J Infect Chemother (2011) 17:254–263
DOI 10.1007/s10156-010-0121-1

ORIGINAL ARTICLE

Nationwide survey of severe respiratory syncytial virus infection in children who do not meet indications for palivizumab in Japan

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Received: 6 May 2010 / Accepted: 14 August 2010 / Published online: 25 September 2010

Abstract In Japan, palivizumab, a humanized monoclonal antibody specific for respiratory syncytial virus (RSV), has been available since 2002. However, its use is limited to children at risk of severe RSV infection, with specific criteria that have been validated in large-scale clinical studies. The Pharmaceutical Committee of the Japan Pediatric Society established a committee to conduct a nationwide questionnaire survey to determine which diseases place children at risk of severe RSV infection and require preventive measures. A questionnaire sent to 613 medical institutions, including major pediatric hospitals and general hospitals with pediatric services, received 272 responses (44.4%). In total, 1,115 children not meeting current indications for palivizumab therapy were hospitalized for severe RSV infection, 16 (1.4%) of whom died; this suggests that palivizumab therapy should be considered for children with severe immunodeficiency or those at risk of nosocomial RSV infection in whom prevention of RSV infection by standard control measures appears difficult.

Keywords Nationwide survey · Questionnaire · Respiratory syncytial virus · Child · Palivizumab off-label use

Introduction

Respiratory syncytial virus (RSV) is a common virus that is prevalent from fall through spring, and primary RSV infection occurs in almost 100% of children by 2 years of age [1]. RSV may cause lower respiratory tract infection in

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children, and 30–40% of infants <12 months of age may develop severe illness, necessitating hospitalization in 2–3% of cases [2]. It has been estimated that 20,000–30,000 children are hospitalized due to severe RSV infection each year [3]. Immunocompromised children and children with underlying diseases often associated with cardiopulmonary disorders are especially susceptible to developing severe RSV infection. Since there is no specific treatment for RSV infection, management is difficult, and some children have a fatal outcome [4].

In Japan, palivizumab, an anti-RSV humanized monoclonal antibody, has been available since 2002 for the prophylaxis of severe RSV lower respiratory tract infection in high-risk infants. As of December 2009, palivizumab has been indicated only for children at risk of severe RSV infection, with specific criteria that have been validated in large-scale clinical studies. The effects of palivizumab prophylaxis in premature infants and children with chronic lung disease (bronchopulmonary dysplasia) were evaluated in an international Phase II multicenter placebo-controlled double-blind clinical study [5], which demonstrated a 55% reduction in RSV hospitalization for these children, as well as decreases in the duration of hospitalization, days of oxygen therapy, and the prevalence of intensive care unit (ICU) admission. In a Phase I/II bridging study conducted in Japan, it was considered legitimate to extrapolate the international efficacy data to the Japanese population. The Ministry of Health, Labor, and Welfare of Japan reviewed existing clinical trials and domestic data and approved palivizumab prophylaxis for: (1) infants ≤12 months of age born at ≤28 weeks of gestation, (2) infants ≤6 months of age born at 29–35 weeks of gestation, and (3) infants or young children ≤24 months of age who had been treated for bronchopulmonary dysplasia at any time during the previous 6 months. The use of palivizumab for children ≤24 months of age who have hemodynamically significant congenital heart disease (CHD) was additionally approved on the basis of the results of a Phase III placebo-controlled double-blind clinical study in children with CHD [6], which demonstrated a 45% decrease in RSV hospitalization and decreases in the duration of hospital stay and oxygen therapy, as well as the results of a Phase III clinical study in Japan which yielded profiles of serum palivizumab concentration in Japanese patients that were similar to those of participants in the international trial.

There are data from descriptive reports and case-control studies that support the use of palivizumab to prevent severe RSV infection in high-risk immunocompromised children and those with airway diseases, neuromuscular disorders, or chromosomal abnormalities/malformation syndromes, and children receiving home oxygen therapy, though no such findings have been reported in Japan. Although cases of serious complications of RSV infection such as sudden infant death syndrome (SIDS), encephalopathy/encephalitis, and cardiomyopathy have recently been documented, the epidemiology of such cases has not yet been clearly determined.

Accordingly, members of the Japan Pediatric Society established an RSV Survey Committee to investigate the types and risks of underlying diseases that could potentially be considered for prophylaxis against severe RSV infection.

Purpose

The present survey was conducted to: (1) identify the diseases and conditions in which prevention of RSV infection might be particularly important, and (2) determine the effects of severe RSV infection in high-risk children.

Patients and methods

Findings for children <4 years of age who did not qualify for palivizumab prophylaxis under existing guidelines and were hospitalized due to or died of laboratory-confirmed RSV infection during the period between August 2006 and July 2008 were retrospectively obtained from medical institutions throughout Japan, using two questionnaire forms.

In Survey A, a survey of RSV hospitalization in children with underlying diseases, physicians were asked to document information on age, sex, duration of hospitalization, treatment, and presence/absence of severe sequelae, defined as conditions requiring support/assistance with daily activities. In Survey B, a survey of severe RSV infection in children without underlying disease, physicians were asked to document data similar to the data involving the hospitalization of children with severe RSV infection, i.e., RSV infection associated with SIDS, apparent life-threatening events, encephalopathy/encephalitis, cardiomyopathy, severe bronchiolitis (defined as bronchiolitis with serious respiratory disorder such as expiratory wheezing, polypnea, chest-wall retraction, and cyanosis), or other diagnoses. The items investigated were the presence/absence and type of underlying disease, month of RSV infection, sex, age, duration of hospitalization, the presence/absence and duration (in days), if present, of oxygen therapy, and the presence/absence and duration (in days), if present, of ventilation (Table 1).

The study protocol was approved by the Ethics Committee of Yokohama City University.

Table 1 Underlying diseases and items of survey

I. Underlying diseases evaluated in the survey	
Respiratory diseases ($n = 414$)	
Asthma	348 (84.1%)
Bronchomalacia	10 (2.4%)
CLD in child over 2 years of age on HOT	10 (2.4%)
Pulmonary hypoplasia	9 (2.2%)
Others	37
Chromosomal abnormalities/malformation syndromes ($n = 130$)	
Trisomy 21 (no CHD)	57 (43.8%)
Congenital anomaly	35 (26.9%)
Other chromosomal abnormalities (no CHD)	30 (23.1%)
Others	8
Neuromuscular disorders ($n = 125$)	
Epilepsy	62 (49.6%)
Sequelae of cerebral hemorrhage/infarction	19 (15.2%)
Cerebral palsy	13 (10.4%)
Sequelae of meningitis/encephalitis	8 (6.4%)
Myasthenia gravis	0 (0%)
Others	23
II. Items of survey	
Underlying diseases[a]	
Severe RSV infection[b]	
Reasons for RSV hospitalization[a]	
Month of RSV infection	
Sex	
Age at RSV infection	
Duration of hospitalization (days)	
Use and duration (days) of oxygen therapy	
Use and duration (days) of ventilation	
Intensive care unit admission[a]	
Presence/absence of sequelae {of RSV infection}	
Heart diseases (did not qualify for palivizumab) ($n = 27$)	
CHD in child over 2 years of age	18 (67%)
Arrhythmia	4 (15%)
Cardiomyopathy	3 (11%)
Others	2
Immunocompromised hosts ($n = 12$)	
Leukemia	3 (25%)
Solid tumor	3 (25%)
Primary immunodeficiency syndrome	3 (25%)
Other transplant recipient	1 (8.3%)
Kidney transplant recipient	0 (0%)
Liver transplant recipient	0 (0%)
Others	2
Congenital metabolic disorders ($n = 8$)	
Other diseases ($n = 40$)	
Kawasaki disease	26 (65.0%)
Rheumatic diseases	0 (0%)
Autoinflammatory syndrome	0 (0%)
Other diseases	14

RSV respiratory syncytial virus, *CHD* congenital heart disease, *CLD* chronic lung disease, *HOT* home oxygen therapy

[a] Investigated only in Survey A

[b] Investigated only in Survey B

Data analysis

The findings for hospitalized patients were tested using univariate logistic regression analysis to evaluate the effect of each factor on the outcome of RSV infection, with p values and crude odds ratios obtained for each factor. Significance was examined using χ^2 tests for categorical variables such as the type of underlying disease, reason for hospitalization, and month of RSV hospitalization; Fisher's exact test for binary variables such as sex and the presence/absence of oxygen therapy; and Student's t-test for continuous variables.

Results

In June 2008, a questionnaire was sent to 613 medical institutions, including teaching hospitals with pediatric residency programs, as well as major pediatric hospitals and general hospitals with pediatric services equivalent to those provided in teaching hospitals, to report cases of RSV hospitalization in children not indicated for palivizumab prophylaxis during the period between August 2006 and July 2008, and 272 institutions (44.4%) responded (Table 2). After the data of Surveys A and B were reconciled to ensure

Table 2 Characteristics of patients evaluated in the nationwide survey

	Survey A ($n = 756$)	Survey B ($n = 359$)
Sex		
Male	447 (69.7%)	194 (30.3%)
Female	273 (63.9%)	155 (36.2%)
Age at RSV infection (months)[a]	20.4 ± 12.17 [0–47]	6.7 ± 8.55 [1–40]
Duration of hospitalization (days)[a]	10.5 ± 21.76 [1–540]	11.5 ± 13.08 [0–210]
≤2 weeks	650 (88.0%)	285 (79.4%)
>2 weeks	89 (12.0%)	74 (20.6%)
Use of oxygen therapy	458 (60.6%)	351 (98.6%) *1
Duration (days)[a]	7.7 ± 27.15 [1–540]	6.8 ± 4.79 [1–51]
Use of ventilation	48 (6.3%)	144 (40.4%) *2
Duration (days)[a]	22.8 ± 83.48 [1–540]	6.4 ± 3.87 [1–22]
Oxygen therapy alone	411 (54.4%)	206 (58.4%) *3
No oxygen/ventilation	297 (39.3%)	5 (1.4%) *3

Data during the period between August 2006 and July 2008 were collected through a questionnaire sent to 613 institutions, 272 (44.4%) of which responded

RSV respiratory syncytial virus, *SD* standard deviation

[a] Values are means ± standard deviation [range]; *1 No data in 3 cases; *2 no data in 3 cases; *3 no data in 6 cases. Cases with no data in *1 and *2 are separate patients

the absence of overlapping cases and to ensure that the data were sufficient, the numbers of patients reported in Surveys A and B were 756 and 359, respectively, and the total number reported was thus 1,115 patients.

The characteristics of the patients enrolled in the study are shown in Table 2. Figure 1 shows the age distribution of the reported patients. Of the children without underlying diseases reported in Survey B, 277 were less than 1 year of age, and the number of reported patients decreased as the age increased. In Survey A, of children with underlying diseases, there were substantial numbers of reported patients throughout the age range evaluated. The relative risk of having an underlying disease was about 1.3 times higher in males than in females, and this difference was statistically significant (1.000 vs. 0.7644, $p = 0.0421$, Fisher's exact test). The mean durations of hospitalization were 10.5 ± 21.76 and 11.5 ± 13.08 weeks in Surveys A and B, respectively. The most frequent duration of hospitalization was 0–2 weeks, and the longest duration of hospitalization was 77 weeks. The distribution of month of RSV infection was consistent with the fact that RSV infection is prevalent during winter months. However, reported cases were distributed through all months of the year, particularly in the patients with underlying diseases. Among the patients with underlying diseases, some were not treated with oxygen therapy or ventilation, while among the patients without underlying diseases, RSV infection was relatively severe, and the number of patients receiving neither oxygen therapy nor ventilation was small.

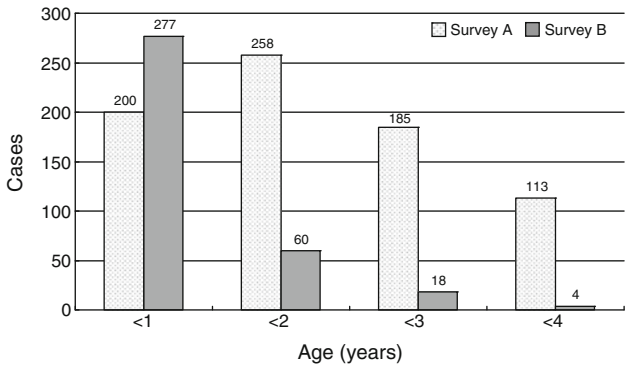

Fig. 1 Age distribution of reported patients

RSV hospitalization in patients with underlying diseases

Respiratory diseases were the most prevalent underlying conditions: 54.8% of reported patients had respiratory diseases, and asthma was the most prevalent respiratory disease (46.0% of the reported patients). Children with chromosomal abnormalities/malformation syndromes, neuromuscular diseases, cardiac diseases, immunocompromised status, and congenital metabolic disorders were also reported (Fig. 2a). Table 1 lists the numbers of patients by underlying disease.

Of the patients with underlying respiratory diseases ($n = 414$), 84.1% had asthma, and the remaining children had various conditions such as bronchomalacia, chronic lung disease (bronchopulmonary dysplasia) in patients over 2 years of age, and pulmonary hypoplasia. The second most prevalent category of underlying diseases was chromosomal abnormalities/malformation syndromes, 130 cases of which were reported, 57 (43.8%) involving children with trisomy 21 without CHD. RSV hospitalization in children with neuromuscular disorders was also common ($n = 125$). About half of these children had epilepsy, and cases of cerebral hemorrhage/infarction, meningitis, and encephalitis were also reported. Among children reported to have cardiac diseases not indicated for palivizumab prophylaxis ($n = 27$), 18 children (67%) had CHD and were over 2 years of age, and 3 children (11%) had arrhythmia or cardiomyopathy. Twelve children were immunocompromised due to treatment for leukemia or solid tumors, primary immunodeficiency syndrome, or post-transplant status. Of the children in the "other diseases" category ($n = 40$; see Table 1), 26 (65%) had a history of Kawasaki disease.

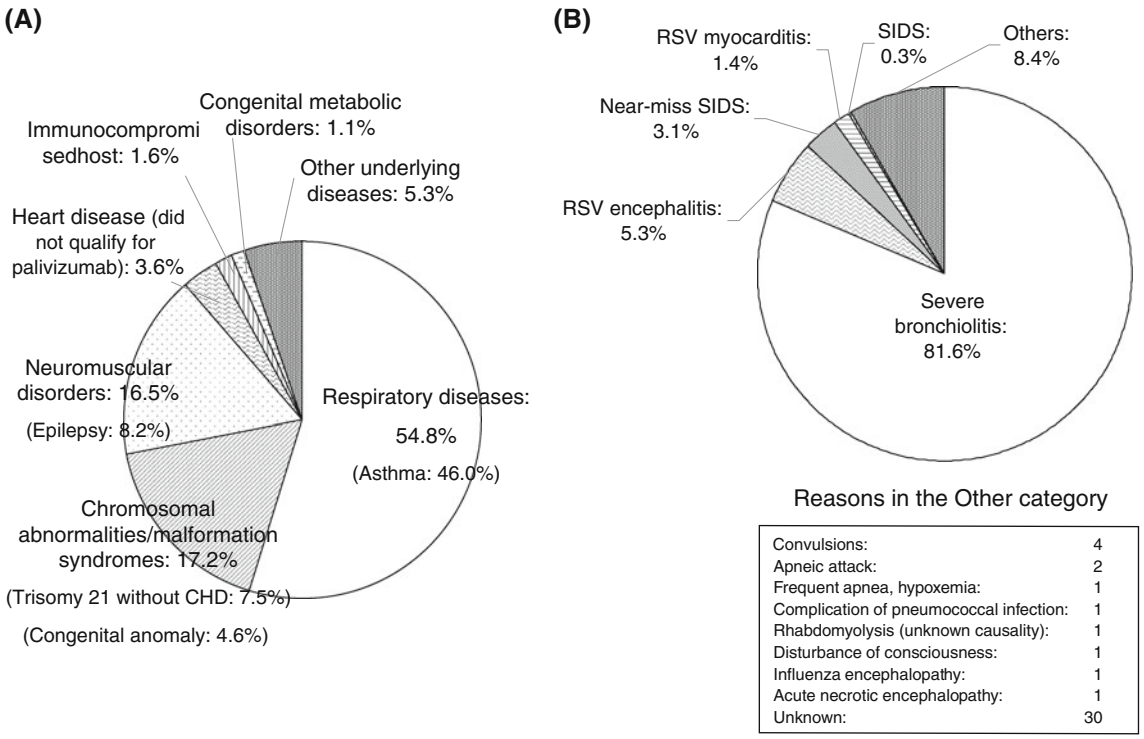

Fig. 2 **a** Types of underlying diseases in children hospitalized for respiratory syncytial virus (*RSV*) infection in Survey A ($n = 756$), and **b** reasons for RSV hospitalization in children without underlying diseases in Survey B ($n = 359$). *CHD* congenital heart disease, *SIDS* sudden infant death syndrome

Table 3 shows the outcome of RSV infection stratified by patient characteristics. When "severe sequelae" and "death" were considered to represent poor outcomes of RSV infection, the risk of poor outcome of RSV infection was about 1,000 times higher in immunocompromised children than in children with respiratory disorders and about 2.8–4.3 times higher than that in patients with other underlying diseases. These findings indicate that immunocompromised status is significantly associated with a poor outcome of RSV infection ($p < 0.0001$, χ^2 test). Oxygen therapy, ventilation, and ICU hospitalization were also significantly associated with poor outcomes of RSV infection ($p < 0.0023$, $p < 0.0001$, and $p < 0.0001$, Fisher's exact test), and the risks of poor outcome were about 11.4, 186.1, and 23.3 times higher in patients receiving oxygen therapy, those receiving ventilation, and those hospitalized in the ICU, respectively, than in patients without the corresponding treatment. The risk of poor outcome was about 1.2 higher in males than in females, but this difference was not statistically significant.

RSV hospitalization in patients without underlying diseases

Of patients with severe RSV infection without underlying diseases, 81.6% had severe bronchiolitis. Cases of RSV encephalopathy/encephalitis, apparent life-threatening events, myocarditis, and SIDS were also reported. Convulsions and apnea were also observed (Fig. 2b). Table 3 lists the results of analysis by patient characteristics. Although a crude odds ratio could not be obtained due to the distribution of cases, the month of RSV infection significantly affected the outcome of RSV infection ($p = 0.0015$, χ^2 test). The relative risk of poor outcome was about 6.5 times higher in patients requiring ventilation, and the use of ventilation was significantly associated with poor outcome of RSV infection ($p = 0.0162$, Fisher's exact test). The relative risk of poor outcome in male patients was about 0.5 times that in female patients, though this difference was not statistically significant.

A total of 16 deaths (Table 4) were reported in children with or without underlying diseases. Seven of the children who died (43.8%) wereunder 1 year of age, and 11 (68.7%) children had underlying diseases, i.e., leukemia and post-transplantation status in 2, neuromuscular disorder in 3, chromosomal abnormalities without CHD in 5, and CHD beyond 24 months of age in 1. The reasons for the RSV hospitalization of these 11 children were pneumonia in 4 patients and bronchiolitis in 1 patient, and nosocomial RSV infection during chemotherapy, unsuccessful resuscitation following cardiopulmonary arrest (CPA), shock, aspiration pneumonia, and deterioration of upper respiratory tract infection with CPA in one patient each.

Table 3 Severity of outcome of RSV infection by patient characteristics—survey in children with and without underlying diseases

Factors	With underlying diseases				Without underlying diseases			
	No/mild sequelae	Severe sequelae[a] or death	Odds ratio	*p* value	No/mild sequelae	Severe sequelae or death	Odds ratio	*p* value
Underlying diseases								
Immunocompromised hosts	9 (81.8%)	2 (18.2%)	1.000	<0.0001				
Respiratory diseases	411 (99.8%)	1 (0.2%)	0.001					
Neuromuscular disorders	116 (95.1%)	6 (4.9%)	0.233					
Chromosomal abnormalities/ malformation syndromes	120 (94.5%)	7 (5.5%)	0.262					
Heart diseases	25 (92.6%)	2 (7.4%)	0.360					
Congenital metabolic disorders	8 (100%)	0 (0%)	–					
Others	39 (100%)	0 (0%)	–					
Severe RSV infection								
SIDS					0 (0%)	1 (100%)	–	<0.0001
ALTE					11 (100%)	0 (0%)	–	
RSV encephalopathy					13 (68.4%)	6 (31.6%)	–	
RSV myocarditis					3 (75%)	1 (25%)	–	
Severe bronchiolitis					283 (99.6%)	1 (0.4%)	–	
Others					29 (96.7%)	1 (3.3%)	–	
Reasons for RSV hospitalization								
Bronchiolitis	374 (98.7%)	5 (1.3%)	1.000	<0.0001				
Pneumonia	171 (96.6%)	6 (3.4%)	–					
Encephalitis	0 (0%)	1 (100%)	–					
Bronchitis	46 (100%)	0 (0%)	–					
Atelectasis	3 (100%)	0 (0%)	–					
Asthma attack	25 (100%)	0 (0%)	–					
Others	55 (91.7%)	5 (8.3%)	6.800					
Sex								
Male	430 (97.3%)	12 (2.7%)	1.000	0.6790	183 (97.9%)	4 (2.1%)	1.000	0.3331
Female	265 (97.8%)	6 (2.2%)	0.811		147 (96.1%)	6 (3.9%)	1.867	
Month of RSV infection								
January	163 (96.4%)	6 (3.6%)	–	0.3994	94 (94.9%)	5 (5.1%)	–	0.0015
February	74 (94.9%)	4 (5.1%)	–		48 (98%)	1 (2%)	–	
March	39 (95.1%)	2 (4.9%)	–		17 (100%)	0 (0%)	–	
April	27 (96.4%)	1 (3.6%)	–		8 (88.9%)	1 (11.1%)	–	
May	12 (100%)	0 (0%)	–		3 (100%)	0 (0%)	–	
June	16 (100%)	0 (0%)	–		3 (75%)	1 (25%)	–	
July	12 (100%)	0 (0%)	–		5 (100%)	0 (0%)	–	
August	18 (94.7%)	1 (5.3%)	–		4 (100%)	0 (0%)	–	
September	23 (100%)	0 (0%)	–		5 (100%)	0 (0%)	–	
October	45 (100%)	0 (0%)	–		6 (75%)	2 (25%)	–	
November	87 (96.7%)	3 (3.3%)	–		25 (100%)	0 (0%)	–	
December	209 (99.5%)	1 (0.5%)	–		119 (100%)	0 (0%)	–	
Age at RSV infection (months) mean (±SD) [range]	20.51 ± 12.10 [0–47]	21.61 ± 16.13 [1–47]	–	0.0538	6.68 ± 8.65 [1–40]	11.2 ± 7.18 [1–21]	–	0.5606
Duration of RSV hospitalization (days) mean (±SD) [range]	9.48 ± 8.65 [1–124]	47.71 ± 129.93 [1–540]	–	0.2427	11.19 ± 12.25 [1–210]	27.9 ± 28.56 [0–94]	–	0.0976
Oxygen therapy								
Present	436	17	11.385	0.0023	332	9	0.1084	0.1371

Table 3 continued

Factors	With underlying diseases				Without underlying diseases			
	No/mild sequelae	Severe sequelae[a] or death	Odds ratio	*p* value	No/mild sequelae	Severe sequelae or death	Odds ratio	*p* value
Absent	292	1	1.000	–	4	1	1.0000	
Use of oxygen therapy	59.9%	94.4%	–	–	98.8%	90.0%	–	–
Duration of oxygen therapy (days) mean (±SD) [range]	6.19 ± 7.33 [1–124]	42.56 ± 132.98 [1–540]	–	0.2912	6.68 ± 4.62 [1–51]	9.88 ± 8.77 [1–23]	–	0.3391
Ventilation								
Present	30	16	186.116	<0.0001	128	8	6.500	0.0162
Absent	698	2	1.000	–	208	2	1.000	
Use of ventilation	4.1%	88.9%	–	–	37.9%	80.0%	–	–
Duration of ventilation (days) mean (±SD) [range]	10.65 ± 11.71 [2–60]	43.20 ± 137.74 [1–540]	–	0.3765	6.33 ± 3.35 [1–15]	9.13 ± 7.99 [1–22]	–	0.3574
ICU hospitalization								
Present	37	10	23.345	<0.0001				
Absent	691	8	1.000	–				
ICU hospitalization rate	5.1%	55.6%	–	–				

SD standard deviation, *SIDS* sudden infant death syndrome, *ALTE* apparent life-threatening events, *ICU* intensive care unit

[a] Severe sequelae were defined as conditions requiring support/assistance with daily activities

In the five children without underlying disease who died of RSV infection, the reason for hospitalization was SIDS in 1 case, severe bronchiolitis in 1, RSV encephalitis in 1, RSV myocarditis in 1, and 'other' (acute necrotic encephalopathy) in 1 case.

Discussion

The present nationwide questionnaire survey was conducted to identify the conditions for which prophylactic treatment may be considered to prevent severe RSV infection and the associated serious sequelae. During the 2-year period of the survey, a total of 1,115 children under 4 years of age were hospitalized due to RSV infection, 16 of whom died. Notably, 756 children had underlying diseases that did not meet the criteria for palivizumab prophylaxis in Japan. This suggests that the current coverage of palivizumab prophylaxis by the National Health Insurance in Japan is perhaps insufficient to protect against the wide spectrum of severe RSV infections in high-risk children.

In the present survey, the outcomes of severe RSV infection were more serious among immunocompromised children than among immunocompetent children with underlying diseases. It has been reported that the mortality rate of RSV infection is 80% when adult bone marrow transplant recipients receive no specific treatment for this infection [7, 8]. Pediatric immunocompromised organ transplant recipients are susceptible to severe RSV infection [9], and are at high risk of developing respiratory failure and death due to RSV infection [10, 11]. The high incidence of poor outcome of severe RSV infection among immunocompromised children in the present survey (2 of 11 children, 18.2%) is consistent with these findings, and indicates the importance of RSV prophylaxis in this population. A recent study using decision analysis modeling indicated that mortality in children receiving bone marrow transplantation was decreased by the addition of palivizumab to protect against RSV lung disease [12]. The American Society of Transplantation has recommended that infants (<1 year) who undergo solid organ transplantation during the RSV season receive immunoprophylaxis to prevent severe RSV infection [13]. Large-scale studies should be conducted in the future to develop guidelines for the prevention of RSV infection after transplantation.

In the present survey, the number of RSV hospitalizations was high among children with trisomy 21 (Down syndrome) without CHD: of the 57 children with trisomy 21 without CHD, two patients died and one had severe sequelae. This finding is supported by Bloemers et al. [14], who have reported that children with Down syndrome are at high risk of RSV hospitalization irrespective of CHD, indicating that patients with Down syndrome with or without CHD should also be considered for prophylaxis. Although the Japanese Society of Pediatric Cardiology and Cardiac Surgery recommends that children under 24 months of age with CHD

Table 4 Characteristics of patients who died due to RSV infection

		Survey A ($n = 11$)		Survey B ($n = 5$)	
Underlying diseases		Leukemia/transplant recipient	2	–	
		Neuromuscular disorders	3	–	
		Chromosomal abnormality without CHD (trisomy 21 in 2, trisomy 31 in 1, 4p-syndrome in 1, Aicardi syndrome in 1)	5	–	
		CHD in child over 24 months of age	1	–	
Reasons for RSV hospitalization		Pneumonia	4	SIDS	1
		Bronchiolitis	1	Severe bronchiolitis	1
		Other (nosocomial pneumonia during chemotherapy)	1	RSV encephalopathy	1
		Other (unsuccessful resuscitation following CPA)	1	RSV myocarditis	1
		Other (shock)		Other (acute necrotic encephalopathy)	1
		Other (aspiration pneumonia)	1	–	
		Other (URTI → CPA)	1	–	
		No data	1	–	
Sex	Male	6 (54.5%)		2 (40.0%)	
	Female	5 (45.5%)		3 (60.0%)	
Age at RSV infection (months)	Mean (±SD) [range]	22.9 ± 15.52 [1–47]		11.2 ± 8.06 [3–21]	
	<12	4 (36.4%)		3 (60%)	
	≥12	7 (63.6%)		2 (40%)	
Duration of hospitalization (days)	Mean (±SD) [range]	18.6 ± 33.34 [1–120]		7.0 ± 8.29 [0–22]	
	≤2 weeks	7 (63.6%)		4 (80%)	
	>2 weeks	4 (36.4%)		1 (20%)	
Oxygen therapy		11 (100%)		11 (100%)	
Duration (days)	Mean (±SD) [range]	8.5 ± 9.23 [1–27]		7.2 ± 8.13 [1–22]	
Ventilation		11 (100%)		11 (100%)	
Duration (days)	Mean (±SD) [range]	7.3 ± 9.17 [1–27]		7.2 ± 8.13 [1–22]	
Oxygen therapy alone		0 (0%)		0 (0%)	
No oxygen/ventilation		0 (0%)		0 (0%)	

CPA cardiopulmonary arrest, *URTI* upper respiratory tract infection

associated with chromosomal aberrations or genetic abnormalities, including trisomy 21, be treated prophylactically to prevent severe RSV infection even when they exhibit no significant signs/symptoms of CHD or have obtained complete cure of CHD [15], such children are not yet officially indicated for RSV prophylaxis in Japan.

The present survey found that severe RSV infections developed throughout the year. We were unable to analyze the relationship between month of RSV infection and corresponding serious outcomes, because of the unequal distribution of cases annually. Patients with underlying diseases should therefore be carefully observed for RSV infection throughout the year. Data in the present study were insufficient to permit analysis by district. In a nationwide epidemiological study, there were no differences in patterns of RSV epidemics among districts of Japan [16]. However, that survey did not include Okinawa Prefecture, which consists of islands in a subtropical zone in which it has been reported that RSV outbreaks also occur in spring and summer [17]. We therefore consider our findings representative of the pattern of RSV infection in most of Japan.

In the present survey, patients with neuromuscular disorders accounted for 16.5% of the children with underlying disease with poorer outcomes than other patient groups (poor outcome in 6 of 116 patients); they thus represent one of the important patient groups in which RSV prophylaxis would be potentially beneficial. In a prospective observational registry of children who received at least one dose of palivizumab injection during the RSV seasons from 2002 to 2004 in the United States, the incidence of RSV

hospitalization was found to be significantly higher in children with congenital airway abnormality or severe neuromuscular disorder than in children without such conditions [18]. Moreover, in a prospective multicenter study conducted in Germany between 1999 and 2005, patients hospitalized with RSV infection and neuromuscular impairment had a greater risk of requiring mechanical ventilation and developing seizures, with a statistically significant, higher attributable mortality compared to controls (5.5 vs. 0.2%) [19].

In the recommendations for the use of palivizumab as prophylaxis against RSV in infants with CHD, the Working Group of the British Paediatric Cardiac Association has included children with cardiomyopathy requiring treatment in the list of children likely to benefit from prophylaxis [20]. Although the number of patients with cardiomyopathy reported in the present survey was too small to examine effects on the outcome of severe RSV infection, this patient group should be carefully evaluated for the presence of congestive heart failure that requires prophylaxis in accordance with the CHD trial [6].

In a cohort study of all children with severe RSV infection in England from 1999 to 2007, all the children who died of RSV infection ($n = 35$) had preexisting diseases (relative risk 2.36), and multiple preexisting diseases (4.38), cardiac anomaly (2.98), and nosocomial RSV infection (2.89) were considered risk factors for death from severe RSV infection. An interaction among preexisting disease, nosocomial RSV infection, and mortality was also found [21].

Although the number of large-scale studies of palivizumab in patients with underlying diseases is limited, in a meta-analysis in 2007, treatment with palivizumab was found to increase the survival of patients undergoing bone marrow transplantation by about 10%, from 83 to 92% [12]; also, the use of palivizumab in children with certain specific diseases is reimbursed in some provinces of Canada and by some insurance companies in Western countries [22–26]. The results of the present survey indicate that palivizumab prophylaxis should be strongly considered in children with severe immunodeficiency and children with nosocomial RSV infection that is uncontrollable with conventional infection control measures.

In the present survey, in children without underlying disease, severe bronchiolitis was the most common reason for RSV hospitalization, though RSV encephalopathy/encephalitis accounted for 5.3% of RSV hospitalizations of otherwise healthy children. The mechanisms of development of severe RSV infection remain unclear in many respects, and it is also unclear which serotypes of RSV cause more severe RSV infection. Since encephalopathy/encephalitis may result in permanent neurological damage and significantly affect the quality of life of patients and their families, it is important to be aware of RSV infection as a cause of encephalopathy/encephalitis.

In summary, this first nationwide Japanese survey of RSV infection in high-risk children who did not receive prophylaxis based on current recommendations provides epidemiological data useful for the determination of additional indications for palivizumab. We hope that our results will help healthcare professionals to investigate the diverse presentations of RSV disease and target patients with RSV infection in pediatric emergency services. The survey also sets the stage for larger prospective studies of underlying medical disorders that place infants at greater risk of compromise from severe RSV infection, and it is such infants who may benefit substantially from prophylaxis.

Acknowledgments The authors wish to thank the physicians at medical institutions who participated in the survey despite their busy schedules.

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