



## Viral infections

# Respiratory virus infections after stem cell transplantation: a prospective study from the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation

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### Summary:

Community-acquired respiratory virus infections are a cause of mortality after stem cell transplantation (SCT). A prospective study was performed at 37 centers to determine their frequency and importance. Additional cases were also collected to allow the analysis of risk factors for severe infection. Forty episodes were collected in the prospective study and 53 additional episodes through subsequent case collection. The frequency of documented respiratory virus infections was 3.5% among 819 allogeneic and 0.4% among 1154 autologous SCT patients transplanted during the study period. The frequency of lower respiratory tract infections (LRTI) was 2.1% among allogeneic and 0.2% among autologous SCT patients. The mortality within 28 days from diagnosis of a respiratory viral infection was 1.1% among allogeneic SCT while no autologous SCT patient died. The deaths of five patients (0.6%) were directly attributed to a respiratory virus infection (three RSV; two influenza A). On multivariate analysis, lymphocytopenia increased the risk for LRTI ( $P = 0.008$ ). Lymphocytopenia was also a significant risk factor for LRTI in patients with RSV infections. The overall mortality in RSV infection was 30.4% and the direct RSV-associated mortality was 17.4%. For influenza A virus infection, the corresponding percentages were 23.0% and 15.3%. This prospective study supports the fact that community-acquired respiratory virus infections cause transplant-related mortality after SCT. *Bone Marrow Transplantation* (2001) 28, 479–484.

**Keywords:** RSV infection; influenza; allogeneic; autologous; SCT

Respiratory viral infections are increasingly recognized as important complications in SCT recipients. RSV has been associated with high mortality despite treatment with ribavirin.<sup>1–4</sup> Recent studies suggest improved outcome with the addition of high dose immune globulin.<sup>5–7</sup> Influenza is also associated with a high morbidity and mortality in SCT patients; Whimbey *et al*<sup>8</sup> reported 17% mortality in patients with lower respiratory tract involvement. Parainfluenza virus infections have also been reported to be associated with significant morbidity and mortality.<sup>9–12</sup>

Despite an increasing number of reports, knowledge is still limited regarding risk factors and management strategies for respiratory virus infections. Therefore, the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT) launched a prospective 1-year study followed by additional case collection to assess frequency and outcome of respiratory virus infections after allogeneic stem cell transplantation.

### Patients and methods

#### Survey

The survey was performed for 1 year from 1 October 1997 to 30 September 1998. Thirty-seven EBMT centers participated in the study. All patients with respiratory viral symptoms were to be investigated for the presence of community-acquired respiratory viruses according to each center's local practices. There was therefore no attempt to standardize the laboratory techniques for detection and identification of respiratory viruses. Nasopharyngeal aspirates, throat swaps, or nasal swabs were used for obtaining upper respiratory specimens. BAL was used for obtaining lower respiratory specimens. Most centers used antigen detection by immunofluorescence, but a few centers used an enzyme immunoassay. Virus isolation was used at some of the centers.

A standardized form was used to collect data including

information about the patient, the transplant procedure, symptoms of a respiratory infection, treatment, and outcome. Information was also collected regarding the number of patients transplanted during the study period to obtain an approximate frequency of respiratory viral infections. Patients transplanted during the year before the study period but developing a respiratory virus infection during the study period were included in the calculations to correct for episodes in patients transplanted within the study period but developing a respiratory virus infection after the study period.

#### Case collection

The number of cases reported was not enough to allow an analysis of risk factors for severe disease, outcome and the results of therapeutic interventions. To get a higher number of cases, additional cases were collected during the subsequent 18 months after the study (until 31 March 2000) using the same case record form.

#### Definitions

The following definitions were used in the study.

An upper respiratory tract infection was defined as detection of a respiratory viral infection from upper respiratory secretions together with symptoms from the upper respiratory tract (nose, throat).

A lower respiratory tract infection was defined as either hypoxia or pulmonary infiltrates together with identification of a respiratory viral infection in BAL or upper respiratory secretions.

Mortality was defined as being either due to a respiratory virus infection or due to another cause. Death due to a respiratory virus infection was defined as patients dying of respiratory failure with no other cause of the pneumonia. Overall mortality during a respiratory virus infection was defined as death from any cause within 28 days of the diagnosis of a respiratory virus infection.

#### Statistics

Multivariate logistic regression models were constructed to analyze the impact of risk factors on the risk of developing a LRTI. Neutrophil and lymphocyte counts were included as continuous variables. Donor status was involved in the models including HLA-identical sibling, unrelated or family mismatch donor, or autologous transplantation as transplant type (allo *vs* auto). Other factors analyzed were age as a continuous variable, type of graft (bone marrow *vs* peripheral cells), and vaccination (influenza only).

## Results

#### Prospective survey

*Incidence of respiratory viral infections:* Forty cases of community acquired respiratory virus infections were documented at participating centers. Thirty-five were diagnosed after allogeneic and five after autologous SCT. Twenty-six

episodes were documented in patients transplanted during the study period, while 14 episodes occurred in patients transplanted between 14 days and 9.5 years before the study period. Of these 14 episodes, six occurred in allogeneic recipients transplanted more than 1 year preceding the study and these were excluded from the incidence calculations.

At the participating centers, 1973 patients underwent SCT during the study period; 819 patients underwent allogeneic and 1154 autologous SCT. Thus, the overall frequency of documented respiratory virus infections was 1.8%. The frequency was significantly higher in allogeneic (3.5%) than in autologous (0.4%) SCT patients ( $P < 0.0001$ ). Eighteen patients had lower respiratory tract infections, 15 occurring in allogeneic patients and three in autologous SCT patients. The frequency of a lower respiratory tract infection was 1.8% in allogeneic and 0.2% in autologous stem cell transplant patients. Frequencies varied from 0 to 17.4% between the participating centers. The frequencies for allogeneic and autologous SCT patients separately varied from 0 to 18.8% and from 0 to 14.3%, respectively. The highest frequencies were found in pediatric transplant centers.

*Documented respiratory virus infections:* Twenty patients had RSV infections (18 allogeneic and two autologous patients). Fourteen were lower respiratory tract infections (LRTI) and six upper respiratory tract infections (URTI). The median time to diagnosis of RSV infection was 91 days (range -20 days to 2220) after SCT.

Sixteen patients had influenza A infection (14 allogeneic; two autologous). Seven patients had LRTI and nine URTI. The median time to diagnosis of influenza A infection was 98 days (range 0-3541 days) after SCT. Four patients had parainfluenza infections (three allogeneic; one autologous). One patient had a LRTI and three patients had URTI infections. One infection was diagnosed before SCT and the others 29-131 days after SCT.

*Outcome of respiratory virus infection:* Nine allogeneic patients, but no autologous patients, died within 28 days of diagnosis of the respiratory viral infection. Thus, the overall mortality was 1.1% after allogeneic and 0% after autologous SCT. Five allogeneic patients died directly of a respiratory virus infection as assessed by the investigators, while four patients died of other causes.

Three of 20 patients died of RSV infection. Two additional patients died of other causes. Thus, the total mortality within 28 days of the diagnosis of RSV infection was 25% and the mortality defined by the investigator as caused by RSV was 15%. Twelve patients diagnosed with RSV had a LRTI of whom four died (33%). Eight patients had RSV URTI at diagnosis; two progressed to pneumonia and one patient died.

Two of 16 (12.5%) patients with influenza A died of the viral infection and two additional patients died of other causes resulting in overall mortality of 25%. All patients with parainfluenza infections survived for 28 days after diagnosis of the infection.

*Analysis of cases obtained through prospective survey and subsequent case collection*

Fifty-three additional cases were obtained using the same case record form as in the prospective survey. Characteristics of the two groups of patients are shown in Table 1. Three patients had double infections with both RSV and influenza A virus. Ninety-six respiratory virus isolates from the 93 patients were therefore included in the study. The types of infection and whether they were URTI or LRTI infections at diagnosis are shown in Table 2.

**Table 1** Patient characteristics

Characteristic	Survey group <sup>a</sup> n = 40	Case collection <sup>b</sup> n = 53
Median age (range)	25.8 (0.6–64.8)	42.3 (0.5–65.5)
Type of transplant		
Allogeneic	35	41
HLA-identical sibling	11	27
Family mismatch	5	4
Unrelated donor	19	10
Autologous	5	12
Graft type		
Bone marrow	30	22
Peripheral blood stem cells	10	31
Type of viral infection		
RSV	20	22
Influenza A	16	20
Influenza B	0	3
Parainfluenza	4	3
Rhinovirus	0	2
Influenza A + RSV	0	3

<sup>a</sup>Survey group: prospective data collection from 1 October 1997 to 30 September 1998.

<sup>b</sup>Case collection: additional case collection performed after 30 September 1998.

**Table 2** Respiratory viral infections

	Survey group <sup>a</sup>	Case collection	Total
RSV			
URTI	8	11 <sup>a</sup>	19
LRTI	12	15 <sup>b</sup>	27
Influenza A			
URTI	9	14 <sup>a</sup>	23
LRTI	7	9 <sup>b</sup>	16
Influenza B			
URTI	0	3	3
LRTI	0	0	0
Parainfluenza			
URTI	3	2	5
LRTI	1	1	2
Rhinovirus			
URTI	1	1	2
LRTI	0	0	0
Total	40	56	93

<sup>a</sup>One patient had both RSV and influenza A.

<sup>b</sup>Two patients had both RSV and influenza A.

*Outcome of respiratory virus infections: all patients*

**RSV:** Fourteen patients with RSV infections died. In eight of these patients, RSV was judged to be the primary cause of death, although two patients had other pathogens (CMV and EBV in one patient and *Pneumocystis carinii* in the other) identified at the time of death. The overall mortality was therefore 14 of 46 (30.4%) and the directly RSV-associated mortality 17.4%. Forty-two of the infections occurred after allogeneic SCT and all patients who died had undergone allogeneic transplantation. Therefore, the overall and RSV-associated mortality in allogeneic SCT patients developing RSV infection was 33.3% and 19.0%, respectively.

**Influenza A:** Nine patients with influenza A died. In six of these patients, influenza A virus was the primary cause of death and in no patient was another pathogen found either at the time of primary diagnosis or subsequently. Thus, overall and influenza associated mortality were 23.0% and 15.3%, respectively. Seven of 30 allogeneic SCT patients (23%) and two of nine (22%) autologous SCT patients died within 28 days from diagnosis of the infection. Seven patients had been previously vaccinated. Vaccination did not influence the risk of LRTI among the patients diagnosed with influenza infection, and there was no difference in the risk of death from influenza or overall mortality within the first 28 days after diagnosis of influenza.

**Other respiratory virus infections:** One of seven patients with parainfluenza virus infection died within the first 28 days. Parainfluenza 3 infection was judged to be the primary cause of death.

*Risk factors for development of lower respiratory tract infection*

In a multivariate logistic regression model analyzing risk factors for development of LRTI, lower lymphocyte count was a significant risk factor (Table 3). In contrast, a lower granulocyte count was borderline significant for a reduced risk of developing LRTI when analyzed as a continuous variable. However, when it was analyzed as a categorical

**Table 3** Risk factors for lower respiratory tract infection

	OR (95% CI)	P value
<i>All episodes</i>		
Lymphocytopenia	2.52 (1.26–5.06)	0.008
Neutropenia	0.82 (0.68–0.99)	0.04
Donor	0.99 (0.57–1.72)	0.99
<i>RSV</i>		
Lymphocytopenia	3.04 (1.26–7.35)	0.01
Neutropenia	0.82 (0.66–1.01)	0.06
Donor	0.75 (0.35–1.59)	0.45
<i>Influenza A or B</i>		
Lymphocytopenia	2.84 (0.73–11.01)	0.11
Neutropenia	0.87 (0.66–1.15)	0.06
Donor	0.99 (0.42–2.40)	0.45

variable (granulocyte count  $<$  or  $>0.5 \times 10^9/l$ ), granulocyte count did not influence the risk of LRTI. Non-significant factors in the analysis were donor type (identical sibling, mismatch, unrelated, or autologous transplantation), and graft type (bone marrow or peripheral blood stem cells). When patients with RSV infections were analyzed separately, lymphocytopenia was also the only significant risk factor (Table 3). No significant factor could be identified for the development of LRTI with influenza A.

### Therapy of respiratory virus infections

Since this was a prospective survey and subsequent additional case collection, and not a controlled treatment study, therapies varied between the different participating centers.

**RSV infections:** The outcome of therapies is shown in Table 4. Three patients died when the RSV infection was first diagnosed as an URTI infection. For infections primarily diagnosed as LRTI infections, there was no clear advantage for any therapy protocol including either ribavirin given alone (11 of 17 survived) or with the combination of ribavirin with intravenous immune globulin (four of eight survived).

**Influenza infections:** Thirteen patients were treated for influenza A infection. Six patients received amantadine of which one patient died of influenza, one died of another cause and four patients survived. Five patients received ribavirin of whom one died of another cause and the other survived. One patient received both amantadine and ribavirin, but died of influenza. No patient in this study received a neuramidase inhibitor.

### Discussion

During the last decade, respiratory viruses, particularly RSV, have been increasingly reported as causing severe infections after SCT.<sup>1,3-5,11</sup> Despite these reports, data regarding the frequency of respiratory virus infections, risk factors for severe infections, and what is the best therapy are lacking.

The present study aimed to provide some of this information. The overall infection rate was low. The frequency of respiratory virus infections was 3.5% in allogeneic and 0.4% in autologous transplant patients. This is much lower

than has previously been reported from the MD Anderson Cancer Center.<sup>4</sup> There are several potential explanations for this low rate of infection. One is that the sampling for respiratory viruses might have varied between the participating centers, despite the agreement to sample all patients with upper or lower respiratory symptoms, since the incidence ranged from 0 to 17% between the centers. However, a frequency of 17%, the highest found at any center, is still lower than that reported from the MD Anderson Cancer Center. A second explanation may be different diagnostic techniques used at the participating centers. It is likely that the true frequency of upper respiratory tract infections has been underestimated in our study since most laboratories did not routinely use virus isolation and instead used antigen detection tests, which are less sensitive compared to virus isolation. In fact, the centers reporting the highest frequencies were pediatric transplant centers and it has been previously shown that the RSV viral load in respiratory specimens obtained from the upper airways of adults is frequently low and therefore false negative antigen tests might result. Too few centers in this study consistently used virus isolation to allow analysis of the impact from using different diagnostic techniques. Alternatively, infection in the lower respiratory tract is likely to be more accurately diagnosed since the false negativity rate is low when tests are performed on bronchoalveolar lavage (BAL) fluid. A third explanation is that the epidemiological situation in each community differed between our study and the study from MD Anderson, since the overall number of cases varies between different years. It is probable that all these explanations might have influenced the results in the study.

However, despite the lower than expected number of documented cases in our study, there are some interesting findings regarding the impact of respiratory virus infections on morbidity and mortality in SCT patients. The incidence of a lower respiratory tract infection caused by community acquired respiratory viruses in the study was 2% in allogeneic and 0.2% in autologous transplant patients, and overall 1.1% of allogeneic patients transplanted at the participating centers died of the infection. In our opinion, the risk for underestimating the respiratory virus-associated mortality is low compared to underestimating the frequency of mild upper respiratory tract infections. The figure of 1.1% can therefore be used as a rough estimate of the overall impact of community-acquired respiratory virus infections on transplant-related mortality in allogeneic transplant patients. This figure could be compared to, for example, CMV-associated mortality. In a recent large prospective

**Table 4** Outcome of therapy in patients with RSV infection

Symptom	No therapy (survived/all)	Ribavirin inhalations (survived/all)	Intravenous ribavirin (survived/all)	Inhaled + intravenous ribavirin (survived/all)	Ribavirin inhalation + i.v. immune globulin (survived/all)	Intravenous ribavirin + i.v. immune globulin (survived/all)	Inhaled + intravenous ribavirin + i.v. immune globulin (survived/all)	Total
URTI (n = 19)	10/10	3/5	0/0	1/2	2/2	0/0	0/0	16/19
LRTI (n = 27)	1/2	6/9	3/3	2/5	3/5	1/2	0/1	16/27

multicenter study, the CMV associated mortality was 2.2%.<sup>13</sup> All allogeneic transplant centers put in much effort to prevent CMV associated mortality. Our study supports previously published studies in that centers should be aware of community-acquired respiratory virus infections and that additional studies are definitely needed to improve management of these infections.<sup>13</sup>

The mortality rate in patients infected with RSV was lower than reported in most studies; 17% of the patients died directly from RSV as assessed by the investigator and 30% died of any cause within 28 days from diagnosis of RSV infection. There have been improvements in outcome of RSV infection since the first report almost a decade ago that reported a mortality of 78% in patients with RSV pneumonia.<sup>3</sup> Studies have suggested that therapy with ribavirin combined with i.v. immune globulin has improved the outcome.<sup>5-7</sup> However, in our series there was no clear positive impact of adding Ig, although the number of patients treated with this combination was small. There have been conflicting results from studies using intravenous ribavirin. Sparreliid *et al*<sup>14</sup> reported possible efficacy and a low risk for toxicity using intravenous ribavirin, while the experience from a study performed by the Seattle group was much less favorable.<sup>15</sup> In our series, there was no clear advantage or disadvantage of adding intravenous ribavirin to either aerosolized ribavirin or to i.v. Ig. However, since there are practical difficulties with administration of aerosolized ribavirin and there are additional risks with staff exposure to the drug, intravenous ribavirin should be considered for additional studies.

There have been few studies published regarding morbidity and mortality in influenza infections in SCT recipients. Whimbey *et al*<sup>8</sup> reported a mortality of 17% in a series from MD Anderson Cancer Center. Our study shows a similar outcome both in the patients reported in the prospective survey and in the total study population and confirming that influenza is a serious disease in SCT recipients. The mortality was similar in allogeneic and autologous recipients in contrast to what was found for RSV infections. Vaccination against influenza is recommended by both the EBMT and the CDC. The efficacy of vaccination in eliciting an antibody response has been poor in both allogeneic and autologous SCT patients.<sup>16,17</sup> Although we could not document any effect on the risk for LRTI or mortality, the number of patients was low and vaccination might, of course, have prevented infections or decreased the severity of disease, so that patients did not seek medical attention and therefore were not included in our survey. However, the fact that vaccinated patients developed severe and even fatal infections, supports considering vaccination of family members and hospital staff to reduce the risk for transmission of influenza. Our study was performed mostly before the new neuraminidase inhibitors became available and shows clearly that studies with these agents are needed in this high risk patient population.

We also attempted to look at risk factors for LRTI. Interestingly, we found that lymphocytopenia increased the risk for LRTI both for all infections (OR 2.54) and for RSV infections (OR 3.04), but we could not find any particular risk factor for development of LRTI in patients with influenza. To our surprise, granulocytopenia did not increase the

risk for LRTI, but in fact, was associated with borderline lower risk for LRTI since it was previously suggested that patients developing respiratory viral infection early after transplant have an increased risk for death.<sup>18</sup> However, the results of this analysis should be taken with caution since the number of cases was limited, but lymphocytopenia as a risk factor for severe disease is in accordance with previous observations for other viral infections such as CMV.<sup>19</sup>

Rhinovirus infections have been suggested to be a cause of severe and potential fatal disease in SCT patients.<sup>20</sup> The number of rhinovirus infections diagnosed in our survey was small, but no severe disease was documented.

The results of this study show that respiratory tract infections, particularly influenza and RSV, are important causes of morbidity after SCT. The overall impact on transplant-related mortality was approximately 1% and therefore an awareness of this risk and prevention strategies against lower respiratory tract infection are necessary. These strategies include an adherence of visitors and staff to hand-washing routines, reducing the exposure of SCT patients to infected individuals, vaccination, and potentially antiviral prevention strategies in the future.

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