

Respiratory syncytial virus and effect of palivizumab prophylaxis in patients with congenital heart disease

 Ayse Ayzit Kilinc¹,  Canan Aygun²,  Metin Sungur³,  Kemal Baysal⁴

¹Department of Pediatric Pulmonology, Cerrahpasa Faculty of Medicine, Istanbul University-Cerrahpasa, Istanbul, Turkey

²Department of Neonatology, Faculty of Medicine, 19 Mayıs University, Samsun, Turkey

³Clinic of Pediatric Cardiology, Kartal Kosuyolu Training and Research Hospital, Istanbul, Turkey

⁴Department of Pediatric Cardiology, Faculty of Medicine, 19 Mayıs University, Samsun, Turkey

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Abstract

Aim: We evaluated the prevalence of Respiratory syncytial virus (RSV), the rates of hospitalization and intensive care unit (ICU) admission due to RSV infection, the need for mechanical ventilation, and the efficacy of palivizumab prophylaxis in children with congenital heart disease (CHD).

Material and Methods: A total of 419 patients under 2 years old who were hospitalized with lower respiratory tract infection (LRTI) were included in this study. Patients were divided into two groups according to the presence of CHD. 241 patients had unstable CHD and 178 patients had no underlying conditions. Palivizumab prophylaxis was administered to 29 of the patients with CHD and RSV infection; 22 of these patients were followed for 1 year.

Results: RSV infection was detected in 19.5% of the patients with CHD and in 20% of those without CHD. Among the 241 patients with CHD and LRTIs, the rate and duration of hospitalization for RSV were 14% and 9.9 days, respectively. The rate of admittance to the ICU was 32% and that of mechanical ventilation was 19% in the CHD patients with RSV infection. Of the patients without CHD, 12% were admitted to the ICU and 8% received mechanical ventilation. These rates were significantly higher among the RSV-infected patients with CHD. The rates of hospitalization for RSV before and after palivizumab prophylaxis were 59% and 14%, respectively; the difference was significant.

Conclusion: RSV infection is a common cause of mortality and morbidity in patients with CHD; palivizumab prophylaxis is effective in these patients.

Keywords: Congenital heart disease; palivizumab; respiratory syncytial virus

INTRODUCTION

Respiratory syncytial virus (RSV) is the most important respiratory pathogen in infancy and childhood (1,2). Children with underlying cardiac, pulmonary, or immunological disorders are at high risk of RSV-related disease, complications, and death (3). For these reasons, prophylaxis with the monoclonal antibody palivizumab is recommended to prevent complications caused by RSV (4,5). Although the rate of hospitalization due to RSV and the efficacy of palivizumab in patients with congenital heart disease (CHD) have been evaluated in developed countries, no such study has been conducted in a developing country. The primary aim of this study was to determine the incidence, risk factors, and complications of CHD in hemodynamically unstable patients under 2 years of age, and the secondary aim was to determine the efficacy of palivizumab prophylaxis in this group of patients.

MATERIAL and METHOD

Patients

A total of 419 patients under 2 years of age admitted to hospital with symptoms of lower respiratory tract infection (LRTI) was analyzed. The LRTI signs were difficulty breathing, cough, tachypnea, cyanosis, wheezing, rale, rhonchus on exam, fever greater than 38C or 100.4F and compatible radiological findings. Patients with histories of premature birth, chronic lung disease, and/or immunodeficiency were excluded. The patients with LRTI were allocated to Group I (241 patients with hemodynamically unstable CHD who needed medical treatment [cyanotic CHD, 64; acyanotic CHD, 177 patients]) and Group II (178 patients diagnosed with LRTI with no underlying chronic disease).

The patients in Groups I and II were followed in terms of the symptoms, physical exams, radiological findings, hospitalization rate and duration and the need for

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Corresponding Author: Ayse Ayzit Kilinc, Department of Pediatric Pulmonology, Cerrahpasa Faculty of Medicine, Istanbul University Cerrahpasa, Istanbul, Turkey **E-mail:** kilincayse203@gmail.com

intensive care and mechanical ventilation. Twenty-nine patients with CHD and RSV infection under 12 months of age underwent prophylaxis with palivizumab, a monoclonal antibody, and 22 were followed for 1 year in terms of recurrent RSV infection and hospitalization. The necessary approval for the study was obtained previously from the 19 Mayis University, Medical Faculty, ethics committee. The informed consent was obtained from the parents or guardians of the patients prior to participation in the study.

Sample collection

Swab samples were collected using a nasopharyngeal brush by a physician. Each sample was added to 0.5 mL Coris test solution and allowed to stand for 15 min. Next, the Coris Bioconcept RSV Respi-Strip was immersed in the sample for 15 min. Single and double lines on the test strip were considered indicative of negative and positive results, respectively. The sensitivity of the Coris Bioconcept Respi-Strip Rapid Diagnostic Kit was 92%, its specificity was 98%, and its diagnostic efficacy was 95% (6).

Statistical analysis

Coded data were transferred to a computer and analyzed using Minitab ver. 16 software. Quantitative data are expressed as means \pm standard deviations, and qualitative

data are expressed as numbers (percentages). The normality of the distribution of the quantitative variables was evaluated by the Kolmogorov–Smirnov test. The Fisher exact test was used for binary comparisons, and the chi-squared test was applied to compare qualitative variables. P values < 0.05 were taken to indicate statistical significance.

RESULTS

Patients

Of 419 patients under 2 years of age diagnosed with LRTI, 190 (45%) were female and 229 (55%) were male. The numbers of hospitalized patients and outpatients with LRTIs were 194 and 225, respectively. In addition, 241 (57%) of the patients had hemodynamically unstable CHD. Of the 241 patients with hemodynamically unstable CHD, 64 (26%) had cyanotic CHD and 177 (73%) had acyanotic CHD. Of the patients with cyanotic CHD, tetralogy of fallot was found in 35 (55%), transposition of great arteries (TGA) in 13 (20%), and other cyanotic heart diseases in 16 (25%). Of the patients with acyanotic CHD, atrial septal defect (ASD) was found in 46 (26.0%), ventricular septal defect (VSD) in 33 (18.6%), patent ductus arteriosus (PDA) in 27 (15.2%), pulmonary hypertension (PHT) and VSD in 15 (8.4%), ASD and PDA in 14 (7.9%), PHT in 11 (6.21%) and other acyanotic heart diseases in 31 (17.5%) (Table 1).

Table 1. Cardiological diagnoses of children with hemodynamically unstable CHD

Diagnosis of CHD	Children with cyanotic CHD N=64, (26%)	Children with acyanotic CHD N=177, (73%)
Tetralogy of fallot	35 (55%)	
Transposition of great arteries	13 (20%)	
Atrial septal defect		46 (26%)
Ventricular septal defect		33 (18.6%)
Patent ductus arteriosus		27 (15.2%)
Pulmonary hypertension + ventricular septal defect		15 (8.4%)
Atrial septal defect + patent ductus arteriosus		14 (7.9%)
Pulmonary hypertension		11 (6.21%)
Other heart diseases	16 (25%)	31 (17.5%)
	Total: 64 (100%)	Total: 177 (100%)

N; Number of Children, CHD; Congenital Heart Disease

While 117 (49%) of the patients with CHD and LRTIs were hospitalized, 124 (51%) underwent outpatient treatment. Of the patients, 178 were children with LRTIs but without CHD; of them, 101 (57%) patients were followed as outpatients and 77 (43%) required hospitalization (Figure 1).

Frequency of RSV infection

Of 419 patients under 2 years of age who had LRTI findings, 83 (19.8%) were infected with RSV. The prevalence of RSV was 25.7% among 194 hospitalized patients under

2 years of age. RSV infection was detected in 19.5% (n = 47) of the 241 patients with CHD. Of the 83 patients infected with RSV, 47 (57%) had CHD and 36 (43%) had no cardiac pathology. The results of statistical analysis on symptoms, physical exams and radiological findings in RSV-infected children in both groups are summarized in Table 2. In those, cyanosis was significantly higher in group 1 than group 2. The frequency of RSV infection peaked from December to April.

Frequencies of hospitalization and mechanical ventilation

Of the 241 patients with CHD, 34 (14%) were hospitalized due to RSV infection. In addition, 83 (43%) of 194 non-RSV-infected patients with CHD were hospitalized due to LRTI, compared with 34 (72%) of 47 RSV-infected patients with CHD ($p = 0.000$). The results of statistical analysis on hospitalization rate in RSV-infected children in both groups are summarized in Table 2. In those, the number of hospitalized children in group 1 were higher than group 2.

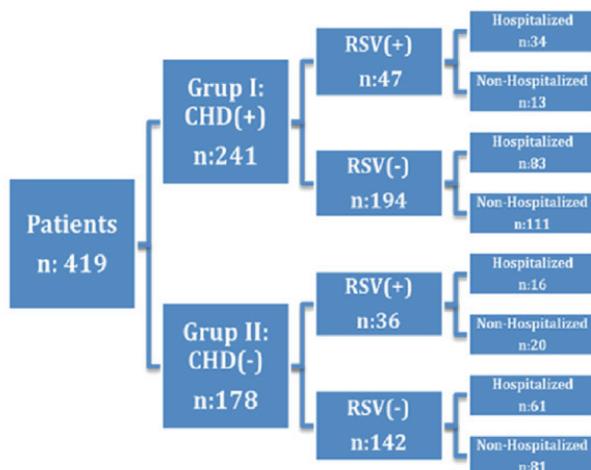


Figure 1. Distribution of the study groups

The mean duration of hospitalization was 9.9 (range 5-17, SD 3.1) days among 34 patients with CHD hospitalized for RSV infection. The mean duration of hospitalization of 16 RSV-infected patients without CHD was 4.2 days (range 2–10, SD 2.6 days; $p = 0.000$). Of the patients with CHD, 32% ($n = 15$) were admitted to the intensive care unit (ICU) due to RSV infection and 19% ($n = 9$) needed mechanical ventilation. In the non-CHD group, the rates of hospitalization in the ICU and mechanical ventilation were 12% ($n = 5$) and 8% ($n = 3$), respectively. The frequency and duration of admission to the ICU differed significantly between RSV-infected patients with and without CHD ($p = 0.011$) (Table 2). The rate of mechanical ventilation could not be analyzed due to the small number of patients. One patient with CHD died due to RSV infection.

Rates of RSV infection and hospitalization in patients with and without cyanotic and acyanotic heart disease

Among the patients with cyanotic CHD, 19 (30%) had RSV infection, 16 (84%) of whom were hospitalized and treated. Among the patients with cyanotic CHD, the frequency of RSV infection was 47% in those with tetralogy of Fallot, 32% in patients with other cyanotic heart diseases, and 21% in those with TGA.

Of the 177 patients with acyanotic CHD, 58 had LRTIs. Among the patients with acyanotic CHD, 28 (16%) had RSV infection, 18 (64%) of whom were hospitalized and treated. Among the patients with acyanotic CHD, the rate of RSV infection was highest in those with VSD ($n = 12$),

Table 2. Comparison of group features in RSV(+) children

	Group 1: RSV (+), CHD (+), N=47	Group 2: RSV (+), CHD (-), N=36	P value
Symptoms			
Fever	21 (45%)	18 (50%)	0.769
Cough	24 (51%)	16 (44%)	0.354
Difficulty breathing	27 (57%)	12 (33%)	0.325
Bruising	11 (23%)	6 (17%)	0.318
Running nose	7 (15%)	9 (25%)	0.924
Physical exams and radiological findings			
Wheezing, rale or rhonchus on exam	41 (87%)	35 (97%)	0.985
Cyanosis	13 (31%)	3 (8%)	0.009*
Abnormal radiologic findings	35 (74%)	29 (81%)	0.35
Follow-up			
Intensive care unit	15 (32%)	5 (14%)	0.046*
Hospitalization	19 (40%)	12 (33%)	0.323
Outpatient	13 (28%)	19 (53%)	0.586
Hospitalization day, mean±SD	9.9±3.1	4.2±2.6	0.000*
Intensive care unit day, mean±SD	6.89±1.83	4.33±0.57	0.011*

N; Number of Children, RSV; Respiratory Syncytial Virus, CHD; Congenital Heart Disease, SD; Standard Deviation

followed by PDA ($n = 4$), ASD ($n = 3$), PHT, VSD ($n = 2$), ASD, PDA ($n = 2$), and other acyanotic heart diseases ($n = 5$). The mean duration of hospitalization was 10.8 days (range 5-17, SD 3.47) in the acyanotic group and 9 days (range 6-14, SD 2.28) in the cyanotic group.

The frequency of RSV infection and the rate and duration of hospitalization due to RSV differed significantly between the patients with cyanotic and acyanotic CHD ($p = 0.015$, 0.000, and 0.043, respectively). Among the patients with CHD who required mechanical ventilation

due to RSV infection (n = 9), two had tetralogy of fallot, four had VSD, one had hypoplastic left heart, one had VSD and pulmonary hypertension, and one had VSD and PDA. One of the patients who died due to RSV had acyanotic heart disease (VSD and pulmonary hypertension).

Control of RSV infection

A total of 70 patients (43 [61%] with CHD and 27 [39%] without CHD) were followed for 1 year. Of those 70 patients, 8 (11%) developed RSV infection during the follow-up period. RSV infection was also detected in 3 (13%) of the 23 patients with CHD with previous RSV infection, and 2 (15%) of the 13 patients without CHD but with previous RSV infection (p = 0.605). None of the RSV-reinfected patients with CHD was hospitalized, whereas three of the patients with CHD were hospitalized and treated for second RSV infections (mean 9 ± 1.52 days, range 9-10 days). Two patients with and one without CHD with no prior RSV infection became infected with RSV.

Follow-up hospitalization rate of patients given palivizumab prophylaxis

Palivizumab prophylaxis was administered to 29 (61%) patients with hemodynamically unstable CHD infected by RSV and under 12 months of age. Twenty-two of these patients attended regular monthly follow-up visits. Before prophylaxis, 17 (59%) of the 29 patients with CHD were hospitalized for RSV. After prophylaxis, only 3 (14%) patients were hospitalized with a diagnosis of RSV LRTI; one did not receive monthly palivizumab injections (Table 3). The rate of hospitalization due to RSV infection was significantly lower among the patients who received palivizumab prophylaxis (p = 0.001). None of the patients hospitalized for RSV infection after palivizumab prophylaxis required mechanical ventilation.

Table 3. Change of Hospitalization Rate Before and After Palivizumab Prophylaxis

	Patients (n)	Hospitalized patients (n %)	
Before prophylaxis	29	17 (59%)	P=0.001
After prophylaxis	22	3 (14%)	

BMI, body mass index

DISCUSSION

RSV is an important agent of LRTIs in children under 2 years of age (1). Whereas RSV infection typically causes mild symptoms in healthy children, CHD increases the severity of LRTI in patients born prematurely who have bronchopulmonary dysplasia. RSV also increases the rate and duration of admission to the ICU and of mechanical ventilation, particularly among patients with hemodynamically unstable CHD requiring daily medical treatment (4). Moreover, patients with CHD are more prone to potential ventilation-perfusion mismatch and more likely to develop alveolar edema do not fully recover from

RSV infection due to, for instance, pulmonary edema and disruption of the ventilation perfusion balance (5).

Several international studies have evaluated the effects of RSV on the incidence and hospitalization rate of CHD. However, information on the incidence of RSV in infants with CHD in Turkey is sparse. Most related studies have involved general populations; thus, epidemiological data on RSV in children with CHD are not available. This study aimed to determine the following:

1. The frequency of RSV in children under 2 years of age hospitalized with LRTIs;
2. The frequency, mortality, and morbidity of RSV in children with CHD under 2 years of age; and
3. The efficacy of palivizumab prophylaxis in children with CHD.

The prevalence of RSV was 20% in 419 patients under the age of 2 years hospitalized for LRTIs and/or followed as outpatients for 1 year. The prevalence of RSV was 25.7% in 194 patients with or without CHD under the age of 2 years who were hospitalized for LRTIs. In Turkey, Gullu et al. (7) detected RSV antigen in 19% of 361 patients under 2 years of age who were hospitalized due to LRTIs. Kanra et al. (8) found RSV infection in 29.5% of 332 patients under 2 years of age with LRTIs. The results of Güllü et al. and Kanra et al. are similar to our findings. In Russia, the prevalence of RSV infection was 38% in 519 children under 2 years of age who were hospitalized due to LRTIs in 2008–2009. This rate is higher than those of other countries, likely due to climate factors (9).

The prevalence of RSV-related LRTI in children with CHD is similar to that in children with no underlying disease. However, RSV infection increases the need for hospitalization and mechanical ventilation among children with CHD, as discovered in the United States (US) by MacDonald et al. (4). From 1976 to 1980, the incidence of RSV infection was 33% and 37% among 699 and 74 children under 2 years of age with and without CHD, respectively (4). These rates are in agreement with our findings. Among the 419 patients under 2 years of age with LRTIs, the prevalence of RSV was 20% and that of CHD was 20%. The rate of hospitalization for RSV was 14% among 241 patients with CHD and LRTIs, compared with 8.9% among patients without CHD.

Feltes et al. (3) reported that 9.7% of 648 patients with CHD in the US and Europe were hospitalized due to RSV infection from 1998 to 2001. Because our hospital is a tertiary health care center, the high frequency of patients with severe CHD and low socioeconomic status may explain the higher rate of hospitalization compared with those in Europe and the US.

In this study, of the 117 patients with CHD diagnosed with LRTI and hospitalized, 73% had acyanotic CHD, 26% had cyanotic CHD, and 29% had RSV infection. In the Spanish multicenter CIVIC study conducted by Medrano et al. (10)

(2004–2005), 45.6% of 79 hospitalized patients with CHD and LRTIs had cyanotic CHD and 54.5% had acyanotic CHD; RSV was the causative agent in 24% of cases.

CHD increases the severity of RSV infection and the duration of hospitalization in children with no risk factor (5,11–15). In this study, the durations of hospitalization in RSV-infected patients with and without CHD were 9.9 and 4.2 ± 2.26 days, respectively. Altman et al. (11) reported that the mean duration of hospitalization of 63 patients with CHD and RSV infection was 7.4 ± 7.5 days, compared with 9.7 days in the CIVIC study. Navas et al. (62) evaluated 260 patients with CHD who were hospitalized due to RSV infection; the rate of admission to the ICU was 33.4%, the rate of mechanical ventilation was 18.8%, and the rate of mortality was 3.4%. In this study, the rate of admission to the ICU due to RSV infection was 30% and that of mechanical ventilation was 18%, consistent with the findings of Navas et al. Also, Altman et al. (11) reported a rate of admission to the ICU of 25%. Of the nine patients in this study who needed mechanical ventilation, two were followed up for tetralogy of fallot, four for VSD, one for hypoplastic left heart, one for VSD and PHT, and one for VSD and PDA. This pattern confirms the notion that RSV infection is more severe in patients with left-to-right shunt (11). In addition, the rate of RSV infection was higher in patients with left-to-right shunt. The mean duration of mechanical ventilation was 6.89 ± 1.83 days in patients with CHD and 4.3 days in patients with RSV without CHD. In the study of Altman et al. (11), seven patients with RSV infection were on mechanical ventilation for 13 ± 6.4 days. In this study, one patient with VSD and PHT died due to RSV infection.

RSV infection increases the morbidity and mortality of CHD, and palivizumab prophylaxis significantly reduces the rate of hospitalization due to RSV in patients with CHD (12). In this study, 29 hemodynamically unstable patients with CHD and RSV infection were recommended to receive 15 mg/kg palivizumab monthly during the RSV season; 22 of them were followed up for one year. The rate of hospitalization for RSV before prophylaxis (59%) was significantly higher than that after prophylaxis (14%). Of the three patients hospitalized after palivizumab prophylaxis, one did not receive monthly palivizumab injections. Feltes et al. (3) reported that among 639 and 648 patients who received prophylaxis and placebo, palivizumab prophylaxis reduced the rate of hospitalization by 45%.

In the Palivizumab Outcomes Registry study (2000–2004), the rate of hospitalization for RSV was 1.9% of 1500 patients with CHD who received prophylaxis. Patients with cyanotic CHD receiving prophylaxis (2.6%) were hospitalized due to RSV more frequently than were patients with acyanotic CHD (1.6%) (13,14,15). The decreases in the hospitalization rate after prophylaxis were 5.6% in the cyanotic group and 11.8% in the acyanotic group (3). In our study, there were two patients with cyanotic and one patient with acyanotic CHD who were infected with RSV while receiving prophylaxis.

The main limitation of our study is the small number of patients with RSV infection who received palivizumab prophylaxis. Further studies of the effect of palivizumab on CHD are thus needed.

CONCLUSION

RSV infection is a frequent and important cause of mortality and morbidity in patients with CHD in developing countries. Palivizumab prophylaxis is effective in such patients. Moreover, the 20% rate of RSV infection among children with LRTIs emphasizes the importance of RSV diagnosis, particularly in tertiary care centers. Such diagnosis will prevent unnecessary antibiotic usage and enable the implementation of appropriate isolation measures.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: Ethical protocol was approved by the medical ethics committee of 19 Mayıs University, Faculty of Medicine, Samsun, Turkey (2009/94).

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