

# A Randomized Trial of Nebulized Epinephrine vs Albuterol in the Emergency Department Treatment of Bronchiolitis

Colette C. Mull, MD; Richard J. Scarfone, MD; Lara R. Ferri, MD; Teresa Carlin, MD; Christy Salvaggio, MD; Kirsten A. Bechtel, MD; Mary Ann Hanes Trephan, MD; Raquel L. Rissman, MD; Edward J. Gracely, PhD

**Objective:** To determine if nebulized epinephrine is more efficacious than nebulized albuterol in the emergency department (ED) treatment of moderately ill infants with bronchiolitis.

**Methods:** Sixty-six patients between 0 and 12 months of age with new-onset wheezing, an antecedent upper respiratory tract infection, and a clinical score (Respiratory Distress Assessment Instrument) of 8 to 15 were randomized in a double-blind fashion to receive either 0.9 mg/kg of nebulized 2.25% racemic epinephrine (n=34) or 0.15 mg/kg of nebulized 0.5% albuterol sulfate (n=32) at 0, 30, and 60 minutes.

**Main Outcome Measures:** Primary outcome measures were clinical score and respiratory rate. Secondary outcome measures were room air oxygen saturation, elapsed time to meeting clinical criteria for ED discharge, hospitalization rate, and proportion of patients relapsed within 72 hours of ED discharge (relapse rate).

**Results:** Both treatment groups experienced a similar

pattern of change in mean clinical score, respiratory rate, and room air saturation over time. There were no significant differences between the groups by these same measures at any time. The median time at which infants were well enough for ED discharge was 90 minutes in the epinephrine-treated group vs 120 minutes in the albuterol-treated group ( $P = .01$ ). Sixteen infants (47.1%) in the epinephrine-treated group were hospitalized compared with 12 infants (37.5%) in the albuterol-treated group (relative risk, 1.25; 95% confidence interval, 0.71-2.22). Relapse rate was 18.8% (3/16) in the epinephrine-treated group and 42.1% (8/19) in the albuterol-treated group (relative risk, 0.45; 95% confidence interval, 0.14-1.41). Adverse effects occurred infrequently.

**Conclusions:** Although the patients treated with epinephrine were judged well enough for ED discharge significantly earlier than the patients treated with albuterol, epinephrine was not found to be more efficacious than albuterol in treating moderately ill infants with bronchiolitis.

*Arch Pediatr Adolesc Med.* 2004;158:113-118

**D**ESPITE WIDESPREAD USE OF inhaled  $\beta_2$ -agonists for bronchodilation in infants with bronchiolitis since the late 1950s, the efficacy of these drugs remains unproven.<sup>1-3</sup> In 1978, Wohl and Chernick<sup>4</sup> suggested that epinephrine, a combined  $\alpha$ - and  $\beta$ -receptor agonist, would be an ideal bronchodilator. At the time of our manuscript preparation, only 3 emergency department (ED)-based studies comparing nebulized epinephrine with nebulized salbutamol (albuterol) or placebo had been published in the English-language literature.<sup>5-7</sup> A study of 41 infants (aged, 6 weeks to 1 year), with first-time wheezing and "symptoms of viral respiratory infection,"<sup>5(p1004)</sup> demonstrated a greater improvement in the mean percent oxygen saturation and a lower hospital admission rate in infants treated with epinephrine. The epinephrine was found to be superior to salbutamol in a study of 91 children, 0 through

2 years of age, presenting to an ED with "wheezing associated with respiratory tract infection."<sup>6(p13)</sup> In contrast, no benefit was demonstrated among 38 infants treated with just 1 dose of either epinephrine or placebo in an acute care setting.<sup>7</sup>

In our ED at St Christopher's Hospital for Children, Philadelphia, Pa, nebulized albuterol has been the standard of care used for the treatment of children with bronchiolitis. In this study, we sought to determine if 2.25% racemic epinephrine was more efficacious than 0.5% albuterol sulfate in the treatment of bronchiolitis in moderately ill infants, as measured by the degree of clinical improvement (change in clinical score [Respiratory Distress Assessment Instrument] and change in respiratory rate), change in room air oxygen saturation (RAO<sub>2</sub>), elapsed time to meeting clinical criteria for ED discharge, hospitalization rate, and the proportion of patients returning to medical attention for clinical deterioration within 72 hours of ED discharge (relapse rate).

The author affiliations are listed at the end of the article.

**Table 1. Respiratory Distress Assessment Instrument\***

Variable	No. of Points					Maximum Points
	0	1	2	3	4	
Wheezing						
Expiration	None	End	1-2	3-4	All	4
Inspiration	None	Part	All	NA	NA	2
Location	None	Segmental $\leq$ 2-4 lung fields	Diffuse $\geq$ 3-4 lung fields	NA	NA	2
Retractions						
Supraclavicular	None	Mild	Moderate	Marked	NA	3
Intercostal	None	Mild	Moderate	Marked	NA	3
Subcostal	None	Mild	Moderate	Marked	NA	3

Abbreviation: NA, not applicable.

\*Within each variable the subscores are summed to give a total score. The maximum total points for wheezing is 8, and for retractions is 9. Reproduced with permission from Lowell et al.<sup>8</sup>

## METHODS

We conducted a prospective, randomized, double-blind study of epinephrine vs albuterol in the ED treatment of infants moderately ill with bronchiolitis. Candidates for the study were patients younger than 12 months who presented to the St Christopher's Hospital for Children with an acute episode of wheezing, an antecedent upper respiratory tract infection, and a moderate degree of illness (Respiratory Distress Assessment Instrument [RDAI]<sup>8</sup> score, 8-15 [Table 1]). Patients older than 1 year were not enrolled in an attempt to avoid including patients with reactive airway disease who will ultimately be diagnosed as having asthma. Other exclusion criteria were a history of wheezing or chronic cardiorespiratory disease (eg, bronchopulmonary dysplasia), suspected cardiac disease, prior bronchodilator use, and a temperature of 38.0°C or higher in infants younger than 2 months. The ordering of respiratory syncytial viral enzyme-linked immunosorbent assays and chest radiographs was left to the discretion of the ED physician. This study was approved by the hospital's institutional review board.

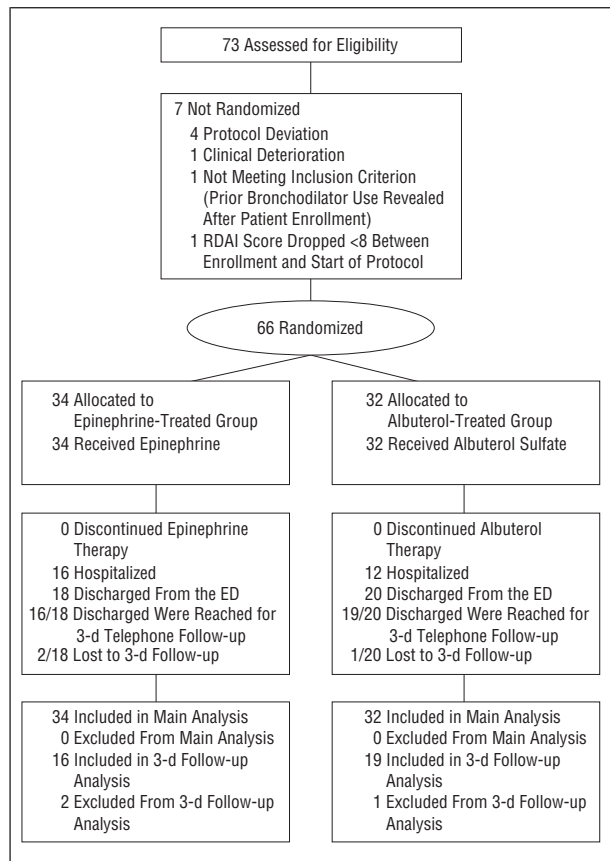
On arrival to the ED, eligible infants were identified by a research assistant who then notified the physician investigator (C.C.M., R.J.S., L.R.F., T.C., C.S., K.A.B., or M.A.H.T.) on call. The investigator examined the infant and assigned an RDAI score. Infants meeting inclusion criteria were invited to participate in the study and written informed consent was obtained from a parent or guardian. Each infant's weight, respiratory rate, RAO<sub>2</sub> (as determined by pulse oximetry), and heart rate were recorded. To test the study hypothesis that epinephrine is more efficacious than albuterol in the ED treatment of infants moderately ill with bronchiolitis, enrolled patients were randomly assigned to receive a dose of either 2.25% racemic epinephrine (0.9 mg/kg) or 0.5% albuterol sulfate (0.15 mg/kg) combined with 2 mL of a 0.9% isotonic sodium chloride solution, delivered by nebulizer using a face mask with continuous flow of 100% oxygen at 6 L/min.

Randomization of patients to receive either epinephrine or albuterol was achieved using a table of random numbers, prepared by a hospital pharmacist. The research assistant calculated, prepared, and administered all study drug doses. Neither the investigator nor the parent or guardian was present for the drug preparation and administration. At no time did the research assistant reveal the drug's identity to either party. In this way, both parties remained blinded. The adverse effect profiles of the 2 study medications are similar enough that unblinding, by noting identifiable drug-specific effects, was highly unlikely. Compliance with medication administration was assured by the research assistant's direct observation of each nebulization and, if need be, by the research assistant's administration of each one. All infants with an RAO<sub>2</sub> of 95% or less received supplemental oxygen when not receiving nebulizations. The

study drug was administered at 0, 30, and 60 minutes. Prior to each drug administration and at 90, 120, and 150 minutes, the investigator assessed the infant's condition and recorded the RDAI score, respiratory rate, RAO<sub>2</sub>, heart rate, and presence or absence of pallor, vomiting, and tremor.

Patients were excluded from the study if the administration of the study drug was delayed by 10 minutes or more (protocol deviation) or if clinical deterioration mandated escalation of therapy and/or support. Patients were in the ED for at least 150 minutes. At the end of that period, the blinded investigator determined the need for admission based on his or her clinical assessment of the infant's condition. Other than supplemental oxygen requirement, there were no absolute admission criteria. In this way, the study sought to model ED disposition decisions as they are made by ED physicians assessing infants with bronchiolitis, that is, by clinical judgment. The investigator was permitted to use factors other than the RDAI score, such as the infant's general appearance or ability to feed, in making disposition decisions. Although all patients completed the 150-minute protocol, if a patient was judged well enough to be discharged from the ED prior to this time, the blinded investigator recorded this as "time well enough for discharge." The primary study outcome measure was the degree of clinical improvement in the infant's condition, as reflected by the RDAI score and respiratory rate. The RDAI score is a clinical score based on the 2 variables of wheezing and retractions<sup>8</sup>; it is the most frequently used clinical scoring instrument in the study of epinephrine for bronchiolitis.<sup>5-7,9</sup> Secondary outcome measures were RAO<sub>2</sub>, time well enough for ED discharge, hospitalization rate, and relapse rate. Discharge medications and instructions were determined by the ED physician caring for the infant; this physician was not involved in the study. The investigators contacted the parents or guardians of discharged study infants via telephone 3 days after their ED visit to determine a relapse rate.

A 2-week pilot study was conducted from January 7, 1998, through January 21, 1998, to help identify the degree of change in the RDAI score that may be considered clinically significant. Based on the findings of previous studies<sup>5,8,9</sup> and the pilot study, an improvement of 3 or more in the RDAI score was determined to be clinically significant. A power analysis revealed that, for detection of this difference of 3 or more in RDAI score with a power of 80%, the total number of study infants required was 66. The study was not powered to detect other outcome measures. In an interobserver reliability exercise for the RDAI, conducted in parallel to the study, combinations of 2 to 5 investigators participated in the joint examination of 18 infants. Using the variance components approach and generalizability methods, analysis of the resulting data using the SPSS/PC + V8 software<sup>10</sup> yielded an interobserver reliability coefficient of 0.73.



**Figure 1.** Study flow diagram. RDAI indicates Respiratory Distress Assessment Instrument; ED, emergency department.

The following data were analyzed using SPSS/PC + V8 software.<sup>10</sup> The difference between the study groups (mean RDAI scores, respiratory rates, and RAO<sub>2</sub>s) at each time point was evaluated with 95% confidence intervals (CIs). Similarly, CIs were used to compare the mean RDAI scores of infants admitted vs those discharged from the ED, and to compare the study groups' hospitalization and relapse rates. The Mann-Whitney test was used to study the time well enough for ED discharge. For some nonnormally distributed variables, the median (50th percentile) and interquartile range (25th and 75th percentiles) were used for descriptive statistics.

## RESULTS

### PATIENT ENROLLMENT

Data collection occurred during 3 consecutive winters (1998-2000). Seventy-three infants were enrolled in the study (**Figure 1**). No parent or guardian approached for enrollment refused to participate in the study. Seven infants were excluded after enrollment. Thus, 66 children were studied.

### PATIENT CHARACTERISTICS

Among the 66 study infants, 1 through 10 months of age, 34 (51.5%) were assigned to the epinephrine group; 36 (54.5%) were boys. Fifty-five infants (83.3%) were products of full-term pregnancies and 9 (13.6%) were born prior to 37 weeks' gestation. At enrollment, no significant differences were noted between the 2 study groups

**Table 2. Patient Characteristics at Study Enrollment\***

Variable	Patients Who Received Epinephrine (n = 34)	Patients Who Received Albuterol Sulfate (n = 32)
Patient age, mo	4.7 (2.6)	4.1 (2.0)
Gestational age, wk	39.0 (2.7)	39.4 (2.1)
Male patients, No. (%)	19 (55.9)	17 (53.1)

\*Data are given as mean (SD) unless otherwise indicated.

**Table 3. Patient's Degree of Illness at Study Enrollment\***

Variable	Patients Who Received Epinephrine	Patients Who Received Albuterol Sulfate
Heart rate, beats/min	157.9 (19.4)	158.5 (15.2)
Respiratory rate, breaths/min	53.8 (13.5)	55.7 (16.5)
RAO <sub>2</sub> , %	96.6 (4.1)	97.5 (2.3)
RDAI score	10.1 (1.4)	10.0 (2.0)

\*Abbreviations: RAO<sub>2</sub>, room air oxygen saturation; RDAI, Respiratory Distress Assessment Instrument.

\*Data are given as mean (SD).

with respect to patient characteristics (**Table 2**) or degree of illness (**Table 3**).

### MAIN OUTCOME MEASURES

Mean RDAI score improved significantly with time across the study population ( $P < .001$ ) (**Figure 2**). No time point revealed a significant difference between the study groups (mean RDAI scores) (**Table 4**). At no time did the 95% CIs for the difference between the treatment groups' mean RDAI score support a mean RDAI score difference of more than 2.2 favoring albuterol or 2.6 favoring epinephrine, each less than the clinically significant difference of 3 (Table 4). The mean RDAI score of infants who required admission (7.5, n=28) was higher than that of those who were discharged from the ED (4.3, n=38) (mean difference, 3.2; 95% CI, 1.71-4.66).

Mean respiratory rate improved significantly with time across the study population ( $P < .001$ ) (**Figure 3**). No time point revealed a significant difference between the treatment groups' mean respiratory rates (**Table 5**).

Mean RAO<sub>2</sub> improved significantly with time across the study population ( $P = .02$ ) (**Figure 4**). No time point revealed a significant difference between the treatment groups' mean RAO<sub>2</sub>s (**Table 6**). The median time well enough for ED discharge was significantly less in the epinephrine-treated group, 90 minutes (interquartile range, 60-120 minutes), than in the albuterol-treated group, 120 minutes (interquartile range, 92.5-157.5 minutes) ( $P = .01$ ). Study group hospitalization rates did not significantly differ—epinephrine 47.1% (16/34) vs albuterol 37.5% (12/32) (relative risk, 1.25; 95%CI, 0.71-2.22).

### ADVERSE EFFECTS

Adverse effects were few. No infant experienced tremor. Six infants vomited during the course of the study pro-

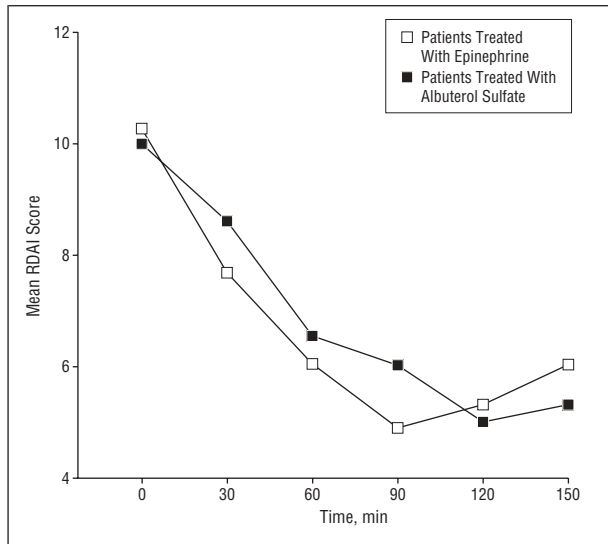


Figure 2. Mean Respiratory Distress Assessment Instrument (RDAI) score by time.

**Table 4. Difference Between Study Groups' Mean RDAI at All Time Points**

Time, min	Mean RDAI <sub>Epi</sub> - Mean RDAI <sub>Alb</sub>	95% CIs	
		Lower	Upper
0	0.06	-0.80	0.91
30	-1.10	-2.37	0.17
60	-0.75	-2.10	0.60
90	-1.27	-2.60	0.04
120	-0.08	-1.62	1.46
150	0.50	-1.17	2.17

Abbreviations: Alb, albuterol; CIs, confidence intervals; Epi, epinephrine; RDAI, Respiratory Distress Assessment Instrument.

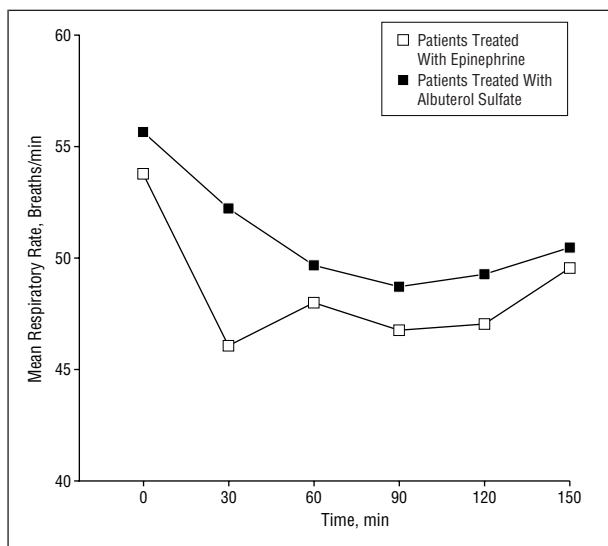


Figure 3. Mean respiratory rate by time.

tolcol; 1 (2.9%) of 34 infants from the epinephrine-treated group and 5 (15.6%) of 32 infants from the albuterol-treated group. One infant from the epinephrine-treated group exhibited pallor.

**Table 5. Difference Between Study Groups' Mean RR at All Time Points**

Time, min	Mean RR <sub>Epi</sub> - Mean RR <sub>Alb</sub>	95% CIs	
		Lower	Upper
0	-1.95	-9.36	5.45
30	-6.26	-11.36	-1.15
60	-1.81	-7.57	3.94
90	-1.89	-8.54	4.75
120	-2.25	-8.87	4.37
150	-1.03	-8.93	6.87

Abbreviations: Alb, albuterol; CIs, confidence intervals; Epi, epinephrine; RR, respiratory rate.

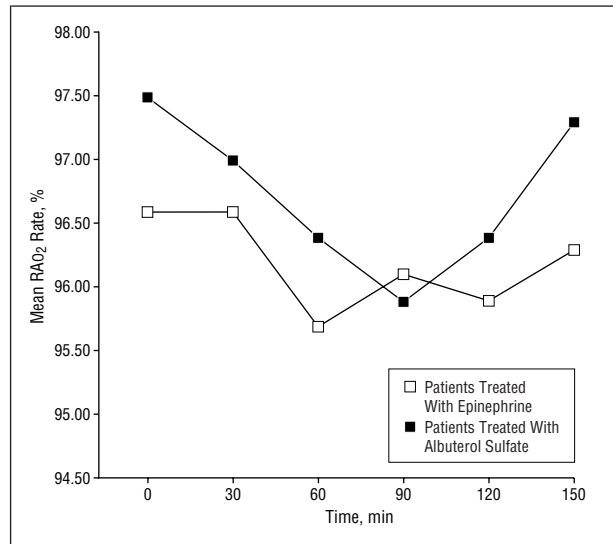


Figure 4. Room air oxygen saturation (RAO<sub>2</sub>) by time.

**Table 6. Difference Between Study Groups' Mean RAO<sub>2</sub> at All Time Points**

Time, min	Mean RAO <sub>2Epi</sub> - Mean RAO <sub>2Alb</sub>	95% CIs	
		Lower	Upper
0	-0.94	-2.59	0.71
30	-0.41	-1.99	1.16
60	-0.73	-2.76	1.30
90	0.18	-1.91	2.27
120	-0.58	-2.68	1.51
150	-1.02	-2.77	0.73

Abbreviations: Alb, albuterol; CIs, confidence intervals; Epi, epinephrine; RAO<sub>2</sub>, room air oxygen saturation.

### FOLLOW-UP DATA

Thirty-eight infants were discharged from the ED. All infants were discharged with instructions to use albuterol. Three days following ED discharge, telephone contact was made with the parents or guardians of 35 treated infants; follow-up rate of 92.1%. Eight (42.1%) of 19 infants in the albuterol-treated group returned to medical attention; 6 returned to an ED (4 were admitted to a hospital) and 2 to their primary physician's office (1 was hospitalized). Three

(18.8%) of 16 infants in the epinephrine-treated group returned to medical attention; all 3 returned to an ED (2 were admitted to a hospital). There was no significant difference in the relapse rate between the 2 study groups (epinephrine vs albuterol; relative risk, 0.45; 95% CI, 0.14-1.41).

#### COMMENT

Data from this prospective, randomized, double-blind study demonstrate that infants moderately ill with bronchiolitis treated with epinephrine experienced the same degree of improvement in clinical score, respiratory rate, and RAO<sub>2</sub> over time as those treated with albuterol. Furthermore, there were no significant differences in hospitalization rate, adverse effects, or relapse rate between these treatment groups. There was no trend toward decreased hospitalization in the epinephrine-treated group. However, the median time at which patients were well enough for ED discharge was earlier in the epinephrine-treated group than in the albuterol-treated group.

At our manuscript preparation, 7 prospective, randomized, double-blind studies have compared nebulized epinephrine to nebulized salbutamol, albuterol, or placebo in the treatment of bronchiolitis<sup>5-7,9,11-13</sup>; 3 of these studies were conducted in an ED.<sup>5-7</sup> Menon et al<sup>5</sup> randomly assigned 41 infants to receive either epinephrine or salbutamol. These investigators found that the mean RAO<sub>2</sub>, a main study outcome, was significantly higher among epinephrine-treated children at 60 minutes than among salbutamol-treated children.<sup>5</sup> In addition, their epinephrine-treated group had a lower hospitalization rate and a significantly more rapid rate of ED discharge than their salbutamol-treated group. Menon et al included patients with mild bronchiolitis (RDAI score  $\geq 4$ ), treated patients with just 2 doses of the study drug, and failed to demonstrate significant differences in improvement of the RDAI score or respiratory rate between the epinephrine-treated and salbutamol-treated groups. As such, it is difficult to explain the significantly lower admission rate (33%) of their epinephrine-treated group compared with that of their salbutamol-treated group (81%).<sup>5</sup> Similarly, despite no significant difference in mean RDAI scores between our epinephrine- and albuterol-treated groups, our epinephrine-treated infants had a more rapid rate of ED discharge. Menon et al<sup>5</sup> did not comment on the possible reasons for the difference in ED discharge rates between their 2 study groups. We speculate that there may have been clinical findings other than those assessed by the RDAI score (eg, mental status, aeration, inspiratory-expiratory ratio) that differed significantly enough between our 2 study groups to lead to the earlier ED discharge of epinephrine-treated infants. Future studies will be needed to confirm this hypothesis and identify such factors. There is some subjectivity in the use of a clinical score to assess the degree of clinical improvement. However, the RDAI has frequently been used in studies of the role of epinephrine in bronchiolitis.<sup>5-9</sup> Its internal validity was established previously<sup>8</sup> and excellent interobserver reliability with the RDAI has been reported by ourselves as well as other investigators in this field of study.<sup>5,6,8,9</sup> An alternative means of clinical assessment would have been to perform pulmonary function testing in sedated subjects. This would have been technically

difficult and the results would not have been generalizable to the ED.

Ray and Singh<sup>6</sup> randomized 91 children, age 0 to 2 years, with "wheezing associated with respiratory tract infection to receive either epinephrine or salbutamol."<sup>6</sup> (p13) In this study, patients treated with epinephrine had significantly greater improvement in mean RAO<sub>2</sub> and a significantly lower mean RDAI score and admission rate compared with those treated with salbutamol. By enrolling children up to 2 years of age and not excluding those with a history of wheezing, it is likely that Ray and Singh's study population included some children with asthma who may respond differently to epinephrine than do those with bronchiolitis. We attempted to exclude children with asthma by not enrolling children older than 1 year and/or those with a history of wheezing. Furthermore, since Ray and Singh's study subjects were severely ill (mean RDAI score,  $> 13$ ; mean RAO<sub>2</sub>, 91%), their results may not be generalizable to a moderately ill population. In a more recent study, Abul-Ainine and Luyt<sup>7</sup> failed to find a significant difference between the mean RDAI scores of infants treated with epinephrine and of those treated with an isotonic sodium chloride solution. However, because there were just 19 children in each study group and because they were treated with just 1 dose of epinephrine or placebo, it is possible that a clinically significant difference might have been missed.

In addition to using strict enrollment criteria to identify children with bronchiolitis, our study had other strengths. In contrast to the 3 previous ED-based studies, we used a clinical score (RDAI) and respiratory rate as our primary outcome measures. The RDAI is a non-invasive scoring instrument that may be easily adopted by clinicians in a nonstudy setting. Also, since the dose of 2.25% racemic epinephrine used in our study (0.9 mg/kg) was considerably higher than that used by Menon et al<sup>5</sup> (3 mg), Ray and Singh<sup>6</sup> (0.1 mg/kg), and Abul-Ainine and Luyt<sup>7</sup> (3 mg), it is not likely that the demonstrated lack of a clear benefit of epinephrine was caused by our underdosing of the study medication.

Our study had some limitations. Our study population consisted of a convenience sample of patients and potentially eligible children were not enrolled. We have no reason to suspect that moderately ill infants with bronchiolitis in the ED at times when research assistants or investigators were unavailable to enroll them in the study would have responded differently to study medications. The study took parts of 3 winters to complete because it started at the end of the first winter and was not fully completed by the end of the second winter (61 [92%] of study population enrolled by then). Also, these results may not be generalizable to children in a non-ED setting.

We evaluated 66 children in our study. Based on pre-study estimates, this sample size was large enough to exclude the possibility of a type II error. Although it is possible that small differences between the 2 drugs' effects on the subjects may have become apparent with a larger sample size, it is unlikely that these differences would have been clinically meaningful. The study was not powered to detect differences in secondary outcome measures.

The use of albuterol to treat infants with bronchiolitis was the standard of care in our ED at the time this study

### What This Study Adds

Previous studies assessing the use of epinephrine in the treatment of bronchiolitis have left unconfirmed the hypothesis that epinephrine therapy is more efficacious than salbutamol or albuterol in the ED treatment of moderately ill infants with this disease. Our prospective, randomized, double-blind study of epinephrine vs albuterol in the ED treatment of infants moderately ill with bronchiolitis demonstrates that epinephrine is as safe as, but not more efficacious than, albuterol in this setting. The epinephrine-treated patients' more rapid rate of discharge from the ED suggests that a subset of patients may be more responsive to epinephrine. Results of our study suggest that either epinephrine or albuterol may be used by ED physicians in the treatment of moderately ill infants with bronchiolitis.

was initiated. Our study question was whether epinephrine was more efficacious than the current standard of care. Although it is likely that a benefit of epinephrine therapy would have been demonstrated had it been compared with placebo, we believe it would have been inappropriate to compare epinephrine with a placebo.

Finally, our method omitted testing study subjects for nasopharyngeal colonization of respiratory syncytial virus. Albeit the most common pathogen implicated in bronchiolitis, respiratory syncytial virus is one of many viruses associated with this disease.<sup>14,15</sup> We believe that our enrollment criteria were stringent enough to select for a population of children with clinical bronchiolitis and we did not wish to exclude those children with bronchiolitis caused by viruses other than respiratory syncytial virus.

### CONCLUSIONS

Our study has demonstrated that epinephrine is as safe as, but not more efficacious than, albuterol in the treatment of infants moderately ill with bronchiolitis. The use of epinephrine was not found to result in substantial clinical benefits compared with the use of albuterol. Although epinephrine-treated patients were judged well enough to be discharged from the ED significantly earlier than albuterol-treated ones, the clinical relevance of this 30-minute difference between the 2 study groups is debatable. Also, epinephrine has the disadvantage of being unable to be administered at home. These data suggest that use of either epinephrine or albuterol is a reasonable option in the treatment of infants moderately ill with bronchiolitis. Since there may be subsets of infants who will respond preferentially to one drug or the other, it is reasonable to administer epinephrine to infants with bronchiolitis who have a suboptimal response to initial treatments of albuterol.

Accepted for publication October 16, 2003.

From the Division of Emergency Medicine, Alfred I. duPont Hospital for Children, Wilmington, Del (Dr Mull); Emergency Department, Children's Hospital of Philadelphia, Philadelphia, Pa (Dr Scarfone); Division of Emergency Medicine, Children's Hospital, Boston, Mass (Dr Ferri); Department of Emergency Medicine, The Johns Hopkins University, Bal-

timore, Md (Dr Carlin); Section of Emergency Medicine, St Christopher's Hospital for Children, Philadelphia (Dr Salvaggio); Section of Emergency Medicine, Yale-New Haven Children's Hospital, New Haven, Conn (Dr Bechtel); Emergency Department, Kaiser Permanente Medical Group, Woodland Hills, Calif (Dr Hanes Trephan); Department of Pediatrics, Children's Hospital of Orange County (California), Orange (Dr Rissman); and the Department of Community and Preventive Medicine, Drexel University College of Medicine, Philadelphia (Dr Gracely).

This study was supported by a \$5000 grant from Nephron Pharmaceuticals Company; monies were used solely for research assistants (stipends). Nephron Pharmaceuticals Company had no role in the design, conduct, interpretation, and analysis of the study and review or approval of the manuscript.

We are indebted to our research coordinators, Leo T. Kroonen, MD (1998-1999), and Gregory T. Poulter, MD (1999-2000), and our research assistants: Mary Elizabeth Alvarez, MD; Latanya Benjamin, MD; Avnish Bhatia, MD; Carrie Bohenic, MD; Jill Fasciana McCoy, MD; Lisa D. Morrison, MD; Amanda J. Nadelson, MD; Wendy E. Schofer, MD; and Abigail E. Zimskind, MD. We thank Sammy Mellissen for her technical assistance, and St Christopher's Hospital for Children's (1998-2000) pediatric housestaff, pharmacy, and ED nursing staff. We are grateful to Brent King, MD, Zach Kassutto, MD, John Loiselle, MD, and Magdy Attia, MD, for their support of this project.

Corresponding author and reprints: Colette C. Mull, MD, Division of Emergency Medicine, Alfred I. duPont Hospital for Children, 1600 Rockland Rd, Wilmington, DE 19899 (e-mail: cmull@nemours.org).

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