

Respiratory syncytial virus-associated hospitalizations over three consecutive seasons in children with congenital heart disease

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Abstract The purpose of this investigation was to analyze the burden of respiratory syncytial virus (RSV)-related hospitalizations in infants and children with congenital heart disease (CHD) over three consecutive RSV seasons. Retrospectively, all children with hemodynamically significant (HS-CHD) and not significant (HNS-CHD) CHD born between 2004 and 2008 at a tertiary care university hospital and identified by ICD-10 diagnoses were included. Data on RSV-related hospitalizations over the first three years of life covering at least three RSV seasons (November–April) were analyzed. The overall incidence of RSV-related hospitalization was 9.6 % (58/602), without a statistically significant difference between HS-CHD and HNS-CHD (7.3 % vs. 10.4 %; $p=0.258$). Recommendation of palivizumab prophylaxis did not influence the RSV hospitalization rates between groups. Patients with HS-CHD and early surgery were significantly less often hospitalized due to RSV compared to those with delayed surgery (1.3 % vs. 14.3 %; $p=0.003$). The median duration of hospitalization was 8.5 days (HS-CHD: 14 vs. HNS-CHD: 7 days; $p=0.003$). Thirteen patients (22.4 %) were admitted to the intensive care unit (ICU), for a median of 10 days. The

median age at admission was 2 months, with a significant difference between HS-CHD and HNS-CHD (6 vs. 2 months; $p=0.001$). The majority (97 %) of RSV-related hospitalizations occurred before 12 months of age. Patients with HS-CHD had a significantly more severe course of RSV disease and were older at the time of hospitalization. Early surgery seemed to significantly reduce the risk of RSV hospitalization during the first RSV season.

Introduction

The importance of respiratory syncytial virus (RSV)-associated lower respiratory tract infection (LRTI) in infants and children diagnosed as having congenital heart disease (CHD) is well documented [1–12]. In a recent review, children with CHD had a mean RSV hospitalization rate of 7.8 % (range 1.4–16.4 %) and a mean mortality rate of 7.3 % (range 0–37 %) [13]. RSV-related morbidity in infants and children with CHD has been reported in detail by Altman et al. in 2000 [14]. RSV infection resulted in delayed cardiac surgery in 35 %, admission to the intensive care unit (ICU) in 25 %, with an average duration of stay of 9.7 ± 8.8 days, and mechanical ventilation in 11 %, with an average treatment duration of 13.0 ± 6.4 days. Patients with pulmonary hypertension required longer ventilator support, had more costly RSV-related hospitalizations, and tended to have longer ICU stays. There is a lot of controversy regarding the use of palivizumab in high-risk infants like young children with CHD due to the high costs of the product [13].

Currently, no data on RSV-related hospitalizations in infants and children diagnosed as having CHD in Austria exist. Therefore, we aimed to analyze the burden of RSV-related hospitalizations in infants and children with CHD over three consecutive RSV seasons.

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Materials and methods

Retrospectively, all children with a diagnosis of CHD and birth between January 1, 2004 and December 31, 2008, who were treated at the Department of Pediatrics of the Medical University of Graz, a tertiary care center in the southern part of Austria, were included for analysis. Patient charts were identified using a search for International Classification of Diseases (ICD), Tenth Revision.

Children were all followed over three consecutive RSV seasons from November to April according to long-term epidemiologic data from Austria [15]. Exclusion criteria were as follows: death during the study period, admission for heart surgery solely, lost to follow-up during the first three years of life, and closure of a patent ductus arteriosus during the neonatal period. Data were collected regarding gender, date of birth, gestational age, birth weight, small for gestation age (defined as birth weight below the 10th percentile), and prescription of palivizumab prophylaxis as documented in the medical charts and according to the Austrian recommendations for RSV immune prophylaxis in infants and children with CHD [16].

CHD was classified as being hemodynamically significant (HS-CHD) or hemodynamically not significant (HNS-CHD) according to the definition of the pediatric cardiologists (M.K. and A.G.). CHD was additionally classified as cyanotic or acyanotic, and the presence of pulmonary hypertension was documented.

RSV hospitalization was defined as hospitalization associated with LRTI and a positive RSV test result. RSV testing was performed from nasopharyngeal aspirates using RSV-ELISA (Directigen EZ RSV test, Becton Dickinson, USA; sensitivity 66.7–87.2 %; specificity 85.5–91.6 %).

Data were collected regarding days of hospitalization due to respiratory illness, age at admission in months, month of RSV hospitalization, days of oxygen requirement, days at the ICU, and days of respiratory support (either nasal continuous positive airway pressure or mechanical ventilation). The severity of LRTI was measured using the lower respiratory infection (LRI) score [17].

Statistical analysis

Statistical analysis was performed using LibreOffice Calc and SPSS. Interval-scaled and normally distributed characteristics were analyzed using Student's *t*-test. The Mann–Whitney *U*-test was used in ordinal-scaled or interval-scaled data, after checking the normality assumption with the Kolmogorov–Smirnov test. Dichotomous data were analyzed using the χ^2 test. If expected values were too low, Fisher's exact test was used. Statistical significance was set at $p < 0.05$.

Results

The study population comprised 602 out of 798 screened children, of whom 451 (74.9 %) had HNS-CHD, and 102 (16.9 %) had acyanotic and 49 (8.1 %) cyanotic HS-CHD. Pulmonary hypertension was diagnosed in 48 of 151 children (31.8 %) with HS-CHD.

Data of the study population and rates of RSV-related hospitalizations are shown in Table 1.

A total of 58 of the 602 children (9.6 %) were readmitted due to RSV infection. Hospitalization rates between HS-CHD (11 of 151; 7.3 %) and HNS-CHD (47 of 451; 10.4 %) did not differ significantly ($p = 0.258$).

The median length of RSV-related hospitalization was 8.5 days (range 1–70). Twenty-nine children (50 %) required supplemental oxygen therapy. The median duration of supplemental oxygen was 1 day (range 0–38 days). Thirteen children (22.4 %) had to be treated at the ICU. The median length of stay at the ICU was 10 days (range 2–70 days) and the median duration of mechanical ventilation was 4 days (range 0–38 days). The median LRI score was 3 (range 2–5). The median age at admission was 2 months (range 0–26 months).

Data on RSV-related hospitalization comparing children with HS-CHD to HNS-CHD are given in Table 2. Four of 11 children with HS-CHD had cyanosis and five of them had pulmonary hypertension. Two children (3.4 %) died (having had HS-CHD). No death was attributed to RSV infection; one was related to underlying VACTERL syndrome with severe trachea-bronchomalacia and the other to atrioventricular blocking following heart surgery.

The seasonal distribution showed a peak in January, with 15 of 58 (25.9 %) RSV-related hospitalizations. Forty of 58

Table 1 Data of the study cohort and rates of respiratory syncytial virus (RSV)-related hospitalizations

	Total	RSV hospitalization
Study cohort	602 (100)	58 (9.6)
HNS-CHD	451 (74.9)	47 (10.4)
HS-CHD	151 (25.1)	11 (7.3)
Male:female	321 (53):281 (47)	37 (11.5):21 (7.5)
Term:preterm infants	347 (66):182 (34)*	36 (10.4):18 (9.9)
Birth weight ≥ 2500 g	353 (68.1)**	39 (11.0)
Birth weight < 2500 g	163 (31.5)**	12 (7.4)
Birth weight < 1500 g	43 (8.3)**	3 (7.0)
Small for gestational age	61 (11.8)**	4 (6.6)

Data are given as number (percentage)

HS-CHD and HNS-CHD = hemodynamically significant and not significant congenital heart disease

*Data available from 529 children

**Data available from 518 children

All differences regarding RSV hospitalization rates were not significant

Table 2 Data on RSV hospitalization comparing 11 children with HS-CHD to 47 children with HNS-CHD

	HS-CHD	HNS-CHD	<i>p</i> -Value
Length of stay (days)	14 (2–39)	7 (1–70)	0.003
Age at admission (months)	6 (2–26)	2 (0–11)	0.001
Need for supplemental oxygen	7 (64)	22 (47)	0.008
Supplemental oxygen (days)	4 (0–27)	0 (0–6)	ns
LRI score	3 (2–5)	3 (2–5)	ns
Admission to ICU	5 (46)	8 (17)	0.021
Stay at ICU (days)	10 (0–27)	9.5 (0–70)	ns
Mechanical ventilation (days)	8 (0–27)	2 (0–38)	ns

HS-CHD = hemodynamically significant congenital heart disease; HNS-CHD = hemodynamically not significant congenital heart disease; LRI score = lower respiratory tract infection score ranging from 1 to 5; ns = not significant

Data are given as median ± SD (range) or number (%)

children (69 %) were hospitalized during the typical RSV season, and 38 (65.5 %) within the first RSV season. Eighteen children (31 %) were hospitalized outside the typical RSV season, nine before the first and nine between the first and second RSV seasons (see Fig. 1).

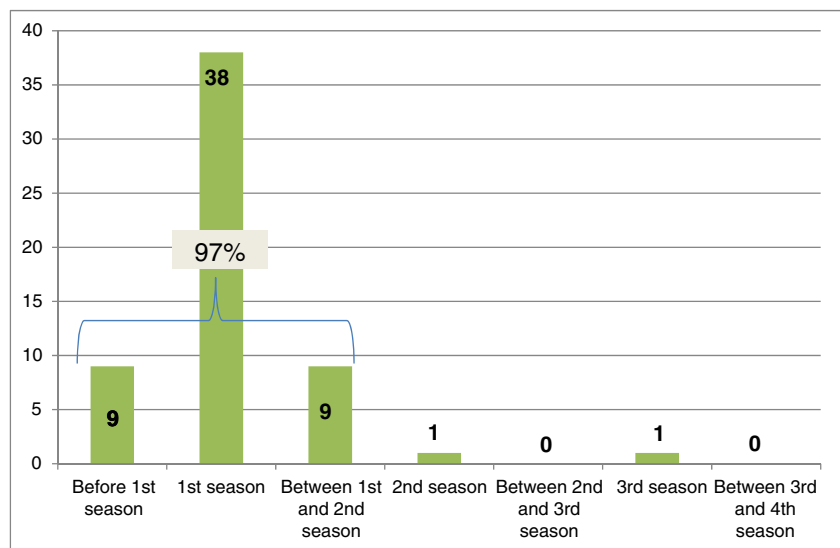
Recommendation of palivizumab prophylaxis was documented in 41 children (27.2 %) with HS-CHD and 10 children (2.2 %) with HNS-CHD. Three of the children with HS-CHD (7.3 %) were hospitalized due to RSV infection compared to 8 of 110 (7.3 %) without recommendation (differences not significant). Children with HS-CHD and early heart surgery were, independent of palivizumab recommendation, significantly less often hospitalized due to RSV compared to those with delayed heart surgery (1.3 % vs. 14.3 %; *p*=0.003).

Discussion

The burden of RSV disease in children with CHD measured by RSV-related hospitalization rates was high, with an overall rate of 9.6 % that increased up to 16.3 % in children without heart surgery before the first RSV season and having no documented palivizumab recommendation compared to the literature [1–12, 18]. As found in most of these studies, our results confirmed the more severe course of RSV disease in children with HS-CHD [1, 2, 5, 6, 18]. Interestingly, prematurity did not significantly alter the course of RSV disease in our study cohort, despite the fact that prematurity was evident in one-third of our study children, thus being significantly higher than the 16.4 % rate reported by a Spanish study group [18]. The duration of RSV-related hospital and ICU stays (median 14 and 10 days, respectively) were found to be higher compared to the Spanish data (median 7 and 6 days, respectively) [18].

Children with HNS-CHD were significantly younger of age compared to those with HS-CHD, and RSV hospitalization rates were astonishingly high (up to 11.7 %). Children with diagnosis of HNS-CHD suffer a substantial burden of RSV disease that seems to be underestimated and underreported in the literature, as far as most studies focused on HS-CHD. A very recent study found an RSV hospitalization rate of only 1.5 % in infants with HNS-CHD compared to 2.1 % in infants with acyanotic HS-CHD and 4.8 % in those with cyanotic HS-CHD, respectively [12]. ICU admission rates and need for ventilator support were high, especially in cyanotic HS-CHD, and, overall, comparable to our findings [12]. Risk factors that may exacerbate the adverse effects of respiratory disease in young CHD patients include compromised cardiorespiratory status at baseline, altered pulmonary mechanics, potential cyanosis, and/or pulmonary hypertension and ventilation–perfusion mismatch, and it is this

Fig. 1 Seasonal distribution of respiratory syncytial virus (RSV) hospitalizations of 58 children with congenital heart disease (CHD). RSV season: November to April



precarious cardiorespiratory baseline that produces increased risk from RSV LRTI [19].

The weighted mean RSV case fatality rate was reported to be 1.2 % among preterm infants, 5.2 % among children with CHD, and 4.1 % among children with bronchopulmonary dysplasia [20]. We found no RSV-attributed mortality, in contrast to most other studies [1–6, 9–12].

The influence of palivizumab on RSV on rates of RSV hospitalizations and the course of disease were found to be low, but our results are limited by the fact that its evaluation was only based on the documentation of palivizumab recommendation in the medical charts and that national recommendations for the use of palivizumab in children with CHD [16] were relatively new during the study period. Cohen et al. reported RSV hospitalization rates of 1.6 % and 2.6 % in acyanotic and cyanotic CHD, respectively [21]. Nevertheless, rates increase significantly by inadequate palivizumab prophylaxis and have been reported to increase from 3.3 % to 7.9 % in one study [18].

The seasonality of RSV hospitalizations was typically peaking in January and comparable to peaks observed in preterm born infants of Austria [15]. Interestingly, a high proportion of RSV hospitalizations, namely more than 30 %, were documented occurring outside the typical RSV season between November and April. Follow-up over three consecutive RSV seasons clearly documented that the highest burden of RSV disease (97 % of all hospitalizations) happened during the first year of life. The second and third RSV seasons showed negligible rates of RSV hospitalizations.

Our findings support only partly the new and restrictive recommendations for the use of palivizumab in children with HS-CHD recently published by the American Academy of Pediatrics [22]. In this statement, children with HS-CHD who might most likely benefit from immunoprophylaxis include either those with acyanotic heart disease receiving medication to control congestive heart failure and requiring cardiac surgical procedures or infants with moderate to severe pulmonary hypertension. The latter is no longer supported by our findings, representing a high rate of RSV hospitalizations in children without evidence of pulmonary hypertension or cyanosis. Efforts are needed in order to improve the mandatory compliance and adherence to palivizumab prophylaxis for infants with HS-CHD and age younger than 12 months at onset of the RSV season in order to yield an effective reduction of the burden of RSV disease in this population.

There are certain limitations of this study that need to be noted. This is a retrospective study performed in a single-center analysis that included patients enrolled over a long period of time and the interpretation of palivizumab prophylaxis results was based solely on medical charts' recommendations. On the other hand, the single-center experience presented here includes homogeneous follow-up data due to the geographical catchment area.

In conclusion, the burden of RSV measured by hospitalization rates was high for both HS-CHD and HNS-CHD, with a more severe course of disease in children with HS-CHD. Early surgery seemed to significantly reduce the risk of RSV hospitalization during the first RSV season, and nearly all RSV-related hospitalizations occurred during the first year of life.

Compliance with ethical standards

Conflict of interest None.

Funding None.

Ethical approval By the Ethics Committee of the Medical University of Graz, number 26-391 ex 13/14.

Informed consent Not applicable due to the retrospective design of the study.

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