Eur J Pediatr (2003) 162: 230–236
DOI 10.1007/s00431-002-1105-7

ORIGINAL PAPER

**Johannes G. Liese · Eva Grill · Birgit Fischer
Irmgard Roeckl-Wiedmann · David Carr
Bernd H. Belohradsky · The Munich RSV Study Group**

Incidence and risk factors of respiratory syncytial virus-related hospitalizations in premature infants in Germany

Received: 21 May 2002 / Revised: 6 August 2002 and 5 September 2002 / Accepted: 4 October 2002 / Published online: 1 March 2003

Abstract Premature infants have an increased risk of developing complicated respiratory syncytial virus (RSV) infections. Epidemiological data on RSV-related hospitalizations are a prerequisite to develop guidelines for the use of preventive measures. The objective of this study was to determine incidence and risk factors of RSV-related rehospitalizations (RSV-RH) of premature infants. We recruited 1,103 infants with a gestational age of less than 35 weeks, primarily admitted to nine neonatologic care units in southern Germany between Nov. 1, 1998 and Oct. 31, 1999. Questionnaires were sent to all parents of infants discharged from neonatal care units to determine the risk of rehospitalization for acute respiratory infections (ARI-RH) and RSV-RH in the 1999-2000 season. The questionnaire response rate was 68.4%. The 717 included infants of the responders had a mean gestational age of 31.6 weeks (Range: 23–35) and a mean birth weight of 1,747 g (range: 430–4,050 g). The risk for an ARI-RH was 10.6% and the risk for RSV-RH 5.2% during the observation period. Premature infants with chronic lung disease (CLD) had a probability of 24.5% for ARI-RH and of 15% for RSV-RH. The following factors were independently associated with an increased risk of RSV-RH: male gender (adjusted Odds-Ratio (OR): 8.7; 95% confidence interval (CI): 2.6–29.1), chronic lung disease (OR: 3.99; 95%CI: 1.4–11.2), discharge between October and December (OR: 2.1; 95%CI: 0.99–4.4), day-care attendance of siblings (OR: 3.9; 95%CI: 1.9–8.3). *Conclusions*: The risk for RSV rehospitalization among premature infants discharged from neonatal care facilities in southern Germany was low. Additional risk factors and high costs of prophylaxis have to be considered when infants are selected for RSV prophylaxis using monoclonal antibodies.

Keywords Respiratory syncytial virus · Premature infants · Hospitalization · Risk factors · Prevention

Abbreviations *RSV* Respiratory syncytial virus · *ARI* Acute respiratory infection · *RSV-RH* Rehospitalization related to RSV infection · *ARI-RH* Rehospitalization related to acute respiratory infection · *CLD* Chronic lung disease · *OR* Odds-Ratio · *95% CI* 95% confidence interval · *GA* Gestational age · *NICU* Neonatal intensive care unit · *PDA* Patent ductus arteriosus

The study was supported by an unrestricted grant from Abbott Laboratories, Germany

Members of the Munich RSV Study group: Münch G, Simbruner G, Universitäts-Kinderklinik im Dr. von Haunerschen Kinderspital, Ludwig-Maximilians-Universität München, Germany; Küster H, Lipowsky G, 1.Universitäts-Frauenklinik, Ludwig-Maximilians-Universität, München, Germany; Schulze A, Genzel O, Klinikum Großhadern, Ludwig-Maximilians-Universität, München, Germany; Roos R, Grimberg B, Kinderklinik im Städtisches Krankenhaus Harlaching, München, Germany; Zimmermann A, Klinkum Rechts der Isar, Technische Universität, München, Germany; Engelsberger I, Peters J, Kinderklinik Schwabing, Technische Universität, München, Germany; Kumlien B, Daunderer, Kinderklinik an der Lachnerstraße, München , Germany; John W, Peller P, Kinderklinik Klinikum Rosenheim, Germany; v. Andrian HC, Schenk W, Klinikum Augsburg, Germany

J.G. Liese (✉) · B. Fischer · D. Carr · B.H. Belohradsky
University Children's Hospital Munich,
Ludwig-Maximilians-Universität,
Lindwurmstr. 4, 80337 München, Germany
Tel.: +49-89-51602811 or +49-89-51603120
Fax: +49-89-51602951

E. Grill · I. Roeckl-Wiedmann
Institute of Medical Informatics,
Biometry and Epidemiology;
Ludwig-Maximilians-Universität, Germany

The Munich RSV Study Group
University Children's Hospital Munich,
Ludwig-Maximilians-Universität,
Lindwurmstr. 4, 80337 München, Germany

Introduction

Premature infants have an increased risk of developing complicated respiratory syncytial virus (RSV) infections [11]. The reported risk of RSV rehospitalization (RSV-RH) in preterm infants after discharge from primary neonatal care ranges between 2.7% and 37% [5, 10, 15,

20, 26, 29]. This wide range can primarily be explained by differences between the populations studied and the time when the study was performed, since a tendency to lower RSV-RH rates was observed in more recent reports [15, 20, 21, 30]. The Impact study, a double-blind, placebo-controlled trial, showed that prophylaxis with the monoclonal antibody palivizumab (Synagis, MedImmune Inc./Abbott Laboratories) in preterm infants with and without chronic lung disease (CLD) can reduce RSV-RH by about 55% [25]. The greatest reduction (78%), however, was found in preterm infants without CLD born at less than 35 weeks' gestational age (GA), whereas preterm infants with CLD demonstrated a smaller reduction of RSV-RH (39%). No reduction was found in the admission rate to intensive-care units, in the requirement of mechanical ventilation, or in the mortality from RSV infection. Nevertheless, the guideline of the American Academy of Pediatrics suggested RSV immunoglobulin (RSV-IG) prophylaxis in a wide range of preterm infants with different underlying conditions [1]. Between 1999 and 2000, palivizumab was approved in several European countries, and the AAP guidelines were adopted without major modifications [4, 8, 9]. However, prophylaxis with monoclonal antibodies is costly, and there is subsequently a continuing discussion about which preterm infants should receive RSV-IG prophylaxis [12, 13, 16, 23, 28]. Furthermore, most published guidelines suggested that the decision should be made on the basis of local RSV rehospitalization data, thus acknowledging the fact that there might be considerable variation in RSV-RH in different populations due to socio-demographic differences. There are currently very limited data on the risk of RSV-RH in Germany, which makes it difficult to assess the potential impact of RSV prophylaxis with palivizumab. We carried out a population-based cohort study in southern Germany to determine incidence and risk factors of RSV-RH to help refine guidelines for the use of preventive measures against RSV infections.

Methods

Study design

The population-based cohort consisted of all neonates born at ≤ 35 weeks' gestation and admitted to one of nine neonatal units in southern Germany. The eligibility criteria for entry into the study consisted of primary admission in one of the nine participating neonatal intensive care units (NICU) between Nov. 1, 1998 and Oct. 31, 1999; gestational age ≤ 35 weeks; discharge alive from NICU before May 30, 2000, and completed medical documentation of primary hospitalization in NICU from computerized databases or medical discharge letters. The study protocol and the questionnaire were reviewed by the ethical board of the medical faculty of the Ludwig-Maximilians-Universität, Munich, Germany, and by the delegate for data protection of the Bavarian government. Informed consent was obtained from all parents or guardians of infants included in the analyses.

Gestational age, birth weight, gender, presence of multiple gestation, dates of primary hospital admission and discharge, length of oxygen and ventilator therapies in the NICU, and presence of CLD (defined as oxygen requirements beyond 36 weeks post-conceptual age), chronic heart disease, or neurological diseases were obtained for all children. The study population covered about 22% of all preterm infants ≤ 35 weeks gestational age (wGA) born in Bavaria, a state with 12.1 million inhabitants and 123,000 yearly live births. Considering baseline risk factors, such as gestational age, birth weight, and main diagnoses of premature infants, this cohort represented the spectrum of premature infants in Germany and Europe to a very high degree [18].

To determine the probability of rehospitalization for acute respiratory infections (ARI-RH) after discharge from primary neonatal care, questionnaires were sent out to all parents in August 2000**.** Parents were asked whether their child had been hospitalized between the date of discharge from primary neonatal care and May 30, 2000. The questionnaire contained questions regarding the presence of any respiratory symptoms at the time of secondary hospitalization, concerning prophylactic treatment with monoclonal antibodies against RSV, breast-feeding of the child, number of siblings, day-care attendance of the child and its siblings, family size, presence of allergic diseases in the family, and presence of smokers in the family. Written informed consent was obtained from parents for all study subjects. In November 2000, the questionnaire was sent once again to those parents who had not responded to the first questionnaire. For all children for whom rehospitalization had been reported by the parents, detailed medical documentation and discharge letters were obtained from the hospitals. Patients were classified as having ARI-RH when at least one of the following symptoms or diagnoses was documented at the time of hospital admission: cough, rhinitis, dyspnea, tachypnea, conjunctivitis, otitis, bronchitis, obstructive bronchitis, bronchiolitis, pneumonia, upper or lower respiratory tract infection. Definite RSV-RH was assumed for all patients with ARI-RH, who had been hospitalized between October and May and had laboratory confirmation via a positive direct RSV antigen test using either an enzyme-linked immunosorbent assay (Directigen RSV, Becton-Dickinson, Sparks, Md., USA) or an immunofluorescence technique (BioMerieux, Marcy l'Etoile, France). RSV tests, however, were not regularly performed in all hospitals where infants had been readmitted for ARI-RH. Therefore, children were classified as having a probable rehospitalization due to RSV infection, if they had been hospitalized between October and May with such clinical diagnoses typical for RSV infection as acute bronchitis, bronchiolitis, obstructive bronchitis, pneumonia, or apnea. The relatively broad period from October to May was chosen in accordance with the distribution of RSV cases diagnosed in a 7-year period from 1994–2001 in the microbiologic laboratory at the university children's hospital in Munich, Germany, where 83% of RSV cases occurred between January and April and 11.4% between October and December. Only community-acquired RSV infections were included in the analyses. Infants with suspected nosocomial RSV-infection who developed clinical respiratory symptoms or a positive RSV antigen test after day 3 of hospitalization were not included. Unless otherwise indicated, all analyses refer to combined definite and probable RSV rehospitalizations. Length of hospital stay, clinical picture, complications, and therapy were documented for all patients with probable or definite RSV-RH.

Statistical analyses

The probability or risk of RSV-RH was calculated as the percentage of infants of the cohort who were admitted for RSV-RH. The length of possible RSV exposure after primary hospital discharge, however, varied among infants, given that their discharge from primary neonatal care occurred at different times throughout the year and the RSV season. Therefore, the incidence rate of RSV-RH was also calculated. The numerator was the number of new RSV cases during the RSV season 1998-1999 and 1999-2000. The denominator was calculated as the sum of person-months that each infant was at a risk of developing RSV disease during the RSV seasons studied. Univariate analyses were conducted to assess whether probable or definite RSV-RH were associated with any of the measured demographic variables and medical risk factors.

Nonparametric comparisons between groups were done by the chi-square test and Fisher exact test, continuous variables were compared using the Student's t-test or the Mann-Whitney U test. Those variables with a p-value < 0.2 were included as possible predictors in the modeling procedure. Multivariate analyses using logistic regression with backward selection were carried out to assess the independent influence of the different risk factors. For logistic regression analyses, twin and triplet births were considered as independent observations, as has been done in all other published RSV cohort studies using regression analyses [5, 15, 20, 24, 27]. Separate explorative analyses showed, in terms of the observed risk factors, that it made little or no difference whether twins and triplets were included as independent observations or not. For all statistical tests, a level of significance of 0.05 was used.

Results

Cohort characteristics

A total of 1,103 infants of ≤ 35 weeks' gestation were enrolled, and questionnaires were sent out to their parents. Completed questionnaires were available for 754 infants (68.4%). Baseline risk factors present at discharge from primary neonatal care were compared between the 754 responders and the 349 infants making up the non-responder group. There were no statistically significant differences for gestational age, birth weight, requirement for oxygen substitution, and presence of CLD or any cardiac, endocrinological, or metabolic abnormalities. Significantly more prevalent among responders versus non-responders were: requirement of mechanical ventilation (28.9% vs. 23.2%; $p = 0.014$), surfactant deficiency syndrome (6.4% vs. 2.9%; $p = 0.032$), intracranial hemorrhage ($p = 0.039$), necrotizing enterocolitis (9.7% vs. 5.4%; $p = 0.031$), retinopathy (13.7% vs. 9.2%; $p = 0.038$) and nosocomial RSV infection during primary neonatal care (1.9% vs. 0.3%; $p = 0.047$). In contrast, stenosis of the pulmonal valve was diagnosed significantly more often in non-responders (4.3% vs. 1.2%; P = 0.003).

Of the 754 responder infants, 37 (4.9%) were excluded because of either prophylactic treatment with palivizumab ($n = 35$, 4.6%) or because they had been discharged from the NICU after May 30, 2000 ($n = 2$, 0.3%). Detailed characteristics of the 717 infants included in the final analyses are given in Table 1 and Table 2.

The 35 infants excluded due to prophylaxis with palivizumab showed the following statistically significant differences compared to the infants included in the analysis: they were born at a mean age ± SD of 28.9 ± 3.9 weeks' gestation (range: 23–35) (compared to 31.7 ± 2.9 weeks; $p < 0.001$) and had a mean birth weight ± SD of 1,336 ± 670 g (compared to 1,747 ± 570 g; $p < 0.001$). Among these 35 infants, 45.7% were born at ≤ 28 weeks' gestation, and 40% had a birth weight of less than 1,000 g. Among the infants, 65.7% required intratracheal mechanical ventilation (compared to 26.9%; $p < 0.001$), and a diagnosis for CLD was made in 54.3% (compared to 7.5%; $p < 0.001$), whereas cardiac abnormalities, including patent ductus arteriosus (PDA), were present in 34.3% (compared to 20%; $p = 0.038$).

Rehospitalization risks and severity of illness

Among the 717 infants included, 76 (10.6%) were hospitalized for ARI-RH after their discharge from primary neonatal care and subsequent to May 30, 2000. Thirty-seven (5.2%) were rehospitalized either for definite, laboratory-proven ($n = 13$, 1.8%) or probable ($n = 24$, 3.4%) RSV-RH at an age of 7.4 ± 4.1 months (mean ± SD). Among the 24 infants with probable RSV-RH, 15 were not tested for RSV infection. Nine infants were tested negative but had a definite, documented clinical diagnosis of RSV infection.

The 717 infants analyzed had a mean follow-up period of 280 days (median: 243 days; interquartile range between 25th and 75th percentile: 243–336.5 days).

Applying the individual follow-up period during the RSV season for each child, the incidence rate of RSV-RH was calculated to be 69.8 cases per 1,000 preterm infants per RSV season (October – May).

Table 3 summarizes the probabilities of hospitalization stratified by GA and CLD. Infants with chronic lung disease had the highest probabilities with an ARI-RH of 25% and an RSV-RH of 15.4%. The distribution of RSV-RH rehospitalization extended over the entire surveillance period from October to May, with 29 cases (75.7%) occurring between January and March and one to three cases occurring in each of the other months. The 37 infants with RSV-RH presented with pneumonia with and without clinical signs of obstructive bronchitis (27%); obstructive bronchitis, bronchiolitis, or acute bronchitis (67.6%) or acute upper airway infection (5.4%). The median length of hospital stay for RSV-RH was 8 days (range: 2–48 days; mean ± SD: 11.6 ± 9.6 days). Thirty-one infants (83.7%) were treated in regular pediatric wards, whereas six infants (16.2%) required intensive-care-unit admission for a median duration of 6.5 days (range: 4–8 days; mean ± SD: 6.8 ± 1.5 days).

Treatment during RSV-RH included inhalation therapy in 34 (91.9%) cases, oxygen therapy in 14 (37.8%) cases, inhalative corticosteroids in 19 (51.4%)

Table 1 Demographic characteristics and risk factors for RSV rehospitalization among 717 preterm infants. Continuous variables

Parameter	Mean ± SD	Range
Birth weight, mean ± SD (g)	1,747 ± 570	430–4,050
Gestational age, mean ± SD (g)	32 ± 3	23–35
Mechanical ventilation, intratracheal (days)	3 ± 9	0–87
Oxygen therapy (days)	9 ± 21	0–145

Table 2 Demographic characteristics and risk factors for RSV rehospitalization among 717 preterm infants. Dichotomous variables

Parameter	*n* =	%
Gestational age ≤ 28 wGA	114	15.9
Gestational age 29–32 GA	228	31.8
Gestational age 33–35 GA	375	52.3
Gender male	375	52.3
Gender female	342	47.7
Single births	484	67.5
Twin births	189	26.4
Triplet births	44	6.1
Oxygen therapy	305	42.5
Mechanical ventilation	193	26.9
Chronic lung disease	53	7.4
Cardiac abnormalities	125	17.4
Patent ductus arteriosus		12.0
Atrial septal defect		4.2
Ventricular septal defect		2.6
Pulmonary stenosis		1.3
Retinopathy	86	12.0
Hemorrhage (intracranial)	69	9.6
Leukomalacia	12	1.7
Neurological disorders	23	3.2
Necrotizing enterocolitis	18	2.5
Congenital malformation	9	1.3
Metabolic/endocrinologic disorders	3	0.4
Breast-feeding	569	79.5
Siblings in the family	423	59.0
Siblings in day care	198	30.5
Allergic family history (asthma, hay fever, atopy)	340	47.8

cases, systemic corticosteroids in 6 (16.2%) and antibiotics in 23 (62.2%) cases.

Twin infants born at 35 weeks' gestation were rehospitalized at 4 weeks of age with RSV bronchiolitis complicated by secondary bacterial infection with *Streptococcus pneumoniae*. Following respiratory insufficiency and recurrent apnea, both infants required mechanical ventilation for 5 and 6 days, respectively. After a total hospitalization of 16 days, both were discharged without sequelae or complications.

Risk factors for rehospitalization

The distribution of potential risk factors among infants with and without RSV-RH is shown in Table 4. Compared with infants who were not hospitalized for RSV, hospitalized infants were more likely to be male, to have a GA ≤ 28 weeks, to have required intratracheal mechanical ventilation during primary neonatal care, to have been discharged from primary neonatal care between October and December, and to have siblings who visited a day-care unit. In addition, hospitalized children demonstrated a diagnosis of CLD and cardiac abnormalities (including PDA) more frequently.

The final multivariate logistic regression model yielded the following statistically significant independent predictors of RSV-RH: Male gender (Odds Ratio: 8.7; 95% Confidence interval: 2.6–29.1; $p < 0.001$), CLD (OR: 3.99; 1.4–11.2; $p = 0.009$) and day-care attendance of siblings (OR: 3.9; 1.9–8.3; $p < 0.001$). Discharge from neonatal care before the RSV season, between October and December, was associated with a risk for RSV-RH (OR: 2.1; 0.99–4.4; $p = 0.0528$) close to statistical significance. No statistically significant association with the risk of RSV-RH was found for cardiac abnormalities, gestational age, or multiple delivery. Based on a multivariate logistic regression model, predicted probabilities of RSV-RH were calculated for the simultaneous presence of significant risk factors for RSV-RH. The estimated probability of hospitalization varied between 0.4% (95% CI: 0.3%–4.0%), for a preterm infant without risk factors, to a maximum of 53.9% (95%CI: 3.5%–98%), for a male preterm with CLD, with siblings visiting day-care units and a discharge from primary neonatal care between October and December. Detailed cost-effectiveness analyses, according to different risk constellations in the preterms of this study, has been published separately in this journal [22].

Discussion

Prophylactic measures, such as palivizumab, offer a possibility of lowering the risk of RSV-RH in preterm infants [25]. The high costs of palivizumab, its limited efficacy [25], and the high variability of the incidence of RSV-RH [5, 10, 20, 21, 27] have stimulated an ongoing discussion concerning which infants should receive this costly prophylaxis [7, 23, 28]. Current recommendations,

Table 3 Acute respiratory infection (ARI) and respiratory syncytial virus (RSV) rehospitalization rates for 717 preterm infants (PT) related to gestational age (wGA) and chronic lung disease (CLD)

	All PT ≤ 35 wGA	PT with CLD ≤ 35 wGA	PT w/o CLD ≤ 35 wGA	PT w/o CLD ≤ 32 wGA	PT w/o CLD ≤ 28 wGA
	717	53	664	290	66
Rehospitalization for ARI	76 (10.6)	13 (24.5)	63 (9.5)	26 (9.0%)	7 (10.6)
Rehospitalization for RSV	37 (5.2)	8 (15.0)	29 (4.4)	11 (3.8%)	3 (4.5)

Numbers in parentheses (percent)
wGA = weeks' gestational age

Table 4 Distribution of potential risk factors for RSV-related rehospitalization

	No RSV-RH $n = 680$	RSV-RH $n = 37$	p-value[a]
Male gender	342 (50.3)	33 (89.2)	< 0.001
Birth weight < 1,000 g	78 (11.5)	8 (21.6)	0.072
Gestational age ≤ 28 weeks	70 (10.3)	9 (24.3)	0.014
Mechanical ventilation, intratracheal	179 (26.3)	14 (37.8)	0.099
Chronic lung disease	45 (6.6)	8 (21.6)	0.006
Cardiac abnormalities	113 (16.6)	12 (32.4)	0.023
Neurological abnormalities	37 (5.4)	5 (13.5)	0.058
Multiple birth			
Single birth	454 (66.8)	30 (81.1)	0.074
Twin birth	182 (26.8)	7 (18.9)	0.343
Triplet birth	44 (6.5)	0 (0)	0.159
Month of discharge			
January – March	174 (26.4)	6 (17.1)	0.146
April – June	171 (25.9)	6 (17.1)	
July – September	145 (22.0)	8 (22.9)	
October – December	170 (25.8)	15 (42.9)	
Breast-feeding	538 (79.2)	31 (83.8)	
One or more siblings	397(58.4)	26 (70.3)	0.173
Siblings in day-care group	176 (28.7)	22 (61.1)	< 0.001
Family history of allergies	318 (47.1)	22 (59.5)	0.176

[a]Fisher exact test

mostly based on the guidelines of the American Academy of Pediatrics [1], include a broad number of possible indications and have rather increased the uncertainty in this decision process [4, 8, 19]. Most guidelines, however, emphasize the importance of determining regional rehospitalization rates for RSV infections among ex-preterm infants and estimate the local average costs of a hospital admission for RSV [12] to administer palivizumab in a most cost-efficient manner. We carried out the first German population-based study to assess the RSV-RH rate in a cohort of 1,105 preterm infants, recruited in nine neonatal care units in southern Germany.

We contacted the parents of 1,103 preterm infants previously discharged from primary neonatal care by questionnaire to determine the rehospitalizaton rate. We chose this retrospective procedure because a prospective study would have taken much more time, would have been a lot more expensive, and following licensure of palivizumab, its increasing use was expected to exclude an essential part of the cohort at risk for RSV-RH.

As in any retrospective study, we had to consider a possible underreporting of RSV-RH and a misclassification of cases not tested for RSV. A recall bias by parents, however, seems unlikely since the questionnaire asked about any hospitalization with any respiratory signs subsequent to discharge from primary neonatal care, and it may be assumed that parents accurately remember a hospitalization of their young child as an important and severe event. The factor that RSV tests might not been regularly performed in all hospitals, may have resulted in a significant number of missed cases. Therefore, in addition to the cases tested RSV-positive, we also included cases with typical clinical signs during the local RSV season as probable RSV cases. We are confident that the sum of our definite and probable cases approximates the real number of RSV-RH, since the proportion of RSV probable and definite cases from all of our cases with respiratory infection was 49%, which is very close to the reported proportions (50%–63%) of RSV infection among respiratory infections determined in several studies [5, 15, 27]. Even if we were to assume that 63% of all hospitalized respiratory infections were caused by RSV (which would be the highest proportion reported in the literature), the overall incidence of RSV-RH would have changed only from 5.2% to 6.7%.

Detailed clinical information on all 1,103 study subjects permitted us to carefully analyze the possible differences between questionnaire responders and non-responders to detect any selection bias. Both groups were very similar with regard to GA and birth weight, and most other known risk factors. However, the proportion of infants in the responder group with mechanical ventilation, necrotizing enterocolitis, intracranial hemorrhage, and retinopathy was slightly larger than in the non-responder group. These patients might be considered to have a slightly higher risk of RSV-RH, thus resulting in an overestimation of the true RSV-RH risk, which might have been observed in the entire cohort including the non-responders. On the other hand, two factors might account for a possible underestimation of the true rehospitalization risk. First, we were not able to assess whether non-responders had a lower socioeconomic status than responders, a factor possibly associated with risk of RSV rehospitalization. Additionally, the exclusion of 35 infants receiving palivizumab may have resulted in an underestimation of the true hospitalization risk, since 54.3% of the 35 infants who received palivizumab had CLD. Even assuming a probability of rehospitalization of 15.4% for all 35 excluded infants, as we found for infants with CLD, the overall rehospitalization risk in the entire cohort would have only increased by 0.4% to a level of 5.6%.

We found an overall risk of 5.2% for RSV-related rehospitalizations in all preterms with ≤ 35 weeks' GA. Reported hospitalization risks due to RSV infections in premature infants with and without CLD range from 2.7% to 37% [5, 10, 20, 21, 27]. This wide range may be explained by differences in the populations studied with regard to such underlying medical conditions as cardiac and pulmonary problems, differences in the socioeconomic status as well as in the virulence and seasonal epidemic variations of regional RSV strains. There has been a clear trend toward lower incidences of RSV-RH evident in recent years [28].

In Germany, epidemiological data on the incidence of RSV in premature infants is limited. A population-based study by Weigl et al. performed in a northern region of Germany estimated the cumulative incidence of RSV-RH in infants to be 1.2%, regardless of prematurity [30]. In a retrospective study by Berner et al. [3], based on the charts of a university pediatric hospital, 8.9% of preterm infants of < 37 weeks' gestation experienced RSV-RH.

Our rehospitalization risk of 5.2% is close to that of recent similar European studies: two from England reported risks of 6.2% [6] and 4% [27], and one from the Netherlands 3.6% and 7.2% for premature infants of 32–36 weeks and less than 32 weeks of age gestation, respectively [21]. A higher incidence of 13.4% was reported from Spain [5], indicating possible differences in criteria for hospital admission, in the virulence of the RSV strains, or in the socio-demographic composition of the cohorts. Lower rehospitalization risks of 3.2% [15] and 2.7% [20] were reported from two recent U.S. studies. The risk of hospitalization for untreated preterm infants in the Impact-RSV Study was 10.4%, and, therefore, clearly higher than in our study [25]. It has to be emphasized that the Impact study group is a non-random cohort of preterm infants, where preterm infants with CLD were included deliberately. In comparison to our population-based cohort, 46.8% of the infants recruited had a diagnosis of CLD, which contrasts with the 7.4% seen in our cohort. The greater risk of preterm infants with CLD may be the major reason for the difference in the rehospitalization risks seen between the Impact study and our study.

The population-based method of our study permitted us to calculate the incidence rate of RSV-RH, which was estimated to be 69.8/1,000 preterm infants ≤ 35 GA/season in our cohort. This estimate is in agreement with the incidence rate of 66/1,000 preterm infants ≤ 36 GA/season reported in a population-based study from Denmark [17], a country with a similar socio-demographic, climatic, and geographic structure to that in Germany. For all of Germany, where the average preterm birth cohort (< 2,500 g) approximates 50,000 infants per year, we, therefore, may estimate about 3,500 RSV-RH among preterm infants per year.

The risk of rehospitalization in our study was clearly increased in patients with CLD (15.4%). This is relatively close to the risks for preterm infants with CLD as found in the Impact Study (12.8%) [25], the study of Clark (15.3%) [6], and the study of Joffe (14.5%) [15] (for patients with > 28 days of oxygen therapy).

Interestingly, we found no correlation between GA and risk of RSV-RH, once infants with CLD were excluded. This was confirmed in the logistic regression analysis where gestational age was not a significant predictor of RSV-RH, once CLD, as a risk predictor, was included in the model. This contrasts with most earlier studies and may be related to the limited sample size of our study. Interestingly, the Impact trial, however, also found no association between gestational age and the risk of RSV-RH when they controlled for CLD [25]. Besides CLD, male gender, the presence of siblings who were visiting a day-care group, and discharge from a primary neonatal care unit between October and December before the RSV season, there were other independent, statistically significant risk factors associated with RSV-RH found in our study. Those factors are well known [14]. The risk of hospitalization increased with the presence of more than one factor. Cardiac abnormalities and GA were risk factors with a tendency to be statistically significant. These and other factors, such as parental smoking, a family history of asthma or day-care attendance, were not identified as significant independent predictors of RSV-RH, possibly due to the limited sample size of our study.

Preterm infants with RSV-RH spent a median duration of 8 days in hospital, which is similar to data from some European countries, whereas patients in the U.S., Australia, U.K., and Finland are usually hospitalized for a shorter median time of only 4 days [2]. The intensive-care admission rate of 16.2% and the mechanical ventilation rate of 5.4% are comparable to those in other European [2, 5] and U.S. studies [15, 25]. Interestingly, the only two infants requiring mechanical ventilation were twins of 35 weeks' gestation without underlying chronic conditions, confirming the small risk of complicated RSV infection even in otherwise healthy infants, especially during the first 2 months of life [7]. There were no deaths or ongoing complications from RSV-RH in this cohort.

The low incidence of RSV-RH in this and other recent studies makes it important to carefully consider the cost of RSV-prophylactic measures and risk factors before administering palivizumab. With an incidence of 5.2% RSV-RH in our cohort and an assumed efficacy of palivizumab of 55%, the number needed to treat is 35, which means that it would have been necessary to administer palivizumab to 35 preterm infants to prevent one rehospitalization for RSV. For preterm infants with CLD, 12 infants would have to be treated to prevent one RSV-RH. A detailed cost-effectiveness analysis based on the data of this study has been published separately in this journal [22].

In conclusion, the results from our and other recent studies [6, 7, 15, 27] do not justify the widespread use of palivizumab in preterm infants, as recommended by the American Academy of Pediatrics and others [1, 4, 8, 9]. We would recommend a restricted use of this expensive

medication in preterm infants with a documented diagnosis of CLD for their first RSV season after discharge from primary neonatal care. These infants carry the highest risk, if they are discharged directly before onset of the RSV season and if siblings visiting a day-care group are living in the same household. It should be emphasized that the continuous education of parents and health-care providers of preterm infants with regard to possible preventive hygienic measures should be standard with regard to the period of postneonatal care. The avoidance of RSV exposure of high-risk infants during the RSV period in larger crowds and day-care groups is an important, effective, and cheap measure, which should be adopted for every preterm infant.

References

1. American Academy of Pediatrics Committee (1998) Prevention of respiratory syncytial virus infections: indications for the use of palivizumab and update on the use of RSV-IGIV. American Academy of Pediatrics Committee on Infectious Diseases and Committee of Fetus and Newborn. Pediatrics 102: 1211–1216
2. Behrendt CE, Decker MD, Burch DJ, Watson PH (1998) International variation in the management of infants hospitalized with respiratory syncytial virus. International RSV Study Group. Eur J Pediatr 157: 215–220
3. Berner R, Schwoerer F, Schumacher RF, Meder M, Forster J (2001) Community and nosocomially acquired respiratory syncytial virus infection in a German paediatric hospital from 1988 to 1999. Eur J Pediatr 160: 541–547
4. Carbonell-Estrany X, Giuffre L, Kimpen JL, Adam D, Calerius NH, Devlieger H, Shaw B, Müller W, Ruuskanen O, Cunha O, Meissner HC (1999) Guidelines for the Use of Synagis (Palivizumab), a Humanized Monoclonal Antibody, for the Prevention of Respiratory Syncytial Virus (RSV) Disease in High-Risk Infants: A Consensus Opinion. Infect Med (Supplement) 16: 29–33
5. Carbonell-Estrany X, Quero J (2001) Hospitalization rates for respiratory syncytial virus infection in premature infants born during two consecutive seasons. Pediatr Infect Dis J 20: 874–879
6. Clark SJ, Beresford MW, Subhedar NV, Shaw NJ (2000) Respiratory syncytial virus infection in high risk infants and the potential impact of prophylaxis in a United Kingdom cohort. Arch Dis Child 83: 313–316
7. Duppenthaler A, Gorgievski-Hrisoho M, Aebi C (2001) Regional impact of prophylaxis with the monoclonal antibody palivizumab on hospitalisations for respiratory syncytial virus in infants. Swiss Med Wkly 131: 146–151
8. Forster J (1999) [Practice guideline by the German Society for Pediatric Infectious Diseases with respect to prevention of RSV infections through immunoglobulin administration]. Klin Padiatr 211: 476
9. Giovannini M, Giovannini M, Giuffre L, Marini A, Rondini G, Rossi G, Salvioli GP (1999) Respiratory Syncytial Virus Infections in Children – State of the Art. Neonatologica 13: 89–92
10. Groothuis JR, Gutierrez KM, Lauer BA (1988) Respiratory syncytial virus infection in children with bronchopulmonary dysplasia. Pediatrics 82: 199–203
11. Hall C (1998) Respiratory Syncytial Virus. In: Feign RD CJ (ed.) Textbook of Pediatric Infectious Diseases. No. 4 ed. W.B.Saunders, Philadelphia, pp 2084–2111
12. Hall CB, Stevens TP, Swantz RJ, Sinkin RA, McBride JT (1999) Development of local guidelines for prevention of respiratory syncytial viral infections. Pediatr Infect Dis J 18: 850–853
13. Hashmi NA, Cosgrove JF, MacMahon P (2000) Prophylaxis in RSV infection (Palivizumab)–is it worthwhile? Ir Med J 93: 284
14. Holberg CJ, Wright AL, Martinez FD, Ray CG, Taussig LM, Lebowitz MD (1991) Risk factors for respiratory syncytial virus-associated lower respiratory illnesses in the first year of life. Am J Epidemiol 133: 1135–1151
15. Joffe S, Escobar GJ, Black SB, Armstrong MA, Lieu TA (1999) Rehospitalization for respiratory syncytial virus among premature infants. Pediatrics 104: 894–899
16. Kneyber MC, Moll HA, de Groot R (2000) Treatment and prevention of respiratory syncytial virus infection. Eur J Pediatr 159: 399–411
17. Kristensen K, Dahm T, Frederiksen PS, Ibsen J, Iyore E, Jensen AM, Kjaer BB, Olofsson K, Pedersen P, Poulsen S (1998) Epidemiology of respiratory syncytial virus infection requiring hospitalization in East Denmark. Pediatr Infect Dis J 17: 996–1000
18. Lack N, Zukunft E (2001) Qualitätssicherung Neonatologie – Ergebnisse 1999. In: Arbeitsgemeinschaft der Krankenkassenverbaende in Bayern BL, editor. Qualitätsbericht – Krankenhaus Bayern 1999/2000. Bayerische Arbeitsgemeinschaft für Qualitaetssicherung in der stationaeren Vorsorge, München, pp 41–62
19. Marini A (2000) Recommendations for the prevention of Respiratory Syncytial Virus Disease. Riv Ital Pediatr (Italian Journal of Pediatrics) 26: 379–381
20. Nachman SA, Navaie-Waliser M, Qureshi MZ (1997) Rehospitalization with respiratory syncytial virus after neonatal intensive care unit discharge: A 3-year follow-up. Pediatrics 100: E8
21. Rietveld E HM, Steyerberg EW, Polder J, de Groot R, Moll HA. Variability of the Incidence of Hospitalisation caused by Infection with Respiratory Syncytial Virus. In: 19th Annual Meeting of the European Society for Paediatric Infectious Diseases; 2001; Istanbul, Turkey, March 26–28, 2001; 2001. p 98
22. Roeckl-Wiedmann I, Liese JG, Grill E, Fischer B, Carr D, Belohradsky BH (2003) Economic evaluation of possible prevention of RSV-related hospitalizations in premature infants in Germany. Eur J Pediatr, DOI 10.1007/s00431-002-1106-6
23. Sharland M, Bedford-Russell A (2001) Preventing respiratory syncytial virus bronchiolitis. BMJ 322: 62–63
24. Stevens TP, Sinkin RA, Hall CB, Maniscalco WM, McConnochie KM (2000) Respiratory syncytial virus and premature infants born at 32 weeks' gestation or earlier: hospitalization and economic implications of prophylaxis. Arch Pediatr Adolesc Med 154: 55–61
25. The IMpact-RSV Study Group (1998) Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. Pediatrics 102: 531–537
26. The PREVENT Study Group (1997) Reduction of respiratory syncytial virus hospitalization among premature infants and infants with bronchopulmonary dysplasia using respiratory syncytial virus immune globulin prophylaxis. Pediatrics 99: 93–99
27. Thomas M, Bedford-Russell A, Sharland M (2000) Hospitalisation for RSV infection in ex-preterm infants: implications for use of RSV immune globulin. Arch Dis Child 83: 122–127
28. Thomas M, Bedford-Russell A, Sharland M (2000) Prevention of respiratory syncytial virus infection with palivizumab. Monaldi Arch Chest Dis 55: 333–338
29. Wang EE, Law BJ, Robinson JL, Dobson S, al Jumaah S, Stephens D, Boucher FD, McDonald J, Mitchell I, MacDonald NE (1997) PICNIC (Pediatric Investigators Collaborative Network on Infections in Canada) study of the role of age and respiratory syncytial virus neutralizing antibody on respiratory syncytial virus illness in patients with underlying heart or lung disease. Pediatrics 99: E9
30. Weigl JA, Puppe W, Schmitt HJ (2001) Incidence of respiratory syncytial virus-positive hospitalizations in Germany. Eur J Clin Microbiol Infect Dis 20: 452–459