial virus, RTI = respiratory tract infection, URTI = upper respiratory tract infection.

Acute and chronic GVHD were diagnosed according to Consensus Criteria.[21,22] Ribavirin-related adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events.[23]

The immunodeficiency scoring index (ISI-RSV), proposed by Shah et al.,[13] was calculated for all episodes, and included the following parameters; absolute neutrophil count, absolute lymphocyte count, age, conditioning intensity, presence of GVHD, corticosteroid treatment within the prior 30 days and timing of RSV infection relative to engraftment. Based on the overall score, infectious episodes were stratified into low (score 0–2), moderate (3–6) or high (7–12) risk group for developing an RSV LRTI.

Mortality attributed to RSV was defined as death caused by respiratory failure in patients with persistent RSV infection without other identified cause.

Management of patients with RSV infection

Patients with RSV-associated URTI were actively monitored in outpatient appointments and via telephone consultations with clinicians/specialist nurses. Anti-RSV treatment was not prescribed for this group (Fig. 1). Patients with RSV-associated LRTI were treated with oral ribavirin in combination with IVIG. Ribavirin was administered at a dose of 15–20 mg/kg divided into three daily doses, rounded to the nearest 200 mg, with appropriate dose adjustment for renal impairment. Patients were given short courses of oral ribavirin until significant symptomatic improvement. IVIG was administered at a total dose of 2 g/kg in split doses over 2–4 days irrespective of patients‘ immunoglobulin levels. Following RSV detection patients were nursed in a single room. Standard infection prevention and control precautions were followed, including wearing gloves and aprons and hand decontamination applied before and after glove use. Isolation was stopped when respiratory symptoms resolved. Repeat microbiology testing was not performed routinely to confirm clearance of RSV.

Table 1
The distribution of risk factors in all, in URTI and in LRTI episodes and comparison of factors in URTI and LRTI.

Variable	All episodes		LRTI		URTI		*p*
	n	%	*n*	%	*n*	%	
Total	49	100	26	100	23	100	
Age							1.0
Below 40 years	4	8.2	2	7.7	2	8.7	
Above 40 years	45	91.8	24	92.3	21	91.3	
HLA							0.692
10/10 matched	42	85.7	23	88.5	19	82.6	
Mismatched	7	14.3	3	11.5	4	17.4	
Donor							0.757
MRD	15	30.6	7	26.9	8	34.8	
MUD	34	69.4	19	73.1	15	65.2	
Conditioning							0.491
MAC	2	4.1	2	7.7	0	0	
RIC	47	95.9	24	92.3	23	100	
Neutropenia (<0.5 × 10^9/l)							0.748
Present	12	24.5	7	26.9	5	21.7	
No neutropenia	37	75.5	19	73.1	18	78.3	
Lymphopenia (<0.2 × 10^9/l)							0.333
Present	12	24.5	8	30.8	4	17.4	
No lymphopenia	37	75.5	18	69.2	19	82.6	
Acute or chronic GVHD							1.0
Present	18	36.7	10	38.5	8	34.8	
No GVHD	31	63.3	16	61.5	15	65.2	
Treatment with corticosteroids							0.382
Yes	16	32.7	10	38.5	6	26.1	
No	33	67.3	16	61.5	17	73.9	
Pre-, or peri-engraftment							1.0
Yes	11	22.4	6	23.1	5	21.7	
No	38	77.6	20	76.9	18	78.3	
ISI-RSV score							0.435
Low risk	17	34.7	9	34.6	8	34.8	
Moderate risk	22	44.9	10	38.5	12	52.2	
High risk	10	20.4	7	26.9	3	13.0	

Abbreviations: GVHD = graft-versus-host disease, HLA = human leucocyte antigen, ISI-RSV = immunodeficiency scoring index for respiratory syncytial virus, LRTI = lower respiratory tract infection, MAC = myeloablative conditioning, MRD = matched related donor, MUD = matched unrelated donor, *n* = number, *p* = probability value, RIC = reduced intensity conditioning, URTI = upper respiratory tract infection.

Statistical analysis

Comparisons for categorical variables were performed by the chi-squared or the Fisher's exact tests and for continuous variables by the Mann–Whitney test. Overall survival (OS, defined as survival from RSV infection until death or last follow-up) was analysed by the log-rank test and Kaplan–Meier estimates were calculated. Probability (*p*) values less than 0.05 were considered statistically significant. The analyses were performed using SPSS Statistics 22 software (Armonk, NY, USA).

Results

Patient and transplant characteristics and risk factors for RSV

During the study period 109 allo-HSCT were performed and the estimated number of patients under regular post-transplant follow-up was 300. Over 26 months 49 RSV RTI episodes were diagnosed in 46 patients, of which 23 were URTI (46.9%) and 26 LRTI (53.1%). Three patients had two separate episodes, 8, 11 and 12 months following their first episode. Nine episodes were considered nosocomial (9/49, 18.4%, three URTI and six LRTI). Most infections (85.7%) presented within the documented peak season, from November through to January. Median age at onset of RSV infection was 52 years (range 19–73). The median time from transplant to developing an RSV RTI was 9 months (range 0–69 months, 63.4% of episodes occurred within the first year). Patient characteristics are outlined in Table 1. The majority of patients presenting with RSV infection had received a reduced intensity conditioning (RIC, 44/46, 95.7%) matched unrelated donor transplant (MUD, 31/46, 67.4%) from a well matched (10/10 HLA-matched at high resolution) donor (40/46, 87.0%).

Shah et al. previously demonstrated that certain risk factors could be used to predict the risk of progression of URTI to LRTI and the risk of RSV-related mortality.[13] We attempted to validate their scoring tool (Immunodeficiency Scoring Index for RSV infection [ISI-RSV]) in our patient cohort (Table 1). A significant number of patients presented with high risk characteristics. Eleven episodes (22.4%) developed in the early transplant period i.e. within 30 days post or prior to engraftment. Concomitant GVHD was present in 18 episodes (36.7%, $n = 4$ acute and $n = 14$ chronic) and 16 patients were receiving corticosteroid treatment at the time of developing RSV infection. ISI-RSV score was calculated for each episode and graded as low, intermediate or high risk in 34.7%, 44.9% and 20.4% of the cases, respectively. No individual risk factor was significantly differently distributed between cases of URTI vs LRTI (Table 1). Similarly, in episodes with available immunoglobulin level measurements within 30 days of infection (49% of cases), the presence of hypogammaglobulinaemia was comparable in the two groups (40.0% in URTI vs. 35.7% in LRTI, $p = 1.0$).

Diagnosis of RSV infection

RSV was detected by throat swab in 91.8% of episodes and BAL specimen in 8.2% of episodes.

Chest X-ray (CXR) was performed in 91.8% of episodes (45 out of 49), and showed new infective changes in 15 cases (33.3%). Of the 15 episodes with new CXR findings 13 patients also under-

Table 2
Disease burden and outcome of URTI and LRTI episodes.

Variable	LRTI		URTI		p
	n/(%)	%/(CI)	*n*/(%)	%/(CI)	
Total	26	100	23	100	
Treatment setting					<0.001
Outpatient	2	7.7	13	56.5	
Inpatient	24	92.3	10	43.5	
ICU admission	3	11.5	0	0	
Length of inpatient stay (for admitted patients)					0.061
Median, range in days	16	1–72	3	1–29	
Overall survival					0.012
1 year post-RSV	63.7	10.4	94.7	5.1	
RSV-related mortality	1	3.8	0	0	

Abbreviations: CI = confidence interval, ICU = intensive care unit, LRTI = lower respiratory tract infection, n = number, p = probability value, RSV = respiratory syncytial virus, URTI = upper respiratory tract infection. For overall survival % and CI are given.

went chest CT imaging, which confirmed the presence of a LRTI in all the investigated cases. A further five patients had a CT chest for clinical signs suggestive of LRTI; in all except one case, the CT confirmed the diagnosis. Altogether 18 episodes were investigated with CT scan, which showed features consistent with infection in 17 cases. Ground glass opacification was the most frequent feature detected in 12 of 17 cases (70.6%), nodularity was present in 11 (64.7%), consolidation in 9 (52.9%) and pleural effusion in 4 cases (23.5%). Overall, LRTI was confirmed radiologically in 19 of 26 cases (73.1%) and was diagnosed clinically in the remaining seven cases. All seven patients had a productive cough and on examination findings were in keeping with LRTI, and four of seven patients had hypoxia. The ISI-RSV score was low in six, intermediate in six and high in seven of radiologically confirmed LRTI and low in three and intermediate in four cases with clinically diagnosed LRTI.

Management and outcome of RSV URTI

The median follow-up time for the entire cohort from the first RSV RTI was 14 months (range 1–27 months). Of the 27 episodes initially presenting as URTI, four (14.8%) progressed to LRTI. Among those whose infection showed progression, one patient was stratified as having low (25%), two moderate (50%) and one (25%) high risk for progression based on the ISI-RSV risk score. The ISI-RSV risk categorisation showed no significant difference compared to those who did not progress ($n = 8$, 34.8% low, $n = 12$, 52.2% moderate and $n = 3$, 13% high risk, $p = 0.8$). The remaining 22 patients with 23 episodes of RSV URTI (including one patient who experienced two separate episodes of RSV URTI) recovered fully from the infection without specific anti-RSV treatment or IVIG. More than half of the URTI episodes (56.5%) did not require admission to hospital and half of those admitted to hospital (21.7%) were discharged within 24 h. Median length of hospital stay was three days (range 1–29) with no cases requiring admission to intensive care.

No patient died within 100 days of RSV URTI. At last follow up, one patient, who suffered from two RSV infections, died of non-RSV pneumonia 321 days after RSV URTI and 84 days following RSV LRTI.

Management and outcome of RSV LRTI and treatment-related side effects

Twenty-six patients were diagnosed with LRTI. Patients with RSV LRTI were treated with short courses of oral ribavirin until significant symptomatic improvement and they also received IVIG. Significantly more patients ($n = 24$, 92%, $p < 0.001$) required admission to hospital compared to those with URTI. Median duration of inpatient stay was 16 days (range 1–72 days, Table 2).

Two patients with clinical signs of LRTI did not receive anti-RSV treatment as per attending clinician's decision. Both patients were found to be RSV positive from throat swab and suffered from LRTI, but it was felt clinically that the LRTI was possibly related to bacterial infection and patients were treated with antibiotic therapy and recovered. Twenty-four patients (92.3%) received oral ribavirin for a median duration of 7 days (range 3–12 days), and IVIG was given to 22 (84.6%) patients. Ribavirin was generally well tolerated. The most common side effect observed with ribavirin treatment was transfusion-dependent haemolytic anaemia that developed in four patients (16.7%) and occurred early, within the first week of administration with the nadir during the second week. The haemoglobin drop was marked in three cases (from 152, 120 and 150 g/l baseline to 74, 79 and 78 g/l respectively) and mild in one case (from 101 to 83 g/l). The mean ribavirin dose in patients with no evidence of haemolysis was 17.0 mg/kg/day (range 15.0–19.4), whereas in those with haemolysis it was higher at 19.0 mg/kg/day (range 17.6–19.8, $p = 0.027$). Patients received 2–3 units of red blood cells with no further interventions required. All patients fully recovered from this complication. During treatment with ribavirin and IVIG, four patients developed acute kidney injury (AKI), in three of whom the role of anti-RSV treatment was unlikely: however in one patient ribavirin-induced haemolysis was likely to contribute to stage 1 AKI. This patient had a severe haemolytic reaction with a haemoglobin drop from 150 g/l to 78 g/l, a lactate dehydrogenase (LDH) level over 3000 IU/l (normal range 90–235) and reticulocyte count of 16%. Renal function returned to baseline within three weeks. Interestingly, 11 of 24 patients (45.8%) had abnormal liver function tests (LFTs), mainly mild transaminase elevation ($n = 8$ grade 0, $n = 1$ each grade 1, 2 and 3) at the time of RSV diagnosis prior to any treatment. LFTs worsened in five patients (20.8%) during or after the course of ribavirin and IVIG. In four of the five cases, LFT abnormalities were considered independent of anti-RSV treatment. The cause for deranged LFT was thought to be due to GVHD in two patients, toxicity of chemotherapy in one and due to adenovirus infection in one case. In the fifth patient alanine aminotransferase (ALT) level showed a sudden rise from normal to the grade 4 range (maximum 1216 IU/l, normal range 10–45) with normal bilirubin levels, ALT then normalised within four weeks. Anti-RSV treatment might have played a role in this latter reaction.

Three patients (11.5% with LRTI, 6.5% of all) were admitted to the intensive care unit (ICU), all of whom required mechanical ventilation. One patient died (only RSV-attributable death in the cohort) and two recovered. The ISI-RSV score was high in two (including the deceased patient) and moderate in one of these patients.

Although no death was attributable to nosocomial RSV infection, the survival of patients who developed nosocomial RSV infection was inferior to those with community-acquired infection (1-year estimated OS 46.7 ± 19.0% vs. 85.3 ± 6.1%, $p = 0.016$).

The survival of patients with LRTI was significantly worse compared to patients with URTI (1-year OS: 63.7 ± 10.4% vs. 94.7 ± 5.1%, $p = 0.012$, Table 2). Among LRTI patients three patients (11.5%) died within 100 days: in one patient, death was attributable to RSV (RSV-related mortality 3.8% in LRTI; 2.0% of all RSV-infections). In the other two patients, the cause of death was non-RSV infection (pneumonia and sepsis). Six patients in the LRTI group died beyond 100 days from onset of RSV infection, mortality was associated with GVHD ($n = 3$), disease relapse ($n = 2$) or non-RSV infection ($n = 1$). The patient who died of RSV infection was diagnosed with RSV URTI in the early transplant period, during the end of the conditioning treatment. Given the pre-transplant high-risk presentation the patient was started on ribavirin and IVIG and this was the only patient in our cohort in whom treatment was initiated for URTI. Despite treatment the RSV infection progressed to a LRTI, with detectable RSV on BAL, then to respiratory failure and death.

Discussion

This cohort is one of the largest series to date reporting on outcome of allo-HSCT recipients with RSV infection treated with oral ribavirin and IVIG based on clinical presentation. The results confirm favourable outcomes with the approach of treating patients with oral ribavirin and IVIG for LRTI and close monitoring for those with URTI. Our patients were defined as having lower respiratory tract infections on the basis of radiological findings, hypoxia, auscultatory signs or productive cough. It is important to highlight this definition since not all patients had radiological evidence of lower respiratory tract infection which is in contrast with the study by Shah et al. which defines the ISI for RSV. The prognosis of patients treated accordingly was not inferior to literature data where LRTI and URTI cases received routine anti-RSV treatment.[17,20] Furthermore we demonstrate low RSV-attributable mortality (2%) using a restrictive treatment strategy. Short course oral ribavirin was generally well tolerated. Consistent with other reported data the most common adverse effect included acute transfusion-dependent haemolytic anaemia (16.7%).[17] Ribavirin dose varies greatly in literature (from 10 to 60 mg/kg/day).[17] In our centre we used a dose of 15–20 mg/kg/day and our findings suggest that haemolysis might be associated with higher ribavirin dose, however it is quickly resolving following the cessation of the drug.

The radiological findings from our study were similar to those described by Ariza-Heredia et al. showing that the most common CT abnormalities in RSV infection were ground-glass opacification and nodularity.[24]

There is weak evidence to support the clinical management of RSV infection in haematopoietic stem cell transplant recipients. The only RCT that attempted to assess the efficacy of aerosolised ribavirin on the progression of RSV URTI to LRTI was hindered by slow patient accrual and was stopped prematurely. Eventually the trial was unable to confirm a statistically significant difference despite trends toward reduced pneumonia rate.[25] Oral ribavirin has been increasingly implemented in clinic practice, but data are scarce. A recent publication reported similar outcomes in autologous and allogeneic HSCT patients with RSV URTI or LRTI when treated with aerosolised or oral ribavirin suggesting that oral ribavirin may be an effective alternative to aerosolised ribavirin.[20]

Some retrospective reports suggest a survival benefit with ribavirin, but results are not consistent across all reported studies.[14,15,26] Reflecting on the existing therapeutic uncertainties, treatment guidelines are not standardised amongst institutions. Pilie et al. reported that according to their institutional policy inhaled ribavirin treatment was restricted to patients with recent HSCT or with chronic GVHD requiring immunosuppressive treatment.[27] In a Spanish cohort a risk-adapted approach to guide therapeutic intervention with oral ribavirin was applied taking into consideration risk factors and co-infective viruses.[28] In a report from Karolinska University Hospital, all patients with a LRTI and patients with URTI during early post-transplant and those on immunosuppression were treated with ribavirin.[29]

Due to the lack of strong evidence national and international consensus guidelines face challenges when making management recommendations. The Fourth European Conference on Infections in Leukaemia (ECIL-4) guideline states that "Currently, there is only limited evidence for effective treatments. However, pooling of published studies suggests that treating URTI in HSCT and leukaemia at risk for LRTI and treating manifest LRTI with ribavirin and IVIG improves outcome."[7] The recent national (UK) guidelines published in 2016 recommend treatment with ribavirin for all patients with LRTI and for patients with URTI who have multiple risk factors for progression to LRTI. The guideline also recommends the administration of IVIG for all RSV cases.[30]

RSV-related URTI has a good prognosis in the majority of cases, however, previous reports suggest a high risk of progression to LRTI in HSCT patients. RSV LRTI is proven to be associated with higher risk of complications, late respiratory dysfunction and mortality.[29,31] Khanna et al. reviewed the literature from 1981 to 2007 and found 38% progression rate to LRTI in patients treated with ribavirin and 68% in untreated patients.[32] More recent publications report significantly lower figures, even as low as 0% with treatment.[29,33] In our cohort, despite no treatment being given for URTI, the rate of progression was lower (14.8%) compared with many other reports.[27,32,34] We acknowledge that since patients presenting clinically with URTI did not routinely undergo CT investigation, occasional cases with mild LRTI might have been missed.

Studies show conflicting results as to what factors qualify for high risk of progression. Older age, smoking history, mismatched and unrelated donor type, myeloablative conditioning, acute and chronic GVHD, corticosteroids use, neutropenia, lymphocytopenia, hypogammaglobulinaemia and pre-, or periengraftment presentation have all been found to be associated with progression.[7,13,15,27,32,34] Shah et al. proposed an immunodeficiency scoring index (ISI-RSV) for risk stratification of patients with RSV.[13] In a cohort of 237 allo-HSCT patients the score predicted the progression to LRTI and mortality. Patients in the high risk group benefitted most from aerosolised ribavirin therapy. Other studies were unable to demonstrate the same risk factors.[15,29] A good example of inconsistencies between studies is the age cut-off of 40 years, which weighs more in the ISI-RSV score than the presence of GVHD, corticosteroids treatment or pre-engraftment status.[13] In the study by Lehners et al. age over 65 years was determined as high risk instead of 40, whereas the ECIL-4 guideline only refers to older age as risk factor for progression without further specification.[7,15] Nevertheless, certain risk factors such as lymphopenia have consistently been identified.[35,36] In our study we have been unable to confirm the role of the suggested risk factors. Only one patient at the high risk category progressed to LRTI and there was no difference in progression rate between the three risk groups. However we acknowledge that this may be reflective of our modest sample size. Though statistically data did not differ, it is noteworthy that in the high risk group, seven of ten patients developed LRTI, and two of three patients treated on ICU had high risk scores. Treatment of URTI in the high risk category can therefore be justified. It is possible that treatment of URTI would have reduced the chance of developing a LRTI. Nonetheless, more evidence is required to determine whether progression can be accurately predicted and prevented. In the only fatal case of this cohort early initiation of treatment did not translate into survival benefit.

The benefit of using IVIG in RSV infection has not been well demonstrated. As a result of this IVIG use and dosing varies significantly across transplant centres. Gross and Bryson found in their systematic review that only 25% of cases with non-influenza respiratory viral infection were treated with IVIG.[17] Some units restrict IVIG use to patients with hypogammaglobulinaemia.[15,37] In the latter publication RSV-attributable mortality was low (4%) although only three out of 23 patients received IVIG replacement.[37] During a transplant unit outbreak affecting 56 patients, hypogammaglobulinaemia was a significant risk factor for fatal outcome. However, treatment with polyvalent immunoglobulin preparation at a dose of 0.2–0.4 g/kg did not reverse poor prognosis.[15] In contrast, our policy was to use IVIG at a dose of 2 g/kg, which may have contributed to improved survival in our cohort.

Overall, we believe that the good prognosis observed in our cohort can be attributable to a combination of factors such as 24-h access to local emergency services, rapidly available microbiology results, availability of imaging studies including out-of-hours periods, excellent collaboration of teams involved in patient care and prompt initiation and escalation of treatment when indicated. Our approach could provide several benefits to the busy transplant units by managing patients as outpatients and via telephone monitoring and by using oral as opposed to intravenous or nebulised ribavirin for the convenience of patients and saving nursing time. Our approach might not be feasible in other centres with more restricted access to emergency care and outpatient follow-up.

In this large cohort study we demonstrate comparable outcomes with active monitoring of allo-HSCT patients presenting with RSV URTI to published data where the majority of patients were actively treated. As most high risk patients in our cohort were diagnosed with LRTI we advise caution in extrapolating data to the high risk group. Short course oral ribavirin in combination with IVIG is shown to be an effective and well-tolerated treatment for patients with LRTI making it a practical alternative to aerosolised ribavirin that has the greatest amount of supporting evidence in this sparsely researched area. Prospective randomised trials are warranted to address the therapeutic uncertainties in the management of RSV infection among allo-HSCT recipients.

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Conflict of interest

The authors declare no conflict of interest in relation to the work.

Authorship contributions

AP and VR designed the survey; KB and AP co-ordinated the study; KB, DB, RD, ML, RP, AP, LR, RS, BT and EW treated patients and collected clinical data; NM collected treatment data; KJ led the laboratory work and provided expert microbiology input; SM provided expert immunology input and authorised IVIG treatment; RB provided expert radiology input; KB analysed data; KB, NM and RS wrote the manuscript; all authors critically reviewed and revised the manuscript and approved the final version of the paper.

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