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High-Dose Albuterol by Metered-Dose Inhaler Plus a Spacer Device Versus Nebulization in Preschool Children With Recurrent Wheezing: A Double-Blind, Randomized Equivalence Trial

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ABSTRACT. Inhaled albuterol is the most frequently used bronchodilator for acute wheezing, and nebulization is the standard mode of delivery in hospital setting. However, recent guidelines consider spacer devices as an easier to use, and cost-saving alternative and recommend the high-dose metered-dose inhaler bronchodilator.

Objective. To demonstrate clinical equivalence between a spacer device and a nebulizer for albuterol administration.

Design. Randomized, double-blind, parallel group equivalence trial.

Setting. Pediatric emergency wards at 2 tertiary teaching hospitals.

Patients. Sixty-four 12- to 60-month-old children with acute recurrent wheezing (32 per group).

Interventions. Albuterol was administered through the spacer device (50 µg/kg) or through the nebulizer (150 µg/kg) and repeated 3 times at 20-minute intervals. Parents completed a questionnaire.

Outcome Measures. Pulmonary index, hospitalization, ease of use, acceptability, and pulse oximetry saturation.

Results. The 90% confidence interval of the difference between treatment groups for the median absolute changes in pulmonary index values between T0 and T60 was [-1; +1] and was included in the equivalence interval [-1.5; +1.5]. Clinical improvement increased with time. Less than 10% of the children (3 in each group) required hospitalization (2 in each group attributable to treatment failure). Parents considered administration of albuterol using the spacer device easier (94%) and better accepted by their children (62%).

Conclusions. The efficacy of albuterol administered using the spacer device was equivalent to that of the nebulizer. Given its high tolerance, repeated 50-µg/kg doses of albuterol administered through the spacer device should be considered in hospital emergency departments as first-line therapy for wheezing. *Pediatrics* 2000;

106:311-317; recurrent wheezing, asthma, preschool children, inhaled albuterol, spacer device, metered-dose inhaler, nebulizer, equivalence trial, randomized trial, acceptability.

ABBREVIATIONS. ASD, asthma spacer device; MDI, metered-dose inhaler; SaO₂, pulse oximetry saturation; I/E ratio, inspiration/expiration ratio.

Inhaled albuterol is the most frequently used bronchodilator for acute wheezing, and nebulization is considered standard for hospital emergency care.¹⁻⁹ Asthma spacer devices (ASDs) have rapidly achieved widespread use in pediatrics, given children's poor coordination when using aerosol inhalers.¹ National and international guidelines recommend these spacer devices for home management of asthma. ASDs suitable for infants and preschool children have recently been designed, but only a few studies have compared ASDs and nebulizers.¹⁰ The albuterol dose of 150 µg/kg is widely accepted for nebulization. For treatment with the metered-dose inhaler (MDI), the currently used standard is 2 puffs, but several guidelines now recommend for children with severe wheezing dose up to 8 puffs,⁷ 10 puffs,⁴ and even up to 20 puffs.⁵

The Babyhaler spacer (Glaxo Wellcome France, Marly le Roi, France), a device suitable for children <5 years old, has not yet been compared with the nebulizer for first-line albuterol administration in hospital emergency departments.

The main objective of this study was to compare the efficacy of albuterol administered using the MDI through the ASD to that of ultrasonic nebulized albuterol in young children with acute recurrent wheezing. A randomized, double-blind, parallel group equivalence trial was designed for this purpose.

PATIENTS AND METHODS

Patients

Twelve- to 60-month-old children with acute wheezing and a history of at least 1 episode of wheezing were eligible for the study. Children were excluded from the study if 1) their pulse oximetry saturation (SaO₂) was <90%, 2) if they had received inhaled or systemic corticosteroids within the previous 24 hours, 3) if they presented with an underlying chronic disease (respiratory, cardiac, renal or liver insufficiency, immunodeficiency, en-

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Fig 1. A mother using the ASD.

cephalopathy), 4) if their height and weight were >2 standard deviations below the standard for their age.

The study, considered a single-center trial, took place in the pediatric emergency departments of 2 adjacent teaching hospitals (Lyon, France) serving the same population of patients, with the same principal investigator. All investigators were volunteer physicians from the pediatric emergency wards. They were in charge of the entry, treatment, assessment, admission decision, and further clinical management of the children. To minimize variability in evaluation, the principal investigator trained the 8 other investigators, their first patient being assessed in the presence of the principal investigator. The patients were admitted if, at the end of the study, they presented 1) abnormal clinical respiratory signs or low SaO_2 values, or 2) nonrespiratory reasons: other abnormal clinical signs, or other reasons such as the parents' inability to treat or to recognize the severity of the disease or inadequate home conditions).

The study was approved by the Comité Consultatif de Protection des Personnes se prêtant à la Recherche Biomédicale Lyon A. Written informed consent was obtained from either the parents or the legal guardian before inclusion in the study.

ASD

The Babyhaler spacer (Fig 1) is an ASD first manufactured in the early 1990s. It was designed to improve on nebulization by providing a more convenient inhaled therapy with more rapid delivery of medication in the treatment of infants and young children.¹¹ This ASD was designed following the physical and physiologic requirements for aerosol delivery to children <5 years old with lung disease. The technical characteristics include a high-grade soft silicon mask available in two sizes with a handle for ease of use and insertion of the MDI, a tubular chamber 230 mm long with a volume of 350 mL, low-resistance inspiratory and expiratory valves, and instrumental dead space of 36 mL.

Randomization and Treatments

Randomization was performed in blocks of 4 and was generated using software. Patients were assigned to treatment according to the randomization schedule: either albuterol administered using the MDI coupled with the ASD and ultrasonic nebulized placebo, or ultrasonic nebulized albuterol and placebo administered through the ASD. The order of treatment modes, nebulizer

first or ASD first, was randomized within each treatment group, as shown in the study's flowchart (Fig 2).

All study medications were packed individually for each child. Each package comprised 1 vial of albuterol (Ventolin [Glaxo Wellcome France, Marly le Roi, France] solution for inhalation at 50 mg/10 mL or its placebo), 1 single-use nebulizer kit (pediatric face mask, bacteriologic filter, nebulizer cup, and tubing), 1 new Babyhaler spacer, and one MDI (Ventolin 100 μ g or its placebo). Placebo or albuterol vials and MDI packages were identical. Investigators, patients, and parents were unaware of the group assignments. A supply of treatment packages was maintained in the emergency departments to avoid delays in treatment. The investigators participating in the study treated the children.

Nebulizations were conducted in room air, using an ultrasonic nebulizer (ARP 70 Pierre Medical, Nellcor Puritan Bennett France, Les Ulis, France); the face mask was held close to the child's face. The technical specifications of the nebulizer provided a quartz frequency of 2.4 MHz, air flow of 0 to 16 L/min, and a particle size of .5 to 5 μ m.

The quantity of nebulized albuterol (150 μ g/kg) or placebo was .03 mL/kg body weight (minimum dose .3 mL diluted in isotonic saline to give a final volume of 4 mL. Nebulizer air flow was set at 8 L/min, and the particle size cursor was set at 4 on a scale ranging from 0 to 8. The MDI was coupled with the untreated-prior-to-use ASD to deliver 1 puff per 2 kg body weight of albuterol (50 μ g/kg) or placebo (maximum 10 puffs). Each puff was followed by 8 breaths. Each treatment administration lasted 10 minutes (about 8–9 minutes for nebulization, 1–2 minutes for MDI + ASD) and was followed by a 10-minute rest period before assessment. Treatments were given 3 times at 20-minute intervals, for a total study duration of 60 minutes.

The children's body temperature was systematically measured before inclusion, and if the temperature was $>38^\circ\text{C}$, the investigator administered paracetamol and/or aspirin.

Evaluation

Clinical assessment was based on physical examination and monitoring of the child's cardiorespiratory status every 20 minutes—at baseline, T20, T40, and T60 (end of treatment) (Fig 2). SaO_2 was measured using the Nellcor Symphony N3000 pulse oxygen meter (Nellcor Puritan Bennett France, Les Ulis, France). The values of SaO_2 , heart rate, respiratory rate, and respiratory trace generated by measurement of impedance were printed using the Nellcor Symphony N3200 monitor. The duration of the inspiration and expiration phases were measured from the printouts and used to calculate the inspiration/expiration (I/E) ratio. The dated and timed printouts of the monitored parameters allowed data verification.

After having observed the 3 administrations of treatment to their children, parents were requested to give their opinion on the mode of administration. The investigator asked 2 questions: "Which treatment mode looked easier to administer?" and "Which treatment mode looked more acceptable to your child?" Parents chose 1 of 3 proposed answers: the ASD, the nebulizer, or no preference.

The degree of severity of the child's wheezing was determined using the pulmonary index score (Table 1).¹² Interrater reliability was not measured, but 2 of the 4 items of the index (respiratory rate, I/E ratio) were double-checked on the timed printouts obtained from the cardiorespiratory monitor. Severity of wheezing was assessed using the pulmonary index as an asthma severity scale: mild when between 1 and 6; moderate when between 7 and 9; and severe when between 10 and 12.

The primary endpoint was the change in pulmonary index between the beginning of the first treatment administration (T0) and the end of the third and final rest period (T60). Secondary efficacy criteria were 1) improvement in the pulmonary index score after each of the 3 treatment administrations to evaluate the effect of repeated administrations (T0–T20/T0–T40/T0–T60); 2) whether the subject was admitted to the hospital and reasons for admission (decided by the investigator after T60 assessment); 3) which treatment mode parents reported as easier to use and more willingly accepted by the child; and 4) improvement in SaO_2 (T0–T60).

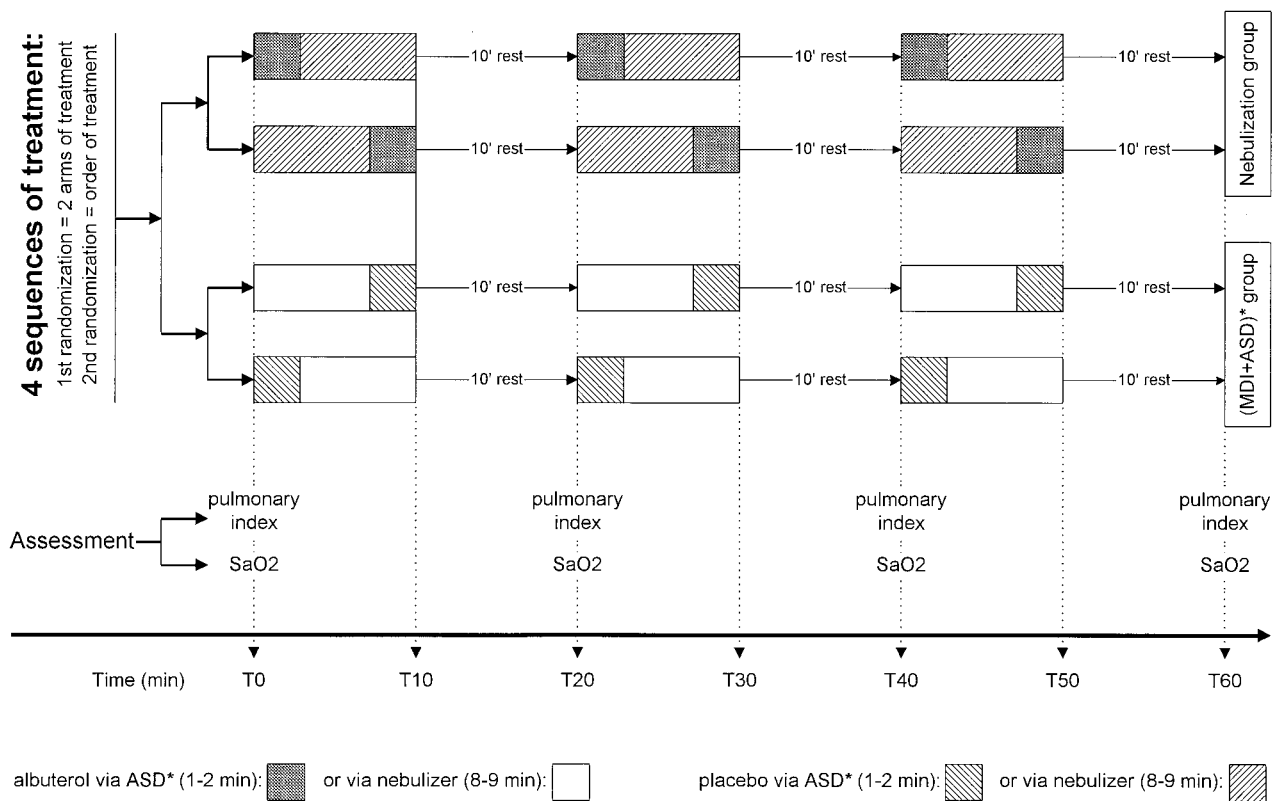


Fig 2. Randomization and sequences of treatment. *MDI + ASD.

Statistical Analysis

This trial was designed as an equivalence trial. A 2-sided 90% confidence interval of the difference between treatment groups for the absolute changes in pulmonary index included in the [-1.5; +1.5] interval was our equivalence hypothesis. Assuming a power of 90% and a change in the pulmonary index standard deviation of 1.7,¹³ a sample size of 56 assessable patients (28 in each treatment group) was needed to conclude equivalence. Given a 15% non-assessable patient rate, a total of 64 children needed to be included in the study.

Three populations were prospectively defined. The randomized population assessed for safety included all children randomized and treated with at least 1 administration of albuterol. The intent-to-treat population included all children randomized, treated, and evaluated. The per-protocol population included all children from the intent-to-treat population who did not present any major deviations from the protocol. Statistical analysis was performed on the intent-to-treat population and verified in the per-protocol population for primary endpoint.

Comparisons were performed between the nebulizer and the ASD treatment groups. Within each group, the order of the treatment administration was equilibrated by a specific randomization. Nevertheless, a time-to-treatment interaction was tested.

Statistical analyses were performed by Laboratoire Glaxo Wellcome France, using SAS (SAS Institute, Cary, NC) software version 6.11.

RESULTS

Between December 22, 1995, and March 22, 1997, a total of 64 patients were enrolled in the study. All children received the 3 scheduled treatment administrations and were evaluated 4 times. One child was randomized twice. Consequently, the efficacy data from the second randomization (ASD group) were not taken into account in the intent-to-treat analysis. Three children were excluded from the per-protocol population for the following reasons: defective recording of SaO_2 values in 1 child in the ASD group and delivery of only half the scheduled dose of nebulized albuterol at each of the 3 administrations (.075 mg/kg instead of .15 mg/kg) in 2 children. None of the patients dropped out of the study, and none had respiratory physiotherapy during the study. The trial profile is presented in Fig 3. The baseline characteristics of the 63 evaluated children can be found in Table 2. The principal investigator (D.P.) assessed 44 children and the remaining 20 children were assessed by the 8 other investigators. Timing of evalu-

TABLE 1. Pulmonary Index*

	Respiratory rate (breaths/min)	Wheezing	I/E Ratio†	Use of Accessory Respiratory Muscles†
Score 0	≤30	None	2:1	None
Score 1	31-45	End expiration	1:1	Minimal use
Score 2	46-60	Entire expiration	1:2	Moderate use
Score 3	>60	Inspiration and expiration without stethoscope	1:3	Marked use

* The pulmonary index is the sum of the score for each of the 4 sections.¹⁰

† Assessed by observing jugular, supraclavicular, intercostal, and subcostal areas.

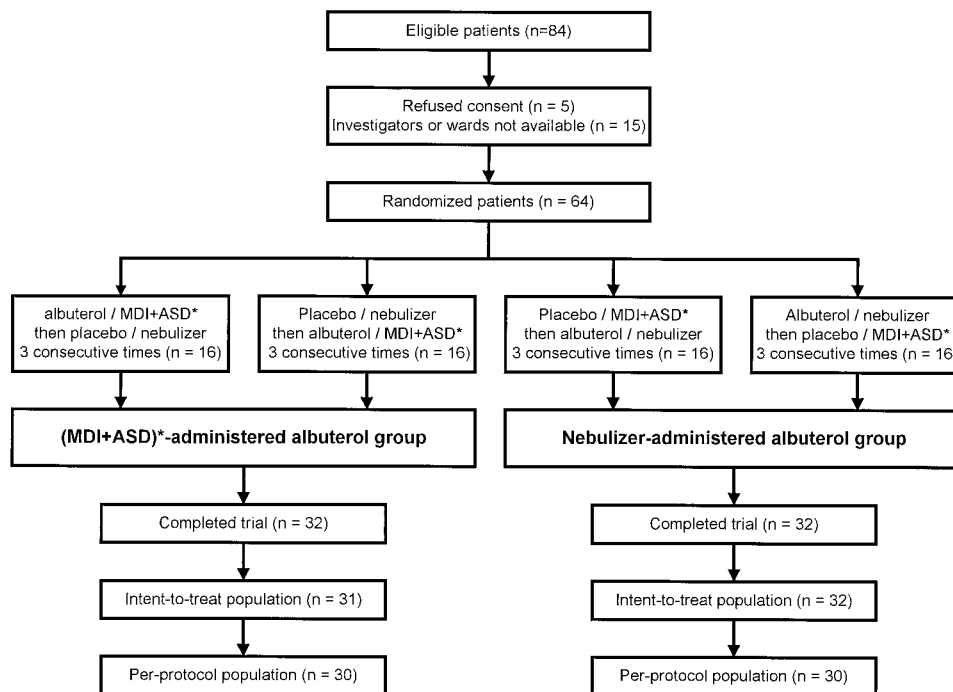


Fig 3. Flowchart of the study. *MDI + ASD.

TABLE 2. Baseline Characteristics of 63 Children (Intent-to-Treat Population)

	(MDI + ASD)* Group (n = 31)	Nebulization Group (n = 32)	P
Male: n (%)	21 (68%)	18 (56%)	.81
Age: mean in months (range)	24.8 (12–51)	25.5 (11–56)	.41
Weight: mean in kg (range)	13.1 (9–21)	12.5 (9–18)	.41
Family history			
Asthma: n (%)	17 (55%)	22 (69%)	.26
Atopy: n (%)	7 (23%)	12 (38%)	.20
Eczema: n (%)	10 (32%)	15 (47%)	.24
Personal history			
Number of previous wheezing episodes: mean (range)	3.3 (1–7)	2.2 (1–6)	.08
Asthma: n (%)	19 (61%)	13 (41%)	.10
Atopy: n (%)	5 (16%)	6 (19%)	.78
Eczema: n (%)	9 (29%)	12 (38%)	.48
Present wheezing			
Pulmonary index: median (range)	9 (6–12)	7 (4–11)	.08
Severity†: mild wheezing: n (%)	3 (10%)	7 (22%)	
moderate wheezing: n (%)	19 (61%)	17 (53%)	.32
severe wheezing: n (%)	9 (30%)	8 (25%)	
SaO ₂ : mean (range)	94.6% (90–99)	95.9% (90–100)	.02

* Pulmonary index was used as an asthma severity scale: mild when 1 to 6; moderate when 7 to 9; and severe when 10 to 12.

ations was the same in the 2 groups: T20 evaluation was performed after a mean time of 21 minutes in both groups, T40 after 45 minutes in the MDI + ASD group, 44 minutes in the nebulizer group, and T60 after 65 minutes in both groups.

No difference ($P = .91$) was observed between the mean temperature of the ASD group ($37.7 \pm .9$) and the nebulizer group (mean temperature $37.7^\circ\text{C} \pm .7$). Investigators administered a mean dose of 19 mg/kg paracetamol to 29 febrile children (fever $\geq 38.0^\circ\text{C}$) before beginning the study. Three patients remained febrile and received a complement of 23 mg/kg aspirin. Causes of the fever were: otitis media in 1 child

and viral respiratory tract infection in the other children.

The 90% confidence interval of the difference between treatment groups for the median absolute changes in the pulmonary index value was $[-1; +1]$.¹⁴ This interval was found to be within the predefined equivalence interval $[-1.5; +1.5]$. It was therefore concluded that the 2 treatments were equivalent.

Figure 4 shows the effect of repeated dosing (repeated-measures analysis of variance on ranks). Clinical improvement increased during the course of the 3 administrations (time effect: $P < .01$), regardless

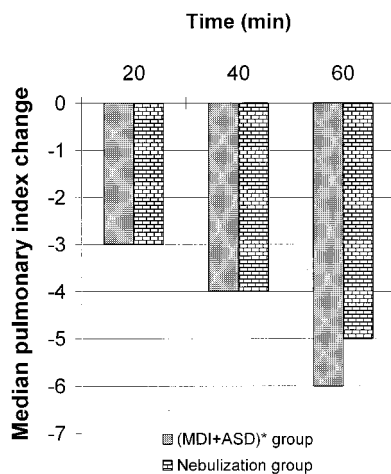


Fig 4. Median decrease from baseline in pulmonary index after each of the 3 treatment administrations (intent-to-treat population). *MDI + ASD.

of the treatment group ($P = .27$), and with no time-by-treatment interaction ($P = .70$).

Six patients (10%) were hospitalized after treatment. A T60 pulmonary index value of 6 or more led to admission of 4 patients (6%) after the end of the study (2 treatment failures in each group). Two patients (3%) could not be discharged for nonrespiratory reasons (1 child in the nebulizer group had a temperature of 38.8°C at T60 despite paracetamol and aspirin administration, and 1 child in the ASD group admitted in order to train the parents to deal with their child's asthma). After resolution of the initial episode, none of the discharged children needed an additional visit in the pediatric emergency department for secondary aggravation of their clinical status.

According to 59 out of 63 (94%) parents, the ASD was the easier mode of albuterol administration, whereas 3 out of 63 (5%) parents preferred the nebulizer, and 1 out of 63 (2%) parents had no preference. The preference distributions were similar between the 2 treatment groups ($P = .24$).

Similarly, 39 out of 63 (62%) parents considered that the ASD was better accepted by their children, while 17 out of 63 (27%) parents preferred the nebulizer treatment, and 7 out of 63 (11%) parents had no preference. However, the preference distributions were significantly different between the 2 treatment groups ($P = .05$). When albuterol was administered by the ASD, 24 out of 31 (77%) parents preferred the ASD, 5 out of 31 (16%) parents preferred the nebulizer, and 2 out of 31 (6%) parents had no preference. When albuterol was administered by the nebulizer, 15 out of 32 (47%) parents preferred the ASD, 12 out of 32 (38%) parents preferred the nebulizer, and 5 out of 32 (16%) parents had no preference.

The 90% confidence interval of the difference in the mean changes in SaO_2 between treatment groups was $[-.57; +1.63]$.

Three children had digestive symptoms: 1 out of 32 (3%) in the ASD group (vomiting), and 2 out of 32 (6%) in the nebulizer group (1 had nausea and 1 had vomiting). Only 1 out of 32 children (3%) in the ASD group had tachycardia after the posttreatment 10-

minute rest period. Tolerance was not different between the 2 groups.

DISCUSSION

In 12- to 60-month-old children with recurrent wheezing, our data showed that efficacy of high-dose albuterol administered using the ASD was equivalent to that of the nebulized albuterol. This main result confirms that MDI + ASD "may be as effective as the nebulizer in delivering high doses of β_2 -agonists during severe exacerbations" as stated in the 1997 National Institutes of Health/World Health Organization guidelines.⁷ Given its tolerance, repeated 50- $\mu\text{g}/\text{kg}$ doses of albuterol administered through the ASD should be considered for use in a hospital emergency department as first-line therapy.

Studied Population

Baseline characteristics were similar in both groups except for the SaO_2 distributions. Lower values were observed in the ASD group. The median T0 pulmonary index was 9 in the ASD group and 7 in the nebulizer group without a statistically significant difference. The observed difference could be attributable to a random effect or may reflect a difference in initial wheezing severity. However, unbalanced values in initial severity were taken into account in statistical analysis by considering only changes from baseline values.

To select children with asthma rather than viral bronchiolitis, we included children older than 1 year with at least 1 previous wheezing episode. Furthermore, excluding children with a SaO_2 lower than 90% ensured that the study did not include children needing immediate admission to pediatric intensive care units.

Albuterol Dosage Regimen

Nebulized albuterol is standard for asthma exacerbation in hospital emergency wards^{1,2,5,8} and a dosage regimen of .15 mg/kg is widely used and recommended.^{3,6-8} Proposed dosage regimens of albuterol administered using an MDI vary widely. The albuterol dose ratio of MDI dose to nebulized dose was 1:3 in our study, as previously used by de Blic et al.¹⁵ In other previous comparative studies, the dose ratio ranged from 1:1 to 1:6.9.¹⁰ The maximum dose was restricted to 10 puffs in accordance with British and US guidelines.^{4,7} Much higher doses than the currently used standard of 2 puffs¹⁶ appear better adapted to the asthma exacerbation requiring hospital management, particularly for cases of severe wheezing. Furthermore, a dose of 1 puff per kg body weight was preferred to a fixed dose for better comparability to the nebulization dose regimen.

Results reported herein associated repeated dosing with an increase in efficacy with no safety concerns, notwithstanding the high doses used. This confirms the relevance of the use of such a high-dose regimen of inhaled albuterol.

Nebulization Mode

The ultrasonic nebulizer was chosen for its rapid delivery and the better particle size obtained. Hess et

al¹⁷ reported that the volume of nebulized solution may have an effect on efficacy. Our experiment used the nebulized volume recommended by the Australian consensus on asthma management.³ The 2 dosing errors observed in our study raise the question of potential mistakes when routine treatments are prepared by physicians, nurses, or parents. The MDI, with or without the concomitant use of the ASD, may represent a safer alternative, as doses are easy to determine and administer, compared with the risks of handling a highly concentrated solution.

Evaluation Criteria

The pulmonary index has already been "successfully used in infants with asthma and showed evidence of validity and responsiveness."¹⁷ The modified pulmonary index, as defined by Scarfone et al,¹² was preferred for its simplicity and the accuracy of the I/E ratio limits.

Sao₂ was stable between T0 and T60 in both treatment groups. Changes in Sao₂ did not reflect the clinical improvement evidenced by the pulmonary index changes. In general, Sao₂ is mainly used as a diagnostic test, providing support for decisions regarding oxygen therapy or hospitalization.^{2-4,6,7} Our study confirms the lack of relevance of Sao₂, as compared with the pulmonary index, in evaluating the therapeutic response in 12- to 60-month-old children in this setting.¹⁹

As nebulizer and MDI + ASD treatment durations were different, we had to perform a specific randomization so as to equilibrate the administration order (nebulizer first or MDI + ASD first) within each group. Lack of time-to-treatment interaction was verified.

Safety Analysis

Overall, treatments were well-tolerated. Tachycardia and digestive disorders may have been related to the respiratory status of the children as well as to albuterol. A total of 10% (6 out of 64) of the children studied were hospitalized, and only 6% (4 of 64) were admitted as a result of treatment failure. The discharge of a large majority of children (58 of 64) may be ascribed, at least in part, to the high dosage regimen used in our study.

Ease of Use and Acceptability

The vast majority of parents considered that the ASD was easier to use than the nebulizer. Furthermore, 62% of them stated that this device, coupled with the MDI, was better accepted by their children (11% not expressing a preference). This figure was 77% when the ASD was used to administer albuterol, whereas it was only 47% when used to administer the placebo. In addition, investigators noticed that, when children did not participate in the treatment, hyperventilation and tachypnea attributable to screaming and crying may have shortened the length of time spent obtaining the 8 breaths, while the long duration of nebulization indeed was more prone to increase the annoyance. Conversely, the children used to the ASD willingly agreed to participate in the treatment administration, some even holding out

their hands to the face mask to bring it into position. With regard to the treatment administered (albuterol or placebo), the parents' opinion confirmed the very high acceptability of the ASD when delivering active treatment.

Overall Strategy

The overall care strategy should include evidence on efficacy, ease of use, acceptability, and cost of each treatment modality. As previously stated by Rees and Price, "nebulizers are expensive, time consuming, and inconvenient, and they are often used incorrectly at home" and "a child should not be discharged from hospital until he is taking the treatment that he will be taking at home."¹ The British guidelines on asthma management in children <5 years old offer the choice of the nebulizer or the MDI + ASD (up to 10 puffs in a community/primary care setting or a dose similar to the nebulization for acute severe asthma); nevertheless, these guidelines state, as much for prevention as for relief, that "nebulizers are rarely needed for young children; spacer devices are as effective, cheaper, and less time consuming."⁴ The guidelines given by the British Thoracic Society Nebuliser Project Group state that "for acute exacerbation, . . . treatment with metered dose inhaler and spacer may be as effective and cheaper than nebulization but is not widely undertaken" with the highest grade of recommendation.⁵

The growing workload in emergency departments and health cost constraints call for controlled studies to define optimal strategies in terms of efficacy and cost. Our efficacy data support the use of high-dose albuterol given through an ASD, even in the hospital, as a first-line mode of treatment for preschool children with recurrent wheezing. Prescribing and demonstrating the use of ASD early rapidly trains families to use the device and thus allows doctors to immediately check parents' skill in delivering the treatment they will administer to the child at home. Furthermore, it shortens the stabilization time and consequently the duration of medical visits, with savings in single-use supplies and nursing and medical staff time. In addition, it may allow early discharge from emergency care, freeing accommodation, the factor limiting the patient turnover in emergency departments. The increasingly widespread use of the ASD and albuterol high-dosage regimens could lead to a decrease in the number of hospitalizations and lower treatment costs.^{7,20}

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THE “RIPE” OLD DAYS

In the period of which we speak, there reigned in the cities a stench barely conceivable to us modern men and women. The streets stank of manure, the courtyards of urine. The stairwells stank of moldering wood and rat droppings, the kitchens of spoiled cabbage and mutton fat; the unaired parlors stank of stale dust, the bedrooms of greasy sheets, damp feather beds, and the pungently sweet aroma of chamber pots. The stench of sulphur rose from the chimneys, the stench of caustic lyes from the tanneries, and from the slaughterhouses came the stench of congealed blood. People stank of sweat and unwashed clothes; from their mouths came the stench of rotting teeth, from their bellies that of onions, and from their bodies, if they were no longer very young, came the stench of rancid cheese and sour milk and tumorous disease. The rivers stank, the marketplaces stank, the churches stank, it stank beneath the bridges and in the palaces. The peasant stank, as did the priest, the apprentice as did his master's wife, the whole of the aristocracy stank, even the King himself stank, stank like a rank lion, and the Queen like an old goat, summer and winter. For in the 18th century there was nothing to hinder bacteria busy at decomposition, and so there was no human activity either constructive or destructive, no manifestation of germinating or decaying life, that was not accompanied by stench.

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Submitted by Student

High-Dose Albuterol by Metered-Dose Inhaler Plus a Spacer Device Versus Nebulization in Preschool Children With Recurrent Wheezing: A Double-Blind, Randomized Equivalence Trial

Dominique Ploin, François R. Chapis, Didier Stamm, Jacques Robert, Louis David, Pierre G. Chatelain, Guy Dutau and Daniel Floret

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