

Bronchodilator Resuscitation in the Emergency Department Part 1 of 2: Device Selection

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Summary [Respir Care 1999;44(11):1353–1374] *Key words: bronchodilator resuscitation, emergency department, pressurized metered-dose inhaler, holding chamber, nebulizer, acute airway obstruction, aerosol therapy.*

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are widely prevalent in the United States, affecting up to 11% of the population.¹ Patients suffering acute exacerbations of asthma or COPD commonly seek medical assistance in the emergency department (ED). This

review examines bronchodilator resuscitation in the ED for symptomatic relief of acute airway obstruction.

Most patients presenting to the ED with acute asthma or COPD have had worsening symptoms for 24–36 hours. They have typically been self-administering whatever relevant medications they have, at greater than prescribed dose and frequency, with little or no effect. The patient is usually uncomfortable, tired, frustrated, and scared. The first order of business for these patients is to relieve the airway obstruction, reduce the work of breathing, and decrease the patient's feeling of panic. Treatment in the ED commonly includes administration of systemic corticosteroids and aerosolized bronchodilators.² The onset of action for steroids, whether given intravenously or orally, occurs

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after 45 minutes, with several hours required for measurable bronchodilator effect. The role of bronchodilator resuscitation is to provide symptomatic relief while waiting for the corticosteroids to reduce airway obstruction.

A careful review of the literature reveals that there are several key components regarding bronchodilator resuscitation in the ED. These components include selection of appropriate device, continuous versus intermittent administration of aerosol, high or low dosing strategies, and the use of beta-2 adrenergic agonists alone, or in combination with anticholinergic bronchodilators. In addition, the severity and the intrinsic reversibility of airway obstruction among patients influence the response to treatment.

The literature abounds with research and opinions about aerosol delivery devices,³ medications, and dosing strategies available for use in the ED to provide symptomatic relief of severe airway obstruction. Despite an impressive amount of literature showing that the pressurized metered-dose inhaler with holding chamber (pMDI/HC) is as effective and efficient, and less costly,⁵⁻¹² many practitioners prefer the use of the nebulizer for bronchodilator delivery in the ED.⁴

In the first part of this review, we examine the impact of device selection on bronchodilator resuscitation. Review of the role of continuous versus intermittent nebulization, dosing strategies, and use of anticholinergics will appear in a subsequent issue of *RESPIRATORY CARE*.

Pressurized Metered-Dose Inhaler Versus Nebulizer

Although the pMDI is the most commonly prescribed aerosol device for patients at home, a bias toward the use of nebulizers in the ED persists. This may be due, in part, to common patient complaints that the use of pMDIs prior to presenting to the ED (after having self-administered more puffs than prescribed) failed to provide adequate relief. In addition, numerous reports in the literature document problems with patient use and a lack of practitioner understanding of proper technique for use of pMDIs.¹³ The limitation of the pMDI is well documented, requiring considerable hand-breath coordination and breath control for optimal therapy, which is difficult for many patients, especially during acute exacerbations. Even patients who demonstrate proper pMDI technique when their dyspnea is under control may not properly self-administer with a pMDI when acutely short of breath.

With this in mind, we present a brief review of salient technical considerations for appropriate use of pMDIs, holding chambers, and pneumatic nebulizers.

Technical Considerations – Pressurized Metered-Dose Inhaler

The pMDI canister contains a pressurized mixture of propellants, surfactants, preservatives, and flavoring agents,

Table 1. Optimal Technique for Using a Pressurized Metered-Dose Inhaler (Bronchodilator Only)

1. Warm pressurized metered-dose inhaler (pMDI) canister to hand or body temperature, shake vigorously.
2. Assemble apparatus, uncap mouthpiece, and make sure there are no loose objects in device.
3. Open mouth wide, keep tongue from obstructing the mouthpiece.
4. Hold the pMDI vertically, with the outlet aimed at mouth.
5. Place canister outlet between lips, or position the pMDI about 4 cm (two fingers) away from mouth.
6. Breathe out normally.
7. As you begin to breathe in slowly (< 0.5 L/s); actuate (fire) the pMDI.
8. Continue to inhale to total lung capacity.
9. Hold breath for up to 10 seconds.
10. Wait 30 seconds between inhalations (actuations).
11. Disassemble apparatus and recap mouthpiece.

with approximately 1% of the total contents being active drug.¹⁴ This mixture is released from the canister through a metering valve and stem, which fits into an actuator boot, designed and tested by the manufacturer to work with that specific formulation. Small changes in actuator design can change the characteristics and output of the aerosol from a pMDI. Whenever a pMDI is being used with an actuator other than the one supplied by the manufacturer, in vitro testing should be performed to determine performance characteristics of the new combination.¹⁵ The output volume of the pMDI varies from 30 to 100 μ l and contains between 20 μ g and 5 mg of drug, depending on formulation. Lung deposition is estimated at between 10% and 25% in adults, with high intersubject variability, largely dependent on user technique.¹⁶⁻¹⁸ When proper technique or an effective accessory device (ie, holding chamber) is used, the pMDI delivers a substantially greater proportion of the nominal dose to the lung than a pneumatic nebulizer.¹⁴

Effective use of the pMDI is technique-dependent. Up to two thirds of patients who use pMDIs and health professionals who teach pMDI use do not perform the procedure properly.^{19,20} Table 1 details recommended steps for administering a bronchodilator using a pMDI.^{21,22}

Common hand-breath coordination problems include actuating the pMDI before or after the breath.^{13,19,20} Some patients, especially infants, young children, the elderly, and patients in acute distress may simply not be able to use a pMDI. In addition, some patients perceive a "cold FREON effect" that occurs when the aerosol plume reaches the back of the mouth, and the patient stops inhaling. All of these problems reduce aerosol delivery to the lung, but can be corrected in part or whole by using the proper pMDI accessory device.

Table 2. Optimal Technique for Using a Pressurized Metered-Dose Inhaler With a Valved Holding Chamber

1. Warm pressurized metered-dose inhaler (pMDI) canister to hand or body temperature.
2. Assemble apparatus and make sure there are no objects in device that could be aspirated or obstruct the flow.
3. Shake canister vigorously and hold canister vertically.
4. Place holding chamber in mouth (or place mask completely over nose and mouth), encouraging patient to breath through mouth.
5. Breath normally and actuate (fire) pMDI at the beginning of inspiration; for small children and infants, continue to breathe through the device for 5 or 6 breaths. Larger breaths with breath-holding may be encouraged in those patients who can cooperate.
6. Allow 30 seconds between actuations.

Spacers and Valved Holding Chambers

The key to successful use of the pMDI in the ED appears to be the use of a holding chamber. Holding chambers range from 130 to 750 mL, with sufficient internal volume to allow the plume of the pMDI to expand, allowing time for the propellants, solvents, and other ingredients to evaporate, increasing the percentage of respirable mass available to the patient. Holding chambers have been shown to improve pulmonary deposition from approximately 10% (with pMDI alone) to $\geq 20\%$.¹⁸ Placement of a valve between the chamber and the patient serves as a baffle impacting large aerosol particles that would otherwise deposit in the oropharynx (reducing oral deposition from 80% to less than 1% of the nominal dose), decreasing the total body dose from swallowed medication. The valve also redirects exhaled gas so that aerosol remaining in the chamber is not "blown away" on exhalation. A patient with a small tidal volume may empty the aerosol from the chamber with 5–6 breaths. A valved holding chamber can also incorporate a mask for use with infants or children. These devices allow effective pMDI administration to patients who are unable to use a mouthpiece because of size, age, coordination, or mental status.^{23–30} For use with infants it is critical that these masks should have minimal dead space, be comfortable for the child's face, and the chamber must have a valve that will open or close with low inspiratory flow. Table 2 details optimal technique for using a pMDI with a valved holding chamber.

While the use of valved holding chambers offers significant advantages in administration compared to the pMDI alone, no device is foolproof. Table 3 summarizes common problems in self-administration with pMDIs and pMDIs with holding chambers. Holding chambers have proven to be the "great equalizer" between pMDIs and nebulizers. Consequently, over the past decade virtually all of the randomized controlled trials comparing the use of pMDIs and nebulizers for treatment of acute, severe asthma in the ED have used pMDIs with valved holding chambers (Fig 1).¹²

Nebulizers

Nebulizer selection affects aerosol delivery. Only nebulizers that have been shown to work reliably under specific conditions with specific medications should be used. Nebulizers producing aerosols with mass median aerodynamic diameter of 1–3 μm are more likely to achieve greater deposition in the lower respiratory tract.¹⁴ European standards specify that an effective pneumatic nebulizer should deliver $> 50\%$ of its total dose as aerosol in the respirable range mass median aerodynamic diameter (1–5 μm) in ≤ 10 minutes of nebulization time. Nebulizer performance varies with diluent volume, operating flow, operating pressure, gas density, and nebulizer model.^{31–34} The amount and percentage of drug nebulized increases as the volume of diluent is increased. The residual volume of medicine that remains in commercial small-volume nebulizers varies from 0.5 to 1.5 mL, depending on the device, so increasing the fill volume allows a greater proportion of the active medication to be nebulized. However, to date no significant difference in clinical response has been shown with varying diluent volumes and flow rates.³³

With so much medication left in the nebulizer, when should the standard nebulizer treatment end? Malone et al found that with 3 different fill volumes, albuterol delivery from the nebulizer ceased following the onset of inconsistent nebulization (sputtering).³⁵ Aerosol output declined by half within 20 seconds of the onset of sputtering. The concentration of albuterol in the nebulizer cup increased significantly once the aerosol output declined, and further weight loss in the nebulizer was primarily due to evaporation. The authors concluded that aerosolization past the point of initial jet nebulizer sputter is ineffective.

Relationship of Deposition and Delivered Dose

Lewis and Fleming³⁶ assessed fractional deposition of aerosol from a nebulizer by having 6 normal and 2 asthmatic subjects inhale aerosol of technetium from a jet nebulizer. They reported that 66% of the nominal dose remained in the nebulizer, while 2% deposited in the mouth, 20% was exhaled, and 12% was deposited in the lung. This is markedly different from the findings of Newman et al¹⁶ in their study of the use of pMDI alone. They found that 9% deposited in the lung, 80% in the oropharynx, 10% in the apparatus, and approximately 1% was exhaled. Subsequent studies using pMDI/HCs showed a reduction in oropharyngeal deposition, to as low as 1%, with 78% of the nominal dose remaining in the chamber, and 20–25% being delivered to the lungs (Fig 2).

Albuterol, like most beta-2 adrenergic bronchodilators, has a log dose response (Fig 3).³⁷ There is an initial steep response to the bronchodilator at relatively low doses, and as the dose is increased the response flattens but continues

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Table 3. Comparison of Errors Associated With the Use of Pressurized Metered-Dose Inhalers and Pressurized Metered-Dose Inhalers with Holding Chambers

Pressurized Metered-Dose Inhaler with Holding Chamber	Pressurized Metered-Dose Inhaler
Major Errors	
Inability to trigger MDI Inability to attach MDI Failure to inhale through device	Inability to trigger MDI MDI actuated after inhalation MDI actuated during exhalation MDI actuation stops inhalation (cold FREON effect) Multiple actions during single breath Failure to inhale through device Failure to remove MDI cap
Minor Errors	
Difficulty with attaching MDI Rapid repetitive actuation of MDI Failure to shake MDI	Triggering MDI late, but during inhalation Failure to hold breath after inhalation Failure to shake MDI

(Adapted from Reference 13.)

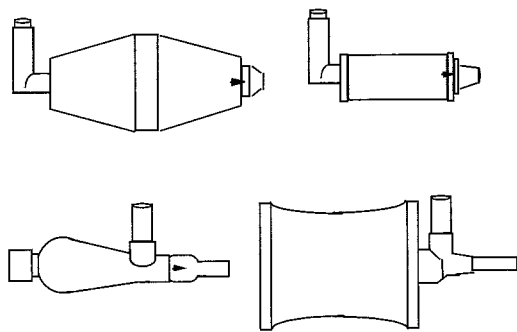


Fig. 1. Examples of valved holding chambers used with pressurized metered-dose inhalers in randomized clinical trials published in the last 12 years. Ranging from 140–750 mL in volume, each device utilizes a one-way valve (designated by the arrow) placed between the holding chamber and the patient's airway.

to improve. The United States Food and Drug Administration's approved standard dose for albuterol via pMDI is 200 μg , while the standard dose with albuterol sulfate solution is 2.5 mg (2,500 μg). Pulmonary deposition of albuterol, eliciting $\geq 10\%$ improvement in the forced expiratory volume in the first second (FEV_1) or peak expiratory flow (PEF) in stable asthmatics is $\approx 20 \mu\text{g}$ with a pMDI and 250–300 μg with a nebulizer. Consequently, the nebulizer delivers more than 10–15 fold more albuterol to the lung than would be required to provide bronchodilation with the pMDI. Use of a holding chamber has been shown to increase pulmonary deposition to 20–25%, representing a $\geq 40 \mu\text{g}$ dose of albuterol to the lungs while reducing oral deposition by 158 μg , substantially reducing the extrapulmonary systemic dose to the patient, reducing the incidence of adverse effects. In small children

and infants, deposition can be less than 1%, representing less than 25 μg delivered to the lung from the nebulizer.

Pressurized Metered-Dose Inhaler with Holding Chamber Versus Nebulizer – Adults

Randomized, controlled clinical studies comparing the use of pMDI/HCs and pneumatic nebulizers for bronchodilator resuscitation have proliferated over the past decade. To provide greater insight into their findings, we begin with a review of the subset of studies of adult patients presenting to the ED with exacerbation of asthma, COPD, or a combination thereof.

Asthma

Salzman et al³⁸ studied bronchodilator response to metaproterenol delivered via pMDI/HC and nebulizer in 44 asthmatic patients who presented to the ED with acute severe airflow obstruction ($\text{FEV}_1 < 50\%$ of predicted). The delivery method was randomized, double-blind, and placebo controlled. The pMDI/HC group received 1 puff of metaproterenol every 5 minutes for a total of 3 puffs (1.95 mg) and the nebulizer group received 15 mg of metaproterenol over 10 minutes. The mean percentage improvement in forced vital capacity (FVC) and FEV_1 trended higher (33.5% and 49.0%, respectively) in the pMDI/HC group than the nebulizer group (22.8 and 33.0%, respectively) but was not statistically significant.³⁸

In 1993, Colacone et al³⁹ reported a randomized, double-blind, placebo-controlled trial of 80 adults presenting to the ED with acute severe asthma (FEV_1 36% of pre-

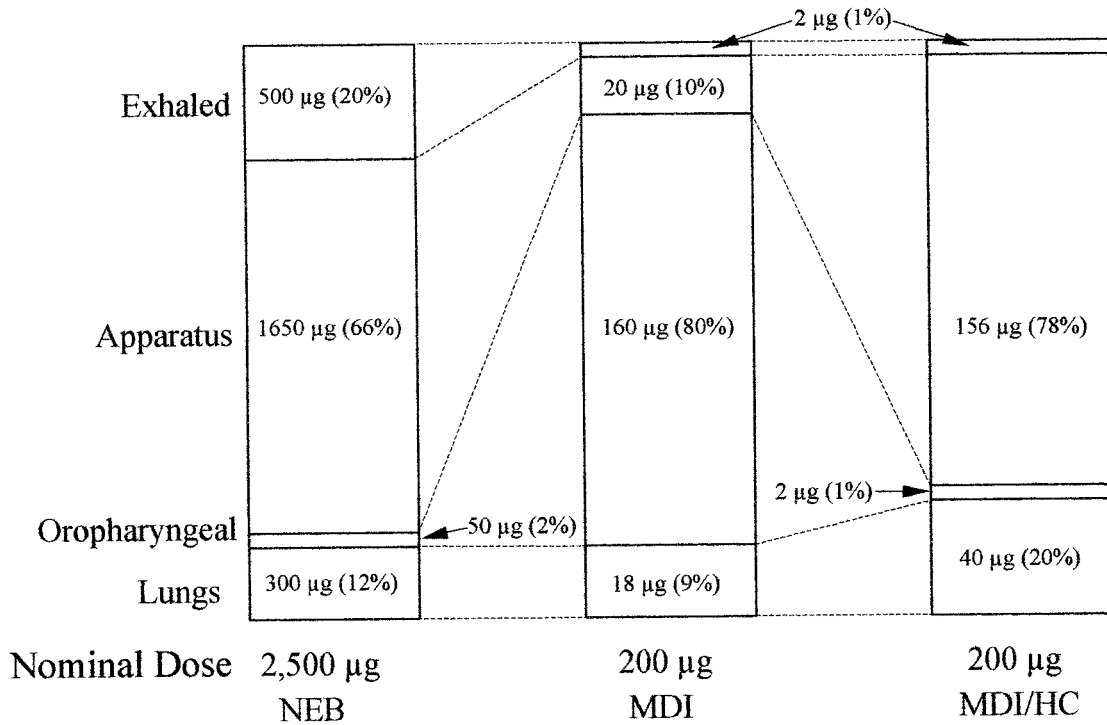


Fig. 2. Analysis of the deposition from a pneumatic nebulizer (NEB) (left), a pressurized metered-dose inhaler (MDI) (center) and a pressurized metered-dose inhaler with holding chamber (MDI/HC) (right), showing the amounts and percents of the nominal albuterol dose deposited in the lungs, oropharynx, apparatus, and exhaled. (Adapted from References 16 and 36.)

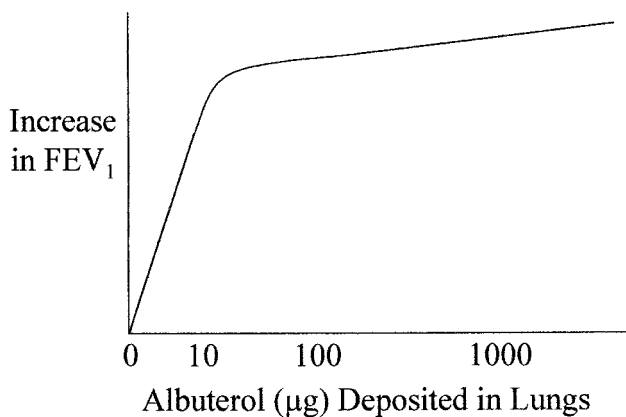


Fig. 3. Conceptual representation of the shallow bronchodilator response curves to albuterol in stable asthmatics. There are 2 phases of response, with the majority of response occurring after lung deposition of 10–20 µg of albuterol in the lung. In Phase 2 the response to increasing lung dose of albuterol is less steep.

dicted). Patients received albuterol via pMDI/HC (0.4 mg) or nebulizer (2.5 mg) every 30 minutes until maximal bronchodilation (Fig 4). Most of the pMDI/HC group (65%) and nebulizer group (75%) achieved maximal bronchodilation after 2 doses, with virtually all patients in both groups reaching maximal bronchodilation by 4 doses. The FEV₁ improved by 0.72 ± 0.49 L for the pMDI/HC group and 0.68 ± 0.61 L for nebulizer group (p = 0.71). A

significant linear relationship (r = 0.94) was found in both groups between the log dose of albuterol and the change in FEV₁.³⁹ About one sixth of the nebulizer dose of albuterol achieved similar response with the pMDI/HC.

Idris et al⁴⁰ reported a randomized, double-blind, placebo-controlled study of 35 patients, age 10–45 years, with FEV₁ < 40% of predicted, in the ED for acute asthma exacerbation. Patients received albuterol or placebo via pMDI/HC (360 µg) or nebulizer (2.5 mg) every 30 minutes until FEV₁ was 80% of predicted or 6 doses had been given. Mean FEV₁ improved for both groups at 30 minutes (p < 0.02) and at 60 minutes (p < 0.02), as did maximum mean FEV₁ (p < 0.001), which occurred at a mean 92 ± 50 minutes (Fig 5). No differences were observed between the groups (p < 0.6), but the time required to administer pMDI/HC (6 minutes first treatment, and 3 minutes for each of the subsequent 6 treatments) was less than the nebulizer (10–15 minutes per treatment). Thirty-three of 35 patients were treated successfully with the study protocol, became asymptomatic, and were discharged home. One patient from each group required further treatment. There was no detectable difference in effectiveness of albuterol administered via nebulizer or pMDI/HC when the dose was titrated to clinical response.

Rodrigo and Rodrigo⁴¹ selected albuterol doses calculated on the basis of the percentage of total dose that

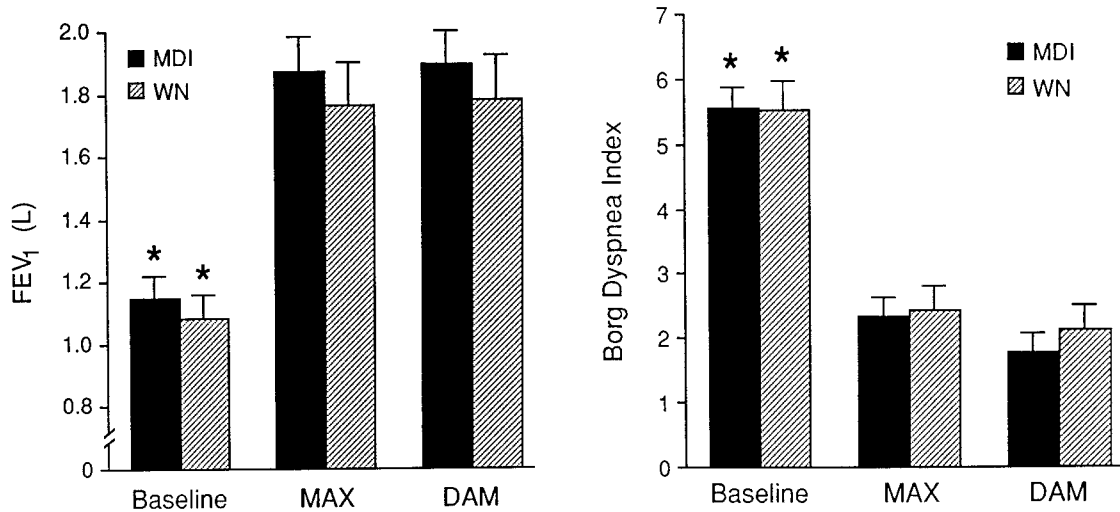


Fig. 4. Mean forced expiratory volume in the first second (FEV₁) (\pm standard of the mean) and Borg Score were similar for patients treated with albuterol delivered via pressurized metered-dose inhaler and via wet nebulizer (WN) at baseline, maximal bronchodilation (MAX), and one dose above maximal bronchodilation (DAM). Both groups showed significant improvement at MAX and DAM compared to baseline values. (From Reference 39, with permission.)

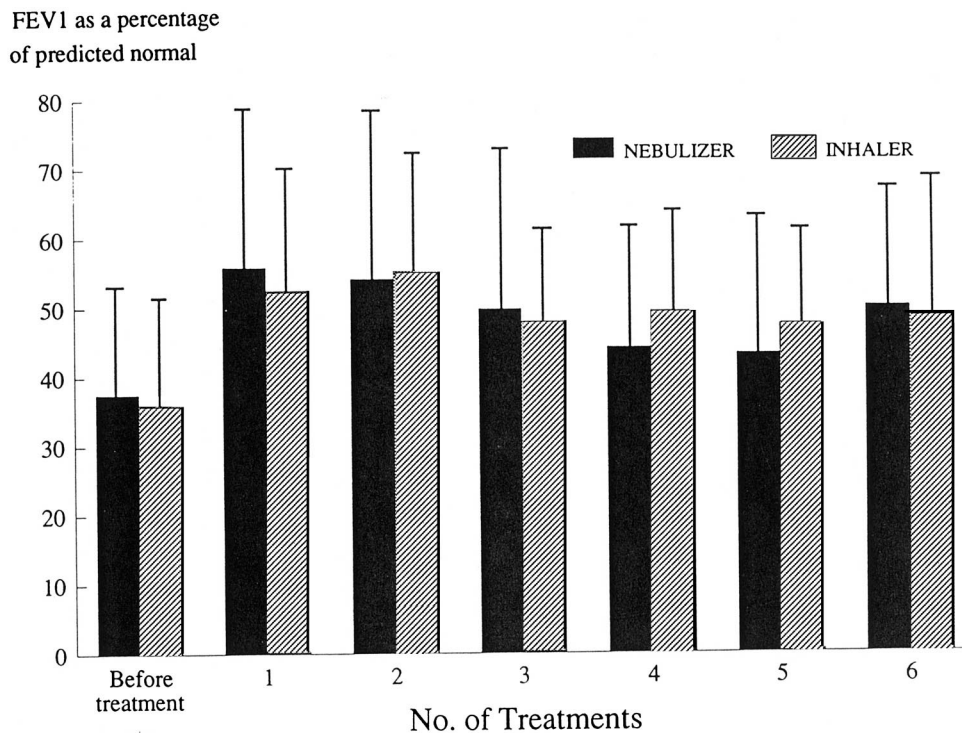


Fig. 5. Percent of predicted forced expiratory volume in the first second (FEV₁) in acute asthmatic patients given albuterol via nebulizer (2.5 mg per treatment) and via pressurized metered-dose inhaler with holding chamber (inhaler) (360 μ g per treatment) at 30-minute intervals. Both groups improved from baseline, with no statistical difference between groups. (From Reference 40, with permission.)

reaches the lower airways with nebulizer (10%) and pMDI/HC (20%). Ninety-seven patients, age 18–50 years, with acute bronchial asthma previously treated at a hospital ED were enrolled in this randomized, double-blind, placebo-controlled trial, receiving albuterol via pMDI/HC

(400 μ g at 10-minute intervals) or nebulizer (1.5 mg at 15-minute intervals) over a 3-hour period. The final mean dose was 5.61 mg for the pMDI/HC group and 11.8 mg for the nebulizer group (2:1 dose ratio). Both groups improved from baseline, with no difference in response, ED treatment

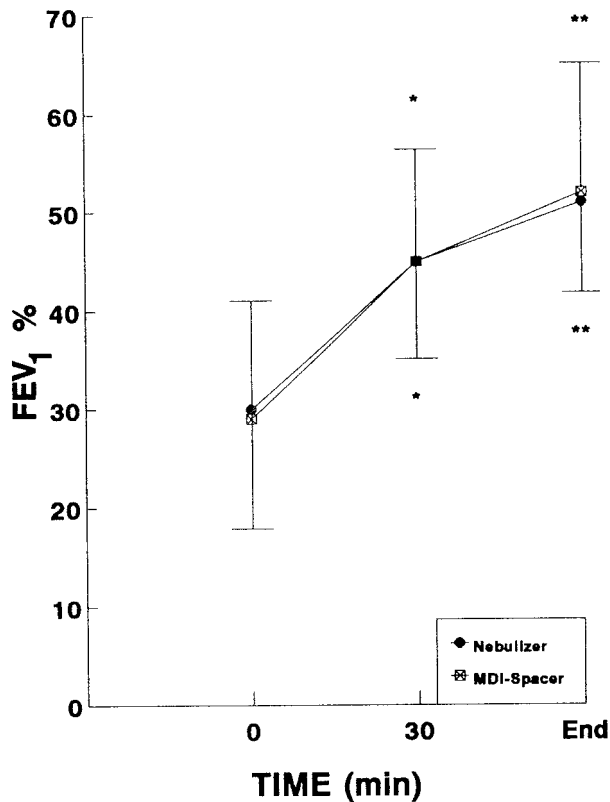


Fig. 6. Percent of predicted forced expiratory volume in the first second (FEV₁) at baseline, 30 minutes, and end of treatment for 97 patients with severe asthma, randomized to receive albuterol via pressurized metered-dose inhaler with holding chamber (MDI) (400 μ g at 10-minute intervals) or nebulizer (1.5 mg, at 15-minute intervals) over a 3-hour period. The final mean dose was 5.61 mg for the MDI group and 11.8 mg for the nebulizer group (2:1 dose ratio). Both groups improved from baseline, with no difference between groups. * $p < 0.01$. ** $p < 0.001$. (From Reference 41, with permission.)

time, or admission rate (Fig 6). Similar patterns were seen in patients with severe airway obstruction (FEV₁ < 0.9 L). Both the pMDI/HC and nebulizer regimens provided similar rates of spirometric and clinical improvement.

Rodrigo and Rodrigo⁴² reported a randomized, double-blind, parallel group study of ED patients suffering severe asthma exacerbation (FEV₁ < 50% of predicted).³⁴ The pMDI/HC group received 400 μ g of albuterol at 10-minute intervals (2.4 mg/h), while the nebulizer group received 1.5 mg of albuterol sulfate at 15-minute intervals (6 mg/h) over 3 hours. PEF and FEV₁ improved significantly over baseline for both groups ($p = 0.01$). There was no difference between either group at any time studied. They found a significant linear relationship between cumulative dose and FEV₁ for pMDI and nebulizer ($r = 0.97$ for both). Regression equations showed that for every 1 mg of salbutamol via pMDI/HC, 2.5 mg were needed via nebulizer for equal therapeutic response. At the end of treatment,

plasma albuterol levels were 10.1 ± 1.6 ng/mL for the pMDI/HC group and 14.4 ± 2.3 ng/mL for the nebulizer group ($p = 0.0003$). The larger systemic absorption of albuterol by the nebulizer group may account for the higher incidence of tremor ($p = 0.03$) and anxiety ($p = 0.04$) experienced. The authors concluded that when the dose of albuterol is calculated on the basis of the percentage of total drug that reaches the lower airway from each device, there was equivalent bronchodilation with either pMDI/HC or nebulizer in patients with acute severe asthma.

In 1994, Robertson⁴³ performed a dose-response study of albuterol via pMDI/HC and nebulizer, concluding that the metered-dose inhaler is as rapid and efficacious as the nebulizer in the treatment of acute asthma.

Chronic Obstructive Pulmonary Disease

In 1987, Jasper et al⁵ compared aerosol bronchodilator delivery with metaproterenol administered every 4 hours via pMDI/HC or nebulizer in 34 patients hospitalized with obstructive airway diseases, enrolled after transfer to the pulmonary ward from the ED or intensive care unit. Daily spirometry indicated that both treatment groups had equivalent bronchodilation initially and equivalent improvement at discharge. The duration of hospitalization for the 2 groups was also the same. The authors reported that in one year, 3,680 patients received a total of 47,038 aerosol treatments, with 16,495 nebulizers. The costs of nebulizers (\$1.00 each), medication (\$0.07), and labor (\$5.94 per treatment) totalled \$299,193. Use of pMDI/HCs represented a one-time cost per admission of \$12.42 (instruction time, holding chamber, and pMDI). They calculated that use of pMDI/HCs rather than nebulizers with adult patients would save their institution \$253,487 per year in labor costs.⁵

Summer et al⁶ studied 36 acutely ill, hospitalized adult patients with acute exacerbation of obstructive airway disease who showed a < 10% increase in FEV₁ after administration of aerosolized bronchodilator. Patients were randomized to receive either a standard dose of metaproterenol sulfate via nebulizer or terbutaline sulfate via pMDI/HC. The changes in FEV₁ and length of stay with pMDI/HC were at least equivalent to changes with nebulizer, with a lower daily charge for therapy and less respiratory therapist time.⁶

Combined Asthma and Chronic Obstructive Pulmonary Disease

In 1988, Turner et al⁴⁴ compared the efficacy of nebulizers and pMDI/HCs in 75 randomly assigned patients (22 COPD and 53 asthma) treated in double-blind fashion with 3 puffs of metaproterenol (0.65 mg/puff) via pMDI/HC plus nebulizer with placebo, or placebo pMDI/HC plus

nebulizer with 15 mg metaproterenol. Either treatment was given 3 times at 30-minute intervals. The FEV₁ and dyspnea scores (using Borg scale) showed no significant outcome difference between the two treatments in either diagnostic group. There was no outcome difference for patients with baseline FEV₁ < 0.9 L.⁴⁴

Levitt, Gambrioli, and Fink⁴⁵ conducted a randomized, double-blind, placebo-controlled study of 40 adult patients in the ED with acute exacerbation of COPD or asthma (FEV₁ < 30% of predicted). Over a 3-hour period patients received continuous nebulization with 15 mg per hour albuterol or normal saline via large-volume nebulizer and intermittent treatment of up to 24 puffs per hour with 2.4 mg/h of albuterol or placebo via pMDI/HC. Both groups had significant improvements in FEV₁, PEF, and Borg score, with no difference between groups, and no incidence of tremor or tachycardia that necessitated discontinuing therapy. Most patients had 100% improvement from baseline of peak flow or FEV₁/FVC (Fig. 7). Many patients in the pMDI/HC group had maximum response with the first 12 puffs (1200 µg). Approximately 66% of each group were discharged from the ED at or before 3 hours, without relapse in 72 hours. No patients required intubation or mechanical ventilation for their asthma.

In 1997, Mandelberg et al⁴⁶ reported results of a randomized, double-blind, placebo-controlled study of 50 adult patients with severe acute obstructive pulmonary event (13 COPD, 37 asthma) with FEV₁ < 32% of predicted.²⁸ The pMDI/HC group received 200 µg of albuterol or placebo and the nebulizer group received 2.5 mg of albuterol or saline solution, repeated 3 times at 15-minute intervals, unless adverse effects appeared. Both groups had significant improvement from baseline, with no difference in spirometry measurements between the two groups at any time (Fig 8). This study demonstrated that with an unselected group of patient referrals to the ED for episodes of severe airflow limitation, clinical and the objective bronchodilator response to albuterol is independent of the method of delivery.

In summary, pMDI/HCs are at least as effective as nebulizers for administration of beta agonist bronchodilators to adult asthmatic and COPD patients presenting to the ED with moderate to severe airway obstruction (see Table 4).

Pressurized Metered-Dose Inhaler With Holding Chamber Versus Nebulizer – Children

In 1986, Fuglsang et al⁴⁷ studied 21 asthmatic children, age 7–14 years, presenting to the ED with a mean FEV₁ of 29% of predicted. The children were randomly assigned to receive a 1.0 mg/kg dose of terbutaline via pMDI/HC

(Nebuhaler*) or nebulizer. Both groups had improvement from baseline, but the pMDI/HC group had a significantly greater increase in FEV₁ than the nebulizer group ($p < 0.05$). A majority of the children expressed a preference for the pMDI/HC over the nebulizer, because of the shorter administration time.

Kerem et al⁴⁸ conducted a double-blind, placebo-controlled study of 33 children, age 6–14 years, seen in the ED with acute asthma and FEV₁ between 20% and 70% of predicted. Patients received albuterol and placebo via pMDI/HC and nebulizer with a dose ratio of 1:5. With the exception of heart rate, which increased in the nebulizer group and decreased in the pMDI/HC group ($p < 0.05$), no difference in the rate of improvement of clinical score, respiratory rate, arterial oxygen saturation, or FEV₁ was observed between the groups during the 40-minute study period.

In 1995, Lin and Hsieh studied 111 children suffering acute asthma treated with terbutaline via pMDI/HC (0.75 mg) versus nebulizer (5 mg).⁴⁹ The pMDI/HC group had better oxygen saturation, better absolute increase of PEF (32.6 L/min vs 10.1 L/min), and better FEV₁ percent increase (22.9% vs 15.4%, respectively). The authors noted that desaturation during acute asthma is a risk when the nebulizer is operated with an air compressor.

Parkin et al⁵⁰ studied 60 hospitalized asthmatic children, age 1–5 years, randomized to receive pMDI/HC (400–600 µg albuterol with 40 µg ipratropium) or nebulizer (0.15 mg/kg albuterol and 400 µg ipratropium bromide). A clinical score was measured at baseline (pMDI/HC 5.7 vs nebulizer 4.8, $p = 0.02$) and every 12 hours. Both groups had significant improvement, with no differences between groups in the score over time or secondary outcome measures (Fig 9).

Similarly, Chou, Cunningham, and Crain studied 152 children, age 2 years and older, presenting to the ED with acute asthma exacerbation (mean PEF 53–56% of predicted).⁵¹ The children were randomly assigned to receive albuterol via pMDI/HC (180–360 µg) or nebulizer (2.5–5 mg) at 20-minute intervals. There were no significant differences between the groups in outcomes, including mean change in respiratory rate, asthma severity score, PEF, oxygen saturation, number of treatments given, administration of steroids in the ED, or admission rate. However, the pMDI/HC group required shorter treatment times in the ED than did the nebulizer group (66 minutes vs 103 minutes, $p < 0.001$), while patients in the nebulizer group had more episodes of vomiting in the ED (20% vs 9%, $p < 0.04$) and greater mean percent increase in heart rate (15% vs 5%, $p < 0.001$).

*Suppliers of commercial products are identified in the Product Sources section at the end of the text.

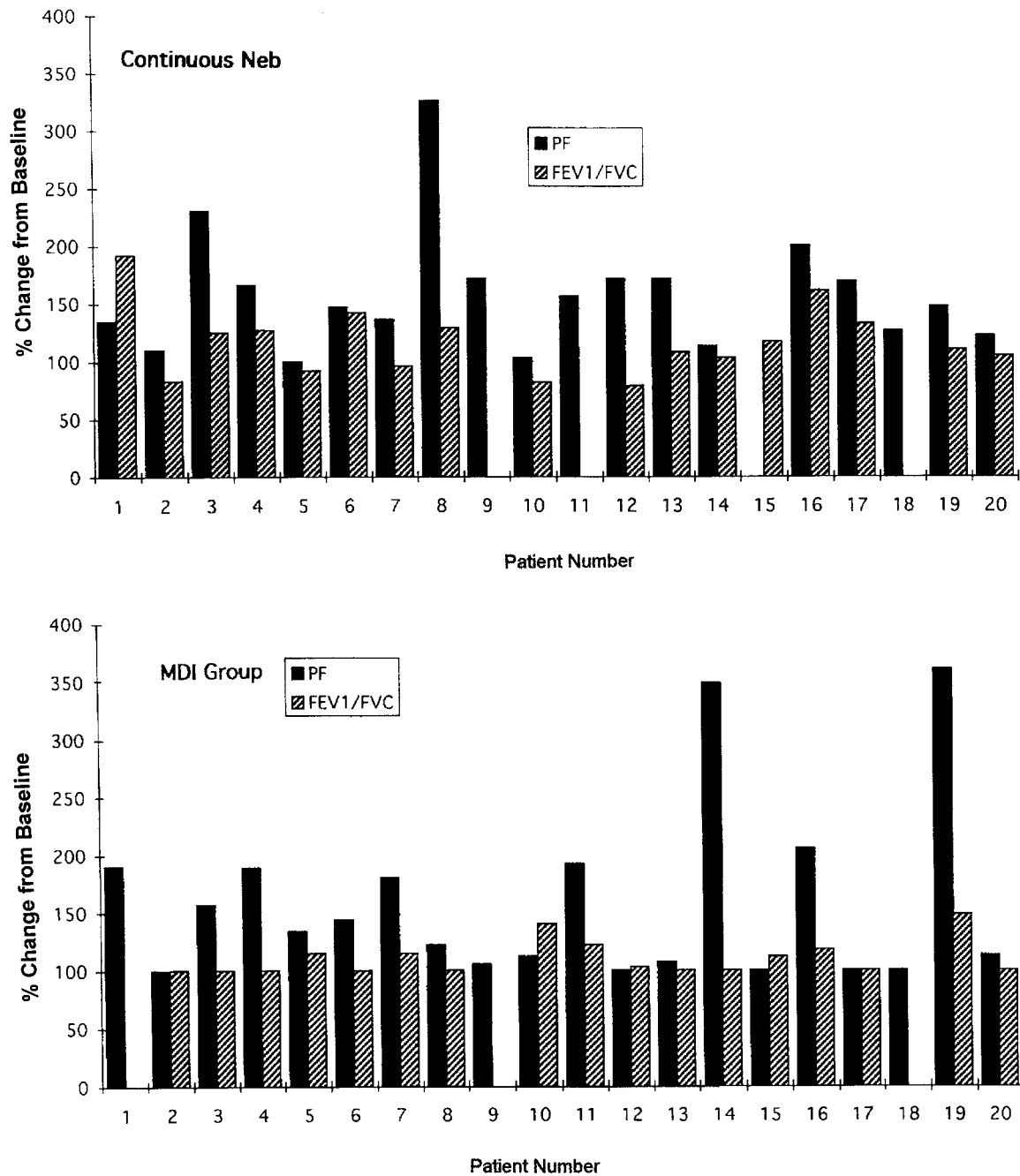


Fig. 7. Change from baseline in the ratio of the forced expiratory volume in the first second to the forced vital capacity (FEV₁/FVC) and peak flow (PF) for patients with severe asthma or chronic obstructive pulmonary disease treated with albuterol via continuous nebulizer (Neb) (15 mg/h) (upper histogram) or pressurized metered-dose inhaler with holding chamber (MDI) (lower histogram) (2.4 mg/h) over a 3-hour period.⁴⁵ (Modified from Reference 93, with permission.)

In 1996, Williams et al⁵² randomized 60 children with acute asthma exacerbation (mean PEF 46% ± 20% percent of predicted) who had not had corticosteroid administration within the preceding 7 days. Children received either nebulizer or one of two pMDI/HC treatment groups (two spacers were evaluated). The dose ratio for albuterol via nebulizer (2.5 mg per treatment) versus pMDI/HC (360

µg) was 6.9:1, and 3 treatments were administered evenly over 1 hour. All groups improved following albuterol therapy in both PEF percent of predicted and respiratory rate, with no significant difference between the 3 treatment groups.

Batra et al⁵³ studied 60 children, age 1–12 years, suffering acute asthma, randomized to receive albuterol via

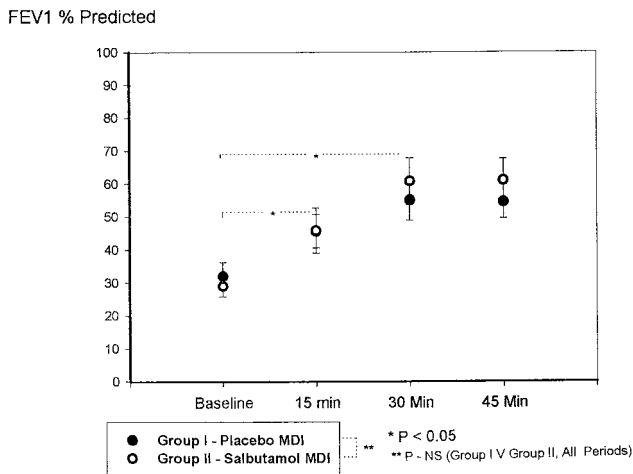


Fig. 8. Percent of predicted forced expiratory volume in the first second (FEV_1) (mean \pm standard error) at baseline and after each intervention. The nebulizer group (Group I) received 2.5 mg of albuterol or saline solution, and the inhaler group (Group II) received 200 μ g of albuterol or placebo. All treatments were repeated 3 times at 15-minute intervals, unless adverse effects appeared. Both groups had significant improvement from baseline, with no difference in spirometric measurements between the two groups at any time. (From Reference 46, with permission.)

nebulizer or pMDI/HC. A greater number of subjects in the pMDI/HC group ($p < 0.02$) presented with severe dyspnea and intercostal muscle retraction (subjective assessment) at baseline, but the objectively-evaluable outcome parameters were comparable ($p < 0.05$) in both groups. All the outcome measures showed a significant ($p < 0.05$) improvement in both the groups, with comparable recovery parameters ($p < 0.05$) at different time periods. These authors pointed out that for developing countries, distinct advantages (economic and power requirement) argue strongly for utilization of pMDI/HCs in preference to nebulizers.

Robertson et al⁵⁴ reported in 1998 on a multicenter ($n = 5$), double-blind, randomized study of 160 children, age 4–12 years, that compared albuterol administration via pMDI/HC and nebulizer. Children ≤ 25 kg received 2.5 mg albuterol via nebulizer or 600 μ g via pMDI/HC, while children over 25 kg received 5 mg or 1200 μ g (12 puffs). There was improvement in severity score and peak flow in both groups, but greater with the nebulizer than the pMDI/HC. A complicating factor in this study was the procedure of firing 3 puffs of albuterol from the pMDI into the holding chamber in rapid succession while the patient breathed tidally for 15 seconds. Rapid actuation of the pMDI dramatically reduces the output of the pMDI, and loading the holding chamber with multiple actuations can reduce aerosol available to the patient by another 65%.⁵⁵ Unfortunately, this methodologic complication in delivery technique obscured other factors of interest such as the use of tidal breathing and dose distinctions by weight. James and

Masters⁵⁶ had previously found no difference in bronchodilator response in asthmatic children between a panting technique and a single-breath technique for delivery of albuterol via pMDI/HC, but confirming this in a large, multicenter study would be of considerable interest.

Closa et al⁵⁷ studied 34 infants, age 1–24 months, in the ED for acute wheezing. Each patient received two treatments of terbutaline at 20-minute intervals via nebulizer (2 mg/dose) or via pMDI/HC (0.5 mg/dose). The clinical score 20 minutes after treatments revealed significant improvement, with no difference in rate of improvement between groups.

Schuh et al⁵⁸ compared treatment with a single dose of albuterol delivered via pMDI/HC or via nebulizer in either a weight-adjusted high dose or a standard low-dose regimen. Ninety children, age 5–17 years, presenting to the ED with mild asthma (FEV_1 50–79% of predicted) were randomly assigned to receive either 6–10 puffs or 2 puffs via pMDI/HC, or 0.15 mg/kg albuterol via nebulizer. All patients had improvement in clinical indices, with no significant differences between groups. The nebulizer group had a significantly greater change in heart rate ($p = 0.0001$).

In summary, pMDI/HC has been proven to be at least as effective as nebulizer in the treatment of children and infants presenting to the ED with acute asthma, with pMDI/HC having some advantages in reduction of adverse systemic effects and time of treatment, compared to nebulizer (see Table 5).

Published Reviews and Meta-Analyses

Several reviews of the literature and meta-analyses have been published in recent years, involving extensive examination of available evidence comparing the use of pMDI/HCs and nebulizers for treatment of acute airway obstruction in the ED.

Turner et al¹² published a meta-analysis comparing the effect of bronchodilator delivery by use of a metered-dose inhaler or wet nebulizer on objective measurements of acute airflow obstruction in adult patients. From 159 potentially relevant citations, 12 studies with a total of 507 patients had sufficient data to calculate an effect size (in standard deviation units) for improvement in airflow obstruction after bronchodilator delivery. All but two studies used pMDI/HCs. The overall treatment effect size was -0.02 (95% confidence interval [CI], -0.20 to 0.16), favoring the pMDI, but the magnitude of the effect size was not clinically or statistically significant. No significant effect was observed in the subgroup analyses that compared the diagnosis: asthma, -0.17 (CI, -0.41 to 0.07) compared with COPD, 0.23 (CI, -0.35 to 0.81); bronchodilator dose; or methodological quality. The results of a sensitivity analysis that included 5 of 6 excluded studies supported the findings from the primary analysis: 0.05 (CI, -0.11 to

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Table 4. Randomized Controlled Studies Comparing Pressurized Metered-Dose Inhaler to Nebulizer for Bronchodilator Resuscitation in the Emergency Department—Adults

Study (year)	Population (n)	Devices	Dose	Frequency	Remarks
Salzman (1989) ³⁸	Asthma, adults, FEV ₁ < 50% of predicted, (44)	MDI/HC (AC) Nebulizer	1.95 mg MET 15 mg MET	One treatment	No significant trend to improved FVC and FEV ₁ with MDI/HC.
Colacone (1993) ³⁹	Asthma, adults, FEV ₁ < 36% of predicted, (85)	MDI/HC (AC) Nebulizer	0.4 mg ALB 2.5 mg ALB	Every 30 min to maximum response	No significant difference between groups.
Idris (1993) ⁴⁰	Asthma, ages 10–45 y, ED, FEV ₁ < 40% of predicted, (35)	MDI/HC (IE) Nebulizer	0.4 mg ALB 2.5 mg ALB	Every 30 min times 6	No significant difference between groups. Less time with MDI/HC.
Rodrigo (1993) ⁴¹	Asthma, adults, ED, FEV ₁ < 50% of predicted (97)	MDI/HC (V) Nebulizer	0.4 mg ALB 1.5 mg ALB	Every 10 min Every 15 min over 3 h	No significant difference between groups.
Rodrigo (1998) ⁴²	Asthma, adults, FEV ₁ < 50% of predicted (22)	MDI/HC (V) Nebulizer	0.4 mg ALB 2.5 mg ALB	Every 10 min Every 15 min times 3 h	No significant difference in lung function improvement. Nebulizer group had greater serum albuterol levels, increased tremor, and anxiety.
Turner (1988) ⁴⁴	Asthma, COPD, adults, FEV ₁ < 50% of predicted, (75)	MDI/HC (IE) Nebulizer	1.95 mg MET 15 mg MET	Every 30 min times 3	No significant difference between groups.
Levitt (1995) ⁴⁵	Asthma, COPD, adults, FEV ₁ < 30% of predicted, (40)	MDI/HC (AC) Nebulizer	≤ 2.4 mg/h ALB 15 mg/h ALB	Dose/h for 3 h	No significant difference between groups.
Mandelberg (1997) ⁴⁶	Asthma/COPD, adults, FEV ₁ < 32% of predicted, (50)	MDI/HC (V) Nebulizer	0.2 mg ALB 2.5 mg ALB	Every 15 min times 3	No significant difference between groups.

MDI/HC = pressurized metered-dose inhaler with holding chamber. AC = Aerochamber. MET = metaproterenol. ALB = albuterol. FVC = forced vital capacity. FEV₁ = forced expiratory volume in the first second. ED = emergency department. IE = InspirEase. V = Volumatic. COPD = chronic obstructive pulmonary disease.

0.20). They concluded that bronchodilator delivery via pMDI/HC or nebulizer is equivalent in the acute treatment of adults with airflow obstruction. The authors noted that pMDI/HCs were used in most studies (all studies in the ED) and pMDI/HCs were recommended for the treatment of acute airflow obstruction.

Looking at the COPD side, Kuhl, Agiri and Mauro⁵⁹ conducted a meta-analysis to critically evaluate the following issues regarding the use of beta agonists in the treatment of acute exacerbations of COPD: (1) optimal dose, and (2) use of nebulizers versus pMDI/HCs limited primarily to ED settings. Journal articles published between 1977 and 1993 were reviewed, with 9 studies evaluated that included beta agonists alone or in combination with other bronchodilators in the treatment of acute exacerbation of COPD. Dosing studies in patients with stable disease show a relationship between dose and the various pulmonary function tests. Dose also correlated with duration of action and incidence of adverse effects. Four studies compared nebulizers versus pMDI/HC, revealing significant improvement in pulmonary function tests for both

treatments, with no significant difference between groups noted.

In 1999, a review by Cates⁶⁰ further supported the equivalence of nebulizers and pMDI/HCs for administration of beta agonists in the treatment of acute asthma. That review suggested that pediatric patients receiving beta agonists via pMDI/HC may have shorter ED stays, less hypoxia, and lower pulse rates compared to patients receiving the same beta agonist via wet nebulization. No outcomes were worse with the pMDI/HC in either adults or children (down to 2 years), even with adults with more severe asthma. Cates found no significant difference in hospital admission rate in either adults or children when the two delivery methods were compared. (Adults: odds ratio = 1.12; 95% CI: 0.45 to 2.76. Children: odds ratio = 0.71; 95% CI: 0.23 to 2.23.) Significant differences were observed in other outcomes, with pMDI/HC resulting in less ED time for children (weighted mean difference = -0.62 hours; 95% CI: -0.84 to -0.40 hours). pMDI/HC also resulted in lower pulse rates in children (weighted mean difference = -10.0% baseline; 95% CI: -14.13% to -5.87% baseline).

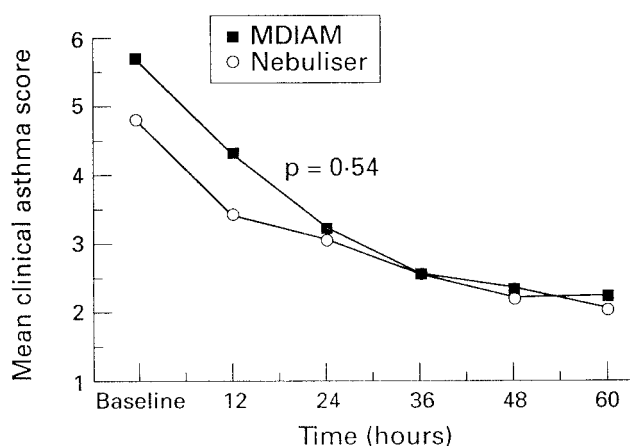


Fig. 9. Mean clinical asthma score over time for 60 pediatric patients, age 35 ± 1.9 months, receiving albuterol via pressurized metered-dose inhaler with holding chamber (MDIAM) (400–600 μg) with 2 puffs of ipratropium bromide (40 mg), or via nebulizer (0.15 mg/kg albuterol and 125 μg ipratropium bromide via face mask). All children received systemic steroids. Although the MDIAM group had higher initial scores, there was no difference in response between groups. (From Reference 50, with permission.)

The author noted that uncertainty over the dose required through any delivery method was overcome in several of the studies by using short treatment intervals (10–30 minutes) with either 2.5 mg of albuterol in saline or 4 puffs (400 μg) via holding chamber.^{39–41,50} Dosage in the studies reviewed varied from 1:1 to 1:8 (with the lower dose being the pMDI). Colacone³⁹ plotted a log dose-response curve, finding an equivalent dose ratio of 1:6. Rodrigo, in more severe asthmatics, found an equivalent ratio of 1:2.⁴¹

Evidence suggests that the pMDIs should be actuated into the holding chamber in individual puffs that can be inhaled by tidal breathing or single breaths.⁶¹ Some children were reported to cooperate better with either pMDI/HCs or nebulizers, so this may be a significant factor in choice of delivery method for the individual patient. None of the studies compared large-volume holding chambers with small-volume holding chambers.

Cates⁶⁰ concludes that pMDI/HCs produced outcomes that were at least equivalent to nebulizer delivery of beta agonists in acute asthma. Uncertainty over delivery of equivalent doses may be overcome by administering beta agonists at short intervals with titration of number of treatments to the patient's response. Adverse effects in children may be more pronounced with nebulizers.

In summary, these published reviews and meta-analyses support the view that pMDI/HCs are at least as effective as nebulizers for administration of beta agonist bronchodilators to infants, children, and adults presenting to the ED with moderate to severe airway obstruction. These data

show that pMDI/HCs are equivalent to nebulizers in eliciting clinical response, and they offer a range of advantages in terms of reduced time for administration, reduced adverse effects, and better portability and convenience.

Role of Ultrasonic Nebulizers

Ultrasonic nebulizers (USNs) have been advocated by some for use in the acute care setting. Just as pneumatic nebulizers vary in performance based on design, operating flow, operating pressure, and fill volume, ultrasonic nebulizer models differ greatly in particle size and output.

The use of ultrasonic nebulizers has proliferated in treatment of ambulatory patients at home. Early work with these nebulizers and their high-density output of small particles was associated with precipitation of bronchospasm, raising the question of their place in the treatment of acute severe asthma. Sears⁶² reported that the bronchodilator effect of fenoterol in 20 adults with moderately severe acute asthma was not enhanced by use of a USN, compared to a pneumatic jet nebulizer (JN), and that response to ipratropium bromide was significantly reduced with USN versus JN. Olivenstein et al⁶³ compared response to albuterol with pMDIs and USNs in 19 adult outpatients with stable obstructive pulmonary disease. Only the pMDI group had significant improvement, and absolute increase from baseline was greater with pMDIs (0.21 ± 0.05 L) than with USNs (0.07 ± 0.03 L; $p < 0.02$). The authors speculated that the inferior response was secondary to superimposed bronchospasm associated with the USN. In contrast, Ballard et al⁶⁴ reported on 17 adults with stable asthma in whom albuterol given via USN appeared to produce greater bronchodilation than the same dose of albuterol given by JN.

To better understand the role of the USN, Nakanishi et al⁶⁵ administered albuterol (0.15 mL/kg) to pediatric ED patients with severe asthma exacerbation using ultrasonic and pneumatic nebulizers. The USN was used with 46 children (initial FEV₁ 36.1% of predicted) and the JN with 67 children (initial FEV₁ 38% of predicted). The difference in the change in FEV₁ (USN +0.22 L vs JN +0.37 L) was significant ($p < 0.05$) and favored JN. There was no difference in the improvement in pulmonary function between JN and USN therapy in children with an initial FEV₁/FVC > 75% of predicted, but when FEV₁/FVC was < 75% of predicted the improvement in FEV₁ favored the JN (USN +0.2 vs JN +0.47; $p < 0.05$).

While USN may be comparable to JN in stable asthmatics, these reports do not support the use of USN in treatment of severe acute asthma in a comprehensive strategy of bronchodilator resuscitation.

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Table 5. Randomized Controlled Studies Comparing Pressurized Metered-Dose Inhaler to Nebulizer for Bronchodilator Resuscitation in the Emergency Department—Children

Study (year)	Population (n)	Devices	Dose	Frequency	Remarks
Fuglsang (1986) ⁴⁷	Asthma, age 7–14 y, FEV ₁ 29% of predicted (21)	MDI/HC (N) Nebulizer	0.10 mg/kg TERB 0.10 mg/kg TERB	Once	MDI/HC > nebulizer increased FEV ₁ (p < 0.05). More children expressed preference for MDI/HC because of shorter treatment time.
Kerem (1993) ⁴⁸	Asthma, age 6–14 y, FEV ₁ 40 ± 10% of predicted (33)	MDI/HC (V) Nebulizer	0.6–0.8 mg ALB 0.15 mg/kg ≤ 5 mg ALB	Once	No significant difference in improvement, but heart rate decreased in MDI/HC group.
Lin (1995) ⁴⁹	Asthma, children (111)	MDI/HC (AC) Nebulizer	0.75 mg TERB 2.5 mg TERB	Once	MDI/HC group had higher O ₂ saturations and greater increase in PEF and FEV ₁ . Nebulizer group had increased risk of O ₂ desaturation when nebulizer was operated with air compressor.
Parkin (1995) ⁵⁰	Asthma, age 1–5 y (60)	MDI/HC (AC) Nebulizer	0.4–0.6 mg ALB +40 μg IB 2.5–5 mg ALB +0.4 mg IB	Not specified	No significant difference between groups.
Chou (1995) ⁵¹	Asthma, age ≥ 2 y, PEF < 56% of predicted, (152)	MDI/HC (AC) Nebulizer	0.2–0.4 mg ALB 0.15 mg/kg ≤ 5 mg ALB	Every 20 min	MDI/HC had shorter treatment time. Nebulizer group had more episodes of vomiting and higher heart rate.
Williams (1996) ⁵²	Asthma, age ≥ 6 y, PEF 46 ± 20% of predicted (96)	MDI/HC (AC) MDI/HC (ACE) Nebulizer	0.4 mg ALB 2.5 mg ALB	Every 20 min times 3	No significant difference between groups.
Batra (1997) ⁵³	Asthma, severe, age 1–12 y (60)	MDI/HC (C) Nebulizer	0.2 mg ALB 2.5 mg ALB	Once	No significant difference between groups.
Robertson (1998) ⁵⁴	Asthma, age 4–12 y (160)	MDI/HC (V) Nebulizer	0.6–1.2 mg ALB 2.5–5 mg ALB		Greater improvement in lung function with nebulizer.
Closa (1998) ⁵⁷	Asthma, age 1–24 mo (34)	MDI/HC (AC) Nebulizer	0.5 mg TERB 2 mg TERB	Every 20 min times 2	No significant difference between groups.
Schuh (1999) ⁵⁸	Asthma, age 5–17 y, FEV ₁ 50–79% of predicted	MDI/HC Nebulizer	0.2 mg ALB 0.6–1.0 mg ALB 0.15 ng/kg ALB	Once	No significant difference in clinical improvement between devices or doses. Nebulizer group had higher heart rate.

FEV₁ = forced expiratory volume in the first second. MDI/HC = pressurized metered-dose inhaler with holding chamber. N = Nebulizer. TERB = terbutaline. V = Volumatic. ALB = albuterol. PEF = peak expiratory flow. AC = Aerochamber. IB = ipratropium bromide. ACE = Aerosol Cloud Enhancer. C = M/s Cipla (ns) 750 mL valved holding chamber.

Dry Powder Inhalers and Breath-Actuated Inhalers

Over the past decade, there has been increasing availability and use of dry powder formulations in the ambulatory setting, where dry powder inhalers (DPIs) have been shown to be comparable to both pMDIs and nebulizers. There is less information on the efficacy of DPIs in treating acute severe asthma. Concerns about the use of DPIs center on the inspiratory flow rate required to draw the drug powder out of the inhaler and the effect of flow reduction on patients experiencing severe acute airway obstruction. Because the energy from the patient's inspiratory flow draws the drug powder out of the inhaler, the

magnitude and duration of the patient's inspiratory effort influence aerosol generation from a DPI.^{66,67} Failure to perform inhalation at a fast inspiratory flow reduces the dose of the drug emitted from a DPI,⁶⁸ and increases the distribution of particle sizes within the aerosol.⁶⁹ Furthermore, the inspiratory flow influences the dose emitted from some DPIs to a greater extent than from others.⁷⁰ For example, the Diskus delivered approximately 90% of the labeled dose at inspiratory flow rates ranging from 30 to 90 L/min, whereas the dose delivered by a Turbuhaler DPI was significantly lower at 30 L/min than at 90 L/min, and variability between doses at various inspiratory flow rates was higher with the Turbuhaler.⁷¹ Similar concerns are

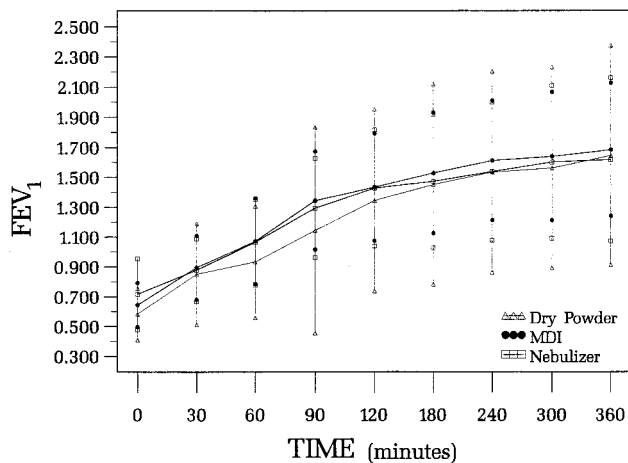


Fig. 10. Absolute changes in forced expiratory volume in the first second (FEV_1) (mean \pm standard deviation) following cumulative doses of inhaled albuterol in 27 ED patients with $FEV_1 < 30\%$ of predicted. Subjects (9 in each group) were treated with albuterol via nebulizer (5 mg), pressurized metered-dose inhaler with holding chamber (MDI) (400 μ g), or dry powder inhaler (DPI) (Rotahaler, 400 μ g). All groups received treatments on arrival in the ED, every 30 minutes during the first two hours, and then hourly until the sixth hour. The total dose of inhaled albuterol administered during the 6-hour treatment was 45 mg of nebulized solution or 3,600 μ g via MDI or DPI. All groups improved from baseline, with no difference between groups. (From Reference 73, with permission.)

associated with the use of breath-actuated pMDI devices that require ≥ 30 L/min inspiratory flow to trigger the device.

Roman et al⁷² studied adult asthmatics admitted from the ED with acute asthma exacerbation and who received either 200 μ g of albuterol via DPI or 2.5 mg of albuterol via nebulizer. They found greater absolute improvement with the nebulizer than with the DPI.

In a prospective, randomized, open design, Raimondi et al⁷³ studied the response to inhaled albuterol in 27 adult asthmatics with severe airway obstruction, presenting to the ED with $FEV_1 < 30\%$ of predicted. Subjects (9 in each group) were treated with either albuterol via nebulizer (5 mg), pMDI/HC (400 μ g), or DPI (Rotahaler; 400 μ g). All groups received treatment on arrival in the ED, every 30 minutes during the first two hours, and then hourly until the sixth hour. Clinical parameters and FEV_1 were recorded on ED admission and 15 minutes after each dose of albuterol. All patients received continuous oxygen and one dose of intravenous steroids (dexamethasone, 8 mg). The total dose of inhaled albuterol administered during the 6 hours of treatment was 45 mg of nebulized solution or 3,600 μ g via pMDI/HC or DPI. FEV_1 improved significantly in all patients after the 6 hours of treatment (Fig 10). The 6-hour area under the FEV_1 curve improved similarly with the 3 delivery methods, despite differences in the total dose administered. Despite the relatively small num-

ber in each treatment group, these data support the view that the 3 delivery methods appear adequate to treat adult subjects with acute severe asthma.

Tonnesen et al⁷⁴ compared the bronchodilating effect of terbutaline (2.5 mg of terbutaline administered at 15-minute intervals) via DPI (Turbuhaler) or via pMDI/HC in 68 consecutive ED patients suffering acute severe bronchial obstruction. The mean baseline FEV_1 values were 0.81 ± 0.64 L (standard deviation) in the DPI group ($n = 33$), and 0.90 ± 0.90 L in the pMDI/HC group ($n = 29$). The mean increases in FEV_1 from baseline were 0.4 ± 0.40 L and 0.21 ± 0.25 L ten minutes after the last inhalation via DPI and pMDI/HC, respectively ($p = 0.0004$).

Nana et al⁷⁵ studied 86 adult asthmatics with severe obstruction ($FEV_1 < 37\%$ of predicted). Patients were randomized to receive albuterol via DPI (Turbuhaler) or pMDI/HC. The clinical response improved with both groups, with no significant differences between groups. A larger decrease in serum potassium levels occurred with the pMDI/HC group.

Sole et al⁷⁶ studied 47 ED pediatric patients, age 6–14 years, suffering acute mild or moderate asthma exacerbation (clinical score 3 or $FEV_1 < 50\%$ of predicted) treated with terbutaline sulphate via DPI or nebulizer. Both groups had significant improvement in clinical score (starting at 15 minutes) ($p < 0.05$) and in FEV_1 , vital capacity, and forced expiratory flow (25–75%) (starting at 5 minutes) ($p < 0.05$). At the end of the first treatment, the number of patients with $FEV_1 < 80\%$ was similar in both groups.

In an open random study in parallel groups, Rufin et al⁷⁷ assessed 30 children, age 4–14 years, presenting with asthma exacerbation. After a baseline measure of pulmonary function, the children inhaled 500 μ g of terbutaline via DPI (Turbuhaler) or pMDI/HC. There was significant improvement in both groups, measured at 15 minutes and 30 minutes after the treatment, with no difference between groups.

Ruggins et al⁷⁸ conducted a randomized, double-blind, two-period crossover study comparing the ability of 51 hospitalized asthmatic children with acute exacerbation to use a breath-actuated metered-dose inhaler, the Autohaler, and a DPI (Rotahaler). Peak inspiratory flow was sufficient in all children (30 L/min) to trigger the Autohaler, including the youngest, age 4 years (Fig. 11). No significant difference was found between the two inhalers as assessed by PEFR. However, the Autohaler inhalation device could be successfully actuated 99/100 times, compared with 74/100 for the Rotahaler. There was a consistent but clinically unimportant increase in pulse rate after use of the Rotahaler, compared with the Autohaler. All 11 patients under 6 years of age failed to empty the Rotahaler, but 5 of these patients received a significant benefit from using the Autohaler, compared with after the Rotahaler. A

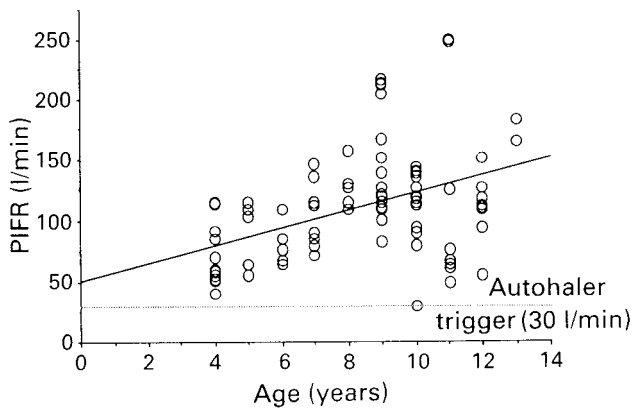


Fig. 11. Relationship between the peak inspiratory flow rate and age of wheezy children, age 4–13 years. The authors noted that these peak inspiratory flow rates were adequate to activate the breath-activated pressurized metered-dose inhaler (pMDI) (Autohaler) 99% of the time, versus 74% for the DPI (Rotahaler). (Not shown in figure.) (From Reference 78, with permission.)

significant drop in oxygen saturation was observed 15 minutes after use of either inhaler.

Different devices with the same medication can result in different levels of in vivo deposition. Lipworth and Clark⁷⁹ compared lung delivery of albuterol from two DPIs, Diskhaler and Diskus, and the Easi-Breathe breath-activated pMDI. In a randomized, single-blind, crossover study, 10 healthy volunteers inhaled 1200 μg of albuterol over 6 minutes. Lung delivery was greater with the Diskhaler and pMDI than with the Diskus. Serum albuterol levels were determined at 5, 10, 15, and 20 minutes after inhalation. Peak concentration for the Diskhaler (4.34 ng/mL) and Easi-Breathe (3.98 ng/mL) were greater than the Diskus (3.22 ng/mL). Similarly, average concentrations were greater for the Diskhaler (3.95) and Easi-Breathe (3.52) than for the Diskus (2.62). Table 6 summarizes the differences in inhalation technique between pMDIs and DPIs, and Tables 7 and 8 summarize the results of studies comparing DPIs with pMDI/HCs and nebulizers.

In a parallel, randomized, placebo-controlled clinical trial of 24 patients, age 18–55 years, in the ED with acute asthma and an initial FEV₁ 40–70% of predicted, Silverman et al⁸⁰ compared the efficacy of the Autohaler with inhaled beta agonist administered via wet nebulizer in treating acute asthma exacerbations. Patients were given either 6 puffs from the Autohaler (1,200 μg pirbuterol) plus saline solution via nebulizer, or 6 puffs placebo plus 2,500 μg albuterol sulfate solution via nebulizer. Treatments were repeated at 30 and 60 minutes, with clinical evaluation before each treatment, and at 120 minutes. Baseline FEV₁ was 53% of predicted for both groups, and at 120 minutes FEV₁ was 66% for the Autohaler group and 64% for the nebulizer group. Time for administration was 2.9 minutes

with the Autohaler versus 9.1 minutes with the nebulizer. No patient was excluded due to inability to use the Autohaler device adequately.

Effect of Positive-Pressure Breathing

While the use of intermittent positive-pressure breathing (IPPB) treatments has been criticized for lack of evidence supporting its use, there has been an increased interest in the use of bi-level and noninvasive ventilation in the ED and intensive care unit. Many of the patients benefiting from these interventions may benefit from bronchodilator resuscitation, raising the question of how such medications should be administered. The relatively high flow rates used in many continuous positive airway pressure (CPAP) and bi-level systems are suspected of increasing aerosol impaction prior to inhalation. Similarly, the use of mask versus mouthpiece is thought to further reduce deposition of aerosol to the lungs, reducing clinical efficacy.

In 1977, Dolovich et al⁸¹ found that aerosol administration with IPPB resulted in 30% less aerosol delivery to the lungs than use of the nebulizer alone. In 1983, the use of IPPB was found not to improve the effect of nebulized bronchodilator.⁸² More recently, Loren et al⁸³ compared administration of isoproterenol hydrochloride via pMDI, pneumatic nebulizer, and IPPB to 23 children with severe bronchospasm (PEF < 25% of predicted) and found all 3 methods to be similar in reversing the bronchospasm. IPPB therapy did not offer any advantage over simple nebulization in patients with severe, reversible airway obstruction, but was no less effective.

Reporting in 1992 on a randomized, single-blind study, Lowenthal and Kattan⁸⁴ compared the use of mouthpieces and face masks with nebulizers for delivery of medication in 64 children, age 6 to 19 years, presenting to the hospital with acute asthma (Fig 12). There was no significant difference in improvement between the groups. Patients with nasal congestion, age < 10 years, or severe airway obstruction did equally well with each method. Patients in the face mask group had a higher incidence of tremor. The authors concluded that the mouthpiece is as effective as the face mask and produces less tremor.

CPAP has been shown to decrease pulmonary resistance and increase expiratory flow in induced bronchial asthma,⁸⁵ indicating that expiratory positive pressure dilates the airways, improves the distribution of ventilation, and might improve deposition of simultaneously-inhaled medication. This was confirmed by Wang et al,⁸⁶ who reported that in asthmatic adults, nasal CPAP (6 cm H₂O for 10 minutes) significantly reversed methacholine-induced bronchoconstriction, increasing FEV₁ by $15 \pm 4\%$ and peak inspiratory flow by $32 \pm 11\%$. Nasal CPAP significantly increased the response to bronchodilators. The im-

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Table 6. Differences in Inhalation Technique Between Metered-Dose Inhalers and Dry Powder Inhalers

	MDI/HC	DPI
Shaking the inhaler	+	–
Actuation with inspiration	Optional	Essential
Inspiration	Slow, deep improves deposition	Fast, prolonged required for deposition
Interval between doses	30–60 s	20–30 s
Exhalation into device	Small decrease in dose	Large decrease in dose

MDI/HC = metered-dose inhaler with holding chamber. DPI = dry powder inhaler.

Table 7. Dry Powder Inhalers in the Emergency Department—Adults

Study (year)	Subjects (n)	Devices	Medication	Results
Roman (1993) ⁷²	Moderate to severe asthma (30)	Nebulizer DPI (Rotahaler)	ALB	Nebulizer group had greater improvement than DPI group
Raimondi (1997) ⁷³	Severe asthma, adults, FEV ₁ < 30% of predicted (27)	Nebulizer MDI/HC (Aerochamber) DPI (Rotahaler)	ALB	No difference between groups
Tonnesen (1994) ⁷⁴	Severe asthma (68)	MDI/HC (Nebuhaler) DPI (Turbuhaler)	TERB	No difference between groups
Nana (1998) ⁷⁵	Severe asthma, FEV ₁ < 37% of predicted (86)	MDI/HC (Volumatic) DPI (Turbuhaler)	ALB	No difference between groups

DPI = dry powder inhaler. ALB = albuterol. FEV₁ = forced expiratory volume in the first second. MDI/HC = metered-dose inhaler with holding chamber. TERB = terbutaline.

Table 8. Dry Powder Inhalers in the Emergency Department—Children

Study (year)	Subjects (n)	Devices	Medication	Results
Sole (1995) ⁷⁶	Mild to moderate asthma, 6–14 y (47)	Nebulizer DPI	TERB	No difference between groups
Ruffin (1993) ⁷⁷	Moderate asthma, 4–14 y (30)	MDI/HC DPI	ALB	1–2 doses twice a day
Ruggins (1993) ⁷⁸	Asthma, 4–12 y (51)	Breath-actuated MDI DPI	ALB	All 11 patients < 6 y failed to empty Rotahaler

DPI = dry powder inhaler. TERB = terbutaline. MDI/HC = metered-dose inhaler with holding chamber. ALB = albuterol.

provement in airflow persisted for at least 5 minutes after nasal CPAP withdrawal and was highly correlated with the response to bronchodilators. There was no significant effect of nasal CPAP on airflow in COPD patients.

CPAP is often applied with high rates of gas flow delivered via nasal or face mask, conditions that would be expected to reduce aerosol availability to the respiratory tract. Parkes and Bersten⁸⁷ used a bench model simulating spontaneous respiration to compare the delivery of technetium-labeled aerosol generated from a jet nebulizer with and without CPAP at 10 cm H₂O at a flow of 50 L/min. CPAP significantly reduced total aerosol delivery to the face mask, from 6.85 ± 1.5% to 1.3 ± 0.4%. However, in a separate in vivo study, incremental doses of albuterol administered to 9 stable asthmatic subjects produced sim-

ilar dose-response curves and identical magnitude of the total increase in FEV₁ for CPAP and control conditions. Despite a 5-fold reduction in aerosol delivered to the face, adequate aerosol was delivered to produced a bronchodilator response.

Frischknecht-Christensen, Norregaard, and Dahl⁸⁸ performed a randomized crossover study with 10 asthmatic adults and 2-week treatment periods to determine the effect of positive expiratory pressure at 10–20 cm H₂O, with and without 2 puffs (0.5 mg) of terbutaline via pMDI/HC, in treatments performed 3 times a day. All treatments increased PEF (p < 0.0001) (Fig 13). The mean increase in PEF was greater with positive expiratory pressure and terbutaline (32 L/min) than with terbutaline alone (25 L/min) or positive expiratory pressure alone (18 L/min). These

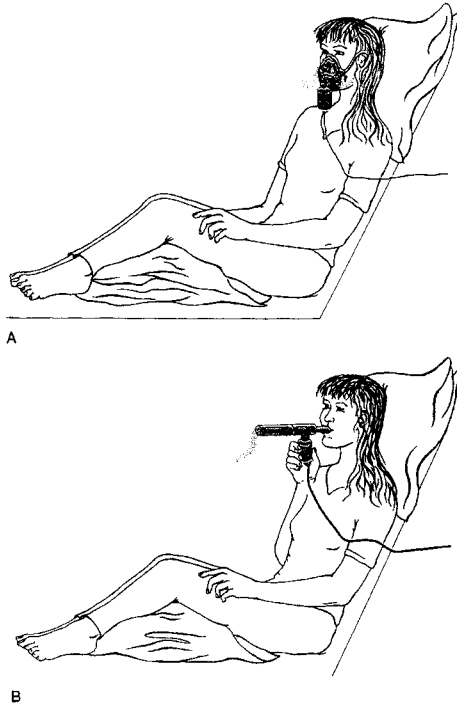


Fig. 12. Lowenthal and Kattan compared use of mouthpieces and face masks with nebulizers in a randomized, controlled study of 64 asthmatic children, age 6–19 years, with no difference in clinical endpoints.⁸⁴ (From Reference 93, with permission.)

data imply a potential benefit of aerosol delivery with positive expiratory pressure in stable asthmatics.

Pollack et al⁸⁹ randomly assigned adult patients with moderate asthma to receive two doses of aerosolized albuterol (2.5 mg in 3 mL normal saline solution) 20 minutes apart, delivered either via nebulizer ($n = 40$) or bi-level ventilation ($n = 60$) via nose mask⁵⁸ or face mask (inspiratory positive airway pressure 10 cm H₂O, expiratory positive airway pressure 5 cm H₂O). They found that bi-level patients had a significantly greater increase in percentage PEF after each treatment ($p = 0.0011$) and from baseline to completion ($p = 0.0013$). Increase in absolute PEF was greater in the bi-level group (from 211 ± 89 [standard deviation] to 357 ± 108 L/min for bi-level, and from 183 ± 60 to 280 ± 87 L/min for nebulizer; $p = 0.0001$). The authors concluded that, in this population, response to initial ED management of bronchospasm, as measured by PEF, was better with aerosols delivered via bi-level ventilation than via nebulizer.

While IPPB and CPAP have been shown to reduce aerosol delivery in vitro and in vivo compared to nebulizers alone, it appears that there is still sufficient delivery to elicit a bronchodilator response. Limited evidence indicates that CPAP, positive expiratory pressure, and bi-level ventilation may actually increase response to bronchodilator aerosols, but further studies are required to establish

any beneficial effects of CPAP and bi-level ventilation with aerosol delivery during bronchodilator resuscitation of severe airway obstruction.

Device Selection

In the face of evidence that a variety of devices, properly applied, have comparable effect, selection should then be based on specific performance, convenience, drug availability, and costs, as shown in Table 9.

Myths or Facts

If clinical efficacy is similar between pMDI/HCs and nebulizers in the ED, when and why would we actually use the nebulizer? Device selection between pMDI/HCs and nebulizers is often premised on the ability of the patient to take a deep breath and to hold that breath for at least 4 seconds. This distinction has been emphasized in several consensus documents^{3,90} that offer “expert opinion” that the inability to take a deep breath and hold it should be used as exclusion criteria for the use of a pMDI in favor of a nebulizer. While evidence supports that deep breaths and breath-holding improve deposition of any inhaled aerosol,¹⁸ it has not been demonstrated that this is unique to the pMDI. A breathing pattern of shallow, rapid breaths without a breath-hold serves to reduce lung deposition of aerosol from any aerosol generator. This limitation is best countered with an increased dose of bronchodilator, titrating to effect.

The evidence clearly establishes that the administration of bronchodilator aerosols with pMDI/HCs is at least as effective as use of nebulizers, with some additional advantages in children. Of course, demonstrating that two aerosol delivery methods are not different does not prove that they have the same effect on every patient. Some patients just respond better to one device than to another. This preferential response, when it exists, can be empirically determined by improvement in lung function or subjectively by soliciting patient preference. We suggest that device selection is best determined by the clinician at the bedside, working with the patient.

Patient Education and Empowerment

Perhaps the paradigm of health care that we value could help guide the selection process. The longstanding paradigm of the patient as passive recipient has long been the standard of hospital-based care.⁹¹ In this paradigm, once the patient enters the ED, the role of the health care team is to take care of the patient. In this case, the pMDI that the patient is prescribed for use at home is taken away in the ED and replaced with a nebulizer until the patient is discharged from the ED or hospital with one or more pMDIs

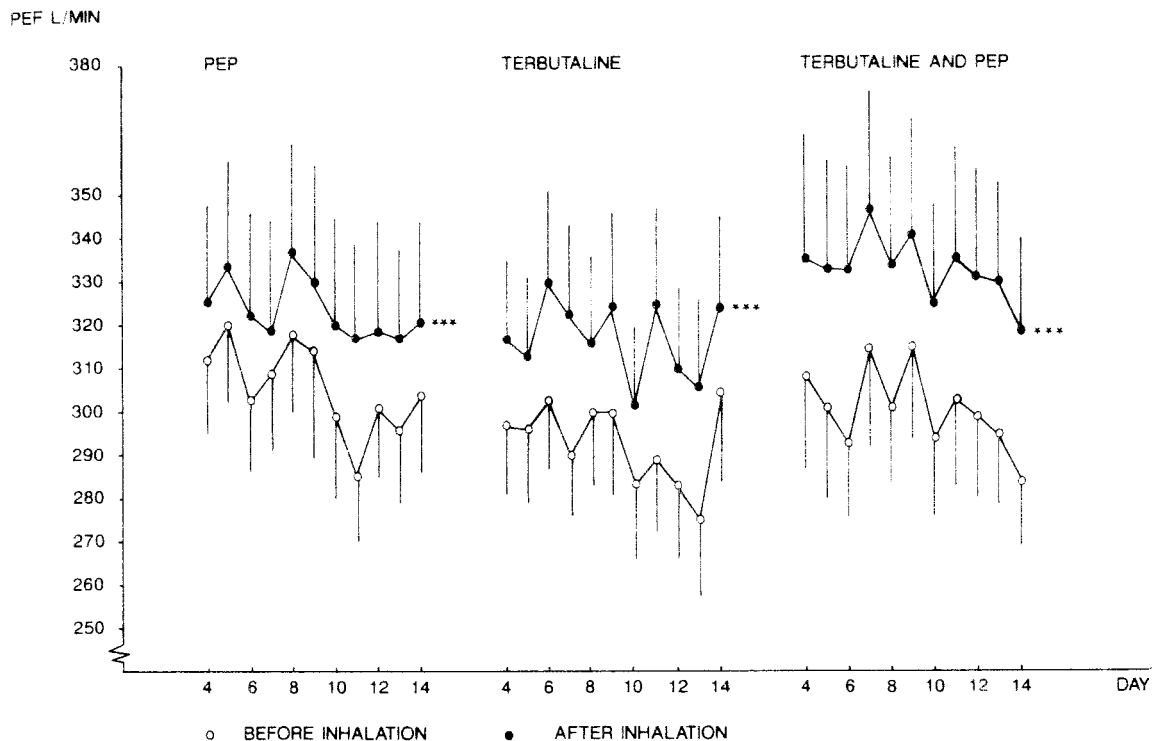


Fig. 13. The peak expiratory flow (PEF) before inhalation (lower curves) and after inhalation (upper curves) with: positive expiratory pressure (PEP) therapy (10–15 cm H₂O) and placebo (left); terbutaline (0.5 mg) via pressurized metered-dose inhaler with holding chamber (middle); or terbutaline (0.5 mg) with positive expiratory pressure (right). Improvement in PEF was greatest with terbutaline plus positive expiratory pressure ($p < 0.005$). (From Reference 88, with permission.)

reordered for home use. This approach creates the perception that the tools the physician prescribes for self-administration are less effective than the nebulizer used in the ED, and that when the patient has trouble breathing he or she needs to go to the ED to get the “good stuff” (the nebulizer) that will make the patient feel better. There is little opportunity in this scenario for the patient to learn how to get the desired therapeutic effects from that same medication (in the pMDI) when the patient is outside the hospital.

The emerging paradigm of health care embraces patients as active participants in the health care team. The patient is educated in many aspects of health and disease, with strategies for self-management that help avoid visiting the ED or hospital. In this paradigm, failure to get relief from bronchodilators is not an issue of device efficacy, but rather of how the device is used, with the possibility that factors such as hand-breath coordination may suffer with increasing dyspnea. Rather than replace the pMDI with a nebulizer, we would add a holding chamber to the pMDI, taking the opportunity to evaluate patient technique, reinforce proper technique, and demonstrate to the patient that the pMDI/HC can in most cases provide relief of symptoms. This approach encourages integration of devices with medication and action plan, reinforces

proper technique, and is best implemented with continuity across the health care organization, from the ED, hospital, and clinic to home.

At our institution, educational consistency for the patient has been a priority, and we have attempted to base our ED bronchodilator resuscitation strategies on the tools and techniques that our patients are asked to use at home.

Staff Knowledge

Another important consideration in device selection is the comfort level and familiarity of staff with the devices and strategies used. Hanania et al⁹² surveyed medical personnel to assess their knowledge of and ability to use 3 widely-used inhaler devices: pMDI, pMDI/HC (Aero-Chamber), and a DPI (Turbuhaler). Thirty respiratory therapists (RTs), 30 registered nurses (RNs), and 30 medical house staff physicians (MDs) were asked to demonstrate the use of each device using placebo inhalers and to answer 11 clinically relevant questions related to the use and maintenance of the tested devices. The RTs' percent mean knowledge score ($67 \pm 5\%$) was significantly higher than that of either the RNs ($39 \pm 7\%$) or the MDs ($48 \pm 7\%$) (for all $p < 0.0001$). Similarly, percent mean demonstration scores for each device were significantly higher for

Table 9. Comparison of Metered-Dose Inhalers With Holding Chambers, Dry Powder Inhalers, and Nebulizers as Aerosol Delivery Devices

Performance	MDI/HC	DPI	Nebulizer
Majority of aerosol particles < 5 μm	+	+	\pm
High pulmonary deposition	+	\pm	\pm
Low mouth deposition	+	\pm	-
Reliability of dose	+	\pm	\pm
Influenced by humidity	-	+	-
Physical and chemical stability	+	+	+
Breath-actuated	-	+	-
Risk of contamination	-	-	+
Convenience Factors			
Lightweight, compact	+	+	-
Multiple doses	+	+	-
Dose indicator	-	+	-
Dose counter	-	+	-
Inexpensive	+	+	-
Easy and quick operation	\pm	\pm	-
Suitable for all ages	+	-	+
Suitable for multiple clinical situations	+	\pm	+

RTs than for either RNs or MDs: for pMDI, $97 \pm 3\%$ versus $82 \pm 13\%$ and $69 \pm 24\%$, respectively ($p < 0.0001$); for the Aerochamber, $98 \pm 2\%$ versus $78 \pm 20\%$ and $57 \pm 31\%$ ($p < 0.0001$); and for the Turbuhaler, $60 \pm 30\%$ versus $12 \pm 23\%$ and $21 \pm 30\%$ ($p < 0.0001$). Knowledge of and practical skills with the devices were roughly proportional to the length of time the device had been in clinical use, Turbuhaler demonstration scores being lower than either pMDI or Aerochamber scores ($p = 0.05$ and $p = 0.09$, respectively). More RTs (77%) had received formal instruction in school on the use of devices than either RNs (30%) or MDs (43%) ($p < 0.05$). The authors concluded that (1) many medical personnel responsible for monitoring and instructing patients in optimal inhaler use lack rudimentary skills with these devices, (2) nurses and physicians seldom receive formal training in the use of inhalers, and (3) newer inhaling devices designed to obviate problems of technique are at present less likely to be used well by medical personnel soon after their introduction. To better familiarize staff with these devices, professional continuing education, especially for the ED staff, would appear to be warranted.

Cost

Cost considerations may dictate which delivery system is used in different settings. For example, a nebulizer (\$1.00) used in the hospital may be less expensive than a pMDI/HC (\$12.00) in terms of acquisition cost, unless the patient is

sent to the floor or home with the pMDI/HC after discharge from the ED. However, continued treatment with a nebulizer at home is much more expensive than a pMDI/HC in terms of medication and supply costs. Labor costs have been shown to be higher with the nebulizer than with the pMDI/HC, both in the ED and during hospitalization.^{5,6} Table 10 costs out 3 common methods of bronchodilator resuscitation in the ED.⁹³ By far, labor is the greatest cost associated with any of the 3 methods, which means that convenience, effort, and time required for administration are paramount.

Summary

The pMDI/HC is equivalent to nebulizer therapy for treatment of infants, children, and adults with moderate to severe asthma. There may be some advantage in reduced treatment time and reduced adverse systemic effects for children with pMDI/HCs. The USN is less effective than the pMDI/HC or pneumatic nebulizer for treatment of severe asthma. The DPI has been shown to work in some ED settings, but dose administration is flow-dependent, which is a concern regarding reduced dose available to smaller children and severely obstructed patients. The administration of aerosol via pMDI/HC or nebulizer, with positive airway pressure appears to offer some additional benefit but requires further study to determine the most effective methods of delivery and the benefit, if any, in treatment of severe airway obstruction.

For treatment of patients with moderate airway obstruction (secondary to acute asthma and COPD) the selection of aerosol device appears to be less of an issue in effecting clinical response than for patients with severe airway obstruction. In treating the most severe asthmatic (adult, child, or infant), the pMDI/HC has been demonstrated to be as effective as the nebulizer (or other available devices) in relief of airway obstruction, and appears to offer some advantage in fewer adverse effects. If the pMDI/HC works in the ED, with the sickest of patients, it should be equally effective in other settings as well. The evidence is abundant and clear: the debate on pMDI/HC versus nebulizer appears to no longer be a relevant issue.

In Part 2 of this review (which will appear in a future issue of RESPIRATORY CARE) we will explore the evidence supporting the use of high-dose and low-dose, intermittent versus continuous treatment, as well as combining beta agonist with anticholinergic agents.

PRODUCT SOURCES

Pressurized Metered-Dose Inhalers:

Autohaler, 3M Pharmaceuticals, Northridge CA
Easi-Breathe, Norton Healthcare UK

BRONCHODILATOR RESUSCITATION IN THE EMERGENCY DEPARTMENT

Table 10. Comparative Costs of Bronchodilator Delivery During Acute Exacerbation for 3 Hours of Treatment in the Emergency Department

	Continuous Nebulizer*	MDI	SVN
Equipment	\$10 (HEART nebulizer)	\$6.00 (holding chamber)	\$1 (nebulizer)
Medication	\$9.50†	\$6.00‡	\$2.67§
Personnel			
Time per hour or number of treatments	20 + 10 + 10 min	45 + 15 + 15 min	15 min × 9
Cost	\$13.33	\$25.00	\$45.00
Total Costs	\$32.83	\$37.00	\$48.67

MDI = metered-dose inhaler. SVN = small-volume nebulizer.

Continuous nebulizer and MDI with holding chamber are comparable in total costs as well as efficacy. Increased equipment and medication costs with continuous nebulizer are offset by reduced time required by the care giver at the bedside. Labor costs for each of the first 3 h drive SVN administration costs to more than 150% of continuous nebulizer or MDI with holding chamber, with no greater clinical benefit.

*All patients on continuous nebulizer should be closely monitored during administration. Cost of EKG and pulse oximetry has not been added.

†Medication costs for continuous nebulizer include 20 mL albuterol solution mixed with 180 mL 0.9% NaCl.

‡Reflects costs of an MDI canister containing 200 doses of 90 µg of albuterol (\$0.03/puff). The actual medication cost of 72 actuations over 3 h is \$2.16.

§SVN costs calculated with three 15-minute treatments each hour, for a 3-h period.

(Table adapted from data in Reference 93.)

Nebulizers:

High-Output Extended Aerosol Respiratory Therapy (HEART) nebulizer, Westmed, Lakewood CO

Dry Powder Inhalers:

Diskhaler, Glaxo Wellcome, Research Triangle Park NC

Diskus, Glaxo Wellcome, Research Triangle Park NC

Rotahaler, Glaxo Wellcome Inc, Research Triangle Park NC

Turbuhaler, AstraZeneca, Wilmington DE

Holding Chambers:

AeroChamber, Monaghan Medical, Syracuse NY

ACE Aerosol Cloud Enhancer, DHD Healthcare Canastota NY

InspirEase, Schering-Plough, Madison NJ

M/s Cipla, Mumbai, India

Nebuhaler, AstraZeneca, Wilmington DE

Volumatic, Glaxo Wellcome, Research Triangle Park NC

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