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ABSTRACT. *Objectives.* **To determine whether the use of albuterol by nebulization enhances physiologic or clinical recovery in hospitalized infants with moderate bronchiolitis.**

Methods. **This prospective, double-blind, placebo-controlled, randomized clinical trial was performed from December 1995 to March 1996. A total of 52 patients <24 months of age with a diagnosis of moderately severe, acute viral bronchiolitis were enrolled and assigned to receive nebulized albuterol or normal saline placebo for 72 hours under a standardized protocol. Primary outcome measures included improvement in oxygen saturation (Sao_2) during hospitalization and survival analysis to assess the time required to reach preestablished discharge criteria on three measures: Sao_2, accessory muscle use, and wheezing. An additional secondary outcome measure was actual length of hospital stay. Adverse outcomes also were compared between treatment groups.**

Results. **There was no significant difference in mean Sao_2 between albuterol and placebo at baseline, 24 hours, or maximum Sao_2 achieved during hospitalization. Both groups showed significant improvement in oxygen saturation over time, but there was no significant difference in improvement between the two groups. The study had a power of 90% to detect a difference in mean percentage point improvement of 2% Sao_2. There was no difference in time to reach discharge criteria as defined by Sao_2, accessory muscle use, or wheezing. There was no difference in length of hospital stay or in the frequency of adverse outcomes.**

Conclusions. **Nebulized albuterol therapy does not appear to enhance recovery or attenuate severity of illness in infants hospitalized with acute, moderate bronchiolitis, as evidenced by improvement in oxygen saturation, time to meet standardized discharge criteria, or length of hospital stay.** *Pediatrics* **1998;101:361–368;** ***bronchiolitis, respiratory syncytial virus infections, infant, wheezing, hospitalization, albuterol, adrenergic β-agonists, bronchodilator agents.***

ABBREVIATIONS. RSV, respiratory syncytial virus; Sao_2, oxygen saturation; Max Sao_2, maximal oxygen saturation achieved during hospitalization.

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Bronchiolitis is an acute inflammatory respiratory illness of children that occurs in the first 2 years of life and is characterized by fever and/or rhinitis, tachypnea, expiratory wheezing, and increased respiratory effort. Bronchiolitis occurs in a seasonal pattern, with peak incidence in the winter to spring months. Several viral agents have been identified as causing bronchiolitis (respiratory syncytial virus [RSV], parainfluenza, adenovirus, influenza, and rhinovirus), with RSV being the most prevalent. The incidence of bronchiolitis has been shown to be as high as 11 cases per 100 children per year for both the first and second 6 months of life.[1,2] In the first 6 months of life, 6 children per 1000 are hospitalized with bronchiolitis per year in the United States.[3] The care of hospitalized infants with bronchiolitis represents a major portion of health care efforts and costs, estimated to be ~$300 million each year. Cost of hospitalization is influenced by illness severity, length of stay, and the specific treatments used in the hospital.[4,5]

The traditional approach to symptomatic management of bronchiolitis has been supportive care with attention to oxygen therapy, hydration, and respiratory support as needed.[6] The use of nebulized albuterol and other β-adrenergic agents in the therapy of bronchiolitis has been debated for over 20 years. In the outpatient setting, short-term benefit from nebulized β-adrenergic bronchodilators has been demonstrated through improvements in oxygen saturation or clinical respiratory scores, and some authors support their use in the treatment of infants with bronchiolitis.[7–10] Using similar methods, other studies evaluating the short-term effects of albuterol have shown no or equivocal benefit.[11,12] Studies evaluating the effects of bronchodilators on pulmonary mechanics in infants with bronchiolitis also have shown mixed results.[11,13–18] None of these studies have evaluated the efficacy of patients receiving nebulized albuterol treatments beyond 4 hours or have advocated the use of bronchodilators as a means of reducing hospitalizations or length of stay.[6]

One previous study has evaluated the effects of albuterol on long-term clinical and physiologic recovery in hospitalized patients with bronchiolitis. Although no benefit of treatment with albuterol was demonstrated, the small sample size limited the power to detect a statistically significant difference between treatment groups. Additionally, study patients had clinically mild bronchiolitis, as shown by normal oxygen saturation (Sao_2 = 96% at enrollment) and low clinical score at admission.[19]

Based on this review of the literature, we felt that a clinical trial with sufficient power was necessary to help clinicians evaluate the efficacy of albuterol in the treatment of the hospitalized infant with moderately severe bronchiolitis. The objective of this study was to evaluate whether the use of albuterol by nebulization in hospitalized patients with bronchiolitis enhances clinical and physiologic recovery as demonstrated by 1) a greater improvement in oxygen saturation on room air during hospitalization when compared with saline placebo; 2) decreased time for patients to reach predetermined discharge criteria based on three measures (oxygen saturation, accessory muscle use, and wheezing); or 3) decreased length of hospital stay.

METHODS

This prospective, double-blinded, placebo-controlled, randomized clinical trial was performed at Maricopa Medical Center, a tertiary medical care facility in Phoenix, AZ. All patients <24 months of age who were admitted to the general pediatric inpatient unit with a first episode of wheezing during bronchiolitis season (November 1995 through March 1996) were eligible for study. Patients were evaluated consecutively for enrollment on the first hospital day (within 12 hours of admission) by one of five on-call study investigators (J.D., S.S., S.M., S.B., or M.S.) using a standardized complete respiratory history and clinical evaluation. Initial history included age, gender, race, duration of illness, history of previous wheezing, current medications, allergies, family history of wheezing or smoking, birth history, history of previous chronic illnesses, cardiac or pulmonary disease, and the presence or absence of cough, fever, rhinorrhea or wheezing. Children meeting criteria for the diagnosis of viral bronchiolitis, defined as an acute infection of the lower respiratory tract, preceded by or accompanied by fever and/or rhinitis, and characterized by tachypnea, expiratory wheezing, and increased respiratory effort, were approached for study enrollment. Children were excluded from the study if they had underlying chronic cardiac or pulmonary disease, significant concurrent illness (sepsis, meningitis, pneumonia, urinary tract infections, gastroenteritis), current gestational age <38 weeks, history of wheezing requiring hospitalization or bronchodilators, history of bronchodilator therapy before current illness, concurrent steroid treatment, or severe bronchiolitis requiring intensive care (mechanical ventilation, documented apnea, heart rate >200 beats per minute, or hypercarbia). Only infants defined as having moderately severe acute bronchiolitis were eligible for study. Moderate severity was defined in this study as having at least one of the following findings on initial evaluation: oxygen saturation on room air <94%, moderate to severe accessory muscle use (clinical score ≥2), or moderate to severe wheezing (clinical score ≥2) (Table 1).

Patients meeting eligibility criteria were enrolled by a study investigator on the first hospital day after obtaining language-appropriate written informed consent (English or Spanish) from the child's parent or guardian. Direct patient care was supervised by the pediatric inpatient team (pediatric inpatient attending and house officers) independent of the study investigators. Both the study investigators and the pediatric inpatient team were blinded to the study drug. Study patients were disenrolled at any time at parental request or if the pediatric inpatient team deemed it necessary to discontinue the study drug for clinical considerations.

Study patients were randomly assigned to receive blinded treatment with either albuterol or normal saline placebo in the following manner: albuterol (1.25 mg for patients <10 kg and 2.5 mg for patients >10 kg in normal saline to make a total volume of 3 mL) or saline placebo (3 mL of normal saline). The study drug, prepared in the hospital pharmacy and supplied in individual identical containers, was administered by a respiratory therapist, also blinded to the identity of the study drug, via nebulized aerosol every 2 hours for the first 24 hours, then every 4 hours for the next 48 hours. Dosage, route, schedule of drug administration, and clinical evaluations were selected to approximate standard regimens used for bronchiolitis. Routine supportive care (oxygen administration, intravenous hydration, nasopharygeal suctioning, and chest physiotherapy) and actual time of discharge were determined by the pediatric inpatient team. No study patient received steroid therapy or other respiratory medications (eg, ipatropium, racemic epinephrine). All study patients were monitored continuously by routine pulse oximetry to detect deteriorating pulmonary status and potential β-adrenergic cardiovascular side effects such as tachycardia. Oxygen was administered as needed by the pediatric inpatient team to keep oxygen saturation ≥94% except during clinical evaluations.

Baseline assessments included chest x-ray and RSV analysis by direct fluorescent antibody testing, with additional viral testing via respiratory panel if RSV test results were negative. Clinical assessments were performed by a study investigator at baseline (time 0) and at 24 hour intervals for a maximum of 72 hours or until the patient's discharge from the hospital (whichever came first). The assessment included separate clinical scores for general appearance, accessory muscle use, and wheezing, adapted from Schuh and colleagues[8] (Table 1). In addition to routine pulse oximetry monitoring, oxygen saturation (Sao_2) was recorded after equilibration to room air over a 15-minute interval and the mean Sao_2 calculated using a cardiorespiratory monitor with trending capabilities (Passport Non-invasive Cardio-respiratory Monitor and Pulse Oximeter, Datascope Corp, Paramus, NJ). During the evaluation of Sao_2 on room air, oxygen therapy was reinstituted if the patient desaturated to <86% for >1 minute, or if the patient developed increasing respiratory distress or tachycardia. Because we were seeking to follow overall recovery and not short-term or transient nebulized study drug effects, all clinical evaluations were made immediately before the next scheduled study drug treatment. To control for increased wheezing or accessory muscle use secondary to excessive secretions or agitation, all study patients received chest physiotherapy and nasal suction 5 to 10 minutes before clinical evaluation, and were only examined when asleep (general appearance score = 0) or awake, calm, and content (general appearance score = 1). During evaluation of accessory muscle use and wheezing, oxygen was administered, if necessary,

TABLE 1. Clinical Score*

General appearance	0	Asleep
	1	Calm, content, happy, and or interactive
	2	Mildly irritable when touched, occasional crying, but able to be consoled
	3	Moderately irritable, difficult to console, less interactive
	4	Extremely irritable, cannot be comforted, crying throughout examination, or not interactive
Accessory muscle use	0	No retraction
	1	Mild retractions (mild intercostal supra, and/or subcostal retractions, but minimal distress)
	2	Moderate retractions (obvious intercostal, supraclavicular, and/or subcostal retractions with moderate distress)
	3	Severe retractions (severe intercostal supraclavicular and subcostal retractions with marked distress)
Wheezing	0	No wheezing or crackles
	1	Wheezing (scattered, end-expiratory wheezes or crackles only)
	2	Moderate wheezing (diffuse expiratory wheezes ± scattered early inspiratory wheezes)
	3	Severe wheezing (diffuse inspiratory and expiratory wheezing

* Adapted from Schuh et al.[8]

to ensure an Sao_2 level ≥94% to control for worsening clinical status induced by hypoxemia.

Primary outcome measures included improvement in oxygen saturation on room air during hospitalization and the time required to independently reach three separate preestablished discharge criteria. For the purposes of this study, clinical criteria compatible with continued need for hospitalization were defined to be hypoxia (Sao_2 on room air <94%), moderate to severe accessory muscle use (clinical score ≥2), or moderate to severe wheezing (clinical score ≥2). Survival analysis was chosen to assess time to reach discharge criteria, because it allowed the incorporation of censored cases (those who were discharged before 72 hours) in the statistical analysis and provided a tool for analysis of noncontinuous (ordinal) data points obtained through the use of clinical scores. An additional secondary outcome measure was actual length of hospital stay as determined by the pediatric inpatient team. The decision to discharge a patient was made by the pediatric inpatient team independent of the study investigator's clinical evaluation of severity of illness. Accordingly, it represented a separate measure of treatment efficacy. Adverse outcome measures, including incidence of cardiovascular side effects or deteriorating respiratory status requiring additional respiratory or intensive care support, also were compared between treatment groups.

To collect the data required for a comprehensive power analysis and to test the reliability of proposed measurement tools and the feasibility of the research protocol, a pilot study was conducted during December 1995, using a total of 20 patients, 10 randomly assigned to each arm. To control for interobserver variability, each patient was evaluated independently by two study investigators during each observation period. All study investigators were shown to reach a concordance of at least 80% in independent evaluation of clinical scores compared with that of the principal study investigator (J.D.). Analysis of the pilot data revealed that ~26 patients per group would be required to achieve a power >80% in the primary outcome measure (improvement in Sao_2). This would detect a difference in improvement of two percentage points in Sao2 between placebo and albuterol treatment groups with a P value < .05.

Between-group comparisons of baseline data were performed using χ^2 tests for categorical indicators and t tests for continuous variables. Distributional properties of continuous data were evaluated to ensure that distributional assumptions were satisfied. Repeated-measures analysis of variance was used to assess changes in Sao_2 at each of the 24-hour observation periods. Each study patient served as his or her own control. The significance of change (criterion) in Sao_2 from baseline was determined using Dunnett's q test. Survival analysis was used to assess the time required for patients to reach preestablished discharge criteria. The Cox proportional hazards model was used to compare the albuterol and saline groups while controlling simultaneously for other factors that might influence recovery, such as number of albuterol treatments before enrollment in the study, age, or duration of illness. The log rank test was used to assess the equality of the distributions. The frequency of adverse outcomes was compared across the two groups, using appropriate nonparametric statistics.

The protocol and informed consent for this study were reviewed and approved by the Institutional Review Board for Human Research of Maricopa Medical Center.

RESULTS

A total of 58 patients were randomized to the study protocol. Of these, three were disenrolled by request, because the parent or guardian desired discontinuation in the study. All three were disenrolled during the first 24 hours of the study protocol and none showed signs of clinical deterioration, thus, they were excluded from the statistical analysis. Three study patients were withdrawn by the pediatric inpatient team because of worsening clinical status. All three study patients had been randomized to receive albuterol. Table 2 shows the baseline characteristics of the remaining 52 study patients by treatment group. There were no statistically significant differences in any measured parameters at baseline.

There was no significant difference in mean Sao_2 between albuterol and placebo at time 0 ($P = .61$), 24 hours after randomization ($P = .77$), or at time of maximal oxygen saturation (Max Sao_2, $P = .85$) achieved during hospitalization (Fig 1). Each group did show significant improvement ($P < .05$) in oxygen saturation on room air over time (Table 3). Improvement in oxygen saturation was measured as the mean percentage point increase in Sao_2 over three separate time intervals (time 0 to 24 hours, time 0 to Max Sao_2, and 24 hours to Max Sao_2). However, when comparing the albuterol and placebo groups for each time period, there was no significant difference in improvement between the two groups ($P = .86$, .48, and .55, respectively, for the three time intervals measured). Although pilot study data predicted a power of 80% to detect a difference in mean percentage point improvement of 2% Sao_2 between treatment groups, analysis of our final data indicated that a power of 90% had been achieved.

The percentage of patients meeting hospitalization criteria on each day in the two treatment groups was evaluated using survival analysis. Figure 2 shows the percentage of patients on albuterol and placebo with an Sao_2 on room air <94% at baseline and at 24-hour intervals. Figures 3 and 4 show the percentage of patients by treatment group meeting hospitalization criteria at each time interval for accessory muscle use and wheezing, respectively. There were no significant statistical differences in time to reach discharge criteria in these three defined categories. Figure 5 compares the percentage of patients on albuterol and placebo discharged from the hospital at 24, 48, and 72 hours by the pediatric inpatient team. Although it appears that a greater percentage of patients on placebo were discharged by 72 hours (69% vs 52.2%), this does not reach statistical significance ($P = .24$). Because baseline data indicated a young mean age of enrolled patients (5.6 months), subgroup analysis of patients <12 months of age was undertaken (45 of 52 study patients, or 86% of the study population). Results and conclusions from this truncated analysis were the same as with the full group.

No patients in either treatment group experienced clinically significant adverse cardiovascular side effects (tachycardia or dysrhythmia). Three patients in the albuterol treatment group were withdrawn by the pediatric inpatient team because of deterioration in respiratory status (oxygen desaturation and increasing respiratory distress). None of the three required mechanical ventilation, and all recovered over time. Comparison of adverse effects for albuterol versus control groups approaches, but does not reach, statistical significance ($P = .10$).

DISCUSSION

A unique feature of this study was the attempt to evaluate whether albuterol enhances overall clinical and physiologic recovery independent of short-term bronchodilator effects. To achieve this, patients were evaluated at the longest possible interval (at least 2 hours in all cases) from their previous nebulized

TABLE 2. Baseline Characteristics of the Study Groups*

	Albuterol (n = 23)	Placebo (n = 29)	P
Age (months)	5.1 ± 3.7	6.1 ± 5.4	.491 (NS)†
Gestational age at birth (months)	39.2 ± 1.6	38.8 ± 2.4	.522 (NS)
Male/female	9/14	16/13	.278 (NS)
Weight (kg)	6.8 ± 1.9	7.2 ± 2.4	.546 (NS)
Viral agent (%)			
RSV	17 (74)	25 (86)	.156 (NS)
Other	6 (26)	4 (14)	
History of (%)			
Fever	15 (65)	20 (69)	1.0 (NS)
Cough	23 (100)	29 (100)	1.0 (NS)
Rhinorrhea	22 (96)	29 (100)	.44 (NS)
Wheezing	20 (87)	23 (79)	.714 (NS)
Duration of (days)			
Fever	2.9 ± 1.5	2.6 ± 1.5	.612 (NS)
Cough	3.6 ± 1.6	3.6 ± 1.8	.977 (NS)
Rhinorrhea	3.5 ± 1.5	3.6 ± 1.8	.786 (NS)
Wheezing	2.3 ± 1.5	2.9 ± 1.9	.292 (NS)
Race			
Latino-American	21	20	.163 (NS)
White	1	6	
African-American	0	2	
Native American	1	1	
Family history of wheezing (%)	7 (30)	14 (48)	.259 (NS)
Exposure to smokers (%)	6 (26)	12 (41)	.379 (NS)
Pretreatment with nebulized albuterol			
Patients (%)	20 (87)	26 (90)	1.0 (NS)
Treatments (no.)	2.1 ± 1.8	2.9 ± 2.4	.214 (NS)
Heart rate	161 ± 16	156 ± 22	.415 (NS)
Respiratory rate	48 ± 9	50 ± 13	.518 (NS)
Sao_2	91.4 ± 3.9	91.9 ± 2.5	.61 (NS)
Accessory muscle score‡			
%	69.6	75.9	
Median	2.0	2.0	.65 (NS)
Wheeze score‡			
%	56.5	69	
Median	2.0	2.0	.66 (NS)

* Plus–minus values are means ± SD.
† Significance level, $P < .05$. NS, not significant.
‡ Percentage of patients meeting criteria for hospitalization and median clinical score.

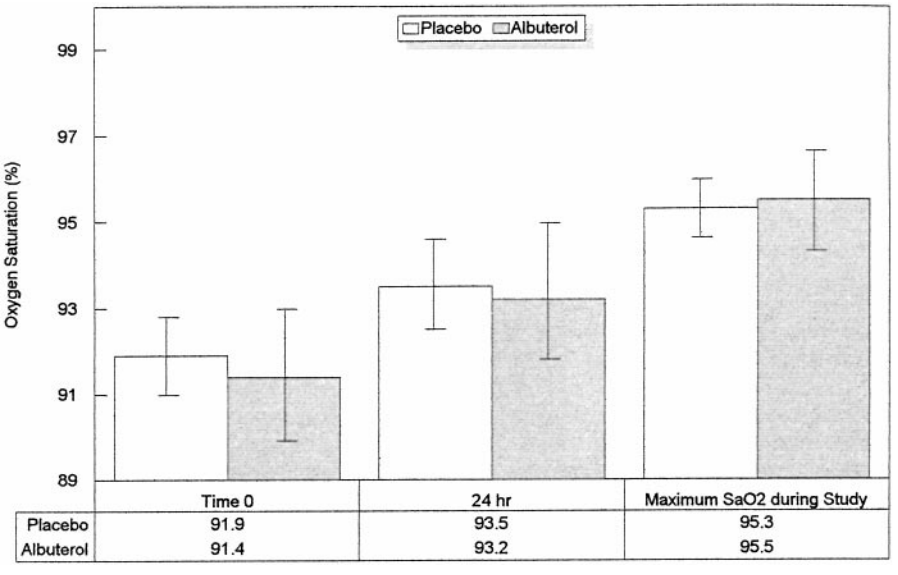

Fig 1. Oxygen saturation on room air at time 0, 24 hours, and Max Sao_2 by treatment group. Error bars are 95% confidence intervals.

drug treatment. Previous studies have evaluated only the short-term effects of bronchodilator administration, with both beneficial and deleterious effects being documented.[7–9,11,20,21] Ho and coworkers, by continuously measuring oxygen saturation on room air after nebulized albuterol administration, demonstrated that 9 of 13 infants with bronchiolitis had a transient desaturation >4% Sao_2 compared with only 2 of 8 after saline administration. The most significant decrease occurred between 5 and 10 minutes after administration and had completely resolved within 60 minutes.[20] Stokes et al demonstrated that

TABLE 3. Improvement in % Sao_2 on Room Air Over Time*

	Albuterol	Placebo
Time 0 to 24 hours	1.8% (0.1%–3.6%)	1.6% (0.2%–3.0%)
24 hours to Max Sao_2	2.2% (1.3%–3.1%)	1.8% (0.9%–2.8%)
Time 0 to Max Sao_2	4.0% (2.6%–5.4%)	3.4% (2.4%–4.5%)

* Results are mean percentage point improvement in Sao_2 with 95% confidence intervals in parentheses.

nebulized albuterol increased the mean work of breathing per minute by 22%, and took an average of 15 minutes to resolve.[22] Transient albuterol-induced adverse effects might explain some of the conflicting results found in previous trials evaluating only the short-term effectiveness of albuterol. This study attempts to evaluate whether bronchodilator administration, independent of short-term effects, alters the overall course of the disease process by decreasing length of hospitalization or attenuating severity of illness.

Analysis of the outcome measures shows no clear benefit to nebulized albuterol treatment in hospitalized patients with bronchiolitis, as evidenced by improvement in oxygen saturation, accessory muscle use, wheezing, or length of hospital stay. Patients enrolled at the time of admission to the hospital were in the early, acute phase of their illness (within 2 to 4 days of onset of upper respiratory symptoms), and had moderately severe bronchiolitis, as demonstrated by a mean oxygen saturation on room air at enrollment of 91.7% and moderate accessory muscle use and wheezing. The average age of study patients was 5.6 months, indicating a relatively young patient population and is consistent with data published previously on the average age of hospitalized infants with bronchiolitis.[3] Both treatment groups demonstrated clear evidence of clinical improvement in oxygen saturation, accessory muscle use, and wheezing over the hospital course, maximizing the opportunity to discern a difference in improvement between treatment groups. A power of 90% was achieved to detect a difference in improvement of as little as 2% Sao_2 between treatment groups, indicating that the study had sufficient power to detect a statistically and clinically significant treatment effect in this outcome measure (Table 3; Fig 1). A comparison of the percentage of patients meeting hospitalization criteria on each day in both treatment groups showed no significant statistical differences in time to reach standardized discharge criteria (Figs 2 to 4). In fact, a greater percentage of patients on placebo (18%) had been discharged by the pediatric inpatient

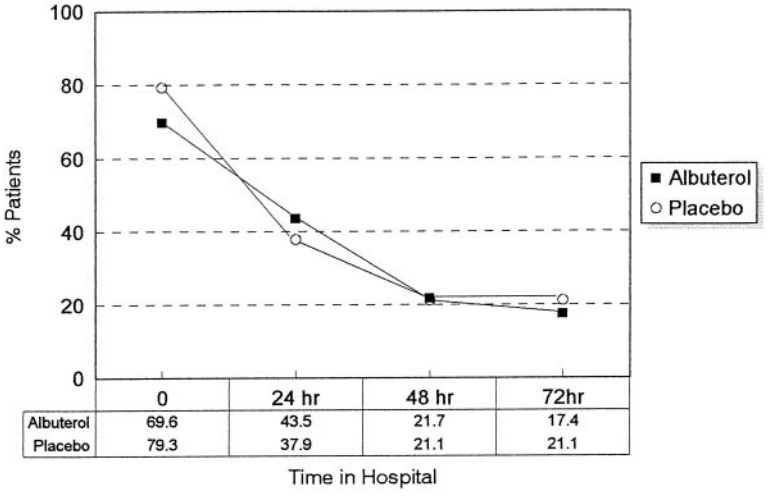

Fig 2. Percentage of patients on albuterol and placebo with oxygen saturation <94% on room air at baseline (time 0), 24, 48, and 72 hours of study. Log rank = 0.04; $P = .84$.

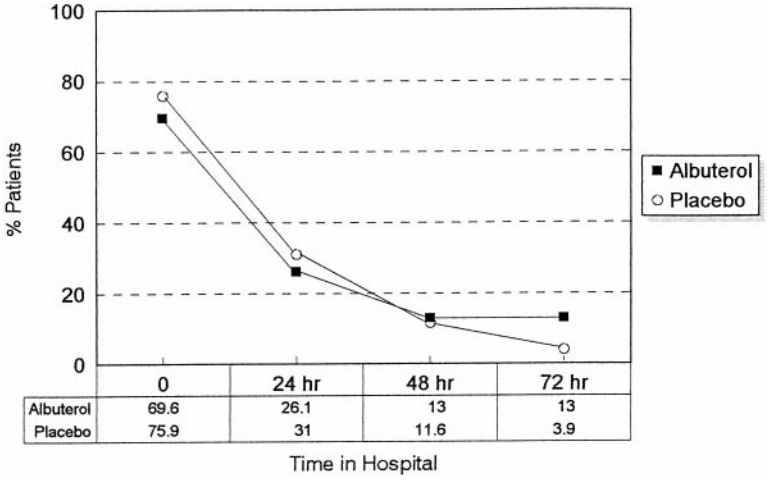

Fig 3. Percentage of patients on albuterol and placebo with moderate to severe retraction at baseline (time 0), 24, 48, and 72 hours of study. Log rank = 0.02; $P = .90$.

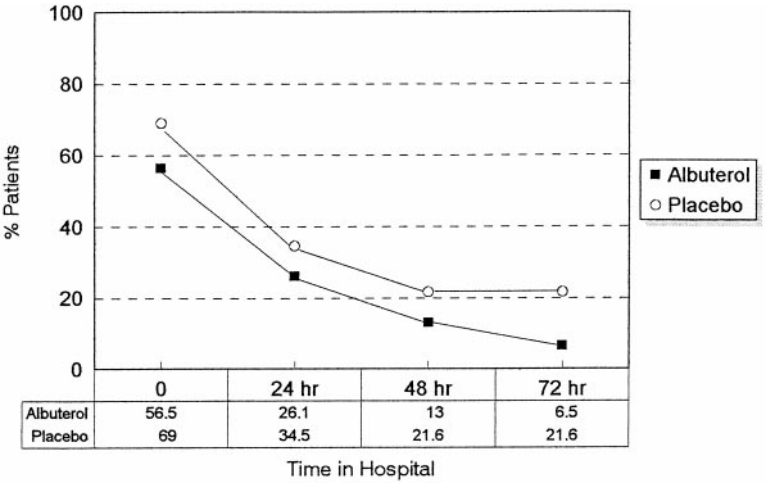

Fig 4. Percentage of patients on albuterol and placebo with moderate to severe wheezing at baseline (time 0), 24, 48, and 72 hours of study. Log rank = 1.29; $P = 0.26$.

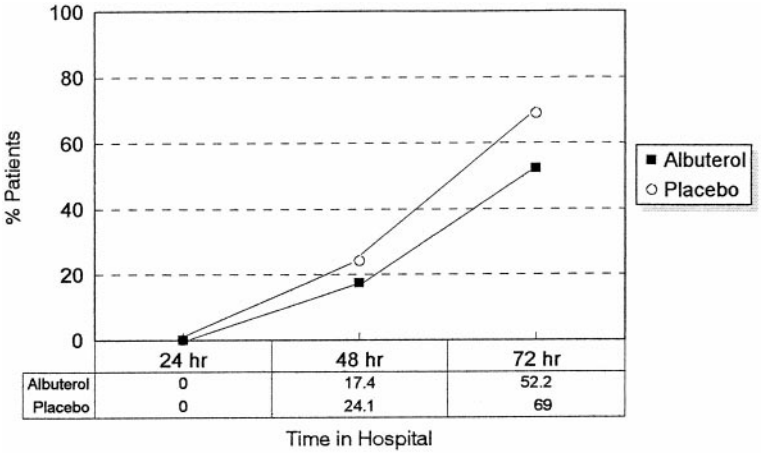

Fig 5. Percentage of patients on albuterol and placebo discharged from the hospital at 24, 48, and 72 hours. Log rank = 1.41; $P = .24$.

team at 72 hours (Fig 5). Given a larger sample size, this difference might have attained statistical significance, but the study lacked sufficient power in this outcome measure to make this conclusion definitively. Additionally, it is possible that uncontrolled variables other than treatment with albuterol or placebo may have had a bearing on the actual time of discharge by the pediatric inpatient team (ie, social considerations, concurrent nonrespiratory illness, or variability in physician practice), making this secondary outcome measure more difficult to interpret.

Outcome measures were selected to represent criteria used commonly in clinical practice in determining severity of illness, clinical improvement, and qualification for discharge. Oxygen saturation, as determined by pulse oximetry, provides a safe and reliable noninvasive measure of pulmonary function and respiratory compromise.[23,24] It allows for an accurate, reproducible, and continuous measure of the level of arterial oxygenation as well as of the adequacy of alveolar ventilation.[25] Accessory muscle use and wheezing are clinical measures of increased small airway resistance from airway edema, secretions, and bronchoconstriction.[25] Clinical scoring systems using accessory muscle use and wheezing, although subject to interobserver and intraobserver variability requiring careful control, have been shown to correlate with measurements of pulmonary mechanics, and provide objective clinical measures in infants in whom measurements of pulmonary mechanics are impractical.[11] Oxygen saturation, accessory muscle use, and wheezing have been shown to correlate with disease severity in infants with bronchiolitis, with oxygen saturation being the single best predictor of more severe disease.[26] Recently, it has been demonstrated that measurements of oxygen saturation and clinical assessment may not correlate immediately after treatment with inhaled bronchodilators.[27] The most likely cause of lack of correlation between these two standard clinical measures of pulmonary compromise is transient arterial oxygen desaturation after treatment with nebulized albuterol, most likely secondary to β-adrenergic-stimulated vasodilatation leading to ventilation-perfusion mismatch with intrapulmonary shunting.[7,20] It is also likely that oxygen saturation and clinical assessment of accessory muscle use or wheezing are evaluating interrelated but distinct aspects of respiratory compromise (ie, arterial oxygenation vs small airway obstruction), and direct correlation between the two might not be expected.[25] This study was designed to evaluate these outcome measures independent of short-term or transient bronchodilator effects such as oxygen desaturation. It supports the use of both oxygen saturation and clinical assessment as valuable and reliable measures of overall clinical and physio-

logic improvement in infants hospitalized with bronchiolitis.

A limitation of the use of clinical scoring systems is the inability to use differences in mean scores as evidence of treatment efficacy. Statistically, a mean score can only be used if the assumption is met that the data points making up the scale are equally interspersed, and can thus be added and divided (ie, that all the data are ratio or interval, and not ordinal). Clinical scoring systems use ordinal (noncontinuous) data points. Many studies using clinical scores to evaluate the efficacy of albuterol in infants with bronchiolitis have not conformed to this statistical tenet or have not attempted to validate this assumption.[7–12,17] Analyzing patients evaluated with clinical scores by survival analysis avoids this statistical violation by transforming the clinical score to a binary clinical outcome (meeting criteria for discharge vs continued hospitalization). Recently, this same methodology has been used to evaluate the efficacy of intravenous steroids in infants with bronchiolitis.[28] Although providing a valuable tool for the evaluation of ordinal data, survival analysis is very demanding statistically, and large sample sizes are needed for sufficient power. To detect a statistically significant difference of 18% in outcome between treatment groups at 72 hours (the largest difference found in this study) with a power of 80% and a P value $< .05$, we would have needed 170 patients equally divided across the two treatment groups. Although the small magnitude of the differences in outcome observed in the survival analysis make it unlikely to represent a clinically significant difference, results of the survival analysis perhaps are better considered descriptive than inferential. A multicenter trial might enable the power necessary to discern smaller differences in outcome measures evaluated by survival analysis such as time to meet discharge criteria or actual time to discharge.

Because of the prevailing practice in our institution, the majority (80%) of infants in the study were given at least one nebulized albuterol treatment in the emergency department or on the inpatient unit before evaluation for enrollment in the study (total mean number of treatments per patient = 2.5). The bronchodilator effect after albuterol inhalation starts at 5 to 10 minutes and can last up to 2 to 4 hours.[20] As noted previously, transient β-adrenergic-induced hypoxemia and increased work of breathing resolves within 60 minutes.[20,22] Any potential short-term effects of albuterol were controlled for by 1)allowing at least 6 hours to elapse since last treatment before baseline clinical evaluation, and 2) verifying that pretreated patients had been distributed equally in both treatment and control groups during randomization. Although it is therefore unlikely that previous albuterol therapy influenced the baseline data or final results, it might be more accurate statistically to refer to the placebo group as a comparison group than as a strict control group. Although not statistically significant, approximately twice as many patients in the placebo group had a family history of wheezing and exposure to smokers in the household. These historical factors have been shown previously not to be associated with disease severity or length of hospitalization.[4,26] Nevertheless, any potential bias would have been in favor of the albuterol group.

Lack of clinically significant improvement after treatment with nebulized albuterol in hospitalized infants with bronchiolitis may be attributable to several factors. Standard methods of nebulization may be an ineffective way of delivering adequate medication to the bronchioles in young infants with high respiratory rates, low tidal volumes, and high dead space ventilation. Depending on stage and degree of illness, there may be some infants with viral bronchiolitis predisposed to reactive airways, and others who predominantly have obstruction from inflammatory edema and mucus.[7,11] Infants responsive to bronchodilators would be more likely to improve selectively with outpatient therapy, leaving the hospitalized population to predominantly represent a subset of patients relatively unresponsive to bronchodilators. It also has been shown that younger age and positive RSV status are significant predictors for nonresponsiveness to albuterol.[29] The mean age of infants in this study was 5.6 months (86% of enrolled patients <12 months of age), and 80% were RSV-positive. The assumption is that younger infants with smaller airways that are compromised further by viral infection are much less likely to respond to bronchodilators than are older infants with viral-induced bronchial reactivity. Subgroup analysis of infants in this study <12 months of age showed no benefit to nebulized albuterol. However, there were insufficient numbers of patients to subgroup further the patients <12 months or to evaluate infants in the 12- to 24-month age category. Because it is possible that older infants might be more likely to have viral-induced bronchospasm amenable to bronchodilator therapy, additional study of this population in the hospital setting is warranted.

In the absence of proven benefit, health care costs and potential adverse side effects of a drug therapy become paramount considerations. In our institution, which is a publicly funded hospital, the cost per patient for administering nebulized albuterol treatments for 72 hours (the median hospital stay for bronchiolitis) is >$1200 per patient. Compared with other institutions treating infants with bronchiolitis, this probably represents a conservative estimate. If this is extrapolated to include all infants hospitalized with bronchiolitis in the United States each winter (~91 000 admissions per year), the treatment of hospitalized infants with albuterol clearly represents a major health care cost.[4,5]

All three patients withdrawn by the pediatric inpatient team for worsening hypoxemia and respiratory distress in the first 48 hours of hospitalization had been randomized to receive albuterol therapy. Although this did not attain statistical significance ($P = .10$), a possible explanation is that cumulative, frequent albuterol dosing might have led to prolonged desaturation in these patients beyond the 60-minute period described by Ho et al.[20] This study, designed to evaluate patients at the longest possible interval from the nebulization administered previously, did not allow discrimination between deterioration secondary to

drug effect as opposed to the natural course of the disease process. Infants in both treatment groups were given oxygen as needed to maintain $Sao_2 \geq 94\%$ except during clinical evaluation by the study investigators, masking any demonstrable transient oxygen desaturation occurring immediately after drug therapy. Future studies evaluating the efficacy of nebulized bronchodilators for bronchiolitis in the hospital setting should be designed to monitor for deterioration attributable to known β-adrenergic-induced adverse side effects. Adverse side effects ranging from oxygen desaturation, tremor, and hypokalemia to cardiovascular side effects including supraventricular tachycardia, sinus tachycardia, premature ventricular contractions, palpitations, and atrial fibrillation have been reported.[7,20,21,30–34]

In summary, infants hospitalized with bronchiolitis represent a subset of all infants affected with bronchiolitis each year. They have a younger average age (5.6 months in this study) and generally have failed standard outpatient therapy. Nebulized albuterol therapy does not appear to enhance recovery in this group of hospitalized infants with acute, moderate bronchiolitis as shown by improvement in oxygen saturation, time to meet standardized discharge criteria, or actual length of hospital stay. Treatment with nebulized bronchodilators has potential adverse side effects and represents a significant health care cost. Because of the lack of convincing evidence documenting the efficacy of albuterol as a means of reducing hospital stay or attenuating severity of illness, its routine use for bronchiolitis in the hospital setting is not supported.

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