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ORIGINAL ARTICLE

Risk factors for hospitalisation due to respiratory syncytial virus infection in children receiving prophylactic palivizumab

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Abstract

Respiratory syncytial virus (RSV) is a common pathogen that causes extremely severe respiratory symptoms in the first few weeks and months of life. In infants with cardiopulmonary diseases, RSV infections have a significant clinical impact. Palivizumab, a humanised monoclonal antibody for RSV, has been shown to significantly reduce the rate of hospitalisation of high-risk infants diagnosed with RSV. However, we have experienced a significant number of RSV infections in our institution that required hospitalisation or intensive care, despite the administration of palivizumab. This study aimed to analyse the risk factors associated with severe RSV despite the use of palivizumab. We retrospectively reviewed the medical records of 688 patients who visited or were admitted to our hospital and received palivizumab. Thirty-seven (5.4%) patients required hospitalisation for RSV, despite receiving palivizumab. In addition, 31 of these patients (83.8%) required hospitalisation out of season for palivizumab injection. Preterm birth (≤ 28-week gestation), bronchopulmonary dysplasia (BPD), and trisomy 21 were risk factors for RSV-related hospitalisation in infected patients, despite receiving palivizumab. Furthermore, subgroup analysis of 69 patients with RSV revealed that hemodynamically significant congenital heart disease (CHD) was also a risk factor for RSV-related hospitalisation.

Conclusion: Preterm birth (≤ 28 weeks of gestation), BPD, trisomy 21, hemodynamically significant CHD, and CHD requiring surgery or cardiac catheterisation/intervention during infancy could be considered when determining whether year-round administration of palivizumab is appropriate.

What is Known:
- *Respiratory syncytial virus causes severe respiratory symptoms in infants, particularly those with cardiopulmonary diseases.*
- *The use of palivizumab has reduced the rate of hospitalisation of infants diagnosed with RSV. Despite this, the rate of hospitalisation is still high.*

What is New:
- *We identified that preterm birth (≤ 28-week gestation), bronchopulmonary dysplasia, trisomy 21, and hemodynamically significant congenital heart disease were risk factors for RSV-related hospitalisation, even after receiving palivizumab treatment.*
- *High-risk infants should be closely monitored and the prolonged use of palivizumab should be considered.*

Keywords Respiratory syncytial virus · Congenital heart disease · Congenital anomaly syndromes · Preterm birth

Abbreviations

AVSD	Atrioventricular septal defect
BPD	Bronchopulmonary dysplasia
CI	Confidence interval
CHD	Congenital heart disease
ICR	Intracardiac repair
MS	Mitral stenosis
MVR	Mitral valve replacement
PAPVC	Partial anomalous pulmonary venous connection
PH	Pulmonary hypertension
PS	Pulmonary stenosis

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RSV	Respiratory syncytial virus
SD	Standard deviation
TOF	Tetralogy of Fallot
VSD	Ventricular septal defect

Introduction

Respiratory syncytial virus (RSV) is the leading cause of respiratory tract infections in infants and young children. Acute lower respiratory tract infections associated with RSV are among the most frequent causes of hospitalisation among patients in this age group [1, 2].

Palivizumab, an anti-RSV humanised monoclonal antibody, was approved by the US Food and Drug Administration in 1998 and formally approved in Japan in 2002 for use in infants and toddlers who meet certain criteria. Human RSV is a medium-sized enveloped virus that contains a linear negative-sense RNA genome. The viral genome encodes for proteins such as F, G, and SH lipoproteins. The F and G lipoproteins target the cell membrane. At the cellular level, RSV infections begin when the envelope G protein binds to its receptor on the plasma membrane. This binding induces a conformational change in the F protein, which causes the RSV coat protein to fuse with the plasma membrane of the host cell [3]. Palivizumab targets the F protein and prevents the entry of RSV into host cells by binding to this protein and inhibiting its conformational change [4].

According to the literature, palivizumab injection is associated with a 72% reduction in the rate of hospitalisation for RSV infection in preterm infants born < 32-week gestation or those with bronchopulmonary dysplasia (BPD) [5]. In addition, there was a 45% reduction in the rate of RSV-related hospitalisation in palivizumab recipients with hemodynamically significant congenital heart disease (CHD) [6]. Thus, palivizumab is effective in preventing severe RSV infections in high-risk infants.

However, we have encountered several infants and toddlers who have contracted severe RSV infections that require hospitalisation, despite a history of palivizumab administration. In the present study, we analysed the clinical course, complications, and risk factors of patients with severe RSV infections who required hospitalisation, despite the palivizumab administration. We hypothesised that several risk factors were associated with severe RSV infections among these patients, and palivizumab would further contribute to preventing severe RSV infections if we could identify these risk factors.

Materials and methods

Patients and ethical considerations

We retrospectively reviewed the electronic medical records of patients who visited or were admitted to Hokkaido University Hospital between February 2013 and February 2020 and received palivizumab for the prevention of severe RSV infection. We included newborns, infants, and young children who met at least one of the following criteria at the beginning of the RSV season, based on their documentation for palivizumab injection in Japan: (1) ≤ 12 months of age and born preterm (≤ 28-week gestation) (criterion 1); (2) ≤ 6 months of age and born between 29- and 3-week gestation (criterion 2); (3) ≤ 24 months of age and treated for BPD within the past 6 months (criterion 3); (4) ≤ 24 months of age diagnosed with CHD with hemodynamic abnormalities (criterion 4); (5) ≤ 24 months of age with immunodeficiencies (criterion 5); and (6) ≤ 24 months of age with trisomy 21 (criterion 6). Palivizumab was administered to all subjects who met the dosing criteria via intramuscular injection at a dose of 15 mg/kg body weight once a month, up to a total of six times, throughout the RSV season. The indication for hospitalisation for RSV infection was needed for oxygen, poor oral intake, respiratory failure, and worsening heart failure. Nine patients were excluded because they had insufficient data ($n = 1$), were diagnosed with RSV infection prior to the initiation of palivizumab ($n = 3$), did not receive approval to use palivizumab ($n = 1$), or died during the observation period ($n = 4$) (Fig. 1). All causes of death were unrelated to RSV infection. Finally, 688 patients were included in the analysis. RSV infections that required hospitalisation were defined as severe RSV infections. Furthermore, RSV infection during the indication period of palivizumab vaccination was defined as RSV infection "during season," and RSV infection during an interval of palivizumab vaccination or after the end of the indication period for palivizumab was defined as RSV infection "out of season" (Fig. 2).

This study was performed in line with the principles of the Declaration of Helsinki. The Institutional Review Board of Hokkaido University Hospital for clinical research approved this study (approval no. 019-0452). Information regarding the present study was disclosed on the Hokkaido University website with an opt-out option because some patients had already died or were lost to follow-up. The requirement for informed consent was waived due to the retrospective nature of the study.

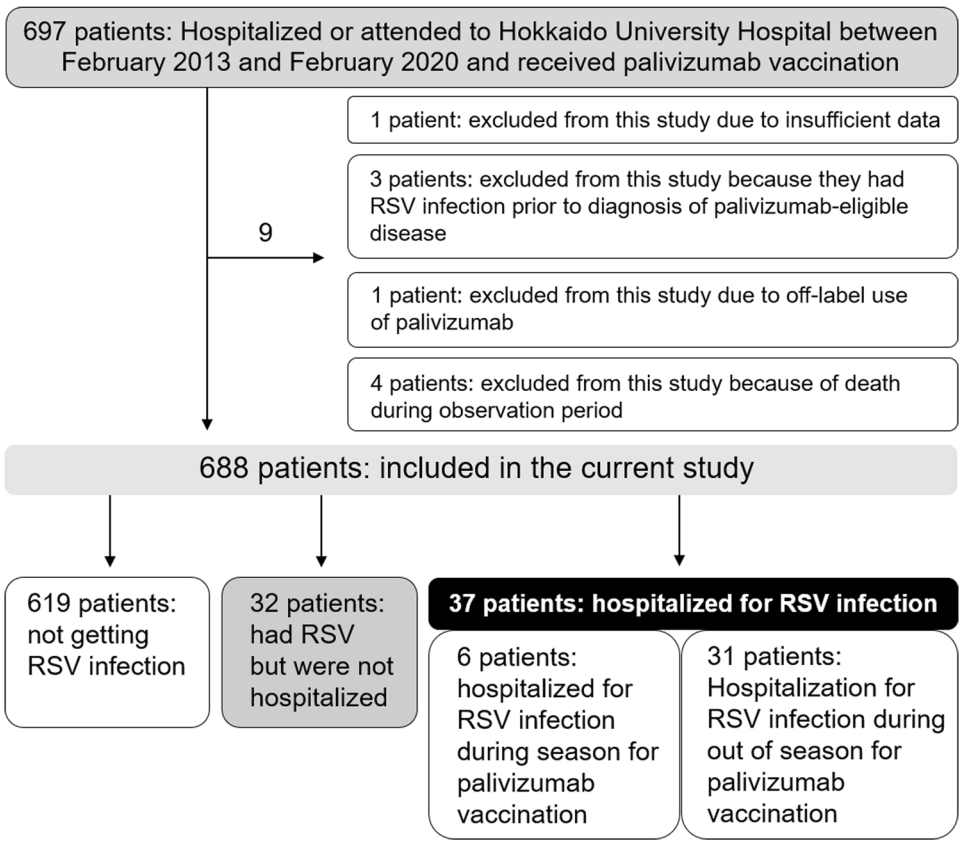

Fig. 1 Flowchart of patient selection. RSV, respiratory syncytial virus

Statistical analyses

Clinical features were presented as mean with standard deviation (SD) or frequency with percentage, as appropriate. For continuous variables, Mann–Whitney test was used. For categorical variables, Chi-squared test was used to compare differences between the two groups. The relationship between hospitalisation due to severe RSV and each clinical feature was evaluated using a univariate logistic regression model. The same analysis was performed for subgroup analyses among the RSV infected cases. Patients born at ≥ 36-week gestation were used as references in the analysis. $P < 0.05$ was considered to be statistically significant, and all values were two tailed. All statistical analyses were performed using SAS University Edition (SAS Institute Inc., Cary, NC, USA).

Results

Out of 688 patients, criterion 1 was met by 28 patients, criterion 2 was met by 258 patients, criterion 3 was met by 46 patients, criterion 4 was met by 420 patients, criterion 5 was met by 25 patients, and criterion 6 was met by 50 patients (Table 1). The median gestational age was 37.0 weeks (IQR 33.9–39.1 weeks), while the median birth weight was 2382 g (IQR 1702.5–2910 g). Forty-six patients (6.7%) had BPD, 420 (61.1%) had hemodynamically significant CHD, 50 (7.3%) had trisomy 21, and 30 (4.4%) had other congenital anomaly syndromes, trisomy 18, 4p deletion syndrome (commonly known as Wolf-Hirschhorn syndrome), 13q deletion syndrome, 16p11.2 deletion syndrome, 22q11.2 deletion syndrome (commonly known as DiGeorge syndrome), VACTERL association, CHARGE syndrome, Williams syndrome, Goldenhar syndrome, Sotos syndrome, branchiootorenal syndrome, Cantrell syndrome, and Moebius syndrome (Table 1). Of the patients with congenital anomaly syndrome, two had congenital anomalies of the respiratory system, eight had congenital anomalies of the digestive system, six had congenital anomalies of the urinary system, and five had congenital anomalies of the cricopharyngeal system.

Sixty nine (10.0%) had RSV infection during the study period (Fig. 1). In addition, 37 patients (5.4%) were hospitalised for RSV infection, three (0.4% of the total number of patients) of whom required intensive care. At the time of the RSV infection, two patients were on home oxygen therapy, and three patients were on tube feeding.

There were significantly more hospitalisations among patients who were born at ≤ 28-week gestation or those

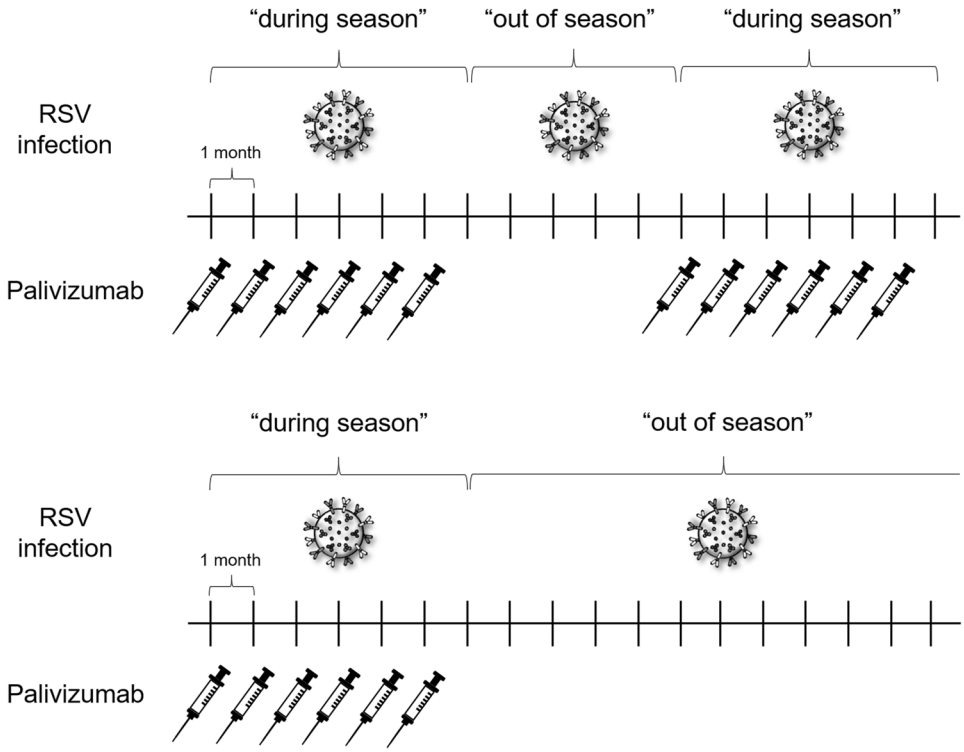

Fig. 2 Definition of the time of respiratory syncytial virus (RSV) infection

who had BPD ($p = 0.0170$) or trisomy 21 ($p = 0.0050$) (Table 2). Logistic regression analysis revealed similar results (Table 3).

Next, we focused on the 69 patients (10%) who were infected with RSV. Table 4 shows the patient details for this group. Thirty seven of these patients required hospitalisation for RSV infection. Furthermore, 31 of these patients were infected outside of the palivizumab injection season. Twenty four of the 31 patients had RSV infection more than 28 days after the last dose of palivizumab or at an age when they were no longer eligible for the vaccination altogether. Hemodynamically, significant CHD and CHD requiring surgery or cardiac catheterisation/intervention during infancy were significant risk factors for RSV-related hospitalisation (Table 5). Logistic regression analysis revealed similar results (Table 6).

Table 7 shows the details of three patients who required intensive care due to RSV infection. All three were prematurely born and had CHD. One patient had bronchial stenosis, while the other two had congenital anomaly syndromes and required heart surgery early after infection.

Table 1 Patient clinical characteristics

Characteristics	***N* = 688**
Gestational age (weeks), median (IQR)	37.0 (33.9–39.1)
≤ 28 weeks, *n* (%)	57 (8.2%)
29–35 weeks, *n* (%)	258 (37.5%)
≥ 36 weeks, *n* (%)	373 (54.2%)
Birth weight (g), median (IQR)	2382 (1702.5–2910)
BPD, *n* (%)	46 (6.7%)
Hemodynamically significant CHD, *n* (%)	420 (61.1%)
CHD requiring surgery or cardiac catheterisation and intervention during infancy, *n* (%)	287 (41.7%)
Cyanotic CHD, *n* (%)	197 (28.6%)
Pulmonary hypertension, *n* (%)	51 (7.4%)
Heart failure, *n* (%)	5 (0.7%)
Immunodeficiency, *n* (%)	25 (3.6%)
Trisomy 21, *n* (%)	50 (7.3%)
Congenital anomaly syndrome, excluding trisomy 21, *n* (%)	30 (4.4%)

CHD congenital heart disease, *BPD* bronchopulmonary dysplasia, *IQR* interquartile range

Table 2 Risk factors for RSV-related hospitalisation despite palivizumab treatment

	Hospitalisation for RSV infection ($n=37$)	No hospitalisation for RSV infection ($n=651$)	p-value
Gestational age (weeks), median (IQR)	35.9 (29.4–38.2)	37.0 (33.9–39.1)	0.0419*
≤28 weeks, *n* (%)	9 (24.3%)	48 (7.4%)	0.0047*
29–35 weeks, *n* (%)	10 (27.0%)	248 (38.1%)	
≥36 weeks, *n* (%)	18 (48.6%)	355 (54.5%)	
Birth weight (g), median (IQR)	2085 (1067–3147)	2390 (1722–2918)	0.0282*
BPD, *n* (%)	6 (16.2%)	40 (6.1%)	0.0170*
Hemodynamically significant CHD, *n* (%)	26 (70.3%)	394 (60.5%)	0.2369
CHD requiring surgery or cardiac catheterisation and intervention during infancy, *n* (%)	17 (45.9%)	270 (41.5%)	0.5916
Cyanotic CHD, *n* (%)	11 (29.7%)	186 (28.6%)	0.8795
Pulmonary hypertension, *n* (%)	3 (8.1%)	48 (7.4%)	0.8682
Heart failure, *n* (%)	1 (2.7%)	4 (0.6%)	0.1458
Immunodeficiency, *n* (%)	0	25 (3.8%)	0.2246
Trisomy 21, *n* (%)	7 (19%)	43 (6.6%)	0.0050*
Congenital anomaly syndrome, excluding trisomy 21, *n* (%)	3 (8.1%)	27 (4.2%)	0.2511

CHD congenital heart disease, *BPD* bronchopulmonary dysplasia, *IQR* interquartile range, *RSV* respiratory syncytial virus

*$P<0.05$

Discussion

The present study revealed that preterm birth, BPD, hemodynamically significant CHD, and trisomy 21 were risk factors for contracting RSV infection, despite the administration of palivizumab for up to a 6-month period. Moreover, this report suggested that administering palivizumab year-round or over a longer period of time may prevent severe RSV infections in high-risk patients. The current indications for other children should be maintained.

Multiple studies have examined the risk factors associated with severe RSV infection. A meta-analysis by Beckhaus et al. revealed that patients with trisomy 21 had a higher risk of hospitalisation and death caused by RSV infection than healthy controls [7]. Furthermore, children with trisomy 21 had an increased length of hospital stay, higher oxygen requirements, more frequent intensive care unit admission, and a greater need for mechanical ventilation [7]. However, there are no known studies reporting the development of RSV in high-risk patients that have previously received palivizumab;

Table 3 Logistic regression analysis of risk factors for RSV-related hospitalisation

	OR (95% CI)	*p*-value
Gestational age ≤28 weeks	3.70 (1.57–8.70)	0.0027*
Gestational age 29–35 weeks	0.80 (0.36–1.75)	0.5697
Gestational age ≥36 weeks	Reference	
BPD	2.96 (1.17–7.50)	0.0225*
Hemodynamically significant CHD	1.54 (0.75–3.18)	0.2401
CHD requiring surgery or cardiac catheterisation and intervention in infancy	1.20 (0.62–2.33)	0.5920
Cyanotic CHD	1.06 (0.51–2.18)	0.8795
Pulmonary hypertension	1.11 (0.33–3.74)	0.8682
Heart failure	4.49 (0.49–41.2)	0.1840
Immunodeficiency	N/A	N/A
Trisomy 21	3.30 (1.37–7.95)	0.0078*
Congenital anomaly syndrome, excluding trisomy 21	2.0 (0.59–7.06)	0.2607

CHD congenital heart disease, *CI* confidence interval, *BPD* bronchopulmonary dysplasia, *N/A* not available due to no patient data, *OR* odds ratio, *RSV* respiratory syncytial virus

*$P<0.05$

Table 4 Clinical characteristics of patients infected with RSV ($n=69$) during the study period

Characteristics	($n=69$)
Age at onset of RSV infection (month), median (IQR)	14 (8.0–20.8)
Gestational age (weeks), median (IQR)	34.7 (28.4–38.1)
≤28 weeks, *n* (%)	18 (26.1%)
29–35 weeks, *n* (%)	23 (33.3%)
≥36 weeks, *n* (%)	28 (40.6%)
Birth weight (g), median (IQR)	2076 (1019–2772)
BPD, *n* (%)	13 (18.8%)
Hemodynamically significant CHD, *n* (%)	38 (55.1%)
CHD requiring surgery or cardiac catheterisation and intervention during infancy, *n* (%)	23 (33.3%)
Cyanotic CHD, *n* (%)	15 (21.7%)
Pulmonary hypertension, *n* (%)	4 (5.8%)
Heart failure, *n* (%)	2 (2.9%)
Immunodeficiency, *n* (%)	0
Trisomy 21, *n* (%)	10 (14.5%)
Congenital anomaly syndrome, excluding trisomy 21, *n* (%)	3 (4.4%)

CHD congenital heart disease, *BPD* bronchopulmonary dysplasia, *IQR* interquartile range, *RSV* respiratory syncytial virus

additionally, no studies have reported improved methods or timelines for administering palivizumab to high-risk patients.

Children with trisomy 21 are susceptible to severe RSV infection [7, 8]; in Japan, these children are eligible to receive palivizumab. Unfortunately, other congenital anomaly syndromes have not been studied sufficiently, and their associations with RSV infection remain largely unknown. However, in cases of congenital anomaly syndromes complicated by CHD, trisomy 13, trisomy 18, 22q11.2 deletion syndrome, and VACTERL association are more likely to complicate pulmonary arterial hypertension, in addition to trisomy 21 [9, 10]. A high incidence of CHD associated with pulmonary arterial hypertension may contribute to the severity of RSV infection.

Table 5 Risk factors for RSV-related hospitalisation

	Hospitalisation for RSV infection ($n=37$)	No hospitalisation during RSV infection ($n=32$)	*p*-value
Age at onset of RSV infection (month), median (IQR)	14 (8.5–21)	15 (7–21)	0.7254
Gestational age (weeks), median (IQR)	35.8 (29.4–37.8)	34.0 (28.0–37.8)	0.3796
≤28 weeks, *n* (%)	13 (35.1%)	10 (31.3%)	0.2994
29–35 weeks, *n* (%)	9 (24.3%)	9 (28.1%)	
≥36 weeks, *n* (%)	10 (27.0%)	18 (56.3%)	
Birth weight (g), median (IQR)	2085 (1067–2765.5)	2027 (961.5–2844)	0.8568
BPD, *n* (%)	7 (18.9%)	6 (18.8%)	0.7586
Hemodynamically significant CHD, *n* (%)	26 (70.3%)	12 (37.5%)	0.0082*
CHD requiring surgery or cardiac catheterisation and intervention during infancy, *n* (%)	17 (45.9%)	6 (18.8%)	0.0220*
Cyanotic CHD, *n* (%)	4 (10.8%)	11 (34.3%)	0.1421
Pulmonary hypertension, *n* (%)	1 (2.7%)	3 (9.4%)	0.6179
Heart failure, *n* (%)	1 (2.7%)	1 (3.1%)	1.0000
Immunodeficiency, *n* (%)	N/A	N/A	N/A
Trisomy 21, *n* (%)	3 (8.1%)	7 (21.9%)	0.3200
Congenital anomaly syndrome, excluding trisomy 21, *n* (%)	0	3 (9.4%)	0.0996

CHD congenital heart disease, *BPD* bronchopulmonary dysplasia, *IQR* interquartile range, *N/A* not available due to no patient data, *RSV* respiratory syncytial virus

*$P<0.05$

Table 6 Logistic regression analysis of the risk factors for RSV-related hospitalisation

	OR (95% CI)	*p*-value
Gestational age ≤ 28 weeks	0.56 (0.17–1.85)	0.3389
Gestational age 29–35 weeks	0.43 (0.14–1.32)	0.1404
Gestational age ≥ 36 weeks	Reference	
BPD	0.69 (0.21–2.32)	0.5501
Hemodynamically significant CHD	3.94 (1.44–10.76)	0.0075*
CHD requiring surgery or cardiac catheterisation and intervention in infancy	3.68 (1.23–11.05)	0.0200*
Cyanotic CHD	2.96 (0.84–10.47)	0.0920
Pulmonary hypertension	2.74 (0.27–27.69)	0.3942
Heart failure	0.86 (0.05–14.34)	0.9167
Immunodeficiency	N/A	N/A
Trisomy 21	2.26 (0.53–9.57)	0.2703
Congenital anomaly syndrome, excluding trisomy 21	N/A	0.9974

CHD congenital heart disease, *CI* confidence interval, *BPD* bronchopulmonary dysplasia, *N/A* not available due to few or no patient data or death, *OR* odds ratio, *RSV* respiratory syncytial virus

*$P < 0.05$

There are variations in the eligibility, timing, and insurance coverage for palivizumab in every country. As mentioned previously, preterm infants born at ≤ 35-week gestation are eligible to receive palivizumab in Japan; in contrast, the American Academy of Pediatrics states that preterm infants born at ≥ 29-week gestation with no BPD- or CHD-related complications cannot receive palivizumab [11]. The American Academy of Pediatrics also argues that prophylaxis with palivizumab is not cost-effective because there are many children who would require prophylaxis to prevent a single RSV hospitalisation, even though the prevalence of RSV is low [11]. However, our data clearly demonstrate that the number of severe RSV infections needs to be reduced as much as possible. Therefore, to reduce the occurrence of severe RSV infections, we believe it is necessary to identify additional high-risk patient groups within patients who receive extended palivizumab administration. The findings of the present study are useful for identifying high-risk target populations, even in other countries, where the specific criteria for palivizumab injection may differ.

In addition, we found that hemodynamically significant CHD and CHD requiring surgery or cardiac catheterisation/intervention during infancy are risk factors of severe RSV infection. All patients who required intensive care due to RSV infection had hemodynamically significant CHD (Table 7). Grambom et al. also reported that children with CHD had a significantly higher risk of developing severe RSV infection year-round [12]. Our findings align with their

Table 7 Clinical features of patients who required intensive care for RSV infection ($n = 3$)

Patient	Gestational age (days)	Birth weight (g)	Major complications	Age at which RSV infection occurred	Timing of RSV infection	Outcome
1	242	1146	VACTERL association, VSD, PAPVC, CHD-PAH, interstitial lung disease	5 mo	During season for palivizumab injection	Needed mechanical ventilation for 18 days and performed ICR
2	257	2476	TOF, absent pulmonary valve, post ICR, bronchial stenosis, congenital duodenal atresia, anal atresia	1 yr, 3 mo	Out of season for palivizumab injection	Needed mechanical ventilation for 23 days
3	267	2982	Trisomy 21, TOF, complete AVSD, severe PS, post Rastelli operation, backward PH due to MS	4 yr, 10 mo	Out of season for palivizumab injection	Needed mechanical ventilation for 6 days and performed MVR

AVSD atrioventricular septal defect, *CHD-PAH* congenital heart disease-associated pulmonary arterial hypertension, *ICR* intracardiac repair, *MS* mitral stenosis, *MVR* mitral valve replacement, *PAPVC* partial anomalous pulmonary venous connection, *PH* pulmonary hypertension, *PS* pulmonary stenosis, *RSV* respiratory syncytial virus, *TOF* tetralogy of Fallot, *VSD* ventricular septal defect

results and stress the importance for improving the administration methods of palivizumab in high-risk patients.

The duration and timing of palivizumab administration for high-risk patients should also be considered. Glick et al. revealed that nearly 10% of RSV-related hospitalisations occurred out of the regional RSV season and suggested that high-risk infants may require RSV immunoprophylaxis more frequently [13]. Another report suggested that it may be effective to administer palivizumab to children with medical complexities until the age of three years [14]. Based on the results of the present study, we believe it would be preferable to extend the duration and/or switch to year-round administration of palivizumab for high-risk patients.

This study has a few limitations that should be addressed. First, this was a retrospective study, and patients were enrolled from a single institution. Therefore, selection bias cannot be denied. In addition, we do not have specific control data for babies born at less than 35 weeks. As such, it is not possible to determine from this study the indications for palivizumab in children born between 29 and 35 weeks or less. Furthermore, the cost-effectiveness of year-round palivizumab administration in our high-risk group was not examined. Prospective multicentre and cost-effectiveness studies are needed in the future to confirm the findings of the present study and further elucidate the clinical efficacy of palivizumab for patients at high risk of contracting RSV.

Conclusions

Preterm birth (≤ 28-week gestation), BPD, congenital anomaly syndromes, hemodynamically significant CHD, and CHD requiring surgery or cardiac catheterisation/intervention during infancy should be considered as very high-risk factors for severe RSV infection, even after the administration of palivizumab. For high-risk infants, year-round and prolonged use of palivizumab should be considered to reduce the rate of hospitalisation; however, additional studies are warranted to determine the long-term efficacy of palivizumab.

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Authors' contributions Collected and analysed the patient data: ACN, IS, MS, DS, GI, HY, KC, and AT. Interpreted the patient data: ACN, HS, and KC. Wrote the draft manuscript: ACN. Revised and edited the final manuscript: ACN, KC, AM, and AT. All authors read and approved the final manuscript.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. The Institutional Review Board of Hokkaido University Hospital for clinical research approved this study (approval no. 019–0452).

Consent to participate The requirement for informed consent was waived due to the retrospective nature of the study.

Consent for publication The requirement for informed consent was waived due to the retrospective nature of the study.

Conflict of interest The authors declare no competing interests.

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