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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