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Respiratory syncytial virus hospitalizations in infants of 28 weeks gestational age and less in the palivizumab era

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ABSTRACT

Objective: To obtain data on respiratory syncytial virus (RSV) associated hospitalization rates in preterm infants of 28 weeks gestational age and less in the era of palivizumab prophylaxis.
Methods: Retrospective single-center cohort study including all preterm infants up to 28 weeks + 6 days gestational age and born between 2004 and 2012 at a tertiary care university hospital. Data on RSV related hospitalizations over the first two years of life covering at least two RSV seasons (November-April) were analyzed.
Results: Ninety-one of 287 (32%) infants were hospitalized due to respiratory illness, and a total of 17 infants (5.9%) tested RSV positive during the first 2 years of life. Fourteen infants (4.9%) were hospitalized during the first RSV season. RSV hospitalization rate in infants with BPD was 4.5% (2/44) compared to 4.9% (12/243) without BPD. Palivizumab prophylaxis was documented in 74.6% of the infants. Infants with RSV compared to other respiratory tract infection were of younger age (6.8 vs. 9.1 months; $p = 0.049$), had longer hospital stays (median 11 vs. 5 days; $p = 0.043$) and more severe respiratory illness (median LRI score 3 vs. 2; $p = 0.043$).
Conclusions: Despite palivizumab prophylaxis the burden of RSV disease and all cause respiratory illness was still remarkable in this vulnerable preterm population and mainly limited to the first season.

Introduction

In 1998 the FDA and in 1999 subsequently the EMEA approved palivizumab, a humanized monoclonal antibody against the F glycoprotein of the respiratory syncytial virus (RSV), for prophylactic use in preterm infants with and without bronchopulmonary dysplasia (BPD) up to 35 weeks of gestational age. The goal was to lessen the burden of severe RSV disease by the reduction of RSV related hospitalization rates, total RSV hospital days, RSV hospital days with increased oxygen, RSV hospital days with a moderate/severe lower respiratory tract illness (LRTI), and reduction of intensive care unit admissions as demonstrated by the results of the Impact trial.[1] The American Academy of Pediatrics published guidelines for the use of palivizumab[2] that were more or less adopted by the Working Group of Neonatology and Paediatric Intensive Care of the Austrian Society of Paediatrics and Adolescent Medicine.[3] There was in general broad consensus regarding its use in infants and children with BPD and very preterm infants accepted as a gestational age of 28 weeks and less. The Impact trial reported on an overall reduction in RSV hospitalization rates by 55% (10.6 vs. 4.8%, $p < 0.001$), and a 78% reduction (8.1 vs. 1.8%, $p < 0.001$) in preterm infants without BPD and a 39% reduction (12.8 vs. 7.9%, $p < 0.001$) in those with BPD over a 150 days study period.[1]

Data from the pre-palivizumab era reported on RSV hospitalization rates for infants and children with BPD ranging from 7.6 to 59% and for preterm infants equal or less than 32 weeks of gestational age without BPD ranging from 2 to 18%.[4] The palivizumab outcomes registry reported on a 5.8% rate in infants with BPD and a 2.1% rate in preterm infants without BPD from a cohort of 2,116 infants enrolled over the 2000/2001 season.[5] These rates decreased in a later report to 1.1% in preterm infants without BPD in the 2003/2004 season and to 1.8% in the BPD group, respectively.[6] The results further improved with home-based administration of palivizumab as reported by a RSV hospitalization rate of 0.4%.[7]

Missing adherence to the dosage and injection interval regimen of palivizumab is a known factor that significantly increases RSV hospitalization rates.[5,8,9] Krilov et al. recently reported on a partial

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palivizumab prophylaxis rate of 67% in 8443 high-risk infants including preterm infants with and without BPD and infants with congenital heart disease.[10]

Aim of our study was to obtain data on respiratory syncytial virus (RSV) associated hospitalization rates in preterm infants of 28 weeks of gestational age and less in the era of palivizumab prophylaxis in Austria.

Methods

Retrospectively all preterm infants of 28 weeks' gestation (up to 28 weeks + 6 days) born between January 1, 2004 and December 31, 2012 at the Department of Pediatrics of the Medical University Graz, a tertiary care center in the southern part of Austria, were included for analysis. The study was approved by the ethic committee of the Medical University of Graz (number 26-467 ex 13/14) and started in April 2014.

Children were all followed over two years including at least two consecutive RSV seasons from November to April according to long-term epidemiological data from Austria.[11] Patients were excluded for analysis when being lost to follow-up during the first two years of life including death. Data were collected from the local electronic database openMedocs regarding gender, date of birth, gestational age, birth weight, small for gestational age (defined as birth weight below the 10th percentile), month of discharge, diagnosis of BPD (defined as oxygen dependency at 36 weeks postmenstrual age), neurological disease (intra-/periventricular hemorrhage, periventricular leukomalacia), presence and number of siblings, multiple birth, tobacco smoking during pregnancy, crowding (more than 3 persons living under poor conditions), and prescription of palivizumab prophylaxis as documented in the medical charts according to the Austrian recommendations for RSV immune prophylaxis in preterm infants with and without BPD.[12] Established risk factors that contribute to RSV were evaluated including discharge during RSV season, male gender, BPD, neurological disease, multiple births, siblings, crowding, and smoking during pregnancy.

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 intensive care unit (ICU), days of respiratory support (either nasal continuous positive airway pressure, or mechanical ventilation). Severity of LRTI was measured using the using a modified lower respiratory illness/infection (LRI) score ranging from 1 to 5.[13] Searching for other respiratory pathogens was not done according to the study protocol.

Statistical analysis was performed using Excel (Microsoft Office Excel 2013, Redmond, USA) and SPSS (IBM SPSS Statistics 22, Armonk, USA). For categorical data chi-square or Fisher's Exact tests and for numerical data t-test or Mann-Whitney-U test were used as appropriate. Normality assumption was checked using the Shapiro-Wilk test. Statistical significance was set at $p < 0.05$.

Results

Of 382 infants born during the study period 88 (23%) died and 7 (1.8%) were lost to follow-up, thus, the study population comprised 287 infants. Basic demographic data are given in Table 1.

Ninety-one infants (32%) were hospitalized due to respiratory illness, and a total of 17 of 287 infants (5.9%) tested RSV positive during the study period. Fourteen infants (4.9%) were hospitalized for proven RSV infection during the first RSV season. One infant (0.36%) had nosocomial RSV infection during the first stay at the NICU that was excluded for analysis, and another infant (0.36%) exhibited two RSV hospitalizations during the first RSV season that was calculated as one case. Three infants (1.04%) were hospitalized for proven RSV infection during the second RSV season and contributed to the above mentioned total RSV rehospitalization rate of 5.9%.

Table 1
Basic demographic data of 287 preterm infants ≤28 weeks of gestational age.

Male: female	170 (59.3): 117 (40.7)
Gestational age (weeks)	26.4 (1.4)
Birth weight (grams)	933 (257)
Discharge during RSV season (November – April)	131 (45.6)
Palivizumab recommendation	214 (74.6)

Data are given as number (%) or mean +/– SD; RSV = respiratory syncytial virus.

RSV hospitalization rate in infants and children with BPD was 4.5% (2/44) compared to 4.9% (12/243) without BPD during the first RSV season; hospitalization rates due to any respiratory illness were 48% (21/44) compared to 29% (70/243), respectively ($p = 0.006$). Seventy percent of RSV cases had diagnosis of bronchiolitis, 18% bronchitis, 9% presented with apneas, and 9% with rhinitis. Seasonal distribution of RSV hospitalizations showed a peak in February followed by March and April, and for all cause respiratory illness (excluding RSV) again a peak in February followed by December and January.

Preterm infants with confirmed RSV compared to other respiratory tract infection were of younger chronological age (6.76 vs. 9.05 months; $p = 0.049$), had longer hospital stays (median 11 vs. 5 days; $p = 0.043$) and more severe respiratory illness (median LRI score 3 vs. 2; $p = 0.043$). Days on supplemental oxygen, ICU admissions rates, and days on mechanical ventilation were all low (median 0 for all groups) and did not differ between groups.

Hospitalization rates due to RSV infection within the first and second RSV season and hospitalization rates due to any respiratory illness in correlation to gestational age, birth weight, and all defined risk factors are shown in Table 2. Discharge during RSV season markedly increased the risk for RSV hospitalization during the first season ($p = 0.056$). Presence of one, two, three, four, and five RSV risk factors led to hospitalization rates of 2.6%, 5.8%, 9.5%, 4.0%, and 0%, respectively ($p = 0.089$).

Ninety-one preterm infants exhibited 164 hospitalizations due to respiratory illness – 52 (32%) due to upper respiratory tract infections and 112 (68%) due to LRTI. Eighty-one percent occurred during the first year of life. Rates of hospitalizations due to any respiratory illness according to gestational age showed lesser hospitalization rates with increasing gestational age except a gestational age of 26 weeks (see Figure 1). Forty-three cases of hospitalization due to respiratory illness (43/164, 26%) had no RSV test done, and 6 (6/164, 3.7%) had diagnosis of bronchiolitis.

Palivizumab prophylaxis was documented in 214 of 287 infants (74.6%). In those with BPD it was documented in 31 of 44 (70.5%) and in those without in 183 of 243 infants (75.3%). Eleven of the 214 infants (5.1%) having documented palivizumab recommendation had RSV infection during the first RSV season.

Discussion

We observed a total 5.9% RSV rehospitalization rate in preterm infants of 28 and less weeks of gestational age during the first 2 years of life. During the first RSV season rates were nearly similar between preterm infants with diagnosis of BPD (4.5%) and those without (4.9%). Palivizumab prophylaxis was documented in 75% of the infants for the first RSV season.

Due to the retrospective study design performed at a single center analysis including patients enrolled over a large period of

Table 2
Hospitalization rates due to RSV infection and any respiratory illness of 287 preterm infants ≤28 weeks of gestational age.

	RSV infection 1st season	RSV infection 2nd season	Respiratory illness (total)	p-value
Male vs. female	4.1: 6.0	1.8: 0	38: 23	ns/ns/0.009
BPD vs. no BPD	4.5: 4.9	0: 1.2	48: 29	ns/ns/0.021
Neurological disease* Y/N	4.7: 5.0	0: 1.7	32: 32	ns/ns/ns
Multiple vs. singleton birth	1.2: 6.3	1.2: 1.0	17: 37	ns/ns/0.001
Siblings Y/N	4.1: 6.0	0.6: 1.7	22: 45	ns/ns/ <0.001
Tobacco smoking during pregnancy Y/N	0: 5.6	2.8: 0.8	31: 32	ns/ns/ns
Crowding Y/N	4.7: 5.2	0.6: 1.7	33: 30	ns/ns/ns
Discharge during RSV season Y/N	7.6: 2.6	1.5: 0.6	28: 33	0.056/ns/ns
23-25 vs. 26-28 weeks GA	3.1: 5.3	0: 1.5	40: 33	ns/ns/ns
<1000 vs. ≥1000 grams	5.2: 4.4	0.6: 1.8	35: 27	ns/ns/ns

Data are given as %, ns = not significant, Y/N = yes/no, GA = gestational age, BW = birth weight.
RSV = respiratory syncytial virus, BPD = bronchopulmonary dysplasia, *Neurological disease includes intra-/periventricular hemorrhage and periventricular leukomalacia.

time interpretation of palivizumab prophylaxis effects remain highly speculative. It might be possible that more infants had received palivizumab via outpatient clinics. Second, we did not collect data on adherence to the monthly injection scheme. Thus, we can interpret only total RSV hospitalization rates in the light of published evidence provided by the literature. An additional limitation is our retrospective study design performed at a single center including patients enrolled over a large period of time. Thus, not all LRTI cases were tested for RSV infection. Again, interpretation of palivizumab prophylaxis results based solely on medical charts' recommendations. Fortunately, guidelines for palivizumab prophylaxis did not change over the study period. On the other hand the single-center experience presented here includes homogeneous follow-up data due to the geographical catchment area.

In comparison to the results of the palivizumab outcome registry having reported RSV hospitalization rates below 2% our findings were disappointing.[5,6] Adherence to the monthly injection scheme of palivizumab is mandatory for successful reduction of RSV hospitalizations, otherwise RSV hospitalization rates significantly increase.[5,8–10] Nevertheless that we were not able to follow closely palivizumab prophylaxis in this population our study results claim for more education on RSV and its prophylaxis.

Among 240 infants with gestational age <28 weeks or birthweight <1,000 grams in Denmark during the years 1994 and 1995 Pedersen et al.[14] reported on 43 infants (18%) that had been rehospitalized 48 times owing to RSV over a two years follow-up. In infants without BPD the risk of rehospitalization for RSV was 16%, whereas in infants with BPD it was 30% (differences not significant). Eighteen infants (38%) required respiratory support (supplemental oxygen only 3, continuous positive airway pressure 14, and mechanical ventilation 1) and no infant died from RSV infection. During the first year of life, the estimated number of RSV hospitalizations per 1000 children was 388 for those with BPDand 70 for children born at 28 weeks and less gestational age compared to 30 for children born at term with no underlying medical condition in a retrospective cohort study of all children <3 years old enrolled in the Tennessee Medicaid program from July 1989 through June 1993.[15] This finding confirmed the important role of BPD as infants at highest risk for severe RSV infection. In the same year Stevens et al.[16] estimated the probability of hospitalization with an RSV-associated illness for infants born at 32 weeks of gestational age or earlier at 11.2% from a cohort of 1029 infants from a 12-county neonatal network in Rochester, NY. The incidence of RSV hospitalization increased with decreasing gestational age and was stated with 13.9% for infants born at 26 weeks or less compared to 4.4% for those born at 30-32 weeks of gestational age. Compared to these data 20 years ago our RSV hospitalization rates underline the significant and promising influence of palivizumab prophylaxis.

In a prospective Peruvian cohort study the incidence of RSV hospitalizations was 116.2 per 1,000 child-years; 244.9 in infants with a birth weight <1000 g and 88.9 in infants 1000–1500 g; $p < 0.05$, thus, 3-times higher in the extremely low birth weight infants.[17] The incidence of RSV LRTI requiring emergency room management was 103.9 per 1,000 child-years.

In infants below or equal to 32 weeks gestational age without BPD RSV rehospitalization rates had been reported to range from 2.0 to 13.4%,[16,18–21] in those with BPD from 7.6 to 19.0%.[1,18–20,22–28] A Spain study[18] reported on 59 preterm infants below 33 weeks of gestational age being rehospitalized for RSV infection of whom 15 (25.4%) required ICU admission for a median of 6 (range 3 to 11) days and three (5.1%) mechanical ventilation for a median of 5 (range 7 to 43) days. In the Impact trial[1] 3% of placebo patients and 1.3% of palivizumab recipients exhibited ICU admissions ($p = 0.026$); total days were 12.7 and 13.3, respectively ($p = 0.023$). The placebo and treated groups did not show significant differences in incidences of mechanical ventilation or total days of mechanical ventilation. Thus, our observations might be satisfying regarding the low rates of severe courses of RSV disease and need for ICU treatment.

The risk factor profile for RSV hospitalization was mainly discussed for the 33 to 35 weeks gestational age' infants in order to tailor the cost-intense palivizumab prophylaxis to the highest vulnerable populations. High-risk infants include those with a history of prematurity, BPD, congenital heart disease, neuromuscular impairment, immunodeficiency, and Down syndrome, and host related risk factors that have been identified to be associated with severe RSV related LRTI include young age below 6 months at the beginning of RSV season, multiple birth, male sex, low socioeconomic status and parental education, crowded living

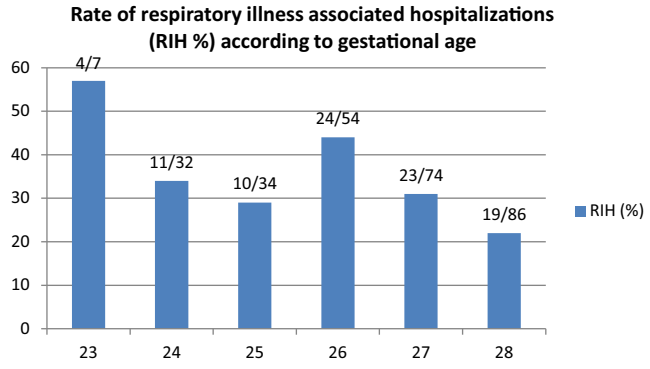

Figure 1. Rates of hospitalizations due to any respiratory illness over two years follow-up in 287 preterm infants ≤28 weeks of gestational age.
Absolute numbers (n RIH/n per GA) are separately given per each column.
GA = gestational age.

conditions, young siblings, maternal smoking and indoor smoke pollution, malnutrition/small for gestational age, family history of atopy or asthma, low cord serum RSV antibody titers, and living at altitude.[29] Additionally, risk factors increasing the risk of acquisition of RSV have been identified to be birth before and/or during RSV season, day care attendance, presence of older siblings in school or day-care, and lack of breast feeding. Some of these risk factors are discussed controversially and some of them are found continuously throughout the literature.[29] Nevertheless, we observed increasing RSV hospitalization rates with increasing number of additional risk factors (up to 3) besides the factor of preterm birth and extremely low gestational age per se. Thus, our study enforces to take into account possible risk factors when recommending palivizumab prophylaxis and advising parents for adequate adherence for the monthly intramuscular injections.

Respiratory morbidity was still high in our study population and did not seem to be altered by palivizumab prophylaxis. Ten years ago, we observed a slightly lower 24% rehospitalization rate in more mature infants of 29 to 32 weeks' gestational age.[30] Underwood et al.[31] reported on a 31% rate in infants below 25 weeks of age and Ralser et al.[32] more recently a 42% rate in infants below 32 weeks.

In conclusion we still found a substantial burden of RSV disease in this population in the era of palivizumab that mainly focused on the first RSV season.

Conflict of interest

BR received honoraria from Abbvie GmbH Austria for oral lectures.

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None.

Ethical Approval

The study was approved by the Ethic Committee of the Medical University of Graz.

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