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ORIGINAL PAPER

Respiratory syncytial virus infection in 406 hospitalized premature infants: results from a prospective German multicentre database

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Abstract Premature birth, chronic lung disease of prematurity (CLD), congenital heart disease and immunodeficiency predispose to a higher morbidity and mortality in respiratory syncytial virus (RSV) infection. This study describes the preterms hospitalised with RSV infection from the prospective German DSM RSV Paed database. The DMS RSV Paed database was designed for the prospective multicentre documentation and analysis of clinically relevant aspects of the management of inpatients with RSV infection. This study covers six consecutive RSV seasons (1999–2005); the surveillance took place in 14 paediatric hospitals in Germany. Of the 1,568 prospectively documented RSV infections, 26% (n=406) were observed in preterms [vs. 1,162 children born at term (74%)] and 3% (n=50) had CLD, of which 49 had received treatment in the last 6 months ('CLDplus'). A significantly higher proportion in the preterm group had congenital heart disease, nosocomial infection, and neuromuscular impairment. There were significantly more children older than 24 months in the preterm group. The attributable mortality was 0.2% (n=2) in children born at term vs. 1.2% (n=5) in the preterm group (p=0.015) [preterm plus CLD 8.0% (n=4 of 50); McIntosh grade 1, 8.6% (n=3 of 35) and McIntosh Grade 4, 15% (n=3 of 20)]. Eight patients were categorized

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as ‘palivizumab failures’. In the multivariate analysis, premature birth, CLD_{plus}, and nosocomial infection were significantly and independently associated with the combined outcome ‘complicated course of disease’. In conclusion, this is the first prospective multicentre study from Germany that confirms the increased risk for severe RSV disease in preterms, in particular in those with CLD treated in the last 6 months before the onset of the infection. From the perspective of our results, the statements of the German Society of Paediatric Infectious Diseases considering the use of passive immunisation (2003) seem reasonable.

Keywords Respiratory syncytial virus · Preterm infants · Nosocomial infection · Illness severity · Palivizumab

Abbreviations

AAP	American Academy of Paediatrics
CG	control group
CHD	congenital heart disease
CLD	chronic lung disease of prematurity
CLD_{plus}	CLD with treatment within the last 6 months
CPAP	continuous positive airway pressure
DSM RSV Paed	database for the inpatient management of RSV-infected children
NI	nosocomial infection
NPA	nasopharyngeal aspirate
PT	preterm (gestational age at birth <37 weeks)
RSV	respiratory syncytial virus
RTI	respiratory tract infection

Introduction

Respiratory syncytial virus (RSV) is the single most prevalent aetiologic agent in paediatric viral respiratory tract infection (RTI) [6, 30]. RSV is responsible for the majority of episodes of acute wheezing triggered by infection [23], bronchiolitis [15], and pneumonia [28] predominantly during the first 24 months of life. About 1–2% of all RSV-infected children require hospital care. The RSV-related hospitalisation rate and the risk of severe complications are increased in prematurely born infants with chronic lung disease (CLD) [29] and in children with hemodynamically relevant congenital heart disease (CHD) [8, 14], other forms of chronic lung disease, or severe neuromuscular impairment [4, 31]. Forster and coworkers estimated (95% confidence interval) a total of 26,524 (23,812–29,432) RSV-related hospitalisations per year in children under 3 years of age in Germany (i.e., 38% of all paediatric hospitalisations for viral lower respiratory tract infection) [16]. The same group calculated €2,772 as the median total cost per hospitalised RSV infection [10, 13, 43]. Others recently calculated even higher costs [37].

Specific therapeutic agents with proven efficacy against RSV are still not available [6, 15]. Meticulous hand hygiene after patient contact together with other barrier precautions are considered to be of utmost importance for the prevention of nosocomial transmission [41, 45].

A specific software tool developed at our institution for the targeted surveillance of hospitalised RSV-infected patients (database for the inpatient management of RSV infections in paediatrics: DSM RSV Paed) was available for data entry in 1999. The primary purpose of the surveillance was to facilitate the collection and analysis of detailed information on the population of hospitalised children with RSV infection in Germany. The additional risk factors neuromuscular impairment [50] and nosocomial RSV infection (Simon et al.; submitted) have been analysed in detail in separate publications.

Materials and methods

Inclusion criteria, surveillance approach, and ethics

All inpatients treated for at least 24 h with a virologically confirmed RSV infection were included irrespective of age, underlying illness, and other comorbidities. Positive RSV results by antigen detection, cell culture methods, or PCR testing were reported within a few hours to the attending physicians. The prospective surveillance period covered 6 months of each year (1 November–30 April). For the primary data collection it did not matter whether the RSV infection had been acquired as an outpatient or in the hospital. A standardised set of 85 clinical and laboratory items was extracted from the files, controlled by a neonatologist, and entered into the DSM RSV Paed database.

All radiological diagnoses were confirmed by a paediatric radiologist. The study protocol was approved by the local study review board and ethics committee; informed consent of the parents or legal guardians was given for the data management.

Definitions

Premature birth was considered to be birth before 37 weeks of gestation. Chronic lung disease in premature infants was defined as the persistent need for supplemental oxygen at a gestational age of 36 weeks and characteristic findings in the chest radiography. A prematurely born patient with ‘CLDplus’ had received oxygen or another specific treatment of his CLD in the last 6 months before the diagnosis of RSV infection [44].

The clinical picture and course (bronchitis, bronchiolitis, central pneumonia, lobar pneumonia, respiratory failure, etc.) were summarised in a final clinical diagnosis by one of the attending physicians who had reviewed the whole episode. A lower respiratory tract infection was documented as pneumonia only if chest radiography, interpreted by a paediatric radiologist, had confirmed the clinical diagnosis [11]. In cases of perihilar and peribronchial infiltrates, the diagnosis of central pneumonia was made. In contrast, lobar infiltrates with or without pleural effusion were documented as "other pneumonia". Vital parameters such as the respiratory rate and oxygen saturation were compared with age-related normal values to identify the patients with tachypnea or hypoxaemia [19]. Apnoea was defined as lack of breathing activity for at least 20 s (plus a decrease in oxygen saturation as measured by pulse oximetry on the ward). Hypoxaemia referred to an oxygen saturation <94% (by pulse oximetry; <87% in premature infants before the calculated date of birth), which was the criterion to supplement oxygen; in addition, oxygen was given to all patients with severe tachydyspnoea.

Acute otitis media as a complication, which is sometimes the clinical reason for antimicrobial treatment in RSV-infected patients, was diagnosed only with severe local findings (effusion, inflammation, and bulging of the tympanic membrane in a child with earache).

Taking into account the incubation period, which lasts 3 to 5 days in most patients, a RSV infection was defined as nosocomial if the patient became symptomatic on day 5 or later after admission [25] and community acquired otherwise.

Virological methods

The nasopharyngeal aspirates were collected in a suctioning trap after a nasal washing with 2–5 ml of isotonic NaCl. This procedure yielded a specimen of 2–3 ml [51].

The diagnostic procedure was performed at the discretion of the attending physician, who was instructed by the local investigator to collect at least one nasopharyngeal aspirate sample in each patient with clinical signs of a viral respiratory tract infection (VRTI) during the surveillance period. All RSV infections included were virologically confirmed, but the study protocol did not stipulate the precise method of detection, because this would have been an important obstacle to participation for many centres.

The protocol called for performing the RSV detection assay from these NPA within 6 h after the sampling. The methods involved were antigen detection [36] (membrane-based ELISA, Becton Dickinson, Sparks, MD; alternatively Abbott Test Pack RSV Abbott Laboratories, North Chicago, IL) [2, 42] and cell culture using a permanent permissive monkey kidney-derived cell line (MS cells) [39]. In some participating institutions, RSV infection was detected following an in-house PCR-based diagnostic protocol.

Passive immunisation

The DSM RSV Paed study was neither designed nor conducted to evaluate the efficacy of palivizumab (Synagis; Medimmune) prophylaxis. In addition, the results in the subgroup of patients who received palivizumab do not confirm or exclude any effect of the passive immunoprophylaxis on the clinical course of the illness. These questions can only be investigated in prospectively randomised controlled studies with clinical endpoints or in meticulously planned cohort studies with matched pairs. Nonetheless, we separately looked at the patients who where hospitalised in spite of passive immunisation (4.8% in the verum group of the IMpact trial) [44]. In our analysis, appropriate palivizumab prophylaxis was defined by means of correct dosing (15 mg/kg) and a correct injection interval (last dose given at least 30 days before the diagnosis of RSV infection) in a patient who had received at least two palivizumab injections [53].

Primary aims of the study and study endpoints

This article concentrates on a detailed description of the risk group of 406 preterms in this prospective multicentre database in comparison to the results of 1,162 children born at term.

Primary endpoints of the study were clinical severity of RSV infection and attributable mortality (please refer to the definitions in the next section). Other outcome variables, including the composite measure 'complicated course of infection', are listed in the section 'Statistic analysis' below.

In 1993 McIntosh and coworkers [27] proposed a practical and reasonable grading of illness severity in RSV-infected patients (1=mechanical ventilation due to RSV; 2=supplemental oxygen, no mechanical ventilation; 3=only supportive care, no oxygen required). Patients with nasopharyngeal continuous positive airway pressure support were allocated to grade 2. In addition, grade 4 was suggested from our group [41, 51] for patients who acquired the RSV infection while on mechanical ventilation if this intervention had not been RSV-related. Mortality attributable to RSV infection was calculated as the proportion of events in which the patient died because of RSV-related complications or in which the RSV infection contributed to the adverse clinical course ultimately leading to death.

Statistical analysis

Clinical variables were prematurity, birth before gestational age of 32 and 28 weeks, respectively, birth weight below

Table 1 Basic characteristics and risk factors from medical history. Terms vs. preterms [1,568 inpatients with RSV infection (1999–2005)]

Item	Terms (n=1,162)	Preterms (n=406)	p value
Gender male (%)	683 (58.8)	229 (56.4)	0.40
Age at diagnosis (days)			
Median	159	142	0.423
IQR[a]	64–340	75–288	
Gestational age (weeks)			
Median	39	33	<0.001
IQR[a]	38–40	30–35	
Range	37–43	23–36	
Birth weight (g)			
Median	3,450	1,950	<0.001
IQR[a]	3,080–3,650	1,235–2,490	
Range	1,870–5,280	460–4,000	
Mech. ventilation med. history (%)	91 (7.8)	146 (36.0)	<0.001
Congenital heart disease (%)	61 (5.2)	70 (17.2)	<0.001
NI [c] (%)	40 (3.4)	50 (12.3)	<0.001
NMI+ (%)	43 (3.7)	30 (7.4)	0.002
Patients with >2 risk factors (%)	7 (0.6)	32 (7.9)	<0.001
Length of hospital stay (days) *without NIs*			
Median	6	8	<0.001
IQR	4–9	6–11	
Mortality no. (%)	6 (0.5)	9 (2.2)	0.002
Attributable mortality no. (%)	2 (0.2)	5 (1.2)	p=0.015

[a] Interquartile range: 25th–75th percentile
[b] Chronic lung disease, medical treatment required in the last 6 months
[c] NI = nosocomial infection (definition see text)
[d] NMI = clinically relevant neuromuscular impairment
[e] Duration of viral shedding in patients with repeated testing (once a week)

1,500 g, CLD_{plus} (chronic lung disease of prematurity and treatment within the last 6 months before the diagnosis of the RSV infection) [20, 44], congenital heart disease, and nosocomial infection [41].

The different outcomes were: need for intensive care treatment, need for mechanical ventilation due to RSV infection, radiologically confirmed pneumonia, and death due to RSV infection. The outcome 'complicated course of infection' represents a summary measure incorporating any one of the secondary outcomes defined as detection of apnoea-bradycardia syndrome, radiologically confirmed pneumonia, need for oxygen supply, need for intensive care treatment, need or for intubation (mechanical ventilation), and death due to RSV infection.

Since partial outcome events were rare and clinical variables were non-normally distributed, exact and wherever possible nonparametric methods were used throughout for data description and analysis despite the large sample size [12]. Exact logistic regression was used for both univariate and multivariate analysis of associations of a set of eight predefined clinical variables with four different outcomes. For multivariate analysis, the stepwise forward variable selection procedure was chosen, which starts with a model with only the variable most significantly associated in univariate analysis and resulting in a model incorporating all variables significantly and independently associated with the respective outcome. LogXact-6 was used for exact logistic regression, and StatXact-6 for the remaining exact analyses (both from Cytel Software Corp., Cambridge, MA).

Results

In 6 consecutive RSV seasons a total of 14 paediatric treatment centres (listed in the attachment) participated in the prospective study for a median time of 2 winter seasons. The median number of reported RSV infections per centre was 49.5 (range, 9–138) per season. Infections were confirmed by antigen detection (n=1,540), immune fluorescence (n=11) or cell culture (n=296). Since 2002, two centres detected 73 RSV infections with an in-house PCR-based diagnostic protocol. In total, 1,568 RSV infections

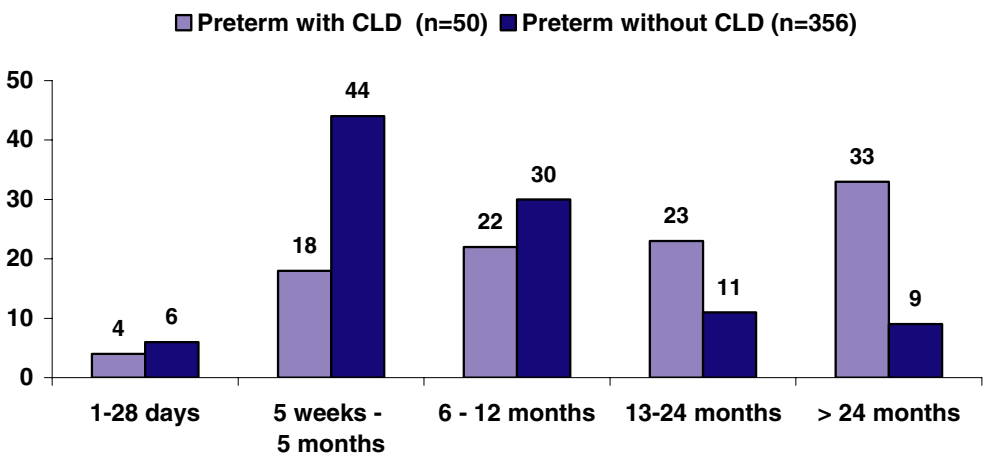

Fig. 1 Age distribution (in %) in prematurely born children with chronic lung disease vs. preterms without CLD [in patients with RSV infection (1999–2005)]

Table 2 Symptoms and complications (in %) in prematurely born children (n=406) vs. children born at term (n=1,162) [proportions in percent; inpatients with RSV- infection (1999–2005)]

Item	Terms (n=1,162)	Prematures (n=406)	p value
General condition (%)			
Good	18	14	
Reduced	78	80	n.s.
Unchanged	4	6	
Airway obstruction	69	59	<0.001
Tachypnoea	44	55	<0.001
Hypoxaemia	30	20	<0.001
Fever	26	20	0.012
Apnoea	7	20	<0.001
Seizure	2	2	n.s.
AOM	6	4	n.s.
ICU admission	8	23	<0.001

AOM = acute otitis media
ICU = intensive care unit

were prospectively documented in 1,541 hospitalised paediatric patients; 27 patients were rehospitalised one to four times during the study after a symptom-free interval (with negative RSV-antigen test) of more than 4 weeks. The number (%) of RSV-infected males and females was 912 (58.1%) and 656 (41.9%), respectively. The following subgroups were differentiated:

– Children with premature birth (gestational age at birth below 37 weeks of gestation) (n=406) vs. children born at term (n=1,162).
– Prematurely born children with (n=50; 12.3%) or without (n=356) chronic lung disease of prematurity (CLD).
– Since 49 of 50 prematurely born children with CLD had received specific treatments (oxygen, diuretics, steroids) in the last 6 months before the onset of the RSV infection, these 49 children were categorised as the 'CLD_{plus}' group.

The basic epidemiological and clinical characteristics of the preterms in direct comparison to the children born at term are shown in Table 1. Very low birth weight (≤1,499 g) was found in 130 (32.0%) and extremely low birth weight (≤999 g) in 62 (15.3%) of all preterms; CLDplus was documented in 49 (12.1%) of all preterms.

A significantly higher proportion in the premature group displayed the following items: mechanical ventilation in medical history, congenital heart disease, nosocomial infection, and neuromuscular impairment. Significantly more preterms had two or more risk factors for a complicated clinical course of the infection. Of all nosocomial infections (n=90), 55% occurred in preterms; 30.6% (15 of 49) of all RSV infections in preterms with CLD_{plus} were nosocomially acquired. When preterms with or without CLD were compared, a significantly higher proportion of the RSV infections in the CLD group was nosocomially acquired (30.0 vs. 9.8%; p<0.001).

While there were no significant differences in the age distribution between terms and preterms (not shown), significantly higher proportions of the preterms with CLD (vs. preterms without CLD) were between 5 weeks and

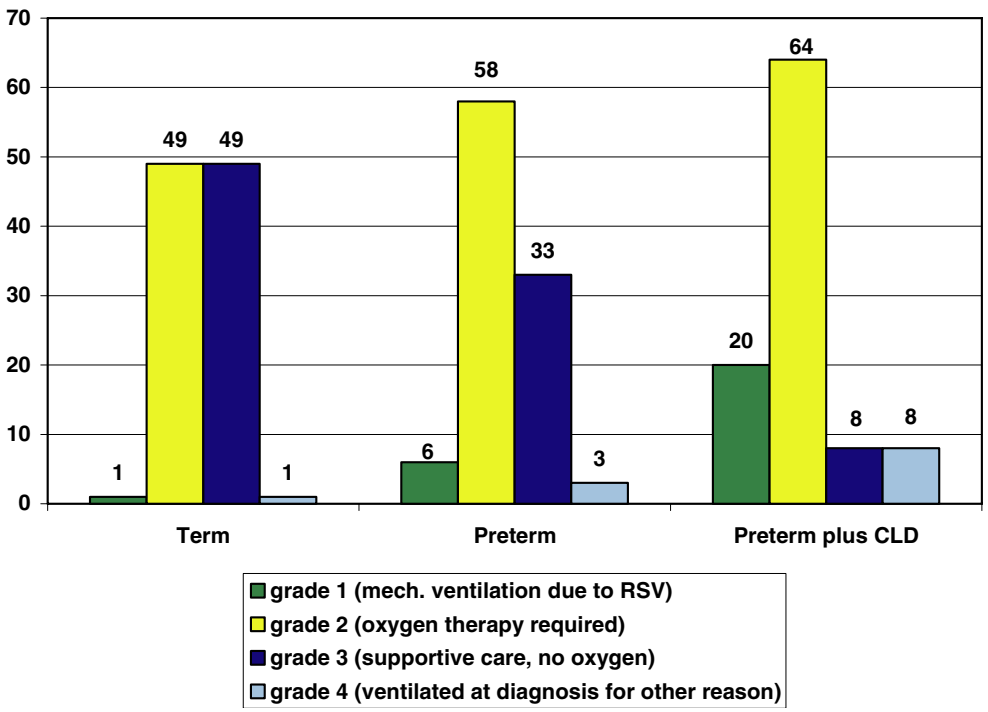

Fig. 2 Modified McIntosh Score (clinical severity grading) in prematurely born children (n=406) vs. children born at term (n=1,162) and in preterms with CLD (n=50) [in patients with RSV infection (1999–2005)] (proportions presented in %)

Table 3 Patients who had received passive immunisation within the last 30 days before rehospitalisation ('palivizumab failures')

Patient	Gender	GA	BW	Age at diagnosis (days)	CLD	Oxygen (for CLD)	Grade 4	Length of stay (days)	Notes of the attending physician	Outcome
1	m	25	550	391	Yes	yes	No	13	s/p severe respiratory distress syndrome, long-term mechanical ventilation, pneumothorax, oesophageal perforation; severe CLD, home oxygen	Death[a]
2	m	30	460	163	Yes	Yes	No	16	s/p SGA preterm, NEC, ileostomasevere apnoea-bradycardia syndrome, hydrocephalus internus. NO- and iloprost treatment for RSV pneumonia.	Death
3	m	39	3,950	618	Yes	Yes	No	4	No specific comments.	Survived
4	m	37	2,390	215	Yes	Yes	Yes	206	No specific comments.	Survived
5	m	32	1,710	207	Yes	Yes	No	5	No specific comments.	Survived
6	m	24	590	418	Yes	Yes	No	30	Dystrophia, oxygen-dependent preterm, long-term mechanical ventilation, spinal muscle atrophy was confirmed after the diagnosis of RSV pneumonia. This resulted in palliative care	Death
7	f	28	1,230	260	Yes	Yes	No	23	High-risk preterm with CLD	Survived
8	f	23	690	510	Yes	No	No	5	High-risk preterm with CLD, severe airway obstruction	Survived

GA = gestational age at birth (weeks); BW = birth weight (g); CLD = chronic lung disease of prematurity; grade 4 = mechanical ventilation at the diagnosis of RSV infection not RSV- related

[a] All deaths were related to the RSV infection. Immunoprophylaxis in patient 7 possibly failed as the result of inappropriate dosing: The patient received in two of three injections only 50 mg instead of 75 mg palivizumab (body weight 5 kg) for unknown reasons.

12 months or older than 24 months (Fig. 1). Without the nosocomially acquired infections in each group, the median length of hospital stay was significantly prolonged in preterms (Table 1).

The median duration of viral shedding was 8 (1–53) days in preterms and 7 (1–41) days in terms, receptively ($p<0.001$). Table 2 compares symptoms and complications in prematurely born children vs. children born at term. The majority of both groups was in a reduced clinical condition at the time of diagnosis, but only 20% of the premature had a temperature >38.5°C. The premature showed significantly more often tachypnoea, apnoea, and need for intensive care admission.

In total, 60% of all premature (vs. 55% of the children born at term; not significant; n.s.) received a chest X-ray examination, which yielded the diagnosis of pneumonia in 46% (vs. 39%; n.s.); 24% of all pneumonias in the preterm group (vs. 19%; n.s.) were 'other pneumonias' with segmental or lobular infiltrates. Comparing preterms with or without CLD, those with CLD had significantly more often a radiologically confirmed pneumonia (46.0% vs. 25.3%; $p=0.02\%$); this referred to a significantly higher proportion of patients with bronchopneumonia in preterms with CLD (30.0% vs. 13.4%; $p=0.003$).

The preterms received significantly more often oxygen (67% vs. 51%; $p<0.001$), antibiotics (51% vs. 35%; $p<0.001$) and systemic steroids (40% vs. 30%; $p<0.001$) related to the RSV infection. Significantly more preterms with CLD received antibiotics compared with preterms without CLD (78.0% vs. 46.6%; $p<0.001$).

Figure 2 illustrates the clinical severity grading (modified McIntosh score) [27, 41] for the different subgroups. The difference between the groups considering the neces-

Table 4 Results of uni- and multivariate logistic regression of clinical variables on course (complicated vs. not)

	Univariate logistic regression		Multivariate logistic regression	
Potential predictor	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Prematurity	2.13 (1.64 to 2.77)	<0.001	1.71 (1.32 to 2.25)	<0.001
Born before gestational week 32	3.45 (2.14 to 5.79)	<0.001	n.s.	–
Born before gestational week 28	6.75 (2.43 to 26.03)	<0.001	n.s.	–
Birth weight <1,500 g	3.41 (2.09 to 5.79)	<0.001	n.s.	–
CLD_{plus}	44.61 (8.10 to infinity)	<0.001	25.03 (4.46 to infinity)	<0.001
Congenital heart disease	1.88 (1.24 to 2.93)	0.0022	n.s.	–

CLD = chronic lung disease of prematurity; CLD_{plus} = CLD with medical treatment in the last 6 months; n.s. = not significant

Table 5 Results of univariate logistic regression of clinical variables on different outcomes, I

	Intensive care		McIntosh 1		McIntosh 1 or 2	
Potential predictor	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Prematurity	3.77 (2.71 to 5.25)	<0.001	7.55 (3.47 to 17.78)	<0.001	1.79 (1.41 to 2.27)	<0.001
Born before gest. week 32	6.87 (4.57 to 10.30)	<0.001	9.77 (4.58 to 20.70)	<0.001	2.22 (1.50 to 3.34)	<0.001
Born before gest. week 28	7.47 (3.92 to 14.16)	<0.001	7.50 (2.41 to 19.78	0.0009	2.29 (1.17 to 4.78)	0.0133
Birth weight <1,500 g	6.17 (4.06 to 9.33)	<0.001	10.45 (4.88 to 22.11)	<0.001	2.04 (1.37 to 3.09)	0.0003
CLD_{plus}	9.85 (5.26 to 18.55)	<0.001	15.23 (6.10 to 35.68)	<0.001	4.57 (2.10 to 11.35)	<0.001
Congenital heart disease	5.39 (3.53 to 8.16)	<0.001	2.84 (1.03 to 6.82)	0.0448	1.38 (0.94 to 2.04)	0.0989

CLD = chronic lung disease of prematurity; CLD_{plus} = CLD with medical treatment in the last 6 months; n.s. = not significant

sity to start a mechanical ventilation related to the RSV infection (grade 1) was significant between children born at term and preterms and furthermore between preterms with and without CLD. The attributable mortality was 0.2% (n=2) in the children born at term group vs. 1.2% (n=5) in the preterm group (p=0.015). This corresponds with the following results for the different subgroups: 8.0% (n=4) of 50 preterm plus CLD patients; 8.6% (n=3) of 35 McIntosh grade 1 patients and 15% (n=3) of 20 McIntosh grade 4 patients.

Palivizumab

In the study population, 45 preterms (2.9%; 11.1% of all preterms included) received at least one dose of palivizumab at any documented time point. Of these patients 21 (47%) received the first dose after admission to the hospital at the discretion of the attending physicians who realised the missing prophylaxis in an eligible patient. The last injection had been delayed for more than 30 days before admission to the hospital (rehospitalisation) in eight patients (18%). Eight patients (18%) had received only one dose before they were readmitted with RSV infection [53]. Taken together, eight patients (18%) who received two (n=4), three (n=3) or four (n=1) intramuscular injections of palivizumab were categorised as 'definite failures'. Details on the patients with palivizumab failure are given in Table 3.

Results of the uni- and the multivariate analysis

The criterion CLD_{plus} showed the strongest association to a complicated clinical course in the univariate analysis (Tables 4, 5, 6, 7 and 8). In multivariate analysis, premature birth and CLD_{plus} were significantly and independently associated with the combined outcome 'complicated course of disease'. Prematurity was an independent predictor in the multivariate analysis of intensive care required, mechanical ventilation due to RSV (McIntosh grade 1), at least oxygen treatment required (McIntosh grade 1 or 2), and of apnoea-bradycardia syndrome related to RSV. CLD_{plus} was an independent predictor of mechanical ventilation due to RSV (McIntosh grade 1), at least oxygen treatment required (McIntosh grade 1 or 2), and of 'pneumonia' related to RSV.

Discussion

This report, extracted from the hitherto largest prospective multicentre clinical database in Germany, confirms the increased risk of hospitalised prematurely born children with RSV infection to experience a complicated severe clinical course. In addition to prematurity (including CLD and CLD_{plus}), a relevant proportion of all preterms showed two or more additional risk factors, such as neuromuscular impairment [31], congenital heart disease [8, 14, 40] and

Table 6 Results of univariate logistic regression of clinical variables on different outcomes, II

	Apnoea bradycardia		Pneumonia		Death due to RSV	
Potential predictor	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Prematurity	3.08 (2.12 to 4.47)	<0.001	1.40 (1.07 to 1.82)	0.0137	2.88 (0.53 to 15.52)	0.2520
Born before gest. week 32	3.65 (2.25 to 5.80)	<0.001	1.90 (1.28 to 2.80)	0.0014	6.37 (0.98 to 33.15)	0.0527
Born before gest. week 28	4.30 (2.03 to 8.63)	0.0002	2.77 (1.46 to 5.19)	0.0016	11.17 (1.07 to 64.70)	0.0439
Birth weight <1,500 g	3.73 (2.28 to 5.96)	<0.001	1.86 (1.24 to 2.76)	0.0027	11.34 (2.09 to 61.65)	0.0049
CLD_{plus}	4.53 (2.19 to 8.92)	0.0001	2.80 (1.50 to 5.18)	0.0011	19.60 (2.96 to 104.3)	0.0029
Congenital heart disease	1.64 (0.89 to 2.85)	0.1131	1.28 (0.83 to 1.94)	0.2724	3.69 (0.36 to 20.92)	0.2782

CLD = chronic lung disease of prematurity; CLD_{plus} = CLD with medical treatment in the last 6 months

Table 7 Results of multivariate logistic regression of clinical variables on different outcomes, I

	Intensive care		McIntosh 1		McIntosh 1 or 2	
Potential predictor	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Prematurity	1.73 (1.08 to 2.72)	0.0218	4.73 (1.96 to 11.94)	0.0003	1.59 (1.24 to 2.05)	0.0002
Born before gest. week 32	2.80 (1.58 to 5.00)	0.0001	n.s.		n.s.	
CLD_{plus}	n.s.		5.42 (2.00 to 14.17)	0.0008	3.18 (1.42 to 8.10)	0.0028
Congenital heart disease	2.97 (1.81 to 4.82)	<0.001	n.s.		n.s.	

nosocomial origin of the infection [10, 18, 21, 22]. Our results underline the indications for passive immunisation stated by the German Society of Paediatric Infectious Diseases (DGPI) in 2003 [17], which were more restrictive than the revised ones of the AAP [3]. The DGPI guideline confined palivizumab use to preterms with CLD_{plus} (up to 24 months) and to preterms with relevant additional risk factors (individual decision of the attending physician; up to 24 months). New detailed German Consensus Guidelines have recently been published (http://www.dgpi.de/pdf/Leitlinie_Palivizumab_27Okt2006.pdf). They consider additional studies on rehospitalisation rates and cost-effectiveness from southern Germany [26, 38]. The data from our study, confirming the increased risk of preterms with 'CLD plus' and with clinically relevant neuromuscular impairment [50], are in accordance with these current recommendations.

A small percentage of all preterms passively immunised with RSV will still be rehospitalised, and some of these children will experience a severe LRTI or will even die because of the infection or its complications [32]. To some extent, this may be explained by the low level of antibodies in the individual preterm infant [53]. It may also be influenced by the pre-existing impaired lung function, which may result in acute clinical deterioration even with an upper respiratory tract infection [7].

There are only very few multicentre trials that have prospectively investigated the clinical course of RSV infection in hospitalised children. Between January 1993 and June 1994, 1,516 hospitalised patients of RSV lower RTI from nine Canadian paediatric tertiary care centres were prospectively entered into the PICNIC-RSV database [48].

The mean length of stay varied among hospitals from 8.6 to 11.8 days in compromised and 4.6 to 6.7 days in patients without underlying diseases; 14–27% of all patients were preterms. There was a pronounced variation among hospitals in receipt of most interventions (bronchodilatators, steroids, antibiotics, ribavirin, PICU admission, and mechanical ventilation) in compromised and previously healthy patients. The same group had published a prospective seven-centre cohort study before that included 689 patients hospitalised with RSV RTI who were younger than 2 years of age, or of any age if they had diseases. The mean hospital stay attributable to respiratory syncytial virus (RSV) was 7 days; 110 patients were admitted to intensive care units, 63 were supported by mechanical ventilation, and 6 patients (0.9%) died [49]. As our data on the age distribution in preterms with CLD demonstrate (Fig. 1), it is not reasonable to exclude children who are older than 24 months from such an analysis. Preterms with CLD were older when they had RSV infection than preterms without CLD. From our data, we can only speculate about the reason for this observation. Is this the case because they get palivizumab or because they are hospitalised longer and therefore are more likely to get RSV in the hospital (see significant difference in terms of NI) compared to preterms without CLD dismissed earlier and getting their RSV infection in the community?

The length of stay for those children with ambulatory acquired RSV infection was within the range of the Canadian results for terms, but not for preterms in our study (Table 1). Unidentified local factors influence the pattern and severity of RSV infection [5] and its management [33]; this may affect the results of multicentre prophylactic and therapeutic studies.

A significantly higher proportion of the preterms in our cohort had to be admitted to the PICU (Table 2). Nonetheless, this subpopulation included 93 patients in each group, respectively. Prais et al. [35] performed a prospective

Table 8 Results of multivariate logistic regression of clinical variables on different outcomes, II

	Apnoea bradycardia		Pneumonia		Death due to RSV	
Potential predictor	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Prematurity	2.80 (1.91 to 4.10)	<0.001	n.s.		n.s.	
CLD_{plus}	n.s.		2.80 (1.50 to 5.18)	0.0011	n.s.	

CLD = chronic lung disease of prematurity; CLD_{plus} = CLD with medical treatment in the last 6 months; n.s. = not significant

national survey before the introduction of palivizumab in which 11 PICUs from tertiary care centres in Israel participated.

One hundred five patients with RSV infection were included in one season; of those, only 30% were preterms. Apnoea was present in 32% of the admitted patients. In the mechanically ventilated group (33 of 105; 31%) 67% were terms as well as 2 of 5 patients who died temporally related to the RSV infection. The authors concluded that most of the infants with severe RSV bronchiolitis who were born at term did not have CLD and were not candidates for RSV prophylaxis with palivizumab.

Since severe bronchitis and bronchiolitis may mimic the clinical picture of pneumonia in particular in infants, a chest radiograph (CXR) should be performed in all hospitalised children with RSV infection if a lower RTI is suspected (respiratory rate, oxygen saturation). Unfortunately, a CXR did not have to be performed in all studies to confirm or exclude 'pneumonia' [9]. RSV is capable of causing pneumonias other than (central) bronchopneumonia even in preterms. The radiological appearance of these lobar or segmental or diffuse pneumonias is highly variable and must not automatically be taken for a bacterial RTI. Nonetheless, due to diagnostic uncertainties it seems reasonable to treat all children with radiologically confirmed 'other pneumonias' initially with an appropriate antibiotic, in particular those admitted to the intensive care unit [46].

Of great concern is the high rate of nosocomial infections [41] in the preterm group, which may result in severe complications, in particular in preterms with severe CLD on prolonged mechanical ventilation or CPAP via a tracheostomy [31] (grade 4) or in postoperative patients [1, 10, 22, 24]. Although preterms with CLD_{plus} face the greatest relative risk, the majority of all patients admitted to the ICU with RSV infection are not candidates for palivizumab prophylaxis [34]. Therefore, clinically more effective alternatives [52] or specific antiviral agents are exigently awaited [47].

Attachment: participating institutions and local investigators

City	Centre	Investigator
Böblingen	Central Hospital Böblingen	Dr. Dieter Klement
Bochum	St. Joseph's Children's Hospital, University of Bochum	Prof. Dr. Christian Rieger, PD Dr. Volker Stephan
Bonn	Children's Hospital Medical Center And Institute for Medical Microbiology, University of Bonn	Dr. med Arne Simon Frau Dr. Wilkesmann Dr. Oliver Schildgen PD Dr. Andreas Müller Dr. Karun Khurana
Datteln	Children's Hospital Datteln, University of Witten Herdecke	Dr. Friedemann Hornschuh
Duisburg	St. Johannis Hospital, Duisburg	Dr. Peter Seiffert Karoline Wadas
Göttingen	Children's Hospital, Georg August University, Göttingen	Prof. Dr. Egbert Herting
Hildesheim	Paediatric Center, St.-Bernward Hospital, Hildesheim	Prof. Dr. Edda Weimann
Lübeck	Children's Hospital, University of Schleswig Holstein, Campus Lübeck	Dr. Thorsten Wygold
Mainz	Children's Hospital Johannes Gutenberg University, Mainz	PD Dr. Wolfgang Kamin
Mannheim	Children's Hospitel, University of Mannheim-Heidelberg	Dr. Angela Süss-Grafeo Prof. Dr. Thomas Schaible
Memmingen	Children's Hospital, Memmingen	Dr. Ralf Pallacks
München	von Haunersches Children's Hospital, University of Munich	PD Dr. Johannes Liese
Oldenburg	Elisabeth Children's Hospital, Oldenburg	Prof. Dr. Jürgen Seidenberg
Salzgitter	Children's Hospital, Klinikum Salzgitter GmbH	Dr. med. Hans U. Peltner

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