

Prednisolone Treatment of Respiratory Syncytial Virus Infection: A Randomized Controlled Trial of 147 Infants

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ABSTRACT. *Objective.* To evaluate the effect of systemic prednisolone as an adjunct to conventional treatment with β 2-agonist, respiratory support, and fluid replacement in hospitalized infants <24 months of age with respiratory syncytial virus (RSV) infection.

Methods. The study was randomized, double-blind, and placebo-controlled. During the winter of 1995–1996, 147 infants <2 years of age, hospitalized with RSV infection, were allocated to treatment with either systemic prednisolone mixture 2 mg/kg daily or placebo for 5 days.

Main Outcome Measures. The acute effect variables were duration of stay in hospital, use of medicine, and supportive measures while in hospital. At follow-up 1 month after discharge, the acute effect variables were duration of illness, start in day care center, morbidity, and use of medicine. At follow-up 1 year after discharge, the acute effect variables were morbidity, use of medicine, and skin prick tests with allergens.

Results. Prednisolone treatment had no effect on any of the outcome measures.

Conclusions. Our randomized prospective study in infants hospitalized with acute RSV infection showed no effect of systemic prednisolone treatment either in the acute state of RSV infection, nor in the follow-up 1 month and 1 year after admission to hospital. We find our results in agreement with the largest studies reported earlier; therefore, corticosteroid, whether by the systemic route or by inhalation, should not be prescribed to infants with RSV infection. *Pediatrics* 1999;104(6). URL: <http://www.pediatrics.org/cgi/content/full/104/6/e77>; *infants, respiratory syncytial virus, prednisolone, corticosteroids, treatment, randomized controlled trial.*

ABBREVIATIONS. RSV, respiratory syncytial virus; IV, intravenous; CPAP, continuous positive airway pressure.

Previous studies have shown that a majority of infants are infected with respiratory syncytial virus (RSV) during their first or second year of life.¹ However, only a minority of these children are admitted to hospital.²

Because of many clinical and presumed patho-

physiological similarities between RSV infection and asthma, corticosteroid has been used widely for treatment of RSV infections.^{3–5} Of the reports of randomized, controlled studies of systemic corticosteroid treatment of RSV infection in infants, 7 have shown conflicting results.^{6–12} However, these studies are not directly comparable because of the differences of diagnostic criteria, exclusion criteria, and measures of effect.

This study investigates the short-term and long-term effects of systemic corticosteroid treatment in a large, unselected group of infants hospitalized with RSV infection.

METHODS

The 3 participating pediatric departments serve the County of Copenhagen and 1 neighboring county with a joint population of ~34 000 infants <2 years of age. A total of 147 hospitalized infants were included prospectively between November 1995 and April 1996.

Inclusion Criteria

Patients <2 years of age hospitalized with respiratory infection and a positive RSV test were included in the study.

Exclusion Criteria

Patients were excluded from the study for any of the following reasons: 1) diseases that contraindicate corticosteroid treatment; 2) corticosteroid treatment within the last month, systemic or local; 3) >48 hours elapsed since the RSV sample was taken; 4) prematurity infants, who at randomization have a gestational age of <40 weeks; 5) communicative problems; or 6) parents not approached because of the absence of a doctor in charge.

Effect Variables

The effect variable included: 1) duration of stay in hospital, duration of illness, and time for start in day care center; 2) use of medicine; 3) supportive measures; 4) morbidity; and 5) a skin prick test.

Study Design

During the winter season (1995–1996), all hospitalized children <2 years of age with symptoms of respiratory infection were examined routinely for RSV in the 3 pediatric departments. The nasopharyngeal secretions were collected and sent in on the morning after the child's admission to hospital. Analysis was by an immunofluorescence test (Merifluor RSV, Meridian, Simoco) in 2 centers and a rapid ELISA assay (Abbott Test Pack; Abbott Laboratories), in the third center. The sensitivity and specificity of both tests range from 80% to 90%.¹

Two clinical microbiology departments performed the analyses. The hospital pharmacy performed the randomization by a computer-generated program in Medstat. Series of 10 patients were allocated randomly to the 2 treatment groups, ensuring equal numbers of patients in each group. All packages of study

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medication (oral mixture and intravenous [IV] formulation for each patient) were prepared and labeled with a study number. The randomization list was concealed until, in May 1997, the study was completed and data analysis had begun.

Informed written consent was obtained from the parents before enrolment of the infants. Included infants were randomly allocated to treatment with either prednisolone hydrate (5 mg/mL) orally or the same volume of quinine hydrochloride (placebo), which has the same bitter taste as prednisolone. Those infants who had an IV line were given methylprednisolone (40 mg/mL) or saline intravenously as 1 daily dose. The first dose of prednisolone or placebo was administered at enrolment in the afternoon, and the subsequent doses were given once daily during the following 4 days at 8 AM. If a patient vomited within 30 minutes, a repeat dose was given. The total treatment period was 5 days. The dose of prednisolone was 2 mg/kg/day. The dose of methylprednisolone was 1.5 mg/kg/day.

The physicians gave their hospitals' routine treatment, with the exception of corticosteroid, at admission and during the stay in hospital in the following 5 days. It included β_2 -agonist inhalation (terbutalin .06 mL/kg or salbutamol .03 mL/kg), respiratory support, fluid replacement, and in some cases antibiotics. Ribavirin and IV immunoglobulin were not used. The routine treatment was recorded before randomization and during the 5 days of experimental treatment.

In hospital the period (in hours) from admission to the time the doctor decided to discharge the child was noted. If infants were discharged before day 5, the parents administered the randomized drugs and filled in a record sheet at home. The parents were asked to record duration of illness, morbidity, and use of medicine (salbutamol, terbutalin, budesonid, fluticasonpropionate) in a special calendar until the clinical follow-up 1 month later. Complication of the calendar was a simple task and needed no special instructions.

The parents received 10 to 11 months after the initial admission a letter and a calendar in which they were asked to record morbidity and use of medicine for 6 weeks preceding the 1-year follow-up. In Denmark, the term asthmatic bronchitis used when infants have recurrent attacks of wheezing. At the clinical follow-up 1 year after discharge (November 1996 to April 1997), a skin test was performed using the prick test method with epicutaneous positive histamine and a negative (saline) control, along with cat, dog, 2 kinds of house dust mite, and milk and egg allergen extracts. A weal diameter of at least 3 mm at 10 minutes was regarded as positive.

Statistical Analysis

Statcon Ltd performed the statistical analysis using the SAS program (SAS Institute, Cary, NC). Wilcoxon's two-sample test and the Fisher's exact test were used for quantitative and qualitative variables, respectively. The survival curves of Fig 1 were calculated by the Kaplan-Meier method and the 2 treatment groups were compared by the log-rank tests or by the proportional-hazards model. The analyses were performed on the total data of all infants, and on 3 subgroups: 1) those infants <6 months of age ($n = 76$); 2) those infants >6 months of age ($n = 69$); and 3) those who either had allergy in the family or had earlier been treated with corticosteroid or β_2 -agonist ($n = 90$). Logistic regression analysis was used to identify risk factors for morbidity after 1 year and to increase the precision of the estimate of the prednisolone effect. The logistic regression analysis was corrected for the effect of other variables such as earlier asthma treatment. Nonsignificant risk factors were eliminated by backward elimination.

RESULTS

Characteristics of the Patients (Tables 1 and 2)

In the study area, 1.4% of all infants <2 years of age were admitted with RSV infection to 1 of the 3 participating centers during the study period (November 1995 to April 1996). Of the 372 eligible infants, 335 were approached, and 147 infants were included (Table 1). A total of 73 infants were randomized to prednisolone and 74 to placebo. Owing to a mistake, 2 patients never received the experimental treatment. None of the infants had underlying medical conditions, such as cystic fibrosis, congenital heart disease, or bronchopulmonary dysplasia. The median age

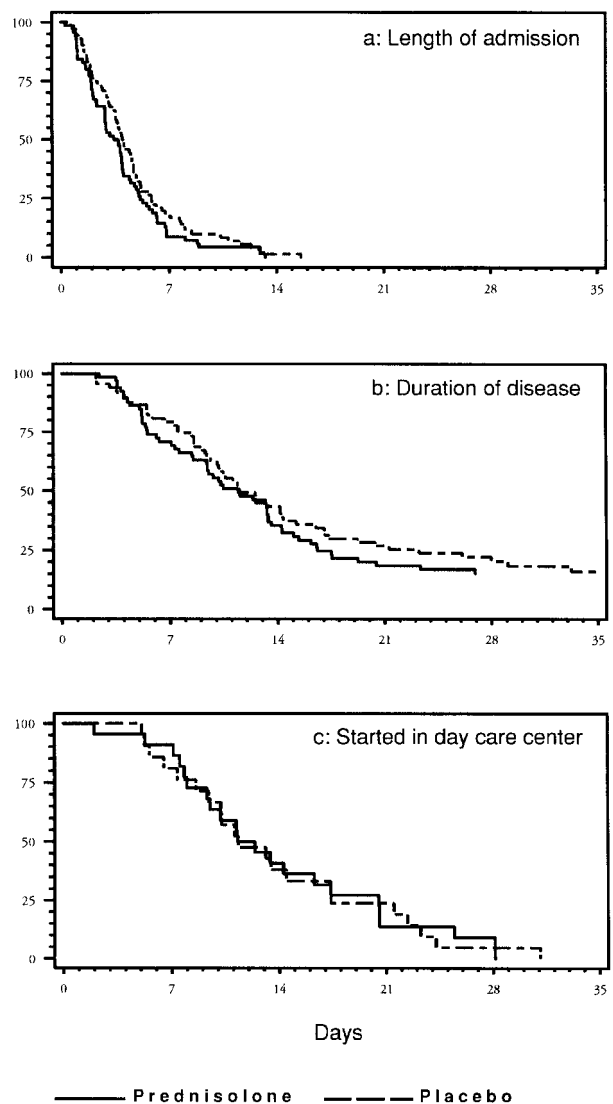


Fig 1. A shows the percentage of infants who are still in hospital \times days after admission. B shows the percentage of infants who are still ill according to the parents' judgment. C shows the percentage of infants not yet back in day nursery. Time zero is at admission to hospital.

was 5.5 months, and 79% were <12 months of age. A total of 24 had respiratory support in the form of oxygen supplementation or nasal continuous positive airway pressure (CPAP) before randomization. There were no statistically significant differences between the 2 groups with regard to any of the variables of Table 2.

A total of 134 infants completed the experimental treatment. Of these, 91 were discharged within the 5-day period of experimental treatment, which was then continued at home with the parents recording the use of β_2 -agonists. A total of 11 patients (7 in the prednisolone group and 4 in the placebo group) did not complete the treatment because of side effects, primarily vomiting (8 patients), which were mild in all cases.

Acute Responses (Table 3; Fig 1)

The treatment with β_2 -agonist, antibiotics, respiratory support, and hydration after the randomization did not differ significantly in the 2 groups. Experimental treatment was given intravenously to 3 of 145 patients, because they were given IV hydration. During the 5 days of experimental treatment, 1 infant was put on a respirator (Table 3). The pattern of hospitalization was very similar in the 2 groups (Fig 1A); the median length of stay was 3.6 days in the prednisolone group and 4 days in the placebo group. The observed difference is not statistically significant (log rank test).

TABLE 1. Infants Hospitalized With RSV Infection During the Study Period, 1995–1996

Approximate number of RSV test performed	1022
Infants <2 years of age with positive RSV-tests	372
Exclusion criterion 6 (doctor not present)	37
Approached	335
Randomized	147
Parents refused	131
Exclusion criteria 1–5	57

Follow-up: One Month After Discharge (Table 3; Fig 1)

A total of 121 infants were seen at the hospital, 15 families were contacted by telephone, and 11 families could not be contacted. During the first month after discharge, no difference between the prednisolone and the placebo groups was seen. The median time from randomization until the parents considered their infants to be completely healthy again was very similar: 11.4 days in the prednisolone group and 11.5 days in the placebo group (Fig 1B), and the time until the infants returned to day nursery was 11.9 and 11.3 days in the prednisolone and placebo groups, respectively (Fig 1C). The number of patients treated with β_2 -agonist or inhaled corticosteroid (asthma treatment) after discharge was almost identical in the 2 groups (Table 3). The frequency of night coughing and the frequency of readmission attributable to respiratory tract infection were also very similar in the 2 groups.

Follow-up: One Year After Discharge (Table 3)

From December 1996 to April 1997, 120 infants were seen at the hospital, 16 families were contacted by telephone, and 11 families could not be contacted. During the 12 months after discharge, there was no difference in morbidity between the prednisolone-treated and placebo-treated groups. At the 1-year follow-up, 60% of the infants had been diagnosed by a doctor as having asthmatic bronchitis at some time after their discharge following RSV infection. In 29 infants otitis media had been diagnosed after discharge. No differences of night coughing and readmission attributable to respiratory tract infection were found between the 2 groups. A skin prick test was performed on 119 children. A positive test result was found in 3 of 58 patients in the prednisolone group and 1 of 61 patients in the placebo group (2 dermatophagoides farinae, 1 dog, and 1 both cat and dog).

Analysis of Subgroups

The analyses of the short-term and long-term effects of prednisolone were repeated on 3 subgroups of infants: 1) those infants <6 months of age ($n = 76$); 2) those infants >6 months of age ($n = 69$); and 3) those who either had a family history of allergy or had received asthma treatment before admission to hospital ($n = 90$). There were no statistical differences in favor of prednisolone in any of the subgroups in any of the tests, and 1 single possible exception in its disfavour: in the subgroup of infants 6–24 months of age, the number of doses of β_2 -agonist was slightly higher in the prednisolone group (median 15 doses) than in the placebo group (median 7; $P = .046$, ie, only just significant at a 5% level). In a fourth subgroup of 15 infants who were treated with CPAP before randomization, we compared the duration of the stay in hospital in the 8 infants who received prednisolone, and the 7 who received placebo. The median duration was 5.6 and 4.7 days, respectively, not statistically significant (Wilcoxon's two-sample test).

Logistic Regression Analysis (Table 4)

Two logistic regression analyses were performed with the purpose of identifying risk factors for respiratory disease at the 1-year follow-up. Odds ratios compare the risks of: 1) having asthma treatment at the 1-year follow-up and 2) being readmitted to hospital for respiratory tract infection within the first year after the admission for the RSV infection, for 2 levels of each risk factor. Asthma treatment before admission was the only risk factor with a significant ($P = .04$) effect on the probability of being in asthma treatment at the one-year follow-up, odds ratio 2.5 ($P = .04$, when all other risk factors are included; $P = .02$, when all other risk factors are eliminated). None of the risk factors influenced the

probability of being readmitted to hospital for respiratory tract disease during the year following RSV infection.

DISCUSSION

This study showed that treatment with systemic prednisolone for 5 days as an adjunct to routine treatment with β_2 -agonist, oxygen, respiratory support, and hydration had effect on neither the short-term nor the long-term course of RSV infection in hospitalized infants <2 years of age.

Earlier randomized, double-blind, placebo-controlled studies have shown conflicting results as to the efficacy of systemic corticosteroid treatment on bronchiolitis and wheezing in infants (Table 5). In 3 studies an effect of corticosteroid treatment was shown,^{10–12} whereas no effect was shown in 4 other studies.^{6–9} Earlier studies differ from ours in a number of respects (Table 5). The proportion with RSV infection varied; the criteria of inclusion varied; and in 6 studies wheezing or bronchiolitis was a requirement and some cases of RSV infection, therefore, were not included.^{6–10,12} Only in 1 study did all included infants have RSV infection.¹¹ In 2 studies infants with earlier episodes of wheezing were excluded.^{7,8} Seriously ill infants who required admission to the intensive care unit also were excluded in 2 of the studies.^{8,12} Only in 1 study were tests of lung function performed.⁹ Some of the studies had a 2- to 4-week follow-up,^{7–9} but none had a long-term follow-up.

Our study differs from the cited studies in the following aspects: 1) all infants with RSV infection ill enough to be hospitalized were eligible; 2) no infant was excluded because of mild or severe illness; 3) all included infants were asked to come for follow-up examinations 1 month and 1 year after admission to hospital; and 4) 10% of the included infants were applied nasal CPAP treatment, this nearly replaced mechanical ventilation.

All the studies cited in Table 5 used clinical scoring and different variables were recorded. The reproducibility of the clinical score was only studied in 2 of the reports in Table 5.^{7,8} We decided against using a clinical score for following reasons: it is difficult to design a study with clinical scoring that is not affected by the treatment given, especially in the form of respiratory support, and clinical scoring is only a proxy variable, the variables of real interest being time to resolution and long-term morbidity.

We believe that the severity of disease in our patients is comparable to that of the other studies cited.^{6–12} The mean duration of hospitalization^{6,7,9,10} and the frequency of respiratory support were equal to those of the other studies.^{6,7,11} The frequency of hospitalization of infants 0 to 2 years of age with RSV infection is 1.4% in our study. This is comparable to the Finnish figures cited by Ruuskanen and Ogra,¹ although similar figures are not mentioned in the studies listed in Table 5.

The study closest to our study in design is that of van Woensel et al¹¹ (Table 5). In that study, all patients were RSV-positive. Furthermore, they all had bronchiolitis, defined as acute tachypnoea, wheezing and/or decreased breath sounds, cyanosis, or the use of accessory respiratory muscles, in the presence of a

TABLE 2. The Characteristics of Randomized Patients

	Treatment According to Randomization		Number With Missing Information
	Prednisolone	Placebo	
Number	73	74	0*
Median age at diagnosis (mo)	5.7	5.1	2
Male/female	38/34	39/35	1
Days of respiratory symptoms before randomization (median)	5	4	8
Exposure to tobacco smoke at home	38	42	3
Doctor's diagnosis of allergy in parents or siblings	31	38	3
Earlier treatment of asthmatic bronchitis†	23	17	3
Number of infants who before randomization were treated with			
β ₂ -agonist	60	53	3
Antibiotics	16	15	3
Oxygen (any method)	13	11	3
Oxygen with mask	7	9	3
Respirator	0	0	3
Nasal CPAP	8	7	3
Hydration (gastro-nasal tube/IV line)	16	19	3

* Of the patients, 2 never received medicine.

† All had had β₂-agonist, 3 infants also had had steroid.

TABLE 3. Effect Variables Recorded During the Five-Day Experimental Treatment Period at the Hospital and One Month and One Year After Discharge From the Hospital

	Prednisolone	Placebo	Number With Missing Information
During the 5 days of prednisolone/placebo treatment			
Number completing treatment	65	69	2
Number not completing treatment	7	4	2
Median duration of stay in hospital (d)	3.6	4.0	5
Median number of doses of β ₂ -agonist*	11	7	5
Number of patients treated with β ₂ -agonist during day 1–5	53	59	5
Antibiotics	20	13	4
Oxygen (any method)	11	16	2
Oxygen with mask	5	10	5
Respirator	0	1	5
Nasal CPAP	6	10	2
Hydration (gastro-nasal tube/IV line)	16	24	5
At 1 mo			
Number in asthma treatment	29	31	11
Number of patients admitted for respiratory tract infection	7	7	2
Median number of nights with cough since discharge	6.0	6.3	16
Number of children coughing at night	59	56	16
Number with otitis media after discharge	7	12	12
At 1 y			
Number in asthma treatment	35	33	11
Number of patients admitted for respiratory tract infection	18	22	2
Median number of nights with cough during the last 6 wk	8	7	18
Number of children coughing at night	47	45	18
Number with otitis media during the last 11 mo	18	11	11
Number with positive prick test	3	1	28
Number with doctor-diagnosed asthmatic bronchitis	38	44	11

* Among those who were treated with β₂-agonist.

viral infection. The study found a significantly shorter duration of stay in hospital in mechanically ventilated patients who received prednisolone, although the number of patients was very small (only 7 in prednisolone and 7 in placebo treatment). In the larger group of patients, who were not mechanically ventilated, the symptom score decreased significantly faster in the prednisolone group, but prednisolone had no effect on the mean duration of hospital stay.¹¹

In our study, prednisolone did not shorten the duration of stay in hospital in the subgroup of infants who received CPAP treatment before randomization.

The logistic regression analysis was performed

with a dual purpose: to identify risk factors for the morbidity during the year following RSV infection and to evaluate the effect of prednisolone treatment in subgroups of patients defined by significant risk factors. The only positive finding was that infants who were treated with β₂-agonist or inhaled corticosteroid before admission had a higher risk of receiving the same treatment at the 1-year control, but the same risk factor did not influence the risk of being readmitted to hospital for respiratory tract infection. The effect of prednisolone treatment was independent of asthma treatment before admission.

In our study, 28% of the children had had asthma treatment before admission and 50% had it at the 1-year control. These figures seem to be very high,

TABLE 4. Logistic Regression Analysis. Response Variables: Asthma Treatment at the One-Year Control and Readmission for Respiratory Tract Infections During the Year Following Admission for RSV Infection

Explanatory Variable	Response Variables	
	Asthma Treatment Odds Ratio*	Admissions to Hospital*** Odds Ratio*
Prednisolone/placebo	1.26 ns.**	0.83 ns.
Sex (male/female)	1.28 ns.	0.88 ns.
Age (≥ 6 mo/ < 6 mo)	0.87 ns.	1.19 ns.
Allergy in family (+/-)	0.87 ns.	1.46 ns.
Tobacco mother (+/-)	0.90 ns.	0.69 ns.
Tobacco in the household (+/-)	1.15 ns.	1.84 ns.
Duration of stay in hospital (≥ 4 d/ < 4 d)	1.02 ns.	1.34 ns.
Duration of illness prior to randomization (≥ 5 d/ < 5 d)	0.80 ns.	0.91 ns.
Asthma treatment before first admission (+/-)	2.54 p = 4%	1.10 ns.

* The relative risk of being in asthma treatment at the 1-year control or to be readmitted to hospital with respiratory tract infection, given that the risk factor is present. For instance, the relative risk of being in asthma treatment at the 1-year control is estimated as 1.26 in the prednisolone group compared to the placebo group, and 1.28 in males compared to females. None of these numbers differ significantly from 1.0, except the last one.

† Not significant.

‡ Only 33 children were readmitted, so we have small numbers.

TABLE 5. Other Randomized Double-Blind Studies of Systemic Corticosteroid Treatment of Children Younger Than Two Years With Bronchiolitis or Wheezing

Studies	Effect	Number	Percentage with RSV	Dose*/Days	Effect Variables
Connolly et al 1969 ⁶	-	43	71	15-2.5 mg/7	Duration of illness Clinical score RSV antibody response
Tall et al 1983 ¹⁰	+	32	Not mentioned	2 mg/2	Duration of hospital stay Clinical score Supportive treatment
Daugbjerg et al 1990 ¹²	+	58	31	6-2 mg/3	Duration of hospital stay Clinical score
Springer et al 1990 ⁹	-	50	Not mentioned	2 mg/3+	Duration of hospital stay Clinical score Lung function Follow-up at 2-4 wk
Van Woensel 1997 ¹¹	+	54	100	1 mg/7	Duration of hospital stay Clinical score
Klassen et al 1997 ⁷	-	61	87	3-2 mg/3	Clinical score Duration of hospital stay Supportive treatment Follow-up at 7 d
Roosevelt et al 1997 ⁸	-	118	67	6 mg/3	Duration of hospital stay Clinical score Supportive treatment Follow-up at 14 d

* Prednisolone equivalent per kg BW per day / duration of treatment.

although a control material does not exist. The population of infants hospitalized with RSV infection may have a higher tendency to bronchial inflammation or hyperreactivity before they are infected with RSV; perhaps the immune response is immature or fewer antibodies are transferred from the mother. Whether asthma is more common after an RSV infection or whether children with predisposition to asthma more often contract severe RSV infection cannot be answered from this study.

Corticosteroids have been used for many years in the treatment of bronchiolitis, asthmatic bronchitis, and wheezing in infants, on the hypothesis that they could reduce a bronchiolar inflammation and bronchiolar hyperreactivity.¹ In this study, we chose to treat with systemic corticosteroid instead of inhaled corticosteroid because of the uncertainty with respect to the uptake of inhaled corticosteroid in infants < 2 years of age.^{3,4,13,14} There are a number of possible explanations for the lack of effect of corticosteroids in

RSV infection. The pathophysiology may differ from that of asthma, where the effect is well-documented.¹⁵ The age of the infants may determine the response to corticosteroid treatment.¹⁶ Finally, the treatment with corticosteroid may have been started too late to have any effect on the response of the child to its RSV infection.

The most commonly used pharmacological treatment of RSV infection is $\beta 2$ -agonist inhalation.¹⁷ In a recent metaanalysis of randomized, controlled trials, Flores and Horwitz¹⁸ conclude that there is no conclusive evidence for its efficacy in bronchiolitis. No comparable metaanalysis of randomized, controlled trials of steroids exists.

Our randomized prospective study in infants hospitalized with acute RSV infection showed no effect of systemic prednisolone treatment either in the acute state of RSV infection, nor in the follow-up 1 month and 1 year after admission to hospital. We find our results in agreement with the largest studies

reported earlier; therefore, corticosteroid, by the systemic route or by inhalation, should not be prescribed to infants with RSV infections.

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This study was approved by the Medical Ethics Committees of the 2 counties and the Danish Medicines Agency.

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