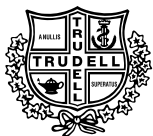


STUDY SUMMARY

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# Use of the *AeroChamber*\* Brand of Valved Holding Chamber

THE EVIDENCE IS CLEAR...



Trudell Medical International

# Comparison of Small versus Large Volume Spacers

1

**Mazhar SHR, Chrystyn H.** *Similar Lung and Systemic Delivery Characteristics of Salbutamol from an AeroChamber Plus\* and a Volumatic.* Presented at the American Thoracic Society Conference, May, 2006.

We have shown that the amount of urinary salbutamol excreted in the first 30 minutes (USAL0.5) represents the relative lung deposition and the 24 hour salbutamol plus its metabolite excretion (USAL24) indicates the total systemic delivery following an inhalation (Hindle and Chrystyn. *Brit J Clin Pharmacol* 1992; 34; 311-5). We have used these in-vivo methods together with in-vitro characterisation of the emitted dose using an Andersen Cascade Impactor (ACI) to compare the Volumatic (VOL) and AeroChamber Plus\* VHC (AERO). Spacers were attached to a salbutamol CFC free metered dose inhaler (MDI). 13 subjects, mean (SD) 31.2(7.6) years and 64.9 (10.9) Kg completed the in-vivo study. The in-vitro and in-vivo results were

**Mean (SD) from two 100µg doses (µg except MMAD µm)**

	MDI	MDI+VOL	MDI+AERO
ACI			
Spacer		74.9 (6.1)	90.6 (6.7)
TED	176.6(7.6)	94.9(4.6)	85.3(4.5)
Throat	93.6(7.4)	11.3(1.9)	11.7(1.2)
FDP	41.5(3.4)	41.8(2.3)	36.8(1.5)
MMAD	2.69(0.03)	2.76(0.07)	2.91(0.10)
Urinary salbutamol			
USAL0.5	5.71(1.9)	16.36(8.2)	14.4(7.6)
USAL24	100.2(16.7)	97.3(12.7)	84.6(25.8)

TED - total emitted dose; Throat - ACI throat+S0+S1; FPD - fine particle dose, ACI S2-filter; MMAD - mass median aerodynamic diameter. Statistical analysis of the USAL0.5 data revealed no difference between the two spacers (mean difference [95% confidence interval] of 1.9[-4.5,8.3]µg). USAL 0.5 VOL and AERO were each greater (p<0.001) than MDI alone (mean difference [95%CI] of 10.6[4.2,17.1] and 8.7[2.3,15.1]µg, respectively). USAL24 amounts were all similar.

The in-vitro characteristics suggest that slightly more salbutamol will be delivered to the lungs from a Volumatic than an AeroChamber Plus\* VHC. The in-vivo data confirms this but the difference, as predicted by the in-vitro data, is only small. The results are consistent with the smaller size of the AeroChamber Plus\* VHC.

2

**Devadason SG, Walker SL, Owen J, Perth, Western Australia, Australia.** *The Effect of Inhalation Technique, Spacer Volume and Training on Aerosol Delivery from Spacers in Children.* Presented at the American Thoracic Society Conference, May, 2005, San Diego, CA.

**RATIONALE:** Variability in the clinical use of inhaler devices is high, particularly in children. Optimisation of inhalation therapy should ensure more consistent dose delivery to the airways of young children. We assessed the effect of spacer volume, inhalation technique and training of the parent/child on drug delivery to children using pressurised inhalers. **METHODS:** Albuterol was delivered via large (Volumatic; VOL) and small (AeroChamber Plus\* VHC; AC+) spacers to 21 children (2-14yrs). Children ≥5yrs either took 5 tidal breaths, or one slow maximal inhalation with 10 sec breath-hold. Children <5yrs used tidal breathing only. Training sessions were scheduled ≥12wks apart. Drug delivery was assessed using a low resistance filter attached to the spacer mouthpiece. **RESULTS:** Mean (SD) drug delivery (% nominal dose) to children of all ages using AC+ [51.5 (14.7)%] was significantly higher (p=0.04) than using VOL [39.3 (10.1)%]. Mean (SD) drug delivery using the single maximal inhalation technique [45.4 (13.7)%] was significantly higher (p=0.01) than that using tidal breathing [32.3 (13.9)]. The improvement in delivery using the single maximal inhalation was most marked in the 5-7yr age group. Training the parent/ child to use the spacer correctly gave a small (3.9%) but significant increase (p=0.04) in drug delivery. **CONCLUSIONS:** AC+ (small volume) delivered more drug than VOL (large volume). This is possibly due to the more efficient construction and design of the AeroChamber Plus\* as delivery is normally improved when using large volume spacers. The single maximal inhalation technique increased drug delivery to patients compared to tidal breathing. However, it is easier for children <5yrs to use the tidal breathing technique. Training of the parent/patient resulted in a smaller than expected (albeit significant) increase in drug delivery.

### 3

**Bates SL, Mitchell JP, Nagel MW, Wiersema KJ.** *Performance of Large- and Small-Volume Valved Holding Chambers with a New Combination Long-Term Bronchodilator / Anti-inflammatory Formulation Delivered by Pressurized Metered Dose Inhaler.* Journal of Aerosol Medicine, Vol 15, Number 4, 2002, Pp. 427-433

The treatment of both the bronchoconstriction and inflammatory aspects of asthma simultaneously by a single pressurized metered dose inhaler (pMDI) represents a significant advance in convenience to the patient. However, a valved holding chamber (VHC) may still be needed to reduce the coarse component of the dose that is likely to deposit in the oropharyngeal region, and a small sized device may offer significant advantages to the patient from the standpoint of compliance with therapy. VHCs representing small (adult AeroChamber Plus\* with mouthpiece, 149-mL) and large (Volumatic™, 750-mL) devices have been compared in an in vitro evaluation with Seretide®/Advair™ (hydro-fluoro alkane [HFA]-formulated fluticasone propionate [FP = 125 µg/dose] and salmeterol xinafoate [SX = 25 µg/dose]) by Andersen Mark-II eight-stage impactor operated at 28.3L/min following compendial methodology. Fine particle fraction, based on the size range from 1.1 to 4.7 µm aerodynamic diameter, from either large or small VHCs with either component (69 – 79%) was similar [p = 0.08], and significantly greater than that from the pMDI alone (approximately 40%) [p < 0.001]. Fine particle dose emitted by the VHCs for SX (8.2 ± 0.8 µg for the AeroChamber Plus\* and 7.7 ± 0.5 µg for the Volumatic™) were comparable, and also similar to the fine particle dose delivered by the pMDI when used without a VHC (7.6 ± 0.6 µg). Fine particle doses for the FP component delivered by the two VHCs (46.4 ± 3.4 µg for the AeroChamber Plus\* and 46.3 ± 2.7 µg for the Volumatic™) were equivalent, but were slightly greater than the corresponding fine particle dose from the pMDI alone (39.1 ± 2.6 µg). However, this difference (approximately 20%) is close to the limit of resolution based on intermeasurement variability and is unlikely to have clinical significance, given the interpatient variability seen with inhaled drug therapy. It is therefore concluded that either of these VHCs has equivalent in vitro performance with this combination formulation in terms of the portion of the dose emitted from the pMDI that is likely to reach the receptors in the lungs.

### 4

**Mitchell JP, Nagel MW, Wiersema KJ, Bates SL, Morton RW.** *Comparison of a Large and a Small Volume Holding Chamber (VHC) for the Delivery of Salmeterol Xinafoate.* Presented at Ann. Meet. Amer. College of Allergy, Asthma and Immunology (ACAAI), Seattle, 2000.

Salmeterol xinafoate is a widely prescribed long-acting beta-adrenergic agonist. Valved holding chambers (VHCs) improve drug delivery from pressurized metered-dose inhalers (pMDI), particularly with patients having poor coordination. The present study compared a large volume VHC (Volumatic™, GlaxoSmithKline - 750-ml, n=5 devices) with a small volume VHC (AeroChamber Plus\*, Monaghan Medical Corp. – 149-ml, n=5 devices) with salmeterol xinafoate (Serevent®: total dose 21 µg ex actuator, GlaxoSmithKline). Measurements were also made with the pMDI without VHC. Total emitted dose (TD), fine particle dose (FPD - particles < 4.7 µm aerodynamic diameter) and fine particle fraction (FPF) were determined by Andersen 8-stage impactor with USP Induction Port at 28.3 ± 0.5 L/min. Assays for salmeterol xinafoate were undertaken by HPLC-fluorescence spectrometry at excitation and emission wavelengths of 226 nm and 296 nm respectively. As expected, both types of VHC greatly reduced the coarse component of the dose from the pMDI (10.5 ± 1.2 µg - pMDI alone; 1.0 ± 0.6 µg - AeroChamber Plus\* VHC; 0.9 ± 0.7 µg - Volumatic™ VHC). Both FPD and TD from the AeroChamber Plus\* (12.7 ± 1.3 µg and 13.6 ± 0.9 µg respectively) and from the Volumatic™ (12.3 ± 1.7 µg and 13.2 ± 2.1 µg respectively) VHCs were comparable (un-paired t-test, p > 0.70). FPD from the pMDI alone was 10.6 ± 1.0 µg, slightly lower but still comparable with the FPD from either type of VHC. The small volume VHC appears to be as effective as the larger chamber for the delivery of this formulation. These data are consistent with the recommendation to use a VHC with this formulation for patients with poor coordination (Demirkan *et al.* Chest 2000; 117, 1314-1318).

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**Mitchell JP, Nagel MW, Wiersema KJ, Bates SL, Morton RW.** *Performance of Large and Small Volume Valved Holding Chambers (VHCs) as a Function of Flow Rate.* UK Aerosol Society, Dec. 2000, pp 52-55

It is useful from the standpoint of the health care provider, if the performance of add-on devices for use with pressurized metered dose inhalers is characterized within the range of flow rates likely to be achieved by users. VHCs representing smaller (adult AeroChamber Plus\*, 149-ml; n = 5) and larger (Volumatic™, 750-ml; n = 5) devices were compared with HFA-formulated fluticasone propionate (125 µg/dose ex metering chamber) at three flow rates, 28.3, 45 and 60 L/min. Measurements were made by Andersen 8-stage impactor. Fine particle fractions (< 4.7 µm, < 4.6 µm and < 4.0 µm aerodynamic diameter at 28.3, 45 and 60 L/min respectively) from both VHCs were close to 90%, significantly greater than that from the pMDI alone. At 28.3 L/min, fine particle dose (FPD) from the smaller VHC (50.5 ± 3.8 µg) was comparable with that from the larger VHC (45.9 ± 7.8 µg) [p = 0.27]. At the higher flow rates, FPD from the smaller VHC (65.5 ± 2.6 µg (45 L/min) and 65.2 ± 6.2 µg (60 L/min) exceeded equivalent values from the larger VHC (53.8 ± 3.7 µg (45 L/min) and 55.3 ± 4.9 µg (60 L/min)) [p < 0.023].

6

**Battistini A, Pisi G, Attanasi G.** *Response to bronchodilator administered directly with spray or with spacer* [Article in Italian]. *Pediatr Med Chir.* 1997 Jul-Aug;19(4):237-42.

If we assume that the only function of a spacer is to facilitate the execution of a spray, its use is limited to small children who do not collaborate (below age 6-7 years). However, spacers seem to improve the effectiveness of drugs and reduce both directly and indirectly the side effects. To assess if these characteristics have a role in clinical practice, the response to 100 micrograms of salbutamol administered directly by Autohaler was compared to that obtained with the same dose administered with three different spacers, AeroChamber\* VHC, Babyhaler, Volumatic. A series of 88 asthmatic subjects with a FEF 25-75 less than 70% of the predicted value was considered. Overall patients provided 118 responses to the bronchodilator: 17 using the Aerotec (Autohaler), 38 the AeroChamber\* VHC, 33 the Babyhaler, 30 the Volumatic. The response was evaluated considering the parameters obtained by spirometry just before, 5 and 20 minutes after the inhalation of salbutamol. Heart rate was also measured at the same time points. Heart rate, but not spirometric parameter were increased by the use of the Autohaler, proving that the drug had been inhaled. All the spacers determined a significant increase in the parameters considered. No significant difference was detected among spacers, although the smallest (AeroChamber\* VHC, Babyhaler) showed a trend to a better response, in particular before age 7 years. The complete ineffectiveness of direct inhalation and the excellent response to inhalation with spacers show the indispensability of the latter, independent of age. Although no substantial difference among spacers was detected, the trend to obtain a better response with smaller spacers inclines us to use them in particular between 4 and 7 years of age. The negative correlation between the increase in spirometric parameters and the age of the patient would allow to have doses aimed to age or to body weight.

## Management of Acute Asthma in Children

7

**Sugerman RW, Teper AM, Girardi G, Scott CA, Clements DS, Wu W, Crim C.** *Fluticasone Propionate HFA Improves Asthma Control in PreSchool Age Children with Asthma.* *J Allergy Clin Immunol*, February, 2005.

**RATIONALE:** To evaluate the efficacy of fluticasone propionate HFA 88mcg BID (FP) vs placebo HFA (PLA) via MDI with the AeroChamber Plus\* spacer with attached facemask for 12 weeks in pre-school age children with asthma. **METHODS:** One to <4 year-olds with ≥ 2 episodes of increased asthma symptoms requiring medical attention and pharmacotherapy ≤12 months prior to screening and a baseline 24-hr daily asthma symptom score (DASS; scale 0 = none to 3 = severe) of ≥1.1 were enrolled in this randomized (120 PLA: 239 FP), double-blind, parallel-group, placebo-controlled trial. Efficacy measures included: mean percent change from baseline to endpoint (last 28 days of treatment) in DASS (primary), mean change from baseline in nighttime asthma symptom scores over the entire treatment period (NASS), change from baseline to endpoint in daily rescue albuterol use (DRAB), and time to treatment failure (TF; i.e., time to first asthma exacerbation). **RESULTS:** Baseline mean DASS and NASS were comparable between groups (DASS=1.7 PLA, 1.8 FP; NASS = 1.2 PLA, 1.4 FP). At endpoint, FP-treated patients experienced a greater reduction (improvement) from baseline in DASS (54% FP, 44% PLA; p=0.036) and NASS (-0.56 FP, -0.44 PLA; p=0.049). Baseline DRAB use was comparable across groups (4 inhalations/day [IPD] PLA;5 IPD FP). DRAB decreased by 2 and 3 IPD for the PLA and FP groups, respectively, at endpoint. More PLA patients (12%) discontinued due to TF compared with FP-treated patients (5%) (p=0.034). **CONCLUSION:** Treatment with FP HFA 88 mcg BID for 12 weeks significantly improves asthma control in 1 to <4 year-olds with asthma.

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**Cates CJ, Bara A, Crilly JA, Rowe BH.** *Holding chambers versus nebulisers for beta-agonist treatment of acute asthma (Cochrane Review).* The Cochrane Library, Issue 3, 2005.

A substantive amendment to this systematic review was last made on 18 February 2003. Cochrane reviews are regularly checked and updated if necessary. Background: In acute asthma inhaled beta-2-agonists are often administered to relieve bronchospasm by wet nebulisation, but some have argued that metered-dose inhalers with a holding chamber (spacer) can be equally effective. In the community setting nebulisers are more expensive, require a power source and need regular maintenance. Objectives: To assess the effects of holding chambers compared to nebulisers for the delivery of beta-2-agonists for acute asthma. Search strategy: We last searched the Cochrane Airways Group trials register in February 2004 and the Cochrane Central Register of Controlled Trials (The Cochrane Library, Issue 1, 2004). Selection criteria: Randomised trials in adults and children (from two years of age) with asthma, where holding chamber beta-2-agonist delivery was compared with wet nebulisation. Data collection and analysis: Two reviewers independently applied study inclusion criteria (one reviewer for the first version of the review), extracted the data and assessed trial quality. Missing data were obtained from the authors or estimated. Results are reported with 95% confidence intervals (CI). Main results: This review has been updated in 2003 and has now analysed 1076 children and 444 adults included in 22 trials from emergency room and community settings. In addition, five trials on in-patients with acute asthma (184 children and 28 adults) have been added to the review. Method of delivery of beta-2-agonist did not appear to affect hospital admission rates. In adults, the relative risk of admission for holding chamber versus nebuliser was 0.88 (95% CI 0.56 to 1.38). The relative risk for children was 0.65 (95% CI 0.4 to 1.06). In children, length of stay in the emergency department was significantly shorter when the holding chamber was used, with a weighted mean difference of -0.47 hours, (95% CI -0.58 to -0.37 hours). Length of stay in the emergency department for adults was similar for the two delivery methods. Peak flow and forced expiratory volume were also similar for the two delivery methods. Pulse rate was lower for holding chamber in children, weighted mean difference -7.6% baseline (95% CI -9.9 to -5.3% baseline). An update search in February 2004 did not identify any new studies. Authors' conclusions: Metered-dose inhalers with holding chamber produced outcomes that were at least equivalent to nebuliser delivery. Holding chambers may have some advantages compared to nebulisers for children with acute asthma. Citation: Cates CJ, Bara A, Crilly JA, Rowe BH. Holding chambers versus nebulisers for beta-agonist treatment of acute asthma. The Cochrane Database of Systematic Reviews 2003, Issue 2. Art. No.: CD000052. DOI: 10.1002/14651858.CD000052.

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**Delgado A, Chou KJ, Johnson Silver E, Crain EF.** *Nebulizers vs Metered-Dose Inhalers With Spacers for Bronchodilator Therapy to Treat Wheezing in Children Aged 2 to 24 Months in a Pediatric Emergency Department.* Arch Pediatr Adolesc Med. 2003; 157:76-80

OBJECTIVE: To determine if administration of albuterol by a metered-dose inhaler with a spacer device is as efficacious as administration of albuterol by nebulizer to treat wheezing in children aged 2 years and younger. DESIGN: Double-blind, randomized, placebo-controlled clinical trial. SETTING: Pediatric emergency department. PATIENTS: From a convenience sample of wheezing children aged 2 to 24 months, 85 patients were enrolled in the nebulizer group and 83 in the spacer group. INTERVENTIONS: The nebulizer group received a placebo metered-dose inhaler with a spacer followed by nebulized albuterol. The spacer group received albuterol by a metered-dose inhaler with a spacer followed by nebulized isotonic sodium chloride solution. Treatments were given every 20 minutes by a single investigator blinded to group assignment. MAIN OUTCOME MEASURES: The primary outcome was admission rate. Pulmonary Index score and oxygen saturation were measured initially and 10 minutes after each treatment. RESULTS: The nebulizer group had a significantly higher mean (SD) initial Pulmonary Index score compared with the spacer group (7.6 [2.5] vs 6.6 [2.0];  $P = .002$ ). With the initial Pulmonary Index score controlled, children in the spacer group were admitted less (5% vs 20%;  $P = .05$ ). Analyses also revealed an interaction between group and initial Pulmonary Index score; lower admission rates in the spacer group were found primarily in children having a more severe asthma exacerbation. CONCLUSION: Our data suggest that metered-dose inhalers with spacers may be as efficacious as nebulizers for the emergency department treatment of wheezing in children aged 2 years or younger.

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**Closa RM, Ceballos JM, Gomez-Papi A, Galiana AS, Gutierrez C, Marti-Henneber C.** *Efficacy of bronchodilators administered by nebulizers versus spacer devices in infants with acute wheezing.* *Pediatr Pulmonol.* 1998 Nov.; 26(5):344-8.

The aim of this study was to compare the response of infants with acute wheezing to treatments with inhaled terbutaline when administered by nebulizer or by metered-dose inhaler and spacer device (MDI-spacer). Thirty-four infants between the ages of 1 and 24 months who were seen in our emergency department for acute wheezing were studied in a double-blind, randomized trial. The participants received two treatments of terbutaline at 20-min intervals, either by a nebulizer (2 mg/dose in 2.8 mL of 0.9% saline solution) or by an MDI-spacer device (0.5 mg/dose). The outcome measure was a clinical score, based on respiratory rate, degree of wheezing, retractions, degree of cyanosis, color, and pulse oximetry data measured before treatment, 20 min after the first treatment, and again 20 min after the second treatment. There was no difference in the rate of improvement in the clinical score between infants who received terbutaline by nebulizer and those who received it by MDI-spacer. We conclude that MDI-spacers and nebulizers are equally effective means of delivering beta-2 agonists to infants and small children with acute wheezing.

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**Schuh S, Johnson DW, Stephens D, Callahan S, Winders P, Canny GJ.** *Comparison of albuterol delivered by a metered dose inhaler with spacer versus a nebulizer in children with mild acute asthma.* *J Pediatr.* 1999 Jul;135(1):22-7.

**OBJECTIVE:** In children with mild acute asthma, to compare treatment with a single dose of albuterol delivered by a metered dose inhaler (MDI) with a spacer in either a weight-adjusted high dose or a standard low-dose regimen with delivery by a nebulizer. **STUDY DESIGN:** In this randomized double-blind trial set in an emergency department, 90 children between 5 and 17 years of age with a baseline forced expiratory volume in 1 second (FEV<sub>1</sub>) between 50% and 79% of predicted value were treated with a single dose of albuterol, either 6 to 10 puffs (n = 30) or 2 puffs (n = 30) with an MDI with spacer or 0.15 mg/kg with a nebulizer (n = 30). **RESULTS:** No significant differences were seen between treatment groups in the degree of improvement in percent predicted FEV<sub>1</sub> (P = .12), clinical score, respiratory rate, or O<sub>2</sub> saturation. However, the nebulizer group had a significantly greater change in heart rate (P = .0001). Our study had 93% power to detect a mean difference in percent predicted FEV<sub>1</sub> of 8 between the treatment groups. **CONCLUSION:** In children with mild acute asthma, treatment with 2 puffs of albuterol by an MDI with spacer is just as clinically beneficial as treatment with higher doses delivered by an MDI or by a nebulizer.

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**Chou KJ, Cunningham SJ, Crain EF.** *Metered-dose inhalers with spacers vs nebulizers for pediatric asthma.* *Arch Pediatr Adolesc Med Vol.* 149 No. 2, Feb., 1995.

**OBJECTIVE:** To determine whether the administration of beta-agonists by metered-dose inhaler (MDI) with a spacer device is as effective as the administration of beta-agonists by nebulizer for the treatment of acute asthma exacerbations in children. **DESIGN:** Randomized trial with two arms. **SETTING:** Urban pediatric emergency department (ED) in Bronx, NY. **PATIENTS:** Convenience sample of 152 children 2 years and older with a history of at least two episodes of wheezing presenting to the ED with an acute asthma exacerbation. **INTERVENTIONS:** Patients were randomly assigned to receive standard doses of a beta-agonist (albuterol) by an MDI with spacer or by a nebulizer. Dosing intervals and the use of other medications were determined by the treating physician. **MEASUREMENTS/MAIN RESULTS:** Baseline characteristics and asthma history were recorded. Asthma severity score, peak expiratory flow rate in children 5 years or older, and oxygen saturation were determined at presentation and before admission or discharge. The groups did not differ in age, sex, ethnicity, age of onset of asthma, or asthma severity score at presentation. There were no significant differences between the groups in outcomes, including mean changes in respiratory rate, asthma severity score, and peak expiratory flow rate, oxygen saturation, number of treatments given, administration of steroids in the ED, and admission rate. Patients given MDIs with spacers required shorter treatment times in the ED (66 minutes vs 103 minutes, P < .001). Fewer patients in the spacer group had episodes of vomiting in the ED (9% vs 20%, P < .04), and patients in the nebulizer group had a significantly greater mean percent increase in heart rate from baseline to final disposition (15% vs 5%, P < .001). **CONCLUSIONS:** These data suggest that MDIs with spacers may be an effective alternative to nebulizers for the treatment of children with acute asthma exacerbations in the ED.

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**Parkin PC, Saunders NR, Diamond SA, Winders PM, Macarthur C.** *Randomised trial spacer v nebuliser for acute asthma.* Archives of Disease in Childhood, Vol 72, 239-240, 1995.

Sixty hospitalised children with asthma aged 1-5 years were randomised to spacer (AeroChamber\*) or nebuliser. A clinical score was measured at baseline and every 12 hours. There were no differences between groups in the score over time, or secondary outcome measures. The spacer is an effective delivery method for young hospitalised asthmatic children.

## Cost Effectiveness of Spacers versus Nebulizers

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**Leversha AM, Campanella SG, Aickin RP, Asher MI.** *Costs and effectiveness of spacer versus nebulizer in young children with moderate and severe acute asthma.* J Pediatr. 2000 Apr;136(4):497-502.

**OBJECTIVE:** To compare the costs and effectiveness of albuterol by metered dose inhaler (MDI) and spacer versus nebulizer in young children with moderate and severe acute asthma. **DESIGN:** Randomized, double-blind, placebo-controlled trial in an emergency department at a children's hospital. The participants were children 1 to 4 years of age with moderate to severe acute asthma. Patients assigned to the spacer group received albuterol (600 microg) by MDI by spacer (AeroChamber\*) followed by placebo by nebulizer (n = 30). The nebulizer group received placebo MDI by spacer followed by 2.5 mg albuterol by nebulizer (n = 30). Treatments were repeated at 20-minute intervals until the patient was judged to need no further doses of bronchodilator, or a total of 6 treatments. **RESULTS:** Clinical score, heart rate, respiratory rate, auscultatory findings, and oxygen saturation were recorded at baseline, after each treatment, and 60 minutes after the last treatment. Baseline characteristics and asthma severity were similar for the treatment groups. The spacer was as effective as the nebulizer for clinical score, respiratory rate, and oxygen saturation but produced a greater reduction in wheezing (P = .03). Heart rate increased to a greater degree in the nebulizer group (11.0/min vs 0.17/min for spacer, P < .01). Fewer children in the spacer group required admission (33% vs 60% in the nebulizer group, P = .04, adjusted for sex). No differences were seen in rates of tremor or hyperactivity. The mean cost of each emergency department presentation was NZ\$825 for the spacer group and NZ\$1282 for the nebulizer group (P = .03); 86% of children and 85% of parents preferred the spacer. **CONCLUSION:** The MDI and spacer combination was a cost-effective alternative to a nebulizer in the delivery of albuterol to young children with moderate and severe acute asthma.

## Effect of Electrostatic Charge

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**Dompeling E, Oudesluys-Murphy AM, Janssens HM, Hop W, Brinkman JG, Sukhai RN, de Jongste JC.** *Randomised controlled study of clinical efficacy of spacer therapy in asthma with regard to electrostatic charge.* Arch Dis Child 2001;84: 178-182, February.

**BACKGROUND:** Inhalation therapy using a pressured metered dose inhaler (pMDI) and a spacer is frequently used in the treatment of airway disease in children. Several laboratory studies found a clear negative influence of electrostatic charge (ESC) on plastic spacers on the delivery of aerosol. **AIMS:** To investigate whether ESC on plastic spacers could diminish bronchodilating responses to salbutamol. **METHODS:** Ninety asthmatic children (aged 4-8 years) were randomised into three groups: metal Nebuchamber, plastic Volumatic, and plastic AeroChamber\*. The bronchodilating response was measured by the change in peak expiratory flow rate (PEF) after 100 µg and 400 µg salbutamol. Within the Volumatic and AeroChamber\* groups, a crossover comparison was made between electrostatic and non-electrostatic spacers. **RESULTS:** We found no significant effect of ESC on the bronchodilating response to salbutamol with any of the doses in the AeroChamber\* and Volumatic groups. For the plastic spacers, the mean difference of the change in PEF after 100 µg salbutamol between non-electrostatic and electrostatic spacers was only +1.7% (95% CI 1.3% to 4.7%). After 400 µg salbutamol this was +1.9% (95% CI 1.4% to 5.1%). A comparable efficacy was found for the Nebuchamber, the AeroChamber\*, and Volumatic with respect to the change in PEF after 100 and 400 µg salbutamol. **CONCLUSION:** This study showed no negative influence of ESC on plastic spacers with regard to clinical efficacy of beta-2-agonist (salbutamol) in children with asthma. The metal Nebuchamber, plastic AeroChamber\*, and plastic Volumatic were equally effective.

# Lung deposition

16

**Asmus MJ, Coowanitwong I, Kwon SH, Khorsand N, Hochhaus G.** *In Vitro Performance of Two Common Valved Holding Chambers with a Chlorofluorocarbon-Free Beclomethasone Metered-Dose Inhaler.* Pharmacotherapy 2003;23(12):1538-1544

**STUDY OBJECTIVE:** To compare in vitro aerosol deposition from a beclomethasone dipropionate metered-dose inhaler (MDI) containing hydrofluoroalkane propellant with that of the MDI in combination with two common valved holding chambers (VHCs) to evaluate how these VHCs affect the respirable dose of beclomethasone dipropionate. **DESIGN:** In vitro aerosol deposition study. **SETTING:** University research center. **DEVICES:** Beclomethasone dipropionate hydrofluoroalkane MDI alone, the MDI with OptiChamber VHC, and the MDI with AeroChamber Plus\* VHC. **INTERVENTION:** The respirable dose (1-5-microm aerosol particles) of beclomethasone dipropionate was determined by sampling 10 80-microg actuations from five runs with each configuration (MDI alone, MDI with OptiChamber, and MDI with AeroChamber Plus\* VHC), using a well-established in vitro cascade impactor method. **MEASUREMENTS AND MAIN RESULTS:** Beclomethasone dipropionate aerosol was washed from the impactor with 50% methanol and quantified by means of high-performance liquid chromatography. Differences among outcomes were determined by using analysis of variance. Mean beclomethasone dipropionate respirable dose from AeroChamber Plus\* VHC (27.2 +/- 10.0 microg/actuation) was not significantly different ( $p>0.05$ ) from that of the MDI alone (29.0 +/- 7.0 microg/actuation). OptiChamber respirable dose (12.8 +/- 6.0 microg/actuation) was less than half that produced by either the AeroChamber Plus\* VHC or the MDI alone ( $p=0.013$ ). **CONCLUSIONS:** The OptiChamber and AeroChamber Plus\* VHCs do not demonstrate equivalent in vitro performance when used with a beclomethasone dipropionate MDI that contains hydrofluoroalkane propellant. The respirable dose of beclomethasone dipropionate aerosol from the hydrofluoroalkane MDI was decreased by only 6% when the MDI was mated to an AeroChamber Plus\* VHC and by 56% when used with an OptiChamber VHC.

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**Wildhaber JH, Dore ND, Wilson JM, Devadason SG, LeSouef PN.** *Inhalation therapy in asthma: nebulizer or pressurized metered-dose inhaler with holding chamber (AeroChamber\*)? In vivo comparison of lung deposition in children.* J Pediatr. 1999 Jul;135(1):28-33.

**OBJECTIVE:** To compare lung deposition from a nebulizer and a pressurized metered-dose inhaler (pMDI)/holding chamber to determine their efficiency in aerosol delivery to children. **Study design:** Children with stable asthma ( $n = 17$ ) aged 2 to 9 years inhaled in random order radiolabeled salbutamol from a nebulizer and a pMDI through a nonstatic holding chamber. Body and lung deposition of radiolabeled salbutamol was assessed with a gamma camera. **RESULTS:** Mean (absolute dose) total lung deposition expressed as a percentage of the nebulized dose was 5.4% (108 microg) in younger children (<4 years) and 11.1% (222 microg) in older children (>4 years). Mean (absolute dose) total lung deposition expressed as a percentage of the metered dose was 5.4% (21.6 microg) in younger and 9.6% (38.4 microg) in older children. **CONCLUSIONS:** For the same age groups we have shown equivalent percentages of total lung deposition of radiolabeled salbutamol aerosolized by either a nebulizer or a pMDI/holding chamber. However, the delivery rate per minute and the total dose of salbutamol deposited were significantly higher for the nebulizer.

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**Tal A, Golan H, Grauer N, Aviram M, Albin D, Quastel MR.** *Deposition pattern of radiolabeled salbutamol inhaled from a metered-dose inhaler by means of a spacer with mask in young children with airway obstruction.* J Pediatr. 1996 Apr;128(4):479-84

**BACKGROUND:** The exact amount of drug deposited in the respiratory and gastrointestinal tract in children with airway obstruction, when delivered from a metered-dose inhaler (MDI) via a spacer with mask, and its distribution in children with airway obstruction, are unknown. **METHODS:** We studied 15 children, using salbutamol labeled with technetium 99m. Each patient was imaged with a gamma-camera immediately after one puff of labeled salbutamol was administered via a spacer with mask. Drug deposition was then analyzed to measure the distribution of the labeled spray in the oropharynx, the lungs, the stomach, and the spacer with mask (AeroChamber\*) itself. **RESULTS:** Fifteen infants and children (mean age, 21 months (range, 3 months to 5 years); mean weight, 9.3 kg (range, 3.2 to 15 kg)) were studied. Mean aerosol deposition was 1.97% +/- 1.4% in the lungs, 1.28% +/- 0.77% in the oropharynx, and 1.11% +/- 2.4% in the stomach. The remainder was trapped in the spacer. Lung imaging after inhalation from an MDI via a spacer showed widespread deposition of the drug in central and peripheral intrapulmonary airways. In two adult volunteers the deposition after one puff of the same radiolabeled drug, inhaled from an MDI via a spacer with a mouthpiece, was 19% in the lungs and 2% in the stomach. **CONCLUSIONS:** Infants and toddlers with obstructive lung disease can be reliably and safely treated with inhaled medication administered with an MDI via a spacer with mask. The doses of a drug given from an MDI to infants and toddlers when a spacer with mask is used are not yet well defined but should be higher than the currently recommended doses, perhaps as much as an adult dose.

## Adult Asthma

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**Drollmann A, Nave R, Steinijans VW, Bethke TD, Baumgärtner E.** *Equivalent pharmacokinetics of the active metabolite of ciclesonide with and without use of a spacer for inhalation.* J Allergy Clin Immunol, Feb, 2004, S120

**Rationale:** Ciclesonide, a novel inhaled corticosteroid for the treatment of asthma, is administered via MDI as a solution-aerosol with high lung deposition (52%). Although a spacer is generally not required, some patients may benefit from the use of such a device. Therefore, as a surrogate for lung deposition, the pharmacokinetics of ciclesonide when administered via the MDI with or without spacer was compared. **Methods:** This was an open, randomized, two-period crossover study in patients with persistent bronchial asthma (n=30; age 19 to 52 y; FEV1 ≥70% predicted). A single dose of 320 µg ciclesonide (ex-actuator) was administered in the morning via the MDI with or without spacer (AeroChamber Plus\* VHC). The pharmacokinetic characteristics AUC<sub>(0,inf)</sub>, C<sub>max</sub>, t<sub>max</sub>, and t<sub>1/2</sub> were assessed for the pharmacologically active metabolite, desisobutyryl-ciclesonide (des-CIC), which is formed through bioactivation of the pharmacologically inactive parent compound ciclesonide by esterases in the lung. **Results:** Equivalence of the pharmacokinetic parameters of des-CIC after inhalation of ciclesonide with spacer (Test) or without spacer (Reference) could be demonstrated. The point estimates and 90% confidence intervals for the ratios Test/Reference were 0.96 (0.85, 1.07) for AUC<sub>(0,inf)</sub>, 1.05 (0.94, 1.18) for C<sub>max</sub>, and 1.04 (0.92, 1.18) for t<sub>1/2</sub>, and thus entirely within the stipulated bioequivalence range of 0.80 to 1.25. **Conclusions:** The use of the AeroChamber Plus\* spacer with the ciclesonide-MDI did not influence the pharmacokinetics of the active metabolite des-CIC. Consequently, it is suggested that the lung deposition may be similar when using the ciclesonide-MDI with or without a spacer.

**Dolovich MB, Clelland L, Rhem R, Coates G.** *Salmeterol Administration by MDI Alone Versus MDI Plus AeroChamber\**. European Respiratory Society, Madrid, Spain, October 9-13, 1999

Spacer and valved holding chambers such as the AeroChamber\* (AC) (Trudell Medical Int'l, Canada) have been developed to help patients take their MDI medication correctly. However, not all spacers can be successfully used with every MDI. The objective of this study was to assess clinical efficacy and safety of Serevent (S) (salmeterol) MDI inhaled from the AeroChamber\* in comparison to inhaling Serevent aerosol from the MDI alone. A double-blind, randomized, placebo controlled study was conducted in 5 stable adult asthmatics (3M, 2F), mean age (range) 38 (21-55) yrs, mean baseline FEV1 77.5±8.5% pred. Each subject was maintained on inhaled steroids and pm salbutamol; 2/5 were receiving S prior to enrollment. On entry, subjects underwent a physical exam, pulmonary function testing, EKG, CXR and SMA12. On each of the study days, subjects inhaled 1 dose (2 puffs) of S (50 ug/puff) via the MDI alone (S/MDI) using the open-mouth technique, or the MDI with AC (S/MDI +AC) and 2 puffs of matching placebo, using the opposite inhalation method. FEV1 and vital signs (BP, pulse, respirations (RR)) were measured at baseline and then over the subsequent 12 hrs, along with symptoms and possible side effects (e.g., tremor, headache). An EKG was done pre-and 3 hrs post-dosing. Baseline FEV1s were within 5% between study days: (S/MDI:2.90±0.73L;S/MDI+AC:2.99±0.83L). For both treatments ( $p < 0.05$ ), there was a significant increase in FEV1 compared to baseline, peaking at 4-5 hrs and sustained at these levels until + 12 hrs (mean±sdΔFEV1 from baseline at 12 hrs: S/MDI 0.22±0.35L, S.MDI+AC 0.17±0.28L), but no difference in response (ΔFEV1,AUC) between the 2 treatments at any time during the 12 hrs. BP, RR, pulse were similar, but from 4-12 hrs Δpulse was significantly higher for S/MDI ( $p < 0.05$ ). EKGs were normal at baseline and unchanged at 3 hrs with either treatment. In conclusion, using optimal inhalation techniques, Serevent inhaled via the AeroChamber\* is as clinically effective and safe as treatment with Serevent MDI alone.

## Management of Acute Asthma in Adults

**Cates CJ, Bara A, Crilly JA, Rowe BH.** *Holding chambers versus nebulisers for beta-agonist treatment of acute asthma (Cochrane Review)*. The Cochrane Library, Issue 3, 2005.

A substantive amendment to this systematic review was last made on 18 February 2003. Cochrane reviews are regularly checked and updated if necessary. Background: In acute asthma inhaled beta-2-agonists are often administered to relieve bronchospasm by wet nebulisation, but some have argued that metered-dose inhalers with a holding chamber (spacer) can be equally effective. In the community setting nebulisers are more expensive, require a power source and need regular maintenance. Objectives: To assess the effects of holding chambers compared to nebulisers for the delivery of beta-2-agonists for acute asthma. Search strategy: We last searched the Cochrane Airways Group trials register in February 2004 and the Cochrane Central Register of Controlled Trials (The Cochrane Library, Issue 1, 2004). Selection criteria: Randomised trials in adults and children (from two years of age) with asthma, where holding chamber beta-2-agonist delivery was compared with wet nebulisation. Data collection and analysis: Two reviewers independently applied study inclusion criteria (one reviewer for the first version of the review), extracted the data and assessed trial quality. Missing data were obtained from the authors or estimated. Results are reported with 95% confidence intervals (CI). Main results: This review has been updated in 2003 and has now analysed 1076 children and 444 adults included in 22 trials from emergency room and community settings. In addition, five trials on in-patients with acute asthma (184 children and 28 adults) have been added to the review. Method of delivery of beta-2-agonist did not appear to affect hospital admission rates. In adults, the relative risk of admission for holding chamber versus nebuliser was 0.88 (95% CI 0.56 to 1.38). The relative risk for children was 0.65 (95% CI 0.4 to 1.06). In children, length of stay in the emergency department was significantly shorter when the holding chamber was used, with a weighted mean difference of -0.47 hours, (95% CI -0.58 to -0.37 hours). Length of stay in the emergency department for adults was similar for the two delivery methods. Peak flow and forced expiratory volume were also similar for the two delivery methods. Pulse rate was lower for holding chamber in children, weighted mean difference -7.6% baseline (95% CI -9.9 to -5.3% baseline). An update search in February 2004 did not identify any new studies. Authors' conclusions: Metered-dose inhalers with holding chamber produced outcomes that were at least equivalent to nebuliser delivery. Holding chambers may have some advantages compared to nebulisers for children with acute asthma. Citation: Cates CJ, Bara A, Crilly JA, Rowe BH. Holding chambers versus nebulisers for beta-agonist treatment of acute asthma. The Cochrane Database of Systematic Reviews 2003, Issue 2. Art. No.: CD000052. DOI: 10.1002/14651858.CD000052.

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**Newman KB, Milne S, Hamilton C, Hall K.** *A Comparison of Albuterol Administered by Metered-Dose Inhaler and Spacer With Albuterol by Nebulizer in Adults Presenting to an Urban Emergency Department With Acute Asthma.* *Chest* 2002 Apr 121:1036-41

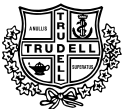
**STUDY OBJECTIVES:** To determine the efficacy of albuterol by metered-dose inhaler (MDI) and spacer (AeroChamber\*) compared to a nebulizer. **DESIGN:** A prospective, open-label study. **SETTING:** Large urban emergency department (ED). **PATIENTS:** All consecutive adult asthma patients over a 2.5-year period. **INTERVENTIONS:** ED personnel used a standardized treatment algorithm, which included albuterol administered by nebulization, for patients presenting to the ED during the first 12 months of the study. The treatment algorithm then was switched to one that utilized albuterol administered by MDI/spacer as the primary mode of delivery for the following 18 months. As part of the conversion to MDI/spacer, ED staff counseled patients on self-management and supplied patients with a peak flowmeter, an MDI/spacer, and an inhaled steroid for home use. **MEASUREMENTS:** Pulmonary function, clinical outcome, laboratory data, and financial data were assembled and analyzed from 2,342 ED visits and 1,420 patients. **RESULTS:** While there was no significant difference in hospital admission rates between patients in the MDI/spacer group and the nebulizer group (13.2% and 14.6%, respectively), there was a statistically greater improvement in peak flow rates in the MDI/spacer group (126.8 vs 111.9 L/min, respectively;  $p = 0.002$ ). The MDI/spacer group also spent significantly less time in the ED (163.6 and 175 min, respectively;  $p = 0.007$ ), had a lower total albuterol dose (1,125  $\mu\text{g}$  and 6,700  $\mu\text{g}$ , respectively;  $p < 0.001$ ), and showed a greater improvement in arterial oxygen saturation ( $p = 0.043$ ). Relapse rates at 14 and 21 days were significantly lower ( $p < 0.01$  and  $p < 0.05$ , respectively) among patients treated with the MDI/spacer and were associated with asthma education and the provision of a peak flowmeter, a spacer, and an inhaled corticosteroid for patients' home use. **CONCLUSIONS:** Albuterol administered by MDI/spacer is an efficacious and cost-effective alternative to nebulization in adults with acute asthma who present at a large urban ED.

## COPD

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**Shortall SP, Blum J, Oldenburg FA, Rodgerson L, Branscombe JM, Harrow EM.** *Treatment of patients hospitalized for exacerbations of chronic obstructive pulmonary disease: comparison of an oral/metered-dose inhaler regimen and an intravenous/nebulizer regimen.* *Respir Care.* 2002 Feb;47(2):154-8

**OBJECTIVE:** Compare the therapeutic efficacy of an oral/metered-dose inhaler used with AeroChamber\* valved holding chamber (oral/MDI) regimen to an intravenous/nebulizer (I.V./neb) regimen of methylprednisolone, cefuroxime, and inhaled albuterol and ipratropium bromide in patients hospitalized for exacerbations of chronic obstructive pulmonary disease (COPD). **DESIGN:** Randomized, nonblinded, therapeutic trial. **SETTING:** Two community hospitals in Bangor, Maine. **PATIENTS:** 34 individuals with severe COPD. The mean admission forced expiratory volume in the first second was 0.75 L (oral/MDI 0.78 L, I.V./neb 0.71 L). **RESULTS:** Baseline demographic, laboratory, comorbidity, and ventilatory values determined in 19 patients who received the oral/MDI regimen and 15 patients treated with the I.V./neb regimen indicated comparability of the two groups. Outcome variables that compared oral/MDI to I.V./neb, including mean change in forced expiratory volume in the first second (0.12 L vs 0.13 L), mean length of stay (4.3 vs 5.1 d), and treatment failures (32% vs 33%), showed no significant differences. **CONCLUSION:** Patients hospitalized for COPD exacerbations can be successfully (and potentially less expensively) treated with an oral/MDI treatment regimen.



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