MAJOR ARTICLE

Respiratory Syncytial Virus Infection in Patients with Hematological Diseases: Single-Center Study and Review of the Literature

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Background. Respiratory syncytial virus (RSV) causes significant mortality in patients with hematological diseases, but diagnosis and treatment are uncertain.

Methods. We retrospectively identified RSV-infected patients with upper or lower respiratory tract infection (RTI) by culture, antigen testing, and polymerase chain reaction from November 2002 through April 2007. Patients with severe immunodeficiency (SID; defined as transplantation in the previous 6 months, T or B cell depletion in the previous 3 months, graft-versus-host disease [grade, ⩾2], leukopenia, lymphopenia, or hypogammaglobulinemia) preferentially received oral ribavirin, intravenous immunoglobulin, and palivizumab. The remaining patients with moderate immunodeficiency (MID) preferentially received ribavirin and intravenous immunoglobulin.

Results. We identified 34 patients, 22 of whom had upper RTI (10 patients with MID and 12 with SID) and 12 of whom had lower RTI (2 with MID and 10 with SID). Thirty-one patients were tested by polymerase chain reaction (100% of these patients had positive results; median RSV load, 5.46 $\log_{10}$ copies/mL), 30 were tested by culture (57% had positive results), and 25 were tested by antigen testing (40% had positive results). RSV-attributed mortality was 18% (6 patients died) and was associated with having ⩾2 SID factors ($P = .04$), lower RTI ($P = .01$), and preengraftment ($P = .012$). Among 12 patients with MID (7 of whom received treatment), no progression or death occurred. Nine patients with SID and upper RTI received treatment (7 patients received ribavirin, intravenous immunoglobulin, and palivizumab); infection progressed to the lower respiratory tract in 2 patients, and 1 patient died. Ten patients with SID and lower RTI were treated, 5 of whom died, including 4 of 6 patients who received ribavirin, intravenous immunoglobulin, and palivizumab. The duration of RSV shedding correlated with the duration of symptoms in patients with SID but exceeded symptom duration in patients with MID ($P < .05$).

Conclusions. Lower RTI, ⩾2 SID criteria, and preengraftment are risk factors for RSV-attributed mortality. Polymerase chain reaction may optimize diagnosis and monitoring. Oral ribavirin therapy seems safe, but trials are needed to demonstrate its efficacy.

Respiratory syncytial virus (RSV) causes significant morbidity and mortality in adult patients with hematological diseases when upper respiratory tract infection (RTI) progresses to lower RTI [1, 2]. Progression from upper to lower RTI has been estimated to develop in up to 50% of patients who have received chemotherapy for leukemia or undergone hematopoietic stem cell transplantation (HSCT), with mortality rates of 20%–60% [3, 4]. The frequency of progression to lower RTI may be associated with lymphopenia, allogeneic HSCT, graft-versus-host disease, and diagnosis within 1 month after transplantation [2, 3, 5, 6], justifying delaying HSCT [7]. Detection of RSV by antigen testing, culture, and RT-PCR is now available, but these tests have rarely been compared in hematology clinics.

Treatment of RSV infection in patients with hematological disease includes ribavirin aerosol inhalation,

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intravenous immunoglobulin (IVIG), RSV hyperimmunoglobulin, or palivizumab (a monoclonal IgG that neutralizes RSV by binding the envelope protein F) [1, 2, 8]. These treatments have been available for more than a decade, but clear evidence of efficacy is lacking. Aerosolized ribavirin might improve outcome when administered early, before lower RTI develops [6, 9, 10]. However, most patients are infected as outpatients—before or after hospitalization for chemotherapy or HSCT—when RSV circulates in the community. Oral ribavirin has a bioavailability of 30%–74% [11] and was successfully administered to 4 patients with upper RTI [12]. Aerosolized or intravenous ribavirin has been combined with IVIG or RSV hyperimmunoglobulin to treat RSV infection in pediatric patients and adult HSCT recipients, but the efficacy of these treatments has not been established [13, 14]. Palivizumab is registered for the treatment and prophylaxis of RSV bronchiolitis in small infants, but high costs and uncertain efficacy question its use in adult patients with hematological diseases [15]. We proposed a management scheme according to the presumed risk of immunodeficiency [16]. Here, we report the retrospective analysis of RSV infection in the patients with hematological diseases and review the literature.

METHODS

Setting. The hematology unit at the University Hospital Basel (Basel, Switzerland) is a referral center for adults (age, ⩾18 years) receiving myeloablative chemotherapy and undergoing autologous and allogeneic HSCT. From February 2002 through April 2007, 212 myeloablative chemotherapy treatments and 402 transplantations (119 autologous and 283 allogeneic) were performed. A high-resolution CT is routinely done in cases involving neutropenic fever and respiratory symptoms and is performed weekly when antiviral or antifungal agents are administered. In cases of suspected respiratory infection, bronchoalveolar lavage (BAL) is performed within 24 h after onset of symptoms.

Patients and definitions. A retrospective chart review was performed for all inpatients and outpatients who received diagnoses of symptomatic RSV infection during the period November 2002–April 2007. Upper RTI was defined as detection of RSV in upper respiratory secretions, together with symptoms involving the upper respiratory tract (nose and throat), according to Ljungman et al. [3]. Lower RTI was defined as the presence of either hypoxia or pulmonary infiltrates, together with identification of RSV in upper or lower respiratory secretions and exclusion of other causes [3].

Severe immunodeficiency (SID) was defined as HSCT ⩽6 months prior to diagnosis of RSV infection, T cell depletion ⩽3 months prior to diagnosis, B cell depletion ⩽3 months prior to diagnosis, graft-versus-host disease (grade, ⩾2), leukopenia (leukocyte count, $\leqslant 2.0 \times 10^9$ cells/L, lymphopenia (lymphocyte count, $\leqslant 0.1 \times 10^9$ cells/L), or hypogammaglobulinemia (immunoglobulin level, ⩽6.5 g/L). Moderate immunodeficiency (MID) was defined as HSCT >6 months prior to diagnosis of RSV infection, graft-versus-host disease (grade, <2), leukocyte count $>2.0 \times 10^9$ cells/L, lymphocyte count $>0.1 \times 10^9$ cells/L, receipt of maintenance immunosuppressive drugs, or T cell or B cell depletion >3 months prior to diagnosis of RSV infection. RSV-attributable mortality was defined as death due to respiratory failure, with no cause other than RSV pneumonia identified.

Table 1. Baseline characteristics of study patients.

Characteristic	HSCT recipients (n = 27)	All patients (n = 34)
Sex		
Male	17 (63)	20 (59)
Female	10 (37)	14 (41)
Age, mean years ± SD	41.9 ± 17	41.7 ± 16.7
Underlying disease		
Leukemia		
Acute lymphocytic	9 (33)	11 (32)
Acute myelogenous	5 (18.5)	6 (18)
Chronic myelogenous	2 (7)	2 (6)
Non-Hodgkin lymphoma	5 (18.5)	6 (18)
Hodgkin disease	1 (4)	1 (3)
Multiple myeloma	3 (11)	3 (9)
Aplastic anemia	1 (4)	3 (9)
Other	1 (4)	2 (6)
Underlying disease state at RSV diagnosis		
Remission	14 (52)	20 (59)
Minimal residual disease	3 (11)	3 (9)
Persistent or relapse	8 (30)	9 (26)
Unclear	2 (7)	2 (6)
T cell depletion[a]	7 (26)	9 (26)
Donor type		
Autologous	3 (11)	…
Allogeneic		
Matched, related	14 (52)	…
Matched, unrelated	5 (18)	…
Mismatched, related	4 (15)	…
Mismatched, unrelated	1 (4)	…
Conditioning regimen		
Myeloablative	18 (67)	…
Reduced intensity	9 (33)	…
Time from receipt of HSCT to engraftment, median days (IQR)	14 (13–20.5)	…
Time from receipt of HSCT to diagnosis of RSV infection, median days (IQR)	210 (127–475)	…
Graft-versus-host disease	13 (48)	…
Immunsuppressive therapy		
Cyclosporin	10 (37)	…
Cyclosporin and corticosteroids	6 (22)	…
Cyclosporin, corticosteroids, and cellcept	6 (22)	…

NOTE. Data are no. (%) of patients, unless otherwise indicated. HSCT, hematopoietic stem cell transplant; IQR, interquartile range; RSV, respiratory syncytial virus.

[a] T cell depletion is defined as treatment or conditioning regimen with anti–T cell globulin, anti–CD3 antibody, anti-CD52, and/or T cell–depleted HSCT.

Table 2. Characteristics of patients according to immunodeficiency.

Variable	No. (%) of patients
Moderate immunodeficiency	
HSCT ⩾6 months prior to diagnosis of RSV infection	7 (58)
Immunosuppressive treatment	4 (33)
T cell depletion >3 months prior to diagnosis of RSV infection	4 (33)
Severe immunodeficiency	
Acute GVHD (grade, ⩾2)	13 (59)
HSCT <6 months prior to diagnosis of RSV infection	9 (41)
Leukopenia (leukocyte count, $\leqslant 2.0 \times 10^9$ cells/L)	6 (27)
Lymphopenia (lymphocyte count, $\leqslant 0.1 \times 10^9$ cells/L)	6 (27)
T cell depletion <3 months prior to diagnosis of RSV infection	5 (23)
Preengraftment	4 (18)
Hypogammaglobulinemia (immunoglobulin level, <6.5 g/L)	3 (14)
B cell depletion <3 months prior to diagnosis of RSV infection	1 (5)

NOTE. Data are for 12 patients with moderate immunodeficiency and 22 patients with severe immunodeficiency. GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; RSV, respiratory syncytial virus.

Virological techniques. RSV infection was diagnosed by testing for antigen, by isolation in tissue culture, and/or by quantitative RT-PCR after specimen arrival at the laboratory. For microbiological diagnosis, nasopharyngeal aspirate specimens, swab specimens (for upper RTI), and BAL specimens were obtained from the site of clinically active infection (for lower RTI). For a follow-up examination, serial nasal secretion specimens were obtained from 19 patients. For RSV isolation, specimens were collected in 3 mL of viral transport media and then inoculated onto shell vials for tissue cultures (Madin-Darby canine kidney cells, rhesus monkey kidney cells, human lung carcinoma cells, and human fetal diploid fibroblast cells). RSV was identified by the cytopathic effect and diagnosed by staining with a fluorescein-conjugated monoclonal antibody (Virion). For the RSV antigen test, the NOW RSV Test Kit (Binax) was used. RSV RT-PCR was performed according to a previously published protocol detecting type A and type B in separate reactions [17]. The limit of detection was 1000 copies/mL.

Antiviral treatment. Stratified treatment was recommended according to presumed immunodeficiency and site of infection, as published elsewhere [16]. Patients with MID and upper or lower RTI received oral ribavirin (initiated with 10 mg/kg as a loading dose and then increased to 400 mg 3 times daily on day 2 and 600 mg 3 times daily on day 3) plus IVIG (0.5 g/kg weekly). Patients with SID and upper RTI were treated with the same ribavirin regimen as that for patients with MID and upper or lower RTI, IVIG (0.5 g/kg every other day), and palivizumab (15 mg/kg administered as a single intravenous dose). Patients with SID and lower RTI received the same ribavirin regimen as that for the other patients and IVIG (0.5 g/kg every other day). The use of palivizumab in patients with SID and lower RTI was based on the decision of the treating physician.

Switching to intravenous administration of ribavirin was only done in patients receiving mechanical ventilation, using the same dosing as that for oral administration. Treatment was discontinued when patients were asymptomatic and RSV was no longer detectable by RT-PCR.

Infection control and supportive care measures. Hospitalized patients with signs of RTI were isolated in single rooms with laminar air flow. Outpatients were seen in single rooms in a different wing of the hospital. Isolation precautions included hand hygiene with an alcohol-based hand rub, gloves, gowns, and protective goggles [16]. Contact isolation was discontinued when patients were asymptomatic and RSV was no longer detectable by RT-PCR.

Statistical analysis. All statistical analyses were performed with SPSS, version 14.0 (SPSS). Quantitative RSV RT-PCR was compared with antigen testing and culture using a receiver operating characteristics curve. Study groups were compared by Mann-Whitney *U* test or Wilcoxon signed rank sum test. Categorical variables were compared by χ^2 test or Fisher's exact test. A 2-sided *P* value <.05 was considered to be significant.

RESULTS

Patient characteristics. From 2002 through 2007, 34 patients were diagnosed with RSV infection at our hospital; all cases occurred from November through April, when RSV infection is prevalent in Switzerland [18]. Patient characteristics at RSV diagnosis are listed in table 1. Most patients had leukemia, which was in remission in approximately one-half of these patients. HSCT was performed for 79% of the patients, 52%

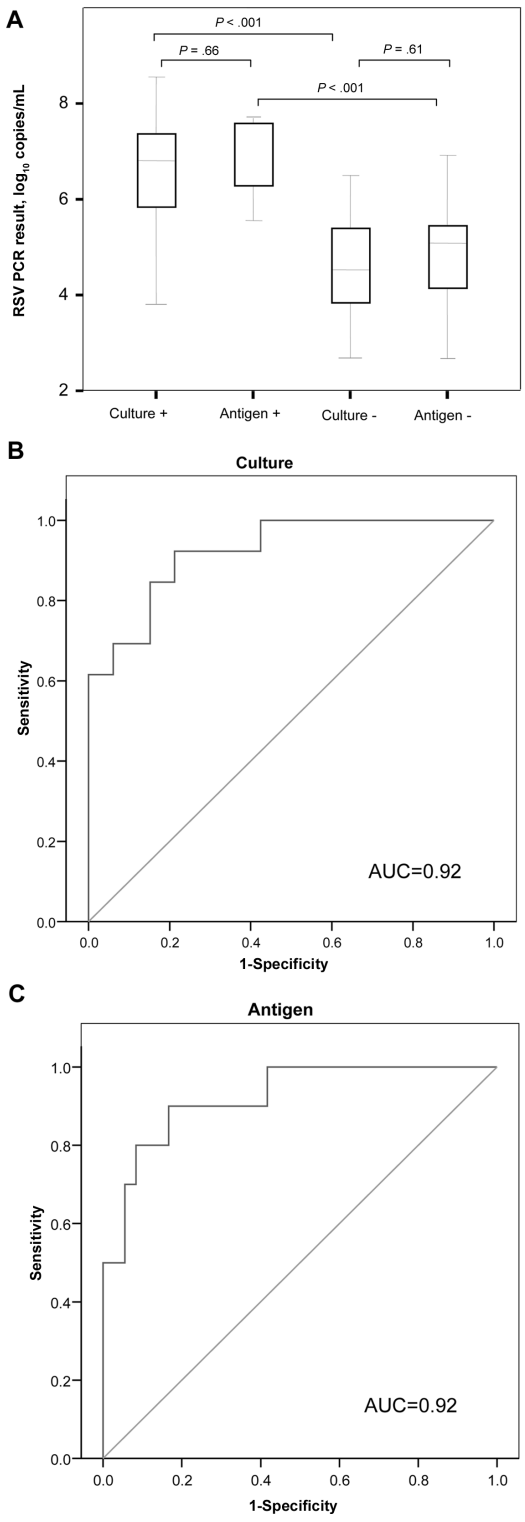

Figure 1. Comparison of respiratory syncytial viral (RSV) PCR with culture and antigen testing. *A,* Box plots of quantitative RSV PCR results for patients with positive or negative culture and antigen test results. *B,* Receiver operating characteristic curve of the RSV RT-PCR to predict culture results (area under the curve [AUC], 0.92; 95% CI, 0.84–1.0). *C,* Receiver operating characteristic curve of the RSV RT-PCR to predict antigen test results (AUC, 0.92; 95% CI, 0.83–1.0).

of whom had a matched, related donor. Eighteen individuals (53%) presented as outpatients. At the time of RSV diagnosis, upper RTI was diagnosed in 22 patients (65%), and lower RTI was diagnosed in 12 patients (35%). All of the patients who had received a diagnosis of lower RTI had a new infiltrate on CT, with hypoxia in 3 patients (25%).

Characteristics according to immunodeficiency. Characteristics of patients according to immunodeficiency are shown in table 2. MID was diagnosed in 12 patients, with 5 patients (42%) fulfilling ⩾2 criteria. SID was diagnosed in 22 patients; 13 patients (59%) fulfilled ⩾2 criteria, and 6 (27%) fulfilled ⩾3 criteria.

Diagnostic results. At diagnosis, RSV was detected in nasal aspirate specimens from 27 patients and in BAL specimens from 7 patients. RSV-specific RT-PCR was performed for samples from 31 patients (91%), and all of the results were positive. Median RSV load at diagnosis was 5.46 $\log_{10}$ copies/mL (interquartile range [IQR], 4.52–6.75 $\log_{10}$ copies/mL), the median RSV load in RSV-positive nasal aspirate specimens was 5.46 $\log_{10}$ copies/mL (IQR, 4.54–6.61 $\log_{10}$ copies/mL), and the median RSV load in RSV-positive BAL specimens was 5.58 $\log_{10}$ copies/mL (IQR, 3.98–6.57 $\log_{10}$ copies/mL). RSV subtypes were available for 30 patients; 16 had subtype A, and 14 had subtype B, without statistically significant differences in RSV load. Culture was performed for samples from 30 patients (88% of total patients tested), and results were positive for samples from 17 (57%) of these 30 patients. Antigen tests were performed for samples from 25 patients (74%), and the results were positive for samples from 10 (40%) of these 25 patients. In total, 105 specimens (84 nasal aspirate specimens and 21 BAL specimens) were obtained from the 34 patients. RT-PCR was conducted for 101 specimens, and the results were positive for 70 (69%) of these specimens. Culture was performed for 74 samples, and the results were positive for 27 (36%) of these samples. Antigen tests were performed for 60 specimens, and results were positive for 12 (20%) of these specimens. For 47 specimens, all 3 tests were performed. RT-PCR results were positive for 32 samples (68%), and results of both culture and RT-PCR were positive for 14 samples (30%). Results of both antigen test and RT-PCR were positive for 11 specimens (23%). All culture- and/or antigen-positive samples were also RT-PCR positive. Among these 47 specimens, the median RSV load was 6.9 $\log_{10}$ copies/mL (IQR, 6.1–7.6 $\log_{10}$ copies/mL) in culture- and RT-PCR–positive specimens and 7.3 $\log_{10}$ copies/mL (IQR, 6.3–7.7 $\log_{10}$ copies/mL) antigen test– and RT-PCR–positive specimens (figure 1*A*). For RSV isolation, receiver operating characteristics curve analysis of the quantitative RSV RT-PCR predicted optimal sensitivity and specificity at 5.21 $\log_{10}$ copies/mL (area under the curve, 0.92; 95% CI, 0.84–1.0). Excluding 2 outliers, the threshold for a positive culture result was an RSV load ⩾5.32 $\log_{10}$ copies/mL (figure 1*B*). For RSV antigen

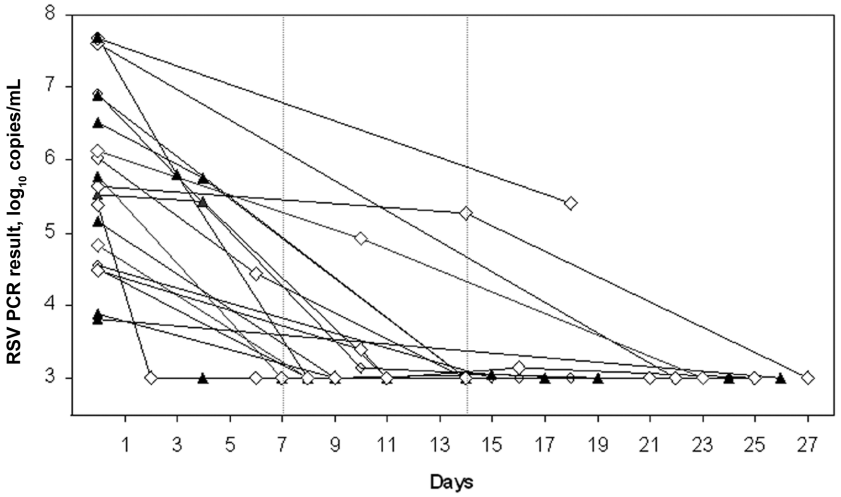

Figure 2. Respiratory syncytial viral (RSV) load in serial nasal swab specimens. Serial quantitative RT-PCR results (log_{10} copies/mL) are shown for 19 patients over a maximal 34 days. Patients with severe immunodeficiency ($n = 11$) are represented by white diamonds, and patients with moderate immunodeficiency ($n = 8$) are represented by black triangles.

detection, optimal sensitivity and specificity was reached at an RSV load of 5.53 log_{10} copies/mL (area under the curve, 0.92; 95% CI, 0.83–1.01). Excluding 1 outlier, the threshold for a positive antigen test result was an RSV load $\geqslant$5.56 log_{10} copies/mL (figure 1*C*).

Site of infection, treatment, and outcome. Upper RTI was identified in 10 patients with MID, 5 of whom did not receive treatment. Five patients with MID were treated with oral ribavirin (median duration of therapy, 14 days; range, 5–21 days) and IVIG (1–3 doses). No progression to lower RTI and no deaths occurred. Lower RTI was identified in 2 patients with MID. Both received oral ribavirin (for 8 and 16 days, respectively), one received IVIG, and both survived. Upper RTI was identified in 12 patients with SID. Three were not treated, 3 received ribavirin and IVIG, and all survived. The remaining 6 patients with SID received ribavirin, IVIG, and palivizumab, but infection progressed to the lower respiratory tract in 2 patients, and 1 patient died. Treatment with ribavirin was applied for a median duration of 16 days (range, 4–64 days). Median duration of IVIG treatment was 2 days (range, 1–6 days). Lower RTI was identified in 10 patients with SID (1 was treated with IVIG only, 2 were treated with ribavirin and IVIG, and 7 were treated with ribavirin, IVIG, and palivizumab). Five patients were admitted to the intensive care unit, and 4 received mechanical ventilation. All 4 patients who received mechanical ventilation died, and 1 patient who died had not been admitted to the intensive care unit (the 1 patient who was not admitted to the intensive care unit received ribavirin and IVIG, and the other 4 patients who died received ribavirin, IVIG, and palivizumab). Overall, lower RTI occurred more frequently in patients with SID than in patients with MID ($P = .068$).

RSV-attributable mortality. RSV-attributable mortality was 18% (6 patients died). Among 6 patients who died, risk factors for mortality were lower RTI at diagnosis in 5 patients ($P = .01$), $\geqslant$2 SID criteria in 6 patients ($P = .046$), $\geqslant$3 SID criteria in 4 patients ($P = .025$), and preengraftment in 3 ($P = .012$). Only 1 of 6 patients with SID who received ribavirin, IVIG, and palivizumab treatment for upper RTI died, whereas 3 of 6 patients treated for lower RTI died ($P = .16$).

RSV load in serial nasal secretions. We observed RSV loads in serial nasal secretions of 19 patients treated with oral ribavirin, 11 of whom had upper RTI (6 patients with MID and 5 with SID) and 8 of whom had lower RTI (1 with MID and 7 with SID) (figure 2). Median RSV load at diagnosis was 6.52 log_{10} copies/mL (range, 3.8–7.7 log_{10} copies/mL). Viral shedding in nasal aspirate specimens remained detectable by RT-PCR for 7–28 days. A >2 log_{10} copies/mL decrease in RSV load was observed in 11 (58%) of 19 patients within 7 days after initiation of treatment, and no progression to lower RTI or death occurred. Another 6 (32%) of 19 patients had >2 log_{10} copies/mL decrease in RSV load within 14 days after diagnosis; lower RTI occurred in 2 patients, and 1 patient died. One of 19 patients died on day 20. Duration of shedding was not associated with site of infection, severity of immunodeficiency, RSV subtype, or treatment modalities. However, symptoms lasted longer in patients with SID than in patients with MID ($P = .002$, by Mann-Whitney *U* test) (figure 3*A*), and duration of viral shedding correlated with the duration of symptoms in patients with SID but exceeded the duration of symptoms in patients with MID ($P = .027$; by Wilcoxon test) (figure 3*B*).

Drug-related adverse events. Ribavirin (1800 mg per day) was given to 19 of 25 treated patients. Transfusion-dependent reversible hemolysis occurred in 5 patients (26%). In 1 patient with RSV infection prior to HSCT and preexisting liver damage,

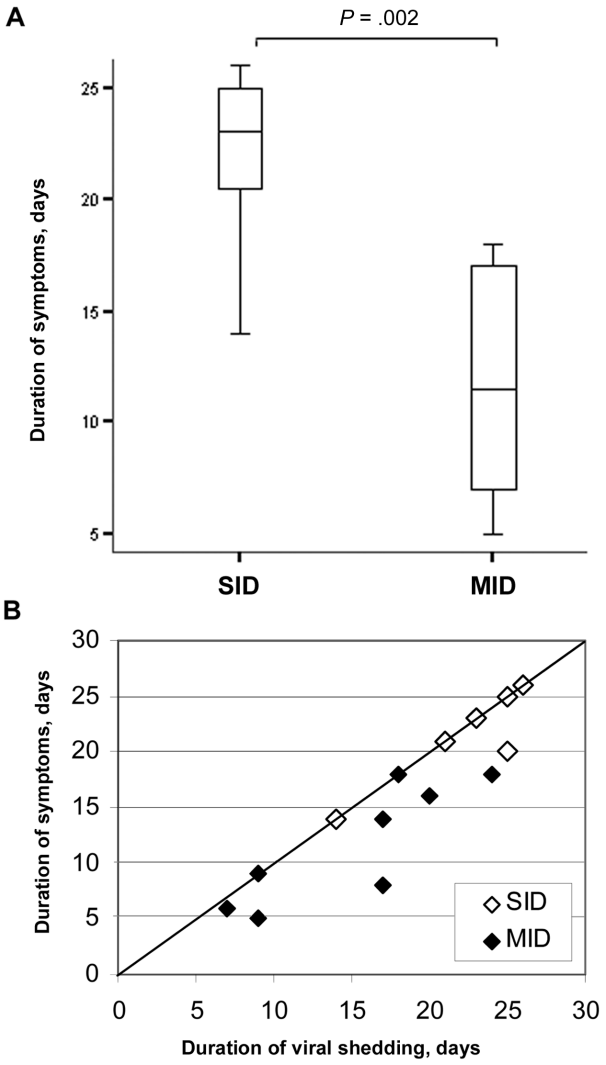

Figure 3. Duration of respiratory syncytial virus shedding and symptoms. *A,* Duration of symptoms. Box plots of patients with severe immunodeficiency (SID; $n = 7$) and patients with moderate immunodeficiency (MID; $n = 8$; $P = .04$, by Mann-Whitney *U* test). *B,* Duration of respiratory syncytial virus shedding and symptoms. Patients with SID ($n = 7$; $P = .18$, by Wilcoxon rank sum test) are represented by white diamonds, and patients with MID ($n = 8$; $P = .027$, by Wilcoxon rank sum test) are represented by black diamonds.

the bilirubin level increased from 100 to 150 μmol/L within 7 days after initiation of treatment. Ribavirin therapy was discontinued, but the bilirubin level remained elevated. Liver biopsy revealed histologic characteristics that were compatible with drug-induced liver damage; thus, we cannot exclude an association with ribavirin. No adverse effects occurred in association with IVIG and palivizumab therapy.

DISCUSSION

RSV is a significant pathogen in patients with hematological diseases, but diagnosis, management, and outcome of RSV infection are subjects of considerable uncertainty. With regard to diagnosis, we found that RSV-specific RT-PCR is more sensitive than culture and antigen testing in the clinical routine. The RSV loads associated with positive culture and antigen test results were 6.9 $\log_{10}$ copies/mL and 7.3 $\log_{10}$ copies/mL, respectively, with a threshold of $\geqslant$5.32 $\log_{10}$ copies/mL and $\geqslant$5.56 $\log_{10}$ copies/mL, respectively. Only 2 of 39 studies reported the use of RSV RT-PCR in patients with hematological diseases [19, 20]. Therefore, the incidence of RSV infection and the risk of nosocomial transmission may have been underestimated. Virus isolation requires 3–5 days and dedicated laboratory expertise but remains the only alternative for detecting respiratory viruses not covered by molecular techniques. RSV antigen testing requires <4 h but detects less then one-third of the RT-PCR–positive cases. Thus, antigen testing could play a role for patients shedding RSV at high levels, to trigger infection-control measures when RSV RT-PCR is not readily available. We conclude that RSV RT-PCR with a turnaround time of <24 h in a quantitative format represents an asset in routine testing and in future studies of patients with hematological diseases.

With regard to management, we report, to our knowledge, the largest number of patients treated with oral ribavirin. Of 25 patients, 16 were seen in an outpatient context. The maximal dosage of oral ribavirin (1800 mg per day) was generally well tolerated. Hemolysis was observed in 5 cases and was readily controlled by blood transfusions. Because of heterogeneous therapy combinations, small sample size, and the retrospective context, we are unable to provide a conclusion regarding whether oral ribavirin therapy affected outcome. However, 2 considerations suggest that oral ribavirin therapy is probably comparable to aerosolized ribavirin therapy. First, analysis of serial nasal secretions from 19 patients treated with oral ribavirin revealed a decrease in RSV load of 2 $\log_{10}$ copies/mL within 7 days after treatment initiation in 58% of the patients and within 14 days after treatment initiation in 90% of the patients. Boeckh et al. [10] reported a mean decrease in RSV load of 0.75 $\log_{10}$ copies/mL at 10 days after treatment initiation in 9 patients with RT-PCR–positive RSV infection and upper RTI who were treated with aerosolized ribavirin, whereas 5 untreated patients had an increase in RSV load of 0.5 $\log_{10}$, to 1.26 $\log_{10}$ copies/mL. Second, rates of disease progression and mortality in our study are comparable to those in studies using aerosolized ribavirin.

Treatment with the neutralizing IgG antibody palivizumab, in addition to ribavirin, was only to be considered for patients with SID and upper RTI, with the underlying rationale being to moderate progression to lower RTI. Although IgG may not modify upper RTI, transudation of IgG in the lower respiratory tract might reduce RSV replication and ameliorate the course of infection in patients with SID. In patients with SID who have established lower RTI, pavilizumab administration was

Table 3. Respiratory syncytial virus (RSV) infection in patients with hematological diseases.

Reference	No. of patients	Site of infection	Diagnostic methods (no. of patients)	Type of ribavirin therapy (no. of patients)	IVIG therapy	RSV-specific immunoglobulin therapy	Palivizumab therapy	Progression to LRTI	RSV-associated mortality, proportion of patients who died among total infected patients	Risk factors for progression to LRTI or death	Comment
[23]	7	No symptoms	Ag, DFA	Aer (7)	No	1	No	…	0/7	…	Children aged 1.5–13.5 years, HSCT recipients, no clinical symptoms developed
[24]	1	URTI	Cul, DFA	No	No	No	No	…	0/1	…	All BMT recipients, 1 child
[22]	13	URTI	Cul, DFA	No	No	No	No	NA	0/13	NA	…
[4]	3	URTI	Cul (3)	No	No	No	No	…	0/3	…	Only patients with leukemia
[25]	16	URTI	Cul, DFA	No	No	No	No	NA	0/16	…	…
[26]	10	URTI	Cul, DFA (10); Ag(3)	No	5	No	No	0	0/10	…	Autologous HSCT for patients with multiple myeloma
[8]	3	URTI	Cul, Ag	Aer (3)	No	No	No	…	…	…	Nosocomial outbreak
[27]	33	URTI	Cul, Ag, DFA	Aer (16 when LRTI)	No	16	No	20/33	12/33	<1 month after BMT, late treatment (>24 h before mechanical ventilation)	All untreated patients died
[28]	25	URTI	Cul, DFA	Aer (25)	No	No	No	8/25	2 or 3/8	…	Aerosolized ribavirin for 7 days
[6]	12	URTI	NA	Aer (12)	12	No	No	2/12	2/12	Autologous BMT	…
[6]	31	URTI	Cul	Aer (17 when LRTI)	17	No	No	17/31	8/17	⩽500 neutrophils/mL	Patients with leukemia
[6]	38	URTI	Cul or autopsy	Aer (23 when LRTI)	23	No	No	23/38	14/23	Late treatment (<24 h before mechanical ventilation)	All BMT recipients
[29]	5	URTI	DFA (5)	Aer (4)	No	No	No	0	0/5	…	…
[30]	14	URTI	Cul, Ag (10); Cul (3); Ag (1)	Aer (14)	14	No	No	4/14	2/14	LRTI <15 days after HSCT	Prospective
[31]	33	URTI	Cul, DFA (22); Cul (6); DFA (3); Ag (1)	Aer (11)	12	6	No	0/33	…	Preengraftment	Retrospective
[32]	27	URTI	DFA (27)	Aer (16)	16	No	No	15/27	1/15 (no treatment)	…	Pulmonary coinfection in 9 of 27 patients (4 with influenza A, 2 with influenza B, 2 with parainfluenza, and 1 with influenza A and B)
[7]	37	URTI	Cul, DFA	Aer (10)	2	No	No	6/37	1/37	HSCT	31 patients before HSCT
[10]	14	URTI	Cul, Ag, DFA	Aer (9)	No	3	No	1/9; 2/5	0/14	…	Randomized, controlled trial
[33]	4	URTI	Cul, Ag	Aer, IV (3); IV (1)	No	No	No	1 or 2/4	…	…	Retrospective
[34]	11	URTI	Cul, Ag	Aer (2); Aer, IV (1)	2	No	No	6/11		Unrelated BMT recipients, 50% untreated	Retrospective
[3]	19	URTI	Cul, Ag	Aer (7); Aer, IV (2)	2	No	No	…	3/19	Lymphopenia	Retrospective and additional case collection
[12]	4	URTI	Cul, DFA	Oral (4)	No	No	No	0	0/4	…	1 patient with 2 episodes
[15]	3	URTI	Cul, DFA (3)	Oral (3)	No	No	3	…	…	…	…
Present study	22	URTI	Cul, PCR, Ag (5); Cul, PCR (4); Cul, Ag (1); PCR, Ag (2); PCR (12)	Oral (14)	14	No	6	2/22	1/22	…	Retrospective
[35]	1	LRTI	Cul of lung biopsy specimen	No	No	No	No	…	1/1	…	Diagnosis after death

[36]	1	LRTI	Cul, DFA (1)	No	No	No	No	…	0/1	…	…
[20]	1	LRTI	Cul, PCR, DFA	No	1/1	No	No	…	0	…	Pediatric patient
[37]	7	LRTI	Cul, Ag	Aer (6)	No	No	No	…	4/7	…	6 BMT recipients and 1 patient with lymphoma
[24]	3	LRTI	Cul, DFA	Aer (1)	No	No	No	…	2/3	…	2 of 4 patients received mechanical ventilation
[22]	18	LRTI	Cul, DFA	Aer (13)	No	No	No	…	14/18	…	4 of 13 treated patients survived; 13 of 18 received mechanical ventilation (all died); 3 of 18 had pulmonary coinfection (1 with *Pneumocystis jiroveci* and 2 with cytomegalovirus)
[4]	6	LRTI	Cul (6)	Aer (6)	No	6	No	…	5/6	…	4 of 9 patients received mechanical ventilation; 3 of 6 had pulmonary coinfection
[8]	16	LRTI	Cul, Ag	Aer (12)	No	12	No	…	9/16	Late treatment or no therapy	…
[38]	2	LRTI	Cul, Ag	Aer (2)	No	2	No	…	0/2	…	…
[29]	3	LRTI	DFA (3)	Aer (3)	No	No	No	…	…	…	…
[39]	4	LRTI	DFA, Cul (3); Cul (1)	Aer (3)	1 (1)	No	No	No	…	1/4	…
[19]	5	LRTI	Cul (4); PCR (5)	Aer (2)	No	No	No	…	1/5	…	…
[31]	25	LRTI	Cul, DFA (22); Cul (2)	Aer (24)	7	18	…	…	3/25	Preengraftment	6 patients received mechanical ventilation; 1 had pulmonary coinfection (with influenza A)
[40]	11	LRTI	Cul (11)	Aer (5)	No	No	No	…	6/11	…	6 received mechanical ventilation, 5 of whom died; 8 had pulmonary coinfection (5 with fungal infections and 3 with bacterial infections)
[41]	3	LRTI	DFA	Aer (2); Aer, IV (1)	No	No	No	…	2/3	…	All autologous HSCT recipients; 2 of 4 received mechanical ventilation, and both died
[25]	12	LRTI	Cul, DFA	IV (10)	No	No	No	…	8/10	…	3 of 10 patients had pulmonary coinfection (with *Aspergillus*, parainfluenza, adenovirus); 2 of 10 patients had acute hemolysis
[33]	2	LRTI	Cul, Ag	Aer, IV (1); IV (1)	No	No	No	…	2/2	…	…
[34]	15	LRTI	Cul, Ag	Aer (2); IV (4); Aer, IV (1)	9	…	…	…	5/15	…	…
[14]	11	LRTI	Ag, DFA	Aer (9); IV (3)	No	11	No	…	1/11	…	Children aged <9 years; patients received steroids; 4 of 11 patients received mechanical ventilation; 1 of 11 survived
[3]	27	LRTI	Cul, Ag	Aer (14); IV (7); Aer, IV (6)	8	No	No	…	11/27	Lymphopenia	14 patients died; however, only 8 of 14 deaths were judged as attributable to RSV infection
[15]	12	LRTI	Cul, DFA(12)	Aer (12)	No	No	12	…	2/12	…	1 patients received mechanical ventilation
Present study	12	LRTI	Cul, PCR, Ag(3); Cul, PCR (4); PCR, Ag (1); Cul (2); PCR (2)	Oral (11)	10	No	7	…	5/12	Preengraftment	Retrospective

[21][a]	3	URTI	Cul (1); Ag (6)	Aer (8)	No	No	No	…	…	Preengraftment, Diagnosis <24 h before respiratory failure	All BMT recipients; 4 of 8 received mechanical ventilation; all died; 1 patient had pulmonary coinfection (with cytomegalovirus and herpes simplex virus)
	5	LRTI	…	…	…	…	…	…	4/8	…	…
[42][a]	10	URTI	Cul, DFA (11); Cul (4); DFA (3)	Aer (8)	1	3	No	…	1/8 not RSV attributable	…	Retrospective, in children with cancer, without HSCT
	8	LRTI	…	…	…	…	…	…	…	…	1 of 18 patients received mechanical ventilation; 4 of 18 had pulmonary coinfection (with *Mycoplasma pneumoniae*, adenovirus, and bacterial pneumonia not specified)
[9][a]	5	URTI	Cul (9)	Aer (9)	3	1	No	2/5	…	Preengraftment	Autologous HSCT recipients with breast cancer
	4	LRTI	…	…	4	1	…	…	2/4	…	…
[43][a]	32	No symptoms	Cul (56)	No	No	No	No	14/56	3/56	Mucositis, elevated LDH, renal failure	Prospective; comparison with RSV-negative patients; only patients with multiple myeloma
	24	URTI or LRTI	…	…	…	…	…	…	…	…	…
[43][a]	11	Unclear	Cul (11)	No	No	No	No	1/11	…	…	Only autologous HSCT recipients
	4	Unclear	Cul (4)	No	No	No	No	1/4	…	…	Only allogeneic HSCT recipients
[44][a]	12	URTI	Cul, DFA	…	No	No	No	4/12	…	Lymphopenia (lymphocyte level, $<0.2 \times 10^9$ cells/L	Prospective
	7	LRTI	…	…	No	No	No	…	2/11	…	…
[2][a]	68	URTI	Cul (6); Ag (59); Cul, Ag (42)	Aer (61)	25	No	No	39/107	…	Older age, no ribavirin treatment	Retrospective
	39	LRTI	…	…	…	…	…	…	7/39	…	…

NOTE. Ag, antigen test; Aer, aerosolized; BMT, bone marrow transplant; Cul, culture and shell vial, DFA, direct fluorescent antibody; HSCT, hematopoietic stem cell transplantation; IV, intravenous; LDH, lactate dehydrogenase; LRTI, lower respiratory tract infection; NA, not available; URTI, upper respiratory tract infection.

[a] Patients could not be discriminated as having URTI or LRTI.

deemed to be ineffective but was left to the discretion of the treating physician. Of 6 patients with SID and upper RTI who received a combination treatment with palivizumab, 1 patient (16%) died, compared with 4 (57%) of 7 patients with SID and lower RTI who received such treatment. Although these data emphasize the role of lower RTI, no conclusion on palivizumab efficacy can be made. Our results are comparable to the only other study investigating 15 HSCT recipients using aerosolized ribavirin in combination with palivizumab [15]. In that study, 3 patients with upper RTI recovered without progression to lower RTI, and 17% of patients with lower RTI died, but the SID status is not known [15].

With regard to outcome, we observed an RSV-attributable mortality rate of 18%, which is in the lower range of rates in the literature [1, 21, 22]. Lower RTI was a significant risk factor for a poor outcome ($P = .01$). Mortality was increased during the preengraftment period, indicating that the risk was not uniform but likely depended on the immunologic vulnerability. To approximate the contribution of the "net state of immunosuppression," we developed a simple scheme to identify patients with SID and MID. Patients with $\geqslant 2$ SID criteria had a significantly higher risk for mortality. The overall better outcome in patients with MID suggests that the simple scheme of MID and SID could balance against overtreatment of patients who received a diagnosis on the basis of more-sensitive methods, such as RT-PCR. Clearly, SID criteria warrant further validation and, possibly, refinement in larger, preferably multicenter studies.

After reviewing the literature, we could identify 39 articles with 780 RSV-infected patients from 1981 through 2007 (table 3). With the exception of one study, all were uncontrolled, and most were retrospective case series. Testing by culture was used in 34 of 39 studies, direct fluorescence was used in 19, antigen testing was used in 16, and RT-PCR was used in only 2. Of the 780 RSV-infected patients, 462 patients had upper RTI, and 263 had lower RTI at RSV diagnosis. Aerosolized ribavirin was administered to 337 patients, intravenous ribavirin was given to 24, and oral ribavirin was given to 4. Both aerosolized and intravenous ribavirin were given to 15 patients. IVIG was administered to 163 patients, RSV-specific immunoglobulin was given to 80, and palivizumab was given to 15. Progression to lower RTI occurred in 174 (38%) of 462 patients. Upper RTI progressed to lower RTI in 30 (32%) of 95 patients who were treated with ribavirin. Upper RTI progressed to lower RTI in 76 (68%) of 112 untreated patients, suggesting that early treatment might reduce progression to lower RTI. RSV-attributable mortality was 18% among all 780 patients and 32% among 437 patients with lower RTI. Mortality rates decreased over the years, from 50%–80% to 0%–30% within the same health care centers [2, 8, 21, 22]. This may have occurred because of increased awareness of RSV infection in hematology wards, earlier and more-sensitive diagnostic testing, and possible inclusion of patients with a milder course of infection. The role of treatment is difficult to evaluate. In patients with lower RTI, death occurred for 39 (38%) of 102 patients reported as treated with aerosolized ribavirin, 50 (43%) of 116 patients treated with the combination of ribavirin and IVIG, 18 (64%) of 28 patients treated with intravenous ribavirin, and 15 (42%) of 36 untreated patients. The difference in outcome among these patients seems to be associated less with the efficacy of treatment than with the disease state of the patient. Presumably, patients treated with intravenous ribavirin had more-advanced disease than did the others. In 6 studies, the preengraftment period was associated with progression to lower RTI and RSV mortality. Our study independently confirms preengraftment as a risk factor and points to the potential relevance of the SID criteria.

In conclusion, RSV infection has a significant impact on morbidity and mortality among patients with hematological diseases who have SID. Duration of shedding of RSV coincides with the duration of symptoms in patients with SID but exceeds the duration of the symptomatic phase in patients with MID. RSV RT-PCR is currently the most powerful tool for diagnosis, infection-control measures, and follow-up. Larger, multicenter studies are needed to evaluate the role of SID criteria and of ribavirin-based interventions in this patient population.

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