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BRIEF REPORT

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Observational study of respiratory syncytial virus-associated hospitalizations and use of palivizumab in premature infants aged 29–32 weeks

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The national observational multicenter cohort study presented here was conducted over two respiratory syncytial virus (RSV) seasons (2001–2003) in Austria to collect data on RSV-related rehospitalizations in premature infants of 29–32-weeks' gestational age. The results revealed an overall RSV hospitalization rate of 4.5% (36/801). Risk factors were discharge from the neonatal intensive care unit between the months of October and December, birth between June and December 2002, and neurological disease. Palivizumab prophylaxis was given to 238 (29.7%) infants, and 148 infants received inadequate or incomplete courses.

Respiratory syncytial virus (RSV) infection represents a major cause of rehospitalization during the first year of life in preterm infants [1]. Recommendations for RSV prophylaxis with palivizumab [2] have been adopted without major modifications in Austria [3], and they suggest that decisions regarding this drug's administration should be based on local epidemiological data. Currently, very limited data are available on the risk of RSV-related rehospitalization in Austria [4]. Due to the fact that insurance companies allocate and reimburse prophylaxis with palivizumab in this group of premature infants differently from published recommendations and with great local variation, we initiated a nationwide observational cohort study. The study was aimed at collecting data on RSV-related rehospitalization of premature infants of 29–32-weeks' gestational age in order to analyze associated risk factors and to assess the use of palivizumab prophylaxis in this population.

Infants were included if their gestational age was between 29 (29+0) and 32 (32+6) weeks and if they were born between 1 June 2001 and 31 December 2002. All infants were followed up until 1 June 2003. For the first RSV season, data on all rehospitalizations were collected retrospectively from medical charts and by telephone calls: for the second RSV season, which occurred after the study was initiated in February 2002, data were collected prospectively. In cases of rehospitalization due to respiratory illness, the following data were collected: patient age in months, the month in which rehospitalization occurred, severity of respiratory illness (determined using the modified clinical lower respiratory illness/infection score [5]), length of stay, number of days with supplemental oxygen, number of days at the intensive care unit, and number of days with mechanical ventilation including nasal continuous positive airway pressure. RSV antigen detection was performed on nasopharyngeal aspirates using either enzyme-linked immunosorbent assays or immunofluorescence techniques. Viral cultures were not performed.

Prophylaxis with monthly administered intramuscular injections of palivizumab was usually started at the end of October or beginning of November, with the last injection in March. Recommendations for prophylaxis were influenced by local differences in allocation and reimbursement of prophylaxis by the insurance companies. Prophylaxis administration was not influenced by the study protocol. The study was approved by the local ethics committee, and informed consent was given by the parents of those infants prospectively enrolled into the study.

Statistical analyses were performed using the Pearson chi-square and Yate's corrected chi-square test, as appropriate for categorical data, and the *t*-test and Fisher's exact test, as appropriate for numerical data. Multivariate analysis was performed using a logistic regression model with backward elimination and the Wald criterion. Analysis was done with SPSS (SPSS, Chicago, IL, USA), and StatXact4 (Cytel, Cambridge, MA, USA) software.

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Table 1 Characteristics of the study population

Characteristic	Number (%) of patients[a]
Number of patients	863
Lost to follow-up	49 (5.7)
Death as outcome	13 (1.5)
Study population	801
Male gender	425 (53)
Gestational age	30.75±1.1
Birth weight (g)	1,510±347
BPD	32 (4)
CHD	81 (10.1)
Hemodynamically significant CHD	19 (2.4)
Neurological disease	84 (10.5)
Severe neurological disease	30 (3.8)
Immunodeficiency	0
Cystic fibrosis	0
Multiple birth	249 (31.1)
Siblings	245 (30.6)
Passive tobacco smoking	109 (13.6)
Crowding	448 (55.9)
Daycare attendance	10 (1.3)

BPD Bronchopulmonary dysplasia (supplemental oxygen at 36 weeks corrected age), *CHD* congenital heart disease
[a]Data are given as number (percentage) or mean±SD

During the study period a total of 863 infants with a gestational age of 29 – 32 weeks was included from 20 study centres, including the four existing university hospitals in Austria. Characteristics of the study population are given in Table 1. A total of 104 patients had 146 rehospitalizations due to respiratory illness. Thirty-six (34.6%) infants had 38 rehospitalizations due to RSV infection, with two patients experiencing reinfection; the first occurred 2 months following the original RSV infection, and the second occurred 12 months after the first infection. Infants with RSV-related hospitalization had a mean length of stay of 9.1 days and a mean lower respiratory illness/infection score of 3.3; this compares with 8.2 days (p=0.205) and a score of 2.1 (p<0.001), respectively, for infants with non-RSV-related respiratory illness. Five (13.9%) infants were admitted to the intensive care unit and two (5.6%) needed mechanical ventilation.

The overall rate of hospitalization due to RSV for both seasons was 4.5% (36/801), and for infants aged 5 months and younger it was 5.7% (24/423). Significant differences were found between seasons (3.9 vs. 7.8%, p=0.042). The seasonal distribution is shown in Fig. 1. Risk factors for RSV-related hospitalization were discharge between the months of October and December (p=0.016), date of birth between 1 June and 31 October 2002 (p=0.044), and neurological disease (p=0.036). In the multivariate analysis model, neurological disease doubled the risk for rehospitalization due to RSV infection (OR, 2.157; 95% CI, 0.770-5.247).

Palivizumab injections were given to 238 (29.7%) infants with a mean number of 2.5±1.6 injections per patient and a range of 1–7 injections. Prophylaxis was adequate with regard to the month of discharge and the usual duration of the season in 90 of 238 (37.8%) infants. Most infants with inadequate prophylaxis received only one injection before discharge from the neonatal intensive care unit, and due to refusal by the local insurance companies, no further injections were administered at home. Three of 90 (3.3%) infants with adequate palivizumab prophylaxis had RSV-related rehospitalization compared to 12 of 148 (8.1%) with inadequate prophylaxis (p=0.07). Rates of bronchopulmonary dysplasia and neurological disease were significantly higher in the group with adequate prophylaxis compared with inadequate prophylaxis (15.6 and 18.9% vs. 7.3 and 8.8%; p=0.014 and 0.003, respectively). The total group of infants having received palivizumab had a lower mean gestational age (30.3 vs. 30.9 weeks, p<0.001) and birth weight (1,352 vs. 1,574 g, p<0.001) and higher rates of bronchopulmonary dysplasia (10.1 vs. 1.6%, p<0.001) and multiple births (36.6 vs. 28.6%, p=0.012).

This large national observational cohort study included approximately 60–70% of all infants with a gestational age of 29-32 weeks born during the study period in Austria. The overall rate of RSV-related rehospitalization was 4.5%,

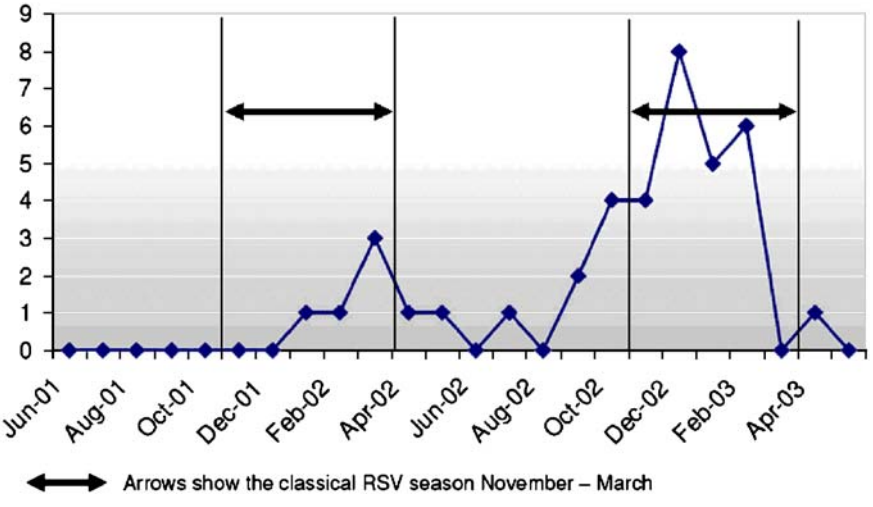

Fig. 1 Seasonal distribution of RSV hospitalizations (n=38) in premature infants of 29–32 weeks' gestational age between 1 June 2001 and 1 June 2003

and this figure increased up to 7.8% depending on the season and date of birth. The Munich RSV study group [6] previously reported a comparable incidence of 5.2%, which would have changed to 6.7% assuming that 63% of all hospitalized respiratory infections were caused by RSV. Rates of RSV-related rehospitalization in this group of preterm infants (gestational age, 29–32 weeks) without bronchopulmonary dysplasia range between 7.6 and 12.9% [7]. It has also been demonstrated that neurological and neuromuscular diseases are associated with a high risk of hospitalization due to severe RSV infection [8]. Missing or delayed palivizumab injections have been shown to increase the incidence of RSV-related hospitalization significantly, from 2.4 to 4.4%, and the interval between the first and second injection has been identified as a high-risk period [9]. In different populations, up to 68% of infants have had palivizumab concentrations below the optimal serum concentration of $\geq$ 40 μg/ml 20–30 days after the first dose [10]. The high number of inadequate or incomplete courses of palivizumab prophylaxis administered in our observational study indicates further efforts are required in order to improve compliance and to educate parents, physicians and third-party insurers.

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