Objective: To determine if administration of albuterol by a metered-dose inhaler with a spacer device is as efficacious as administration of albuterol by nebulizer to treat wheezing in children aged 2 years and younger.

Design: Double-blind, randomized, placebo-controlled clinical trial.

Setting: Pediatric emergency department.

Patients: From a convenience sample of wheezing children aged 2 to 24 months, 85 patients were enrolled in the nebulizer group and 83 in the spacer group.

Interventions: The nebulizer group received a placebo metered-dose inhaler with a spacer followed by nebulized albuterol. The spacer group received albuterol by a metered-dose inhaler with a spacer followed by nebulized isotonic sodium chloride solution. Treatments were given every 20 minutes by a single investigator blinded to group assignment.

Main Outcome Measures: The primary outcome was admission rate. Pulmonary Index score and oxygen saturation were measured initially and 10 minutes after each treatment.

Results: The nebulizer group had a significantly higher mean (SD) initial Pulmonary Index score compared with the spacer group (7.6 [2.5] vs 6.6 [2.0]; \( P = .002 \)). With the initial Pulmonary Index score controlled, children in the spacer group were admitted less (3% vs 20%; \( P = .05 \)). Analyses also revealed an interaction between group and initial Pulmonary Index score; lower admission rates in the spacer group were found primarily in children having a more severe asthma exacerbation.

Conclusion: Our data suggest that metered-dose inhalers with spacers may be as efficacious as nebulizers for the emergency department treatment of wheezing in children aged 2 years or younger.

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Reactive Airway Disease is a major cause of morbidity in infants and young children and is a common reason for emergency department (ED) visits and hospital admissions. Bronchodilators are frequently used to treat reactive airway disease in infants and young children. However, administering bronchodilators by nebulizer in busy EDs is often difficult, given the volume of patients and the limited availability of oxygen ports.

Metered-dose inhalers (MDIs) have provided a quicker and more cost-effective way to deliver aerosolized bronchodilators for asthma treatment in older children and adults. However, younger patients are often unable to coordinate inspiration with activation of the MDI, thereby limiting the amount of drug inhaled. The introduction of spacer devices has helped solve this problem. By holding medication in a chamber, the spacer allows the patient to receive inhaled medications while taking normal breaths through a face mask or mouthpiece.

In children with wheezing, equivalent if not better outcomes have been reported with spacers vs nebulizers for the delivery of aerosolized albuterol. Few studies that have looked at the efficacy of MDIs with spacers in administering albuterol have selectively enrolled children aged 2 years and younger. These studies have focused on drug delivery rather than clinical outcome measures, have not used a double-blind, placebo-controlled design, have not compared the efficacy of an MDI with a spacer with that of a nebulizer, or have included sedated patients. The purpose of this study was to evaluate whether the administration of albuterol by an MDI with a spacer is as efficacious as the administration of albuterol by nebulizer for the ED treat-
measurement of wheezing in infants and children aged 2 to 24 months.

**METHODS**

**STUDY POPULATION**
A convenience sample of wheezing infants and children aged 2 to 24 months who were treated in the pediatric ED of Jacobi Medical Center, Bronx, NY, was enrolled by the principal investigator (A.D.) between August 1995 and December 1996. Exclusion criteria included a history of chronic lung conditions other than asthma (including congenital anomalies, cystic fibrosis, and bronchopulmonary dysplasia), a history of congenital heart disease, intubation for longer than 1 week during the neonatal period, symptoms consistent with croup, oxygen saturation less than 90%, or signs of impending respiratory failure.

**STUDY MEDICATIONS**
Prior to the initiation of the study, albuterol and placebo solutions for nebulization were provided by the hospital pharmacy in identical dark-brown glass medicine bottles. The albuterol (Ventolin; Glaxo Wellcome, Research Triangle Park, NC) and placebo (Schering-Plough Corporation, Kenilworth, NJ) MDIs were prepared by the respective manufacturers in similar canisters. The placebo MDI contained an oleic acid dispersant. The spacer device used was the Aerochamber (Monaghan Medical Corporation, Plattsburgh, NY) with a small or medium-sized mask.

**STUDY PROTOCOL**
After informed written consent was obtained, asthma history and demographic data were collected. A random number table was used to assign patients to 1 of 2 double-blind treatment groups. For patients in the nebulizer group, each treatment consisted of 3 puffs of a placebo MDI with a spacer, followed immediately by a standard dose of 0.15 mg/kg of albuterol in 3 mL of isotonic sodium chloride solution delivered by an oxygen-driven nebulizer (Acorn II; Marquest Medical Products, Englewood, Colo) at a flow rate of 6 L/min. For patients in the spacer group, each treatment consisted of 3 puffs (90 µg per puff) of an albuterol MDI with a spacer, followed by 3 mL of nebulized isotonic sodium chloride solution. All treatments were given at 20-minute intervals.

For administration of the MDI, the investigator dispensed 1 puff of albuterol or placebo into the spacer and held the mask on the child’s face while the child breathed 5 to 6 times through the mask. This process was repeated for a total of 3 puffs per treatment. Between treatments, patients with an oxygen saturation of less than 94% received oxygen by mask with nebulized saline at a flow rate of 6 L/min. All patients were treated by the principal investigator, who determined the total number of treatments, use of steroids, and final disposition.

**RESULTS**
During the study period, 202 acutely wheezing patients aged 2 to 24 months were screened. Of these patients, 34 were excluded for the following reasons: lack of a le-

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**Table 1. Pulmonary Index**

<table>
<thead>
<tr>
<th>Score</th>
<th>Respiratory Rate, Respiration/min</th>
<th>Wheezing*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>≤30</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>31-45</td>
<td>End expiratory</td>
</tr>
<tr>
<td>2</td>
<td>46-60</td>
<td>Entire expiratory</td>
</tr>
<tr>
<td>3</td>
<td>&gt;60</td>
<td>Inspiratory and expiratory, audible without stethoscope</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inspiratory-Expiratory Ratio</th>
<th>Accessory Muscle Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>5:2</td>
<td>None</td>
</tr>
<tr>
<td>5:3 to 5:4</td>
<td>Mild retractions</td>
</tr>
<tr>
<td>1:1</td>
<td>Moderate retractions</td>
</tr>
<tr>
<td>&lt;1:1</td>
<td>Marked retractions</td>
</tr>
</tbody>
</table>

*If there was no wheezing owing to minimal air exchange, the score was 3.

This study was approved by the Committee on Clinical Investigations of the Albert Einstein College of Medicine, Bronx, and Jacobi Medical Center.

**ASSESSMENT**
Demographic data included age, sex, and ethnicity. Historical characteristics included the percentage of patients for whom this was the first wheezing episode, mean number of hospitalizations for wheezing, number of intensive care unit admissions, number of wheezing episodes in the past 3 months, history of prematurity, and asthma medications received in the past 48 hours.

Clinical measurements included room air oxygen saturation measured by pulse oximeter (Nellcor Inc, Hayward, Calif), heart rate, and Pulmonary Index (PI) score. The PI score (Table 1) is a validated asthma severity score that includes 4 measures, each scored from 0 to 3. We divided the PI scores into 3 groups that represented increasing levels of asthma severity. We defined total scores of 0 to 3 as mild asthma, 4 to 7 as moderate asthma, and 8 to 12 as severe asthma. Clinical measurements were obtained at baseline, prior to each treatment, and at the final disposition. The occurrence of vomiting was also recorded.

**PRIMARY AND SECONDARY OUTCOMES**
The primary outcome was admission rate. Secondary outcomes included percentage improvement in PI score, final oxygen saturation, mean number of treatments, whether steroids were given in the ED, percentage increase in heart rate, and percentage of subjects with vomiting in the ED.

**STATISTICAL ANALYSIS**
Bivariate statistical analysis was performed using Epi Info software, version 6.0 (Centers for Disease Control and Prevention, Atlanta, Ga). The Mann-Whitney U test was used to compare the groups on continuous variables, and the χ² and Fisher exact tests were used to compare the groups on categorical variables. P≤.05 was considered statistically significant. We calculated that a sample size of 88 patients per treatment group would provide 80% power to detect a 15% difference in admission rate at α=.05. Analyses of covariance for continuous outcomes and logistic regression analyses for dichotomous outcomes were conducted using SPSS statistical software for Windows 10.0 (SPSS Inc, Chicago, Ill).

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Many infants and young children seek treatment at EDs for acute wheezing episodes. The treatment of these young
The administration of bronchodilator therapy to infants and young children is often difficult in a busy ED. Although MDIs with spacer devices have provided an efficient method of administering bronchodilators to children older than 2 years, their use in young children has not been well evaluated.

This study suggests that MDIs with spacers may be as efficacious as nebulizers for the ED treatment of wheezing in infants and children aged 2 years or younger and may be associated with a lower hospitalization rate and less increase in heart rate in patients with a more severe asthma exacerbation.

Patients often require considerable time and resources. The introduction of MDIs with spacers has provided a more efficient, cost-effective, and easier way of delivering albuterol to infants and young children.

There have been several studies in older children demonstrating equivalent efficacy of nebulized albuterol vs MDIs with spacers. Few studies have examined these treatment modalities exclusively in infants and children aged 2 years or younger. Wildhaber et al assigned 20 wheezing infants between the ages of 4 and 12 months to receive albuterol by nebulizer as well as by MDI with 2 small-volume spacers. A filter was placed between the inhalation systems and the patients, and the amount of albuterol deposited on the filter was measured. The authors concluded that aerosol delivery to wheezing infants via MDIs with spacers is effective and that a higher percentage of the total amount of albuterol is delivered than that from a nebulizer. However, the study was limited by a small sample size and the lack of clinical outcome measures.

Rubilar et al conducted a single-blind, prospective, randomized clinical trial of 123 children younger than 2 years who sought treatment at the ED for “moderate to severe” wheezing. They concluded that in this study population, children who received albuterol via MDI with a spacer responded faster (clinical score $\leq 5$ after 1 hour of treatment) than children in the nebulizer group and were less likely to be admitted. A potential limitation of this study is the lack of a double-blind, placebo-controlled design.

Hickey et al conducted a double-blind, placebo-controlled study of 42 patients aged 1 to 18 months with wheezing in the ED and concluded that albuterol delivered by MDI with a spacer reduced the severity of wheezing and retractions. In addition, there was no significant increase in heart rate over time in either treatment group. The spacer device used was not a standard design, so it is unclear whether this could have affected drug delivery. Furthermore, the number of breaths taken per actuation of the MDI was not indicated.

Clarke et al studied 15 symptom-free infants aged 8 to 23 months with a history of recurrent wheezing in a double-blind study of albuterol vs placebo with an MDI and spacer. All infants were sedated, and bronchoconstriction was induced by methacholine. Lung function was measured before and after the methacholine challenge. Each infant received a single dose of either albuterol or placebo on separate days. The authors found that bronchial responsiveness decreased significantly after the administration of albuterol by an MDI with a spacer. There was no significant increase in heart rate after albuterol administration. The study was limited by a small sample size. Furthermore, the subjects were sedated, and bronchoconstriction was induced. Therefore, the results are not directly applicable to our patient population of awake, acutely wheezing infants.

Studies have found that adverse effects, particularly the mean percentage increase in heart rate and vomiting, are less severe with MDI and spacer therapy compared with nebulizer therapy. In our sample, there was a significant difference in mean percentage increase in heart rate but no difference in the percentage of children who vomited during their ED stay. These results suggest that there may be less systemic absorption of albuterol with MDI and spacer therapy than with nebulizer therapy.

There has been conflicting evidence regarding the efficacy of bronchodilators in the treatment of bronchiolitis. A recent meta-analysis of randomized trials of inhaled $\beta_2$-agonists for bronchiolitis found inconclusive evidence of their efficacy. However, in this study we were primarily interested in investigating the impact of the delivery device.

There were some limitations to our study. Despite random assignment, there was a significantly higher baseline PI score in the nebulizer group. However, after controlling for these initial differences, patients in the nebulizer group still had 3 times the likelihood of admission compared with the spacer group. Moreover, a significant interaction term in the logistic regression analysis suggests that the initial PI score may be a moderating factor. When the analysis was restricted to the subgroup with severe asthma based on the initial PI score, the difference in admission rates between the groups was statistically significant, favoring the use of MDIs with spacers rather than nebulizers. Also, although the odds ratio for admission of patients in the nebulizer group vs the spacer group was higher in children with moderate asthma, it was not statistically significant. Because the overall admission rate was much lower in children with moderate asthma, it was much more difficult to detect a significant treatment effect. We estimated that a sample size of 400 patients per group would be necessary for this difference to be statistically significant.

Some of our outcome measures, such as degree of wheezing and retractions, were subjective. Additionally, the decision to admit a patient with wheezing to the hospital may not be based solely on objective parameters. The use of multiple investigators may have reduced the chance of bias in terms of treatment decisions and determining criteria for admission. However, only one investigator, blinded to the patients’ treatment group assignments, recorded data and made all clinical decisions in order to standardize decision making and eliminate interrater variability.

Our data suggest that MDIs with spacers may be as efficacious as nebulizers for the treatment of wheezing.
in children aged 2 to 24 months in the ED. Compared with nebulizers, they appear to have less impact on heart rate and to be associated with a lower admission rate in those patients with a severe wheezing episode. In addition, the potential to provide an efficient, easier method of delivering albuterol to infants and young children makes MDIs with spacers an attractive alternative treatment modality in the ED.

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REFERENCES


