

# Nebulizers vs Metered-Dose Inhalers With Spacers for Bronchodilator Therapy to Treat Wheezing in Children Aged 2 to 24 Months in a Pediatric Emergency Department

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**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 (5% 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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**R**EACTIVE 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.<sup>1-7</sup> 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.<sup>8-10</sup> 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 hold-

ing 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.<sup>9,11-20</sup> Few studies that have looked at the efficacy of MDIs with spacers in administering albuterol have selectively enrolled children aged 2 years and younger.<sup>19-22</sup> These studies have focused on drug delivery rather than clinical outcome measures,<sup>19</sup> have not used a double-blind, placebo-controlled design,<sup>20</sup> have not compared the efficacy of an MDI with a spacer with that of a nebulizer,<sup>21,22</sup> or have included sedated patients.<sup>22</sup> 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-

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**Table 1. Pulmonary Index<sup>23</sup>**

Score	Respiratory Rate, Respirations/min	Wheezing*	Inspiratory-Expiratory Ratio	Accessory Muscle Use
0	≤30	None	5:2	None
1	31-45	End expiratory	5:3 to 5:4	Mild retractions
2	46-60	Entire expiratory	1:1	Moderate retractions
3	>60	Inspiratory and expiratory, audible without stethoscope	<1:1	Marked retractions

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

ment 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.

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.<sup>23</sup> 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

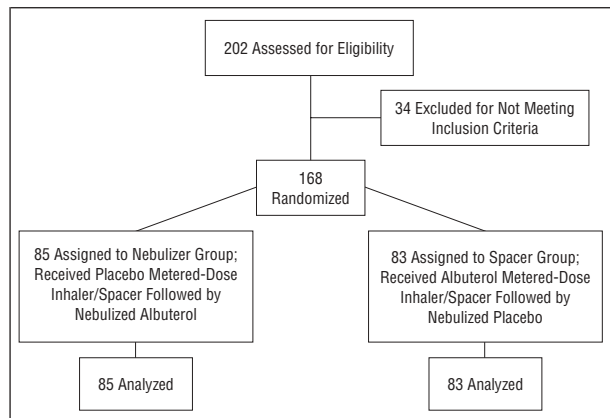
The primary outcome was admission rate. Secondary outcomes included percentage improvement in PI score, final oxygen saturation, mean number of treatments, whether steroids were given in the ED, percentage increase in heart rate, and percentage of subjects with vomiting in the ED.

## 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  $\chi^2$  and Fisher exact tests were used to compare the groups on categorical variables.  $P \leq .05$  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  $\alpha = .05$ . 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).

## 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-



Flowchart of subject progress.

**Table 2. Baseline Characteristics**

Characteristic	Nebulizer Group (n = 85)	Spacer Group (n = 83)	P Value
First wheezing episode, % of patients	26	30	.54
Mean No. of hospitalizations for wheezing	1.4	2.1	.38
No. of patients with history of intensive care unit admissions	0	2	.24
Mean No. of wheezing episodes in past 3 mo	1.2	1.1	.88
No. of patients with history of prematurity	5	7	.52
Steroids in past 48 h, % of patients	14	19	.37
β-Agonists in past 48 h, % of patients	64	61	.78
Pulmonary Index score, mean (SD) <sup>23</sup>	7.6 (2.5)	6.6 (2.0)	.002
Mean oxygen saturation, %	98	97	.38

gal guardian (n=13), intubation for longer than 1 week during the neonatal period (n=15), croup symptoms (n=3), congenital heart disease (n=2), and chronic lung disease (n=1). A total of 168 patients were enrolled: 85 in the nebulizer group and 83 in the spacer group. No parents refused to participate, and all enrolled patients completed the study (**Figure**).

There were no differences between the groups in age, sex, or ethnicity. The mean age was 11.7 months, 66.6% of patients were male, 58.9% were Latino, and 34.5% were African American. Baseline characteristics did not differ between the groups except that the nebulizer group had a significantly higher mean PI score (**Table 2**).

Outcomes for the 2 groups are shown in **Table 3**. There were no significant differences between the groups in percentage improvement in PI score, final oxygen saturation, or percentage of patients with vomiting. However, patients in the spacer group were significantly less likely to be admitted, received fewer treatments, were less likely to receive steroids, and had a lower mean increase in heart rate.

Because differences in the level of the initial PI score in the 2 groups might have contributed to differences in their rates of admission as well as the secondary out-

**Table 3. Outcomes by Treatment Group\***

Outcome	Nebulizer Group (n = 85)	Spacer Group (n = 83)	P Value
Admission rate, % of patients	20	5	.003
Final Pulmonary Index score <sup>23</sup>	4.3 (2.6)	3.7 (1.7)	.30
Improvement in Pulmonary Index score, %	44.7 (28.0)	43.3 (30.9)	.65
Final oxygen saturation, %	96.7 (2.2)	97.0 (1.9)	.51
No. of treatments	2.3 (1.1)	1.9 (1.1)	.006
Given steroids in the emergency department, % of patients	57.6	38.6	.01
Increase in heart rate, %	5.8 (13.1)	1.0 (13.0)	.02
Vomiting in emergency department, % of patients	9.4	13.2	.43

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

comes noted above, we compared the groups again on the significant variables in Table 3 while controlling for baseline PI scores. We used analysis of covariance for the continuous outcome variables (mean number of treatments and percentage increase in heart rate) and logistic regression analysis for dichotomous outcomes (admission rate and given steroids in the ED). With initial PI scores controlled, the groups did not differ in mean number of treatments or percentage of patients given steroids. Children in the spacer group still had significantly lower increases in heart rate than children in the nebulizer group (adjusted means for percentage increase in heart rate were 1.1% and 5.7%, respectively). Patients in the nebulizer group also were more likely to be admitted (odds ratio, 3.22;  $P=.05$ ). Moreover, the analysis of covariance revealed a significant interaction effect between method of treatment and initial PI score, which suggests that they have a joint effect on the likelihood of admission. These findings were unchanged when we controlled for being given steroids in the ED using logistic regression. There were no significant interaction effects found for the other outcomes.

We conducted further analyses to better understand the nature of the interaction. Specifically, we examined whether the delivery device had different effects in subgroups with lower vs higher initial PI scores. The children were classified based on whether they presented to the ED with a moderate (initial PI score, 4-7) or severe (initial PI score, 8-12) asthma exacerbation. Admission rates were compared for the spacer vs the nebulizer groups within these severity categories. In the moderate asthma category, it appeared that slightly more children using the nebulizer (3 [8%] of 36) than children using the spacer (2 [3%] of 58) were admitted, but the groups did not differ significantly (odds ratio, 2.55;  $P=.28$ ). However, when we examined the same outcome for patients having a severe exacerbation, the nebulizer group had a significantly higher admission rate (14 [31%] of 45) than did the spacer group (2 [9%] of 23) (odds ratio, 4.74;  $P=.04$ ).

#### COMMENT

Many infants and young children seek treatment at EDs for acute wheezing episodes. The treatment of these young

### What This Study Adds

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 requires 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.<sup>9,11-14</sup> Few studies have examined these treatment modalities exclusively in infants and children aged 2 years or younger.<sup>19-22</sup> Wildhaber et al<sup>19</sup> 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<sup>20</sup> 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<sup>21</sup> 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<sup>22</sup> 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.<sup>9,11,13,17</sup> 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.<sup>24</sup> 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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