

ORIGINAL ARTICLE

Epinephrine and Dexamethasone in Children with Bronchiolitis

Amy C. Plint, M.D., M.Sc., David W. Johnson, M.D., Hema Patel, M.D., M.Sc.,
Natasha Wiebe, M.Math., Rhonda Correll, H.B.Sc.N., Rollin Brant, Ph.D.,
Craig Mitton, Ph.D., Serge Gouin, M.D., Maala Bhatt, M.D., M.Sc.,
Gary Joubert, M.D., Karen J.L. Black, M.D., M.Sc., Troy Turner, M.D.,
Sandra Whitehouse, M.D., and Terry P. Klassen, M.D., M.Sc.,
for Pediatric Emergency Research Canada (PERC)

ABSTRACT

BACKGROUND

Although numerous studies have explored the benefit of using nebulized epinephrine or corticosteroids alone to treat infants with bronchiolitis, the effectiveness of combining these medications is not well established.

METHODS

We conducted a multicenter, double-blind, placebo-controlled trial in which 800 infants (6 weeks to 12 months of age) with bronchiolitis who were seen in the pediatric emergency department were randomly assigned to one of four study groups. One group received two treatments of nebulized epinephrine (3 ml of epinephrine in a 1:1000 solution per treatment) and a total of six oral doses of dexamethasone (1.0 mg per kilogram of body weight in the emergency department and 0.6 mg per kilogram for an additional 5 days) (the epinephrine–dexamethasone group), the second group received nebulized epinephrine and oral placebo (the epinephrine group), the third received nebulized placebo and oral dexamethasone (the dexamethasone group), and the fourth received nebulized placebo and oral placebo (the placebo group). The primary outcome was hospital admission within 7 days after the day of enrollment (the initial visit to the emergency department).

RESULTS

Baseline clinical characteristics were similar among the four groups. By the seventh day, 34 infants (17.1%) in the epinephrine–dexamethasone group, 47 (23.7%) in the epinephrine group, 51 (25.6%) in the dexamethasone group, and 53 (26.4%) in the placebo group had been admitted to the hospital. In the unadjusted analysis, only the infants in the epinephrine–dexamethasone group were significantly less likely than those in the placebo group to be admitted by day 7 (relative risk, 0.65; 95% confidence interval, 0.45 to 0.95, $P=0.02$). However, with adjustment for multiple comparisons, this result was rendered insignificant ($P=0.07$). There were no serious adverse events.

CONCLUSIONS

Among infants with bronchiolitis treated in the emergency department, combined therapy with dexamethasone and epinephrine may significantly reduce hospital admissions. (Current Controlled Trials number, ISRCTN56745572.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Plint at the Children's Hospital of Eastern Ontario, 401 Smyth Ave., Ottawa, ON K1H 8L1, Canada, or at plint@cheo.on.ca.

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IN INFANCY, BRONCHIOLITIS IS THE MOST common acute infection of the lower respiratory tract, characterized by rhinorrhea, cough, wheezing, respiratory distress, and hypoxemia,^{1,2} and is most often caused by the respiratory syncytial virus (RSV). Hospital admissions for bronchiolitis have almost doubled over the past 10 to 15 years in both Canada and the United States.^{3,4} In the United States, annual hospital costs for RSV-associated bronchiolitis were estimated at \$365 million to \$691 million in 1998.⁵

The current treatment of bronchiolitis is controversial. Bronchodilators and corticosteroids are widely used but not routinely recommended.⁶ A meta-analysis of the treatment effects of nebulized selective beta-agonists⁷ failed to show any consistent benefits, whereas a meta-analysis of the treatment effects of nebulized epinephrine suggested a decrease in clinical symptoms as compared with either placebo or albuterol.⁸ In one small, randomized, controlled trial, treatment with dexamethasone led to a 40% relative reduction in admission rates as compared with placebo.⁹ However, a large, recently published study of dexamethasone failed to show any difference in hospital-admission rates or respiratory clinical scores as compared with placebo.¹⁰

The current study was undertaken in response to the continued controversy concerning the use of nebulized epinephrine and systemic corticosteroids in the treatment of bronchiolitis in infants and in recognition of the substantial burden that the care of infants with this disease adds to the health care system. We conducted a randomized, double-blind, placebo-controlled, clinical trial with a factorial design at multiple sites to determine whether treatment with nebulized epinephrine, a short course of oral dexamethasone, or both resulted in a clinically important decrease in hospital admissions among infants with bronchiolitis who were seen in the emergency department.

METHODS

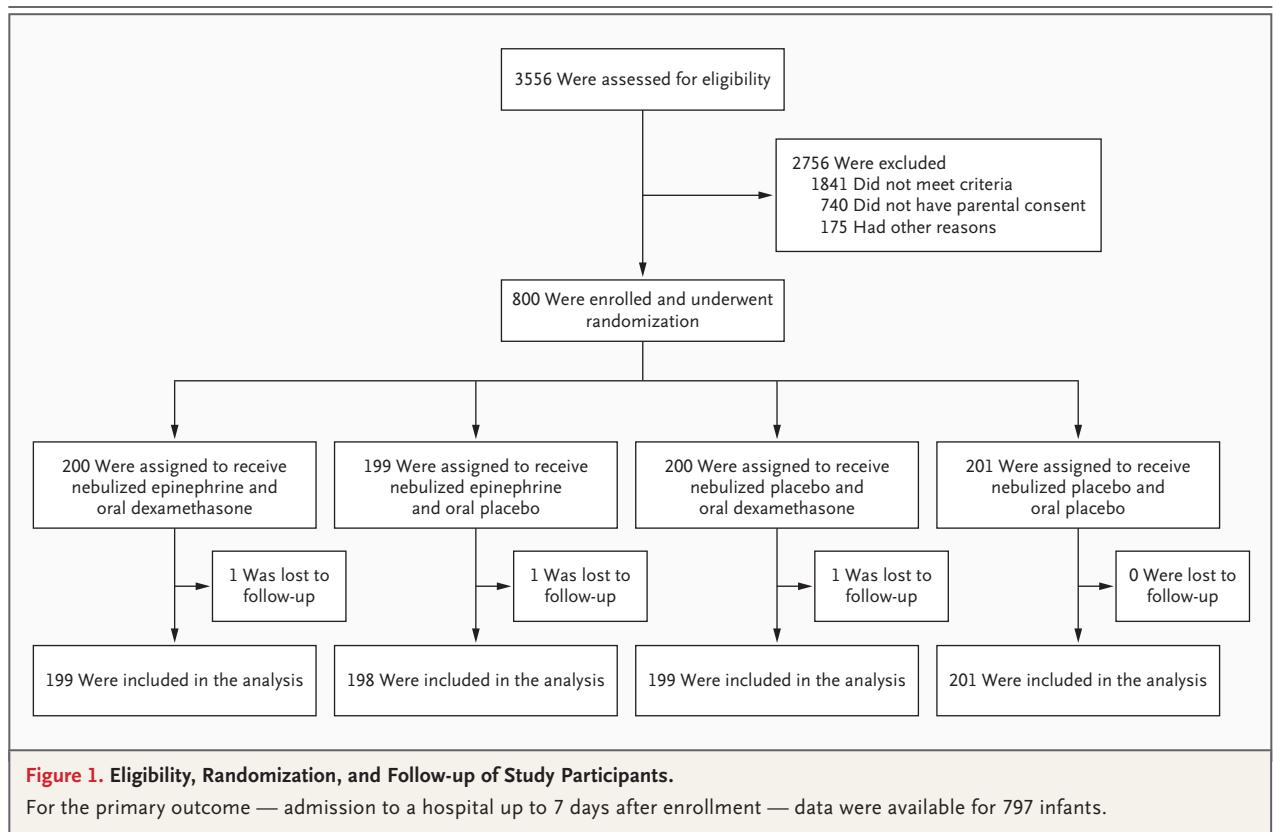
PATIENTS

Patients were recruited during the bronchiolitis season (December through April) at eight Canadian pediatric emergency departments from 2004 through 2007. All hospitals are members of the research group Pediatric Emergency Research Canada (PERC). Written informed consent was obtained

from the parents or guardians of all infants included in the study, and the study was approved by the ethics committee at each site and by Health Canada. The study protocol and manuscript were written by the investigators; data were collected by research nurses and analyzed by PERC statisticians. The granting agencies covered all costs, including the cost of medications, required no confidentiality agreements, and played no role in study design, data analysis, or manuscript preparation.

Infants 6 weeks to 12 months of age with bronchiolitis who were seen at participating emergency departments were eligible for the study if they had a score of 4 to 15 on the respiratory distress assessment index (RDAI).¹¹ The RDAI, which has good interobserver reliability, rates wheezing and respiratory distress on a scale from 0 to 17, with higher scores indicating more severe illness; a score below 4 indicates very mild illness, and a score above 15 very severe illness. Bronchiolitis was defined as the first episode of wheezing associated with signs of an upper respiratory tract infection during the peak RSV season. We excluded infants who received bronchodilator treatment in the emergency department before being assessed by a research nurse, infants who had received oral or inhaled corticosteroids during the preceding 2 weeks, infants with a previous episode of wheezing or a diagnosis of asthma, previous bronchodilator use, any chronic cardiopulmonary disease, or immunodeficiency, and infants in severe distress (defined as a pulse rate >200 beats per minute, a respiratory rate >80 breaths per minute, or an RDAI score >15) or with profound lethargy, and infants who had been exposed to varicella within the preceding 3 weeks. Also excluded were infants born at less than 37 weeks of gestation who had a corrected age of less than 6 weeks at presentation. Finally, infants were excluded if there were insurmountable barriers to communication with the family (a language barrier or lack of a telephone on the part of the parent or guardian).

A research nurse was present in the emergency department up to 16 hours daily to recruit participants. Once a physician had confirmed the diagnosis and parental consent had been obtained, the nurse documented demographic information, obtained a medical history, and obtained a nasal pharyngeal aspirate for RSV testing. Any child with an oxygen saturation of less than 92% while breathing ambient air received supplemental oxy-



gen, and any child with a fever (rectal temperature $>38^{\circ}\text{C}$) received acetaminophen (15 mg per kilogram of body weight).

INTERVENTION

Using a computer-generated randomization sequence, the research nurse assigned participants to one of four study treatments: nebulized epinephrine plus oral dexamethasone (group 1), nebulized epinephrine plus oral placebo (group 2), nebulized placebo plus oral dexamethasone (group 3), or nebulized placebo plus oral placebo (group 4). The two nebulized treatments, administered 30 minutes apart with the use of the 1730 Updraft II nebulizer (Hudson RCI) and an oxygen flow rate of 8 liters per minute, consisted of 3 ml of generic epinephrine in a 1:1000 solution or an equivalent volume of saline.¹²⁻¹⁷ The oral treatments, based on a study by Schuh et al.,⁹ consisted of 1.0 mg of dexamethasone per kilogram of body weight (maximum dose, 10 mg) or placebo given after the first nebulized treatment in the emergency department, followed by five once-daily doses of dexamethasone (0.6 mg per kilogram; maximum

daily dose, 10 mg) or placebo. The dexamethasone suspension consisted of generic dexamethasone phosphate injection solution mixed with Ora-Plus and Ora-Sweet (Paddock Laboratories). The placebo consisted of Ora-Plus and Ora-Sweet. The research nurse administered all drugs in the emergency department and taught parents how to administer the oral drug at home. The treating physician in the emergency department was allowed to provide cointerventions after 90 minutes and independently determined whether to admit or discharge the infant.

RANDOMIZATION

The computer-generated randomization sequence, stratified by center, used randomized permuted blocks of 8 and 12. Codes were secured at each center's pharmacy until enrollment and data entry were complete. In order to conceal the allocation sequence, the pharmacy at each site prepared the study drugs in sequentially numbered, visually identical packets. The active drugs and placebo were identical in appearance, volume, weight, odor, and taste.

ASSESSMENTS

The research nurse recorded the patient's RDAI score, respiratory rate, heart rate, and oxygen saturation in ambient air at baseline, between the two nebulizations, and at 60, 90, 120, 180, and 240 minutes; rectal temperature at 120 and 240 minutes (or at discharge); blood pressure at 240 minutes or at discharge; and any side effects

throughout the observation period in the emergency department. Using a standardized telephone follow-up procedure,¹⁸ the research nurse obtained data regarding compliance with administration of study medication after discharge and health care visits, as well as details about the infant's feeding, sleep, breathing, and coughing. Follow-up by telephone was performed daily until day 7, then

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Epinephrine– Dexamethasone Group (N=200)	Epinephrine Group (N=199)	Dexamethasone Group (N=200)	Placebo Group (N=201)
Age — mo				
Median	5	5	5	5
Interquartile range	3–7	3–7	3–7	3–7
Male sex — no. (%)	124 (62.0)	122 (61.3)	127 (63.5)	120 (59.7)
Clinical characteristics				
RDAI score				
Median	8	8	8	8
Interquartile range	6–10	6–10	6–10	6–10
Respiratory rate — breaths/min				
Median	48	48	50	48
Interquartile range	41–57	44–56	44–60	40–58
Heart rate — beats/min				
Median	150	149	152	150
Interquartile range	138–160	138–160	141–161	137–160
Oxygen saturation — %				
Median	97	97	97	97
Interquartile range	95–98	95–98	95–98	95–98
Temperature — °C				
Median	37.6	37.7	37.6	37.7
Interquartile range	37.3–38.0	37.3–38.0	37.2–38.0	37.2–38.1
Duration of symptoms before enrollment — days				
Median	3	4	3	4
Interquartile range	2–5	3–6	2–5	2–6
RSV-positive — no. (%)	128 (64.0)	129 (64.8)	127 (63.5)	136 (67.7)
History — no. (%)				
Atopy				
Personal history†	28 (14.0)	20 (10.0)	19 (9.5)	22 (10.9)
Family history‡	124 (62.0)	112 (56.3)	113 (56.5)	114 (56.7)
Prematurity§	22 (11.0)	22 (11.1)	23 (11.5)	16 (8.0)
Clinically significant illness¶	7 (3.5)	10 (5.0)	14 (7.0)	11 (5.5)
Previous intubation	6 (3.0)	4 (2.0)	8 (4.0)	6 (3.0)
One or more smokers in home	84 (42.0)	72 (36.2)	67 (33.5)	82 (40.8)

Table 1. (Continued.)

Characteristic	Epinephrine– Dexamethasone Group (N = 200)	Epinephrine Group (N = 199)	Dexamethasone Group (N = 200)	Placebo Group (N = 201)
Previous treatment for current illness — no. (%)				
Bronchodilators	27 (13.5)	21 (10.6)	20 (10.0)	24 (11.9)
Antibiotics	24 (12.0)	20 (10.1)	21 (10.5)	17 (8.5)

* The Respiratory Distress Assessment Index (RDAI) rates wheezing and respiratory distress on a scale from 0 to 17, with higher scores indicating more severe illness; a score below 4 indicates very mild illness, and a score above 15 very severe illness. RSV denotes respiratory syncytial virus.

† A personal history of atopy was defined as a history of eczema or allergies.

‡ A family history of atopy was defined as allergies, asthma, or eczema in a parent or any sibling.

§ Prematurity was defined as birth at less than 37 weeks of gestation.

¶ Clinically significant illness was defined as any illness requiring surgery, hospital admission, or ongoing medical care.

|| Fourteen of the infants who were previously intubated were premature.

every 2 days until day 14, and then every 3 days until day 22. A review of the patient's hospital chart was completed 22 days after enrollment.

OUTCOME MEASURES

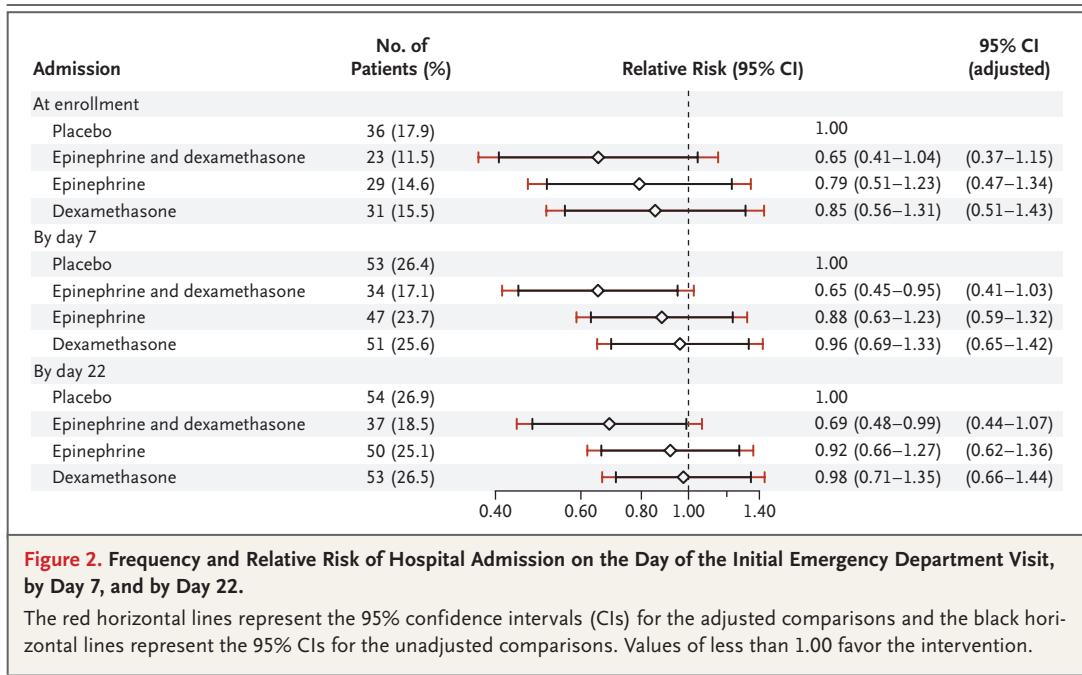
The primary outcome — hospital admission up to 7 days after enrollment, which occurred during the visit to the emergency department — was determined through telephone follow-up and confirmed by chart review, as were rates of admission at enrollment and by day 22. The secondary outcomes of change in heart and respiratory rate, RDAI score, and oxygen saturation from baseline to 30, 60, 120, and 240 minutes were determined by direct measurement by the research nurse. Secondary outcomes of length and severity of symptoms were determined by standardized telephone follow-up. Time to discharge, determined by chart review, was defined as the time between the triage time at the enrollment and the time of discharge from the last emergency department visit or from the last hospitalization for each patient within the next 7 days. Patient return to the health care provider for bronchiolitis symptoms within 22 days of enrollment was determined by telephone follow-up and confirmed by chart review.

STATISTICAL ANALYSIS

A sample size of 800 infants was chosen to provide 80% power (with a 5% type I error rate) to detect an absolute difference of 10 percentage points in admission rates resulting from administration of each drug and assumed no interaction between epinephrine and dexamethasone. Data analysis was performed with the use of Stata soft-

ware, version 10.0. Two interim analyses were planned and conducted with the use of the Haybittle–Peto approach (with a stopping rule that specified a P value of less than 0.001)^{19,20}; both interim analyses had nonsignificant results. Subgroup analyses that were planned a priori included analyses according to the presence or absence of atopy, RSV status, and duration of illness at presentation.

All analyses followed the intention-to-treat principle.²¹ Admission and return visits due to symptoms of bronchiolitis were analyzed with the use of relative-risk regression for binary outcomes. Our analysis plan, as specified by our protocol and based on published recommendations regarding analysis of data in studies with factorial designs,²² was to first conduct a factorial analysis incorporating terms for epinephrine, dexamethasone, and study center, then examine associated interactions, and finally, if evidence of interaction was found, analyze and present our results as separate comparisons of each of the three treatment groups with the placebo group. Evidence of a clinically significant interaction between epinephrine and dexamethasone was found. To accommodate the uncertainty arising from this unanticipated interaction, we provide both unadjusted results and results adjusted for multiple comparisons with the use of the approach described by Westfall²³ and as implemented by Hothorn et al.²⁴ Time to discharge was analyzed with the use of a Cox proportional-hazards model. To allow for intervals between follow-up telephone calls and censoring before the end of the study, time to symptom relief was analyzed by means of para-



metric survival models with Weibull distributions assumed. We analyzed clinical characteristics (e.g., RDAI score) with the use of linear mixed-effects regression, incorporating baseline values. Assumptions such as proportional hazards and normality were examined graphically.

RESULTS

RECRUITMENT AND BASELINE CHARACTERISTICS

A total of 3556 infants were screened for eligibility, 1715 met the criteria for enrollment, and 800 were enrolled (Fig. 1). Of the 1841 ineligible infants, 867 (47.1%) had a previous episode of wheezing or diagnosis of asthma, 90 (4.9%) had an RDAI score above 15, and 343 (18.6%) had an RDAI score below 4. (For more details on patient exclusion, see the Supplementary Appendix, available with the full text of this article at NEJM.org.) A total of 200 patients were randomly assigned to the epinephrine–dexamethasone group, 199 to the epinephrine group, 200 to the dexamethasone group, and 201 to the placebo group. No data were available on the primary outcome for three patients (one each in the first three groups); these patients were not included in the intention-to-treat analysis. Because of a pharmacy error, a total of 23 patients in group 1 and 23 patients in group 3 received dexamethasone at 80% of the planned dose (0.8 mg per kilogram of

body weight in the emergency department and 0.48 mg per kilogram of body weight at home); these patients were included in the analysis. Other deviations from the protocol were minor and equally distributed among the groups. Baseline clinical and demographic characteristics were similar among the groups (Table 1). The additional use of bronchodilators 90 minutes after enrollment was similar across groups, with 18.4% of patients receiving albuterol and 20.6% receiving epinephrine (median number of treatments, 1). At follow-up, the parents or guardians of 19 infants in the epinephrine–dexamethasone group, 13 in the epinephrine group, 20 in the dexamethasone group, and 12 in the placebo group reported that they had stopped administering the study syrup; for all 19 children in the epinephrine–dexamethasone group, all 20 in the dexamethasone group, and 3 of the 12 in the placebo group, the study syrup was withdrawn so that a physician could prescribe oral corticosteroids. The study groups did not differ significantly with respect to use of nonstudy medications at discharge from the initial emergency department visit through day 7.

HOSPITAL ADMISSIONS

By the seventh day, 34 of the 199 infants in group 1 (17.1%) had been admitted to the hospital, as had 47 of the 198 infants in group 2 (23.7%), 51 of the 199 infants in group 3 (25.6%), and 53

of the 201 infants in group 4 (26.4%). The relative risk of admission, unadjusted and adjusted for multiple comparisons, is shown in Figure 2. The relative risk of admission by day 7 in group 1 as compared with group 4 was 0.65 (95% confidence interval, 0.45 to 0.95; $P=0.02$ and $P=0.07$ for the unadjusted and adjusted analyses, respectively); 11 infants would need to be treated to prevent one hospital admission. In contrast, in both unadjusted and adjusted analyses, neither treatment with dexamethasone alone nor treatment with epinephrine alone reduced the rate of admission, as compared with placebo ($P=0.87$ and $P=0.52$, respectively, for the unadjusted analysis). Positive RSV status, personal or family history of atopy, presentation early in the course of illness (≤ 2 days after the onset of symptoms), severe illness (defined as an RDAI score ≥ 6), and the pharmacy error (lower dexamethasone dose) did not affect the primary results. The effects of combining epinephrine and dexamethasone were most apparent in the first 3 days after study enrollment (Fig. 3).

CLINICAL MEASURES

The RDAI score and the respiratory rate improved in all groups during the initial emergency department visit. Infants in the epinephrine group and those in the epinephrine–dexamethasone group had significantly lower RDAI scores during the first hour of the study than did infants in the placebo group; the RDAI scores for infants in the dexamethasone group did not show significant improvement as compared with the change in the scores for infants in the placebo group (Table 2). Infants in the epinephrine–dexamethasone group also had lower respiratory rates during the first hour than did those in the placebo group. As compared with infants in the placebo group, those in the epinephrine group and the epinephrine–dexamethasone group had elevated heart rates during the first hour, whereas infants in the dexamethasone group did not.

OTHER OUTCOMES

The median time until discharge from the emergency department or hospital for group 1 was slightly shorter than that for group 4 (4.6 and 5.3 hours, respectively; unadjusted $P=0.02$), whereas neither group 3 (5.1 hours) nor group 2 (4.9 hours) differed from group 4 on this measure. In group 1, 95 patients (47.7%) returned to a health care provider for bronchiolitis-related symptoms, as did 93

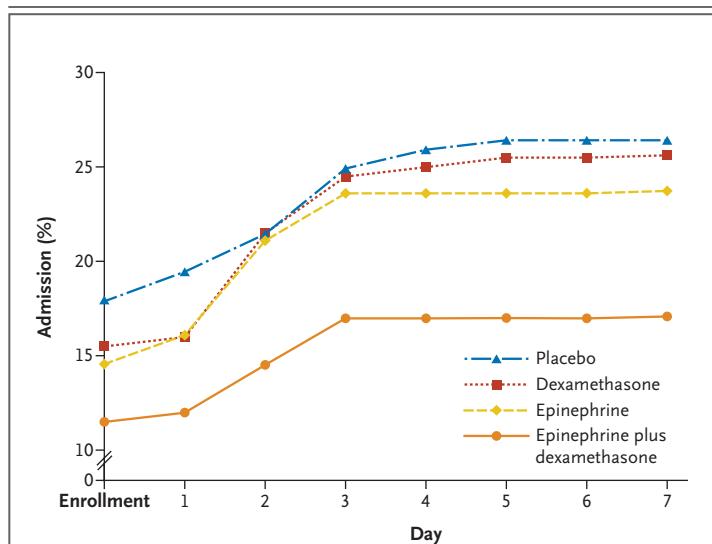


Figure 3. Cumulative Admissions during the First 7 Days after the Initial Emergency Department Visit, According to Study Group.

Enrollment data represent all patients admitted at their initial visit to the emergency department, and data for day 1 represent patients admitted within 24 hours of this visit.

in group 2 (47.0%), 106 in group 3 (53.3%), and 86 in group 4 (42.8%); only the difference between group 3 and group 4 was significant, and only in the unadjusted analysis ($P=0.04$).

Infants in group 1 appeared to return to quiet breathing and normal or almost normal feeding more quickly than those in group 4 (Fig. 4).

ADVERSE EVENTS

Adverse events were uncommon (see the Supplementary Appendix). Pallor was reported in 76 infants (9.5%), tremor in 15 (1.9%), and vomiting in 14 (1.8%), with no significant differences among the groups. One hospitalized infant in group 2 and one in group 3 had mild, transient hypertension, which resolved rapidly.

DISCUSSION

In this randomized, controlled trial of the treatment of acute bronchiolitis in infants, we found an unexpected synergism between epinephrine and dexamethasone. Combined therapy with epinephrine and dexamethasone, as compared with placebo, appeared to reduce the rate of hospital admission in the 7 days after study enrollment by 9 percentage points, with a relative risk reduction of 35%. These results were not modified by RSV status, presence or absence of a history of atopy,

Table 2. Changes in Clinical Characteristics of Patients and Time to Discharge.*

Variable	Epinephrine– Dexamethasone Group (N=199)	Epinephrine Group (N=198)	Dexamethasone Group (N=199)	Placebo Group (N=200)
	<i>change</i>			
RDAl score				
30 min	–1.62±2.23	–1.44±1.94	–0.98±2.07	–1.06±2.16
60 min	–2.50±2.58	–2.45±2.32	–1.75±2.40	–1.65±2.42
P value				Reference
Unadjusted	<0.001	0.003	0.75	
Adjusted	<0.001	0.005	0.75	
Respiratory rate (breaths/min)				
30 min	–2.40±8.29	–1.35±8.53	–1.63±8.32	–0.59±8.34
60 min	–4.04±9.17	–3.68±8.89	–3.30±9.60	–2.88±10.20
P value				Reference
Unadjusted	0.04	0.44	0.83	
Adjusted	0.09	0.66	0.83	
Heart rate (beats/min)				
30 min	3.57±17.40	4.20±15.7	–0.17±17.80	1.65±18.80
60 min	5.20±17.80	4.80±17.60	–3.76±17.70	–3.24±18.80
P value				Reference
Unadjusted	<0.001	<0.001	0.41	
Adjusted	<0.001	<0.001	0.41	
Oxygen saturation (%)				
30 min	–0.35±2.61	0.17±2.09	–0.52±2.45	–0.24±2.77
60 min	–0.73±2.56	0.07±2.70	–1.02±2.57	–0.77±3.23
P values				Reference
Unadjusted	0.59	0.005	0.22	
Adjusted	0.59	0.013	0.36	
Temperature (°C)				
At discharge or at 240 min	–0.19±0.78	–0.17±0.66	–0.10±0.71	–0.29±0.76
P value				Reference
Unadjusted	0.76	0.26	0.18	
Adjusted	0.76	0.42	0.39	
Time to discharge (hr) †				
Median	4.6	4.9	5.1	5.3
Interquartile range	3.5–7.0	3.7–9.6	3.6–17.0	3.8–21
P value				Reference
Unadjusted	0.02	0.78	0.99	
Adjusted	0.94	0.94	1.00	

* Plus–minus values are means SD. The Respiratory Distress Assessment Index (RDAl) rates wheezing and respiratory distress on a scale from 0 to 17, with higher scores indicating more severe illness; a score below 4 indicates very mild illness, and a score above 15 very severe illness. Since almost one third of the patients (283) had been discharged home by 120 minutes and the majority of patients (583) had been discharged by 240 minutes, we do not report clinical measures for times beyond 60 minutes after treatment. P values are for comparisons of treatment with placebo in the linear mixed-effects regression of repeated measures over time.

† The time to discharge was defined as the time between the triage time at the enrollment visit and the time of discharge from the last emergency department visit or the last hospitalization for each patient within the next 7 days.

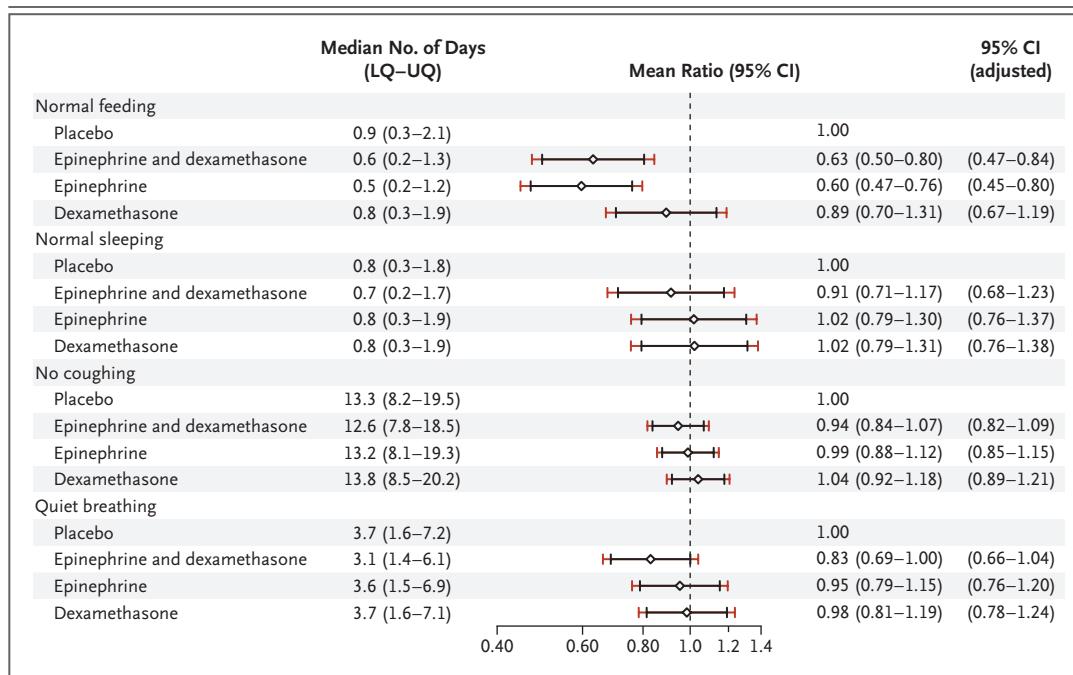


Figure 4. Median Days to Symptom Resolution, with Ratio to Placebo Value.

The red horizontal lines represent the adjusted 95% confidence intervals (CIs), and the black horizontal lines the unadjusted 95% CIs. Values of less than 1.00 favor the intervention. LQ denotes lower quartile, and UQ upper quartile.

or the severity or the duration of illness. The effects of combining epinephrine and dexamethasone were most apparent in the first 3 days after study enrollment. We also found an apparent benefit from combined therapy on our secondary outcomes: infants in this group were discharged earlier from medical care and resumed quiet breathing and normal feeding sooner than did those in the placebo group. In contrast, neither dexamethasone alone nor epinephrine alone had any effect on these outcomes.

Three small studies — two published since our trial began — have also reported a benefit from combining epinephrine and dexamethasone^{25,26} or albuterol and dexamethasone^{25,27} in similar populations and have reported no benefit from the administration of epinephrine or albuterol alone. Furthermore, although the mechanism of action is not known, synergism between corticosteroids and beta-agonists in the treatment of chronic asthma is well documented.²⁸⁻³⁰

Dexamethasone has been studied in a similar population, with conflicting results.^{9,10} Schuh et al.⁹ reported a 40% reduction in admissions in a small, single-site study, whereas Corneli et al.¹⁰ reported no effect in a large, multisite study. The

patients in the study by Schuh et al. were consistently treated with bronchodilators, whereas the patients in the study by Corneli et al. were not.

A meta-analysis has suggested that when epinephrine is used in outpatients with a diagnosis of bronchiolitis, as compared with either placebo or salbutamol, there is short-term improvement in clinical measures.⁸ Our study showed an improvement in the clinical score in the first hour after treatment with epinephrine, as compared with placebo, but with no significant difference in admission rates.

Although there were no serious short-term adverse events among the infants enrolled in our study, we do not have findings from long-term follow-up to establish whether our study treatments caused adrenal suppression, arrest of somatic growth, or neurodevelopmental delay. Adrenal suppression from exogenous corticosteroid use remains a risk; however, with short courses of corticosteroids, any suppression is likely to be transient.³¹⁻³³ Concern has been expressed about possible developmental delay after treatment with corticosteroids.³⁴ To date, this concern has been limited to preterm infants with very low birth weight (<1501 g) who are given corticosteroids in

the first few days of life.³⁵⁻³⁷ The effect of a short course of corticosteroids on otherwise healthy infants is unknown.

Our study has several limitations. First, in order to exclude children with early asthma, we restricted enrollment to infants who had wheezing for the first time. Our results are thus not generalizable to older children or to those with recurrent wheezing, but they are directly pertinent to infants with typical viral bronchiolitis. Second, we enrolled infants at academic centers. Nonetheless, the eligibility criteria were chosen with the intention of enrolling otherwise healthy infants with a wide range in severity of symptoms who did not have complex coexisting conditions, so that our results could be broadly generalized. Third, we did not anticipate the synergism between epinephrine and dexamethasone in our study design, and fourth, our factorial study design raises the issue of multiple comparisons. To address these limitations, we present the results of both unadjusted analyses and analyses adjusted for multiple comparisons. The results of the unadjusted analyses show that combined treatment with epinephrine and dexamethasone led to a significant reduction in hospital admissions, but the results of the adjusted analyses are above the threshold for statistical significance.

In summary, our multicenter study of 800 in-

fants with bronchiolitis suggests that combined treatment with epinephrine and dexamethasone reduces hospital admissions as well as shortening both the time to discharge and the duration of some symptoms. Given the unexpected synergy we found between epinephrine and dexamethasone and the lack of any apparent benefit when either drug is used alone, our results should be considered exploratory. Although some clinicians consider a trial of a bronchodilator to be standard therapy,⁶ published data show, at most, mild transient clinical benefits and no effect on the admission rate. Therefore, confirmation of our findings by a study powered specifically to compare combined epinephrine and dexamethasone therapy with placebo is needed.

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APPENDIX

From the Departments of Pediatrics and Emergency Medicine, University of Ottawa and Children's Hospital of Eastern Ontario, Ottawa (A.C.P.); the Departments of Pediatrics and Pharmacology and Therapeutics, University of Calgary, and Alberta Children's Hospital, Calgary (D.W.J.); the Department of Pediatrics, McGill University, and Montreal Children's Hospital, Montreal (H.P., M.B.); the Departments of Medicine (N.W.) and Pediatrics (T.T., T.P.K.), University of Alberta, Edmonton; the Clinical Research Unit, Children's Hospital of Eastern Ontario Research Institute, Ottawa (R.C.); the Departments of Statistics (R.B.) and Pediatrics (S.W.), University of British Columbia, Vancouver; the Child and Family Research Institute, BC Children's Hospital, Vancouver (R.B.); the Department of Health Studies, University of British Columbia Okanagan, Kelowna (C.M.); the Department of Pediatrics, University of Montreal, and Centre Hospitalier Universitaire Sainte-Justine, Montreal (S.G.); the Departments of Pediatrics and Medicine, University of Western Ontario, and the London Health Sciences Centre and Children's Hospital, London (G.J.); the Departments of Pediatrics and Emergency Medicine, Dalhousie University, and the IWK Health Centre, Halifax, NS (K.J.L.B.); Stollery Children's Hospital, Edmonton, AB (T.T., T.P.K.); and BC Children's Hospital, Vancouver (S.W.) — all in Canada.

REFERENCES

- Welliver JR, Welliver RC. Bronchiolitis. *Pediatr Rev* 1993;14:134-9.
- Milner AD, Murray M. Acute bronchiolitis in infancy: treatment and prognosis. *Thorax* 1989;44:1-5.
- Shay DK, Holman RC, Newman RD, Liu LL, Stout JW, Anderson LJ. Bronchiolitis-associated hospitalizations among US children, 1980-1996. *JAMA* 1999;282:1440-6.
- Njoo H, Pelletier L, Spika J. Infectious diseases. In: Canadian Institute for Health Information, Canadian Lung Association, Health Canada, Statistics Canada, eds. *Respiratory disease in Canada*. Ottawa: Canadian Institute for Health Information, 2001:65-87.
- Stang P, Brandenburg N, Carter B. The economic burden of respiratory syncytial virus-associated bronchiolitis hospitalizations. *Arch Pediatr Adolesc Med* 2001;155:95-6.
- American Academy of Pediatrics Subcommittee on Diagnosis and Management of Bronchiolitis. Diagnosis and management of bronchiolitis. *Pediatrics* 2006;118:1774-93.
- Flores G, Horwitz RL. Efficacy of beta2-agonists in bronchiolitis: a reappraisal and meta-analysis. *Pediatrics* 1997;100:233-9.
- Hartling L, Wiebe N, Russell K, Patel H, Klassen TP. A meta-analysis of randomized controlled trials evaluating the efficacy of epinephrine for the treatment of acute viral bronchiolitis. *Arch Pediatr Adolesc Med* 2003;157:957-64.
- Schuh S, Coates AL, Binnie R, et al. Efficacy of oral dexamethasone in outpatients with acute bronchiolitis. *J Pediatr* 2002;140:27-32.
- Corneli HM, Zorc JJ, Majahan P, et al. A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis. *N Engl J Med* 2007;357:331-9. [Erratum, *N Engl J Med* 2008;359:1972.]

11. Lowell DI, Lister G, Von Koss H, McCarthy P. Wheezing in infants: the response to epinephrine. *Pediatrics* 1987;79:939-45.
12. Klassen TP, Rowe PC, Sutcliffe T, Ropp LJ, McDowell IW, Li MM. Randomized trial of salbutamol in acute bronchiolitis. *J Pediatr* 1991;118:807-11. [Erratum, *J Pediatr* 1991;119:1010.]
13. Menon K, Sutcliffe T, Klassen TP. A randomized trial comparing the efficacy of epinephrine with salbutamol in the treatment of acute bronchiolitis. *J Pediatr* 1995;126:1004-7.
14. Sanchez I, De Koster J, Powell RE, Wolstein R, Chernick V. Effect of racemic epinephrine and salbutamol on clinical score and pulmonary mechanics in infants with bronchiolitis. *J Pediatr* 1993;122:145-51.
15. Kristjánsson S, Lodrup Carlsen KC, Wennergren G, Strannegård IL, Carlsen KH. Nebulised racemic adrenaline in the treatment of acute bronchiolitis in infants and toddlers. *Arch Dis Child* 1993;69:650-4.
16. Wennergren G, Kristjánsson S, Sten G, Bjure J, Engström I. Nebulized racemic adrenaline for wheezy bronchitis. *Acta Paediatr Scand* 1991;80:375-7.
17. Reijonen T, Korppi M, Pitkääkangas S, Tenhola S, Remes K. The clinical efficacy of nebulized racemic epinephrine and albuterol in acute bronchiolitis. *Arch Pediatr Adolesc Med* 1995;149:686-92.
18. Patel H, Gouin S, Platt RW. Randomized, double-blind, placebo-controlled trial of oral albuterol in infants with mild-to-moderate acute viral bronchiolitis. *J Pediatr* 2003;142:509-14.
19. Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. *Br J Radiol* 1971;44:793-7.
20. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observations of each patient. I. Introduction and design. *Br J Cancer* 1976;34:585-612.
21. Fisher LD, Dixon DO, Herson J, Frankowski RK, Hearron MS, Peace KE. Intention to treat in clinical trials. In: Peace KE, ed. *Statistical issues in drug research and development*. New York: Marcel Dekker, 1990:331-50.
22. McAlister FA, Straus SE, Sackett DL, Altman DG. Analysis and reporting of factorial trials: a systematic review. *JAMA* 2003;289:2545-53.
23. Westfall PH. Multiple testing of general contrasts using logical constraints and correlations. *J Am Stat Assoc* 1997;92:299-306.
24. Hothorn T, Bretz F, Westfall P. Simultaneous inference in general parametric models. *Biom J* 2008;50:346-63.
25. Kuyucu S, Unal S, Kuyucu N, Yilgor E. Additive effects of dexamethasone in nebulized salbutamol or L-epinephrine treated infants with acute bronchiolitis. *Pediatr Int* 2004;46:539-44.
26. Bentur L, Shoseyov D, Feigenbaum D, Gorichovsky Y, Bibi H. Dexamethasone inhalations in RSV bronchiolitis: a double-blind, placebo-controlled study. *Acta Paediatr* 2005;94:866-71.
27. Tal A, Baviłski C, Yohai D, Bearman JE, Gorodischer R, Moses SW. Dexamethasone and salbutamol in the treatment of acute wheezing in infants. *Pediatrics* 1983;71:13-8.
28. Pauwels RA, Löfdahl CG, Postma DS, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. *N Engl J Med* 1997;337:1405-11. [Erratum, *N Engl J Med* 1998;338:139.]
29. Barnes PJ. Scientific rationale for using a single inhaler for asthma control. *Eur Respir J* 2007;29:587-95.
30. Giembycz MA, Kaur M, Leight R, Newton R. A Holy Grail of asthma management toward understanding how long-acting beta(2)-adrenoceptor agonists enhance the clinical efficacy of inhaled corticosteroids. *Br J Pharmacol* 2008;153:1090-104.
31. Zora JA, Zimmerman D, Carey TL, O'Connell EJ, Yunginger JW. Hypothalamic-pituitary-adrenal axis suppression after short-term, high-dose glucocorticoid therapy in children with asthma. *J Allergy Clin Immunol* 1986;77:9-13.
32. Wenning GK, Wiethölder H, Schnauder G, Müller PH, Kanduth S, Renn W. Recovery of the hypothalamic-pituitary-adrenal axis from suppression by short-term, high-dose intravenous prednisolone therapy in patients with MS. *Acta Neurol Scand* 1994;89:270-3.
33. Streck WF, Lockwood DH. Pituitary adrenal recovery following short-term suppression with corticosteroids. *Am J Med* 1979;66:910-4.
34. American Academy of Pediatrics Committee on Fetus and Newborn, Canadian Pediatric Society Fetus and Newborn Committee. Postnatal corticosteroids to treat or prevent chronic lung disease in preterm infants. *Pediatrics* 2002;109:330-8.
35. Halliday HL, Ehrenkranz RA, Doyle LW. Moderately early (7-14 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. *Cochrane Database Syst Rev* 2003;1:CD001144.
36. *Idem*. Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants. *Cochrane Database Syst Rev* 2003;1:CD001145.
37. *Idem*. Early postnatal (<96 hours) corticosteroids for preventing chronic lung disease in preterm infants. *Cochrane Database Syst Rev* 2003;1:CD001146.

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Pragmatic research

Epinephrine and dexamethasone in children with bronchiolitis

NEMJ 2009; 360:2079 – 89

1. Provide a summary of this paper (max 200 words, short bullet points are acceptable) (6)

2. What is meant by the term 'factorial design' and what advantage may it have? (2)

3. What is meant by the term 'selection' bias. Give an examples of where this potential source of error may be said to have occurred. How does it effect the validity of the study results? (3)

4. The following quote is taken from the paper:
'a randomized, double-blind, placebo-controlled, clinical trial'
 - a) How was randomization achieved and what purpose does it serve? (1)
 - b) What makes an ideal placebo? (1)
 - c) Why should a placebo or a control be used in a RCT? (1)

5. Why is the 'intention to treat' principle for data interpretation used? (1)
Prevents the effects of allocation concealment & allows for protocol deviations

6. Figure 4 illustrates the effects of treatments on secondary outcome measures. Which secondary outcome measures were significantly improved and by what interventions? (2)
Box 2 white

7. The following quote is taken directly from the paper:
'The relative risk of admission by day 7 in group 1 as compared to group 4 was 0.65 (95% confidence interval, 0.45 to 0.95)'
 - a) What is meant by the relative risk? – illustrate your answer(1)
 - b) What is meant by the phrase '95% confidence interval' (1)

8. What is meant by the term 'median'? Give 2 other alternative measures of central tendency. (2)
9. The following quote is taken directly from the paper:
'our factorial design raises the issue of multiple comparisons. To address these limitations, we present the results of both unadjusted analyses and analyses adjusted for multiple comparisons'
- a) What problem may occur with the use of multiple comparisons? (1)
- b) Do you know of any methods for dealing with this issue? (1)
10. How could this study be improved? (1)

Total (24)
Pass mark 15

5 Allows for protocol deviations / drop outs / crossovers.