

AeroChamber *Plus*

Valved Holding Chamber Devices

Product Monograph



Trudell Medical International[®]

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1 Introduction

Valved Holding Chambers (VHCs), also commonly referred to as “spacers,” are designed to improve medication delivery, reduce oropharyngeal deposition of medication and help patients to overcome difficulties in the co-ordination between actuation of a pressurized metered dose inhaler (pMDI) and inhalation. For these types of patients, VHCs may offer the potential for better clinical outcomes over using their pMDI alone.

VHCs are commonly described as small or large volume according to the size of the holding chamber: **AeroChamber Plus*** VHC is typically referred to as a small volume spacer (149ml) whereas GlaxoSmithKline’s Volumatic[†] is considered to be a large volume spacer (750ml).



AeroChamber Plus* VHCs are manufactured in clean room conditions (ISO Class 8 Standards) by Trudell Medical International at its facilities in London, Ontario, Canada. **AeroChamber Plus*** VHCs are CE marked, in accordance with the European Medical Devices Directive 93/42/EEC for this Class 1 Medical Device. Trudell Medical International operates a quality system approved to ISO 13485.

2 The Role of Valved Holding Chambers (VHCs)

VHCs such as the **AeroChamber Plus*** devices have an important clinical role to play in the management of respiratory disease. They are designed to improve medication delivery, reduce oropharyngeal deposition of medication and help patients to overcome difficulties in the co-ordination between actuation of a pressurized metered dose inhaler (pMDI) and inhalation.

National and international guidelines for the management of asthma and COPD all recommend the inhaled route as the preferred method of delivery for medications to treat asthma and COPD [GINA, 2003; NIH, 2002; BTS/SIGN, 2004; GOLD, 2003]. For asthma, the GINA guidelines draw attention to the requirement for co-ordination of actuation of the pMDI with inhalation and recommend that a spacer device be used where appropriate, particularly in children. In infants and pre-school children, in whom active co-operation cannot be expected, a pMDI used with a spacer and facemask is recommended as the device of choice for maintenance treatment. As co-operation improves, often around the age of 4 to 6 years, it further recommends that the child is encouraged to use a mouthpiece rather than facemask attachment to the spacer [GINA, 2003].

The GINA guidelines (2003) state:

“The disadvantage of pressurized MDI therapy is that training and skill are required to coordinate activation of the inhaler and the inhalation. The use of a spacer (holding chamber) improves drug delivery from an MDI (Evidence A). The spacer device allows discharge of the drug into a chamber where particles of medication are held in suspension for 10 to 30 seconds. During this time, the patient can inhale the drug.

Spacers also reduce deposition in the mouth and oropharynx, decreasing cough as well as the possibility of oral candidiasis when used to deliver glucocorticosteroids (Evidence A). Further, the use of spacers for the delivery of inhaled glucocorticosteroids decreases their systemic bioavailability and the risk of systemic side effects (Evidence B).”

Valved Holding Chambers are widely used for the delivery of inhaled maintenance treatment for asthma and COPD and also as an alternative to nebuliser therapy in the management of acute asthma.

3 Factors That Affect Aerosol Delivery From VHCs

Three main factors affect aerosol delivery via a VHC: VHC characteristics, pMDI characteristics and the characteristics of the patient who uses the VHC.

3.1 VHC Characteristics

The first generation of chambers, including GSK's Volumatic[†] and AstraZeneca's Nebuhaler[†], were large volume devices designed to accommodate the aerosol plume from CFC-formulated pMDIs. These plastic chambers were constructed of polycarbonate, a transparent material, which has been found to be prone to the accumulation of electrostatic charge. This accumulation of charge has been widely reported to cause aerosol to deposit on the inner surfaces of the VHC walls [Wildhaber, 1996; Dewsbury, 1996], reducing the fine particle mass available for inspiration. Although a 'wash but don't rinse' procedure with ionic detergent has been shown to minimise the build-up of electrostatic charge, the frequent washing suggested for maintenance of optimum VHC performance may not be a practical expectation during routine clinical use. Thus, the variability in performance of plastic VHCs may outweigh any small differences seen in the pharmaceutical performance between VHC devices.

Some VHC devices such as Volumatic[†] incorporate heavy plastic one-way valves to prevent exhalation back into the chamber. Patients with small lung volumes, such as infants, may not generate sufficient inspiratory flow rates to open these valves correctly [Kraemer, 1991; Barry, 1996b]. Modern small volume VHCs such as *AeroChamber Plus*^{*} VHC with low resistance inspiratory valves may therefore be more appropriate for use in infants and small children.

The first truly portable, patient-friendly VHC was the *AeroChamber*^{*} VHC which was developed at McMaster University, Canada. It was designed to deliver the same lower respiratory tract dose of medication as the MDI alone when used under optimal conditions [Corr, 1982]. Since then new technologies and materials have become available and these too have been incorporated into the design of *AeroChamber*^{*} VHC range. The *AeroChamber Plus*^{*} VHC has incorporated aids such as the "EZ Flow" exhalation valve and the *FLOWSignal*^{*} whistle, to assist appropriate inhalation patterns through the device. These VHCs are supplied with comfortable latex free *ComfortSeal*^{*} facemasks for infants, children and adults to facilitate an effective seal between the VHC and face.

3.2 pMDI Characteristics

When a VHC is used in conjunction with a pMDI, it is important that the respirable mass of aerosol (i.e. the amount of the actuated dose that comprises particles small enough (<5 micron in diameter) to reach the airways during inhalation), is not significantly affected by the addition of the VHC [Corr, 1982; Cripps, 2000]. In many cases, the reformulation of CFC pMDIs with HFA propellants has not affected the particle size distribution of the drug in the aerosol. However the characteristics of the aerosol plume, in terms of its size and velocity, have been shown to differ from the conventional CFC pMDI. In many HFA products the velocity of aerosol released from the pMDI is lower than that of the corresponding CFC product. Barry [Barry, 1996c] reported that the aerosol delivered from the HFA salbutamol pMDI, Airomir[†], is both slower and contained within a smaller volume than the corresponding CFC product. For these reasons small volume VHCs may be better suited to HFA pMDIs than the older large volume VHC devices such as Volumatic[†], which were designed for use with CFC pMDI formulations.

Electrostatic charge is generated on discharging the aerosol, which can influence deposition in the VHC. The magnitude of this charge is influenced by the nature of the formulation eg. CFC and HFA. HFA pMDIs tend to be more susceptible to static charge on the chamber than the CFC MDIs they have replaced.

Early VHC devices such as GSK's Volumatic[†] were supplied for use in conjunction with company-specific pMDIs and only the actuators of the specified products fitted into the opening of the VHC. If patients were prescribed a combination of different pMDIs from different manufacturers, more than one VHC was required. Newer spacers such as *AeroChamber Plus** VHC have been designed with flexible, universal adapters to accommodate a wide range of actuator mouthpiece designs. In this way the same VHC can be used in conjunction with different pMDIs without affecting the metering performance of the pMDIs used [Berlinski, 2001]. All pMDIs compatible with the Volumatic[†] are also mechanically compatible with the *AeroChamber Plus** VHC range, so a transition from the Volumatic[†] chamber to *AeroChamber Plus** VHC would not require prescription of alternative pMDI medication.

3.3 Patient Characteristics

Large volume VHC devices have been found to be cumbersome and obtrusive, particularly for elderly patients [Jones, 1999]. Studies have shown that patients prefer smaller, more discreet and portable devices [Chapman, 1995; Gunawardena, 1997]. A research study by NOP Healthcare UK in 2000 found that many asthma patients, or parents of children with asthma, do not have a VHC available when at work or school, or when going out socially [data on file, Trudell Medical International]. Patients and parents identified size and ease of use as the most important factors in achieving acceptability of their device. When compared with Volumatic[†] chamber, the *AeroChamber Plus** VHC may lead to improvements in adherence to treatment, due to improved patient acceptability of the device.

The use of VHCs in conjunction with pMDIs is advocated across the spectrum of patient populations, from infants to the elderly. Consequently there is considerable inter subject variability in inhalation techniques, inspiratory flow rates, tidal volumes, breathing frequencies and airways calibre, in addition to variations in other factors such as patient dexterity and ability to self-administer the dose.

Even within an individual patient there is considerable variability on a day-to-day basis in aerosol delivery. In a randomised, cross over, real-life study in children with stable asthma, the mean coefficient of variation of filter dose in children 5-8 years using the Volumatic[†] was 34% versus 23% for AstraZeneca's antistatic Nebuchamber[†] device (p=0.003) [Janssens, 1999].

Patient handling characteristics are therefore of major importance. This may be of greater significance than the small differences seen in pharmaceutical performance between VHCs.

4 *AeroChamber Plus** VHC – Patient Benefits

4.1 All *AeroChamber Plus** VHCs

- The 149 ml holding chamber is manufactured from a shatter-resistant, clear, polymer blend, making it easy to carry and ensure no foreign bodies are in the chamber before use.
- Pictographic usage instructions are permanently printed onto the chamber.
- The universal pMDI adapter fits all commonly prescribed inhalers from major manufacturers.
- The universal pMDI adapter is easily removed and replaced to facilitate cleaning inside the chamber (see cleaning instructions).
- Devices are supplied ready to use after first wash – no assembly required.
- No latex or phthalates are used in the manufacture of *AeroChamber Plus** devices.



4.2 *AeroChamber Plus** Infant and Child Mask

- Pictographic, child-friendly *AEROBEAR** instructions are permanently printed onto the chamber.
- Latex-free infant (orange colour: 0-18 months approx.) and child (yellow colour: 12 months to 5 years approx.) *ComfortSeal** masks minimise dead space and provide a secure, comfortable fit.
- One-way, low resistance inhalation valve opens easily at low inspiratory flow rates and features a protective design to help ensure a long life.
- “*EZ Flow*” exhalation valve in the mask offers low resistance to exhaled flow making device suitable for tidal breathing. The exhalation valve directs exhaled medication away from the patient’s face and eyes.

4.3 *AeroChamber Plus** Mouthpiece and Adult Mask VHCs

- Mouthpiece device designed for patients 5 years and over.
- Mouthpiece device features an integrated inhalation/exhalation valve system to permit tidal breathing and direct exhaled medication away from the patient’s face and eyes.
- *FLOWSignal** whistle alerts patient if they inhale too rapidly, encouraging proper inhalation technique.
- One-way, low resistance inhalation valve opens easily at low inspiratory flow rates and features a protective design to help ensure a long life.
- *ComfortSeal** adult size mask available, with “*EZ Flow*” exhalation valve. The *ComfortSeal** mask is made of medical grade silicone to reduce facial irritation and provides a snug, secure seal, limiting the leakage of ambient air. The “*EZ Flow*” exhalation valve is built directly into the mask to minimise dead space and reduce resistance when patients exhale.

Key Features of the Volumatic[†] and *AeroChamber Plus*^{*} VHCs

Feature	<i>AeroChamber Plus</i> [*]	Volumatic [†]
Manufacturer	Trudell Medical International	GlaxoSmithKline
Transparent Chamber	Polymer blend	Polycarbonate (prone to static)
Flow Rate Alarm	FLOWSignal [*] whistle alerts patient to excessive inspiratory flow rates (adult version)	X
Permanent Instructions on unit	Pictographic, includes AeroBear [*] on child and infant mask devices	X
Compatible with most pMDIs	Mechanically compatible with all widely prescribed pMDIs	X Only GSK pMDIs
Recommended replacement	Replace after 12 months	Replace after 6-12 months
Mask	Three different sizes of latex free, ComfortSeal [*] mask – infant, child and adult, all with “ EZ Flow ” exhalation valve	One paediatric size mask, no exhalation valve
Internal Volume	149 mL	750 mL

5 Review of Scientific Data

5.1 *In Vitro* Data

This section presents published data from *in-vitro* drug delivery studies of the use of pMDIs in conjunction with currently available VHC devices.

Summary

- In vitro data demonstrate comparable medication delivery performance of *AeroChamber Plus*^{*} VHC and Volumatic[†] device.
- In vitro data on a wide range of pMDIs shows acceptable medication delivery performance with *AeroChamber Plus*^{*} VHC.
- Clinical data demonstrate that:
 - *AeroChamber Plus*^{*} VHC performs as expected for a spacer increasing drug delivery versus pMDI alone
 - The increased drug exposure from *AeroChamber Plus*^{*} VHC is within the range of exposure where cortisol is unlikely to be affected
 - At a population level, there appears to be no impact on patient care if transitioning from the Volumatic[†] to *AeroChamber Plus*^{*} VHC
 - *AeroChamber Plus*^{*} VHC is an effective alternative to nebuliser therapy in the beta₂ agonist management of acute asthma in children and adults
 - *AeroChamber Plus*^{*} VHC is effective with tidal breathing

5.1.1 Methodology

In vitro studies performed under controlled laboratory conditions are widely accepted as important in the evaluation of VHCs, by measuring the effect of the VHC on the fine particle fraction delivered by the pressurised metered dose inhaler (pMDI). Recent *in vitro* studies of GSK pMDIs by TMI's aerosol laboratory have directly compared the *in vitro* performance of the Volumatic[†] spacer with **AeroChamber Plus*** VHC using the Andersen Cascade Impactor.

The Andersen Cascade Impactor provides both a measure of the aerodynamic particle size distribution of the drug particles in the discharged aerosol and also a measure of the fraction of the delivered dose which is within a size range suitable for deposition in the lungs. This fraction is defined as the fine particle mass and corresponds to the summed deposition of drug on stages 3, 4 and 5 of the impactor. Under the flow rate conditions of 28.3 litres/minute, this deposition corresponds to material with an aerodynamic particle size range of 1.1 to 4.7 µm.

The performance of each VHC was evaluated against the pMDI alone by assessing the effect of the VHC on both the particle size distribution of drug in the aerosol and the fine particle mass. Each VHC was washed in accordance with the patient instructions, prior to testing in order to minimise the effects of electrostatic charge.

5.1.2 Results

The data [data on file, Trudell Medical International] demonstrate that for both the CFC and HFA products, each of the Volumatic[†] and **AeroChamber Plus*** VHCs has no significant effect on the particle size distribution of the drug in the aerosol, with the fine particle fraction consistently deposited on stages 3, 4 and 5 of the cascade impactor.

These data demonstrate that each VHC gives an increase in the fine particle mass (FPM) compared to the pMDI alone. For GSK's CFC products, Becotide[†] CFC and Becloforte[†] CFC, the magnitude of the percentage increase in FPM is comparable for each of the VHCs. Similarly, the increase in FPM observed for Serevent[†] CFC is similar across the two VHCs. For GSK's HFA products, Flixotide[†] HFA, Ventolin[†] HFA, Serevent[†] HFA and Seretide[†] HFA, the increase in FPM is of the same order for each VHC, although for Ventolin[†] HFA, Serevent[†] HFA and Seretide[†] HFA, the increase in FPM with **AeroChamber Plus*** VHC was lower than that with the Volumatic[†] chamber.

This increase in fine particle mass observed in the laboratory for each of the VHCs is in accordance with expectations and is due to the deceleration of the aerosol plume when discharged into the VHC. However, Volumatic[†] and **AeroChamber Plus*** VHC have been shown to give comparable performance. Although in a few cases statistically significant differences were detectable between the VHCs, driven largely by a small standard deviation, the practical differences between the VHCs for all of the products were small, and in no instance exceeded 10% of the label claim dose.

Other studies, which have compared the aerosol delivery in terms of respirable dose (or FPM) and Mass Median Aerodynamic Diameter (MMAD) of Ventolin[†] HFA, have shown equivalent delivery via GSK's Volumatic[†] or Babyhaler[†] devices [Cripps, 1997] and between the **AeroChamber Plus*** VHC and OptiChamber[†] VHCs [Crim, 2003]. Similar observations were made for Flovent[†] CFC delivered via **AeroChamber Plus*** VHC or Easivent[†] spacers compared to the MDI alone [Asmus, 2002]. With Becotide[†], similar FPM recoveries were made from Volumatic[†] and Babyhaler[†], although for this CFC formulation, FPM was lower from the **AeroChamber*** VHC [Barry, 1996a].

5.2 Clinical Data

5.2.1 Comparative Data of *AeroChamber Plus** VHC and Volumatic†

Summary

There are limited clinical data of direct comparisons between the performance of small and large volume VHCs. At a population level, these data suggest no impact on patient care if transitioning from the Volumatic† to *AeroChamber Plus** VHC. In some individual cases, switching from the Volumatic† to the *AeroChamber Plus** VHC may produce a change in systemic exposure – which may be an increase or decrease – and is influenced by a number of factors including patient inhalation technique, compliance, handling conditions, efficiency and reproducibility of MDI delivery. It is therefore recommended that patients are reviewed whilst changing from one VHC device to another and that pMDI dosage is increased or decreased as appropriate.

The clinical efficacy of Ventolin† HFA delivered via *AeroChamber** VHC, GSK’s Volumatic† or AstraZeneca’s Nebuchamber† was assessed in 90 asthmatic children aged 4 – 8 years. Improvements in peak expiratory flow (PEF) after 100mcg Ventolin† were between 11% and 14% and between 16% and 21% after a cumulative dose of 400mcg Ventolin† with no statistically significant difference between any of the VHCs. The study concluded that all three VHCs were effective for the delivery of Ventolin† and similarly all three devices achieved a high level of patient satisfaction [Dompeling, 2001].

The performance of *AeroChamber Plus** VHC and Volumatic† was assessed in 21 children (age 2-14 years), by measuring mean albuterol (salbutamol) collected in low resistance filter paper attached to the mouthpieces. Inhaler technique was optimised by training of patients and parents. The mean (SD) drug delivery (% nominal dose) to children of all ages in this study using *AeroChamber Plus** VHC [51.5 (14.7) %] was significantly more efficient ($p=0.04$) than using Volumatic† [39.3 (10.1) %] [Devadason, 2005].

5.2.2 Management of Acute Asthma in Children and Adults – VHC versus Nebuliser

Cates *et al* [2005] performed a systematic review of large and small volume holding chambers versus nebulisers for β_2 agonist treatment of acute asthma. The review included 28 clinical studies. Of the studies included 18 involved children and the devices investigated were *AeroChamber** VHC (5), Nebuhaler† (3), Volumatic† (5), unspecified (2) Babyhaler† (1), ACE† spacer (1) and M/S Cipla (1). The 5 *AeroChamber** VHC studies included 443 children (age 1-16 years) [Chou, 1995; Leversha, 2000; Lin, 1995; Parkin, 1995; Williams, 1996]. The review concluded that pMDI with holding chamber produced outcomes that were at least equivalent to nebuliser delivery, although pulse rate was significantly lower when a VHC was used in children (possibly due to a lower total dose of beta₂ agonist). The authors also state that holding chambers may have some advantages compared to nebulisers for children with acute asthma.

5.2.3 Tidal Breathing

The *AeroChamber Plus** VHC devices are suitable for use with tidal breathing [Mitchell 1996]. All four of the *AeroChamber Plus** VHC devices are designed with a one-way, low resistance inhalation valve, which opens easily at low inspiratory flow rates. The “EZ Flow” exhalation valve on *AeroChamber Plus** products with facemask offers low resistance to exhaled flow making the device suitable for tidal breathing. The exhalation valve directs exhaled medication away from the patient’s face and eyes.

Barry *et al* [1996] measured aerosol clearance from five different VHCs, two small volume (< 200ml); GSK's Babyhaler[†] and TMI's *AeroChamber** VHCs, and three large volume (>700ml); GSK's Volumatic[†], AZ's Nebuhaler[†] and Fisons' (now SanofiAventis) Fisonair[†] using a Pari Sinus Breath Simulator, to mimic tidal breathing. The study demonstrated more efficient clearance of aerosol from the Babyhaler[†] and *AeroChamber** VHCs at lower tidal volumes (<300ml), with aerosol still visible in the three larger chambers after 20 seconds (seven breaths). The study suggests that differences in VHC design and volume may affect clearance of aerosol from VHCs, and may mean that large volume VHCs are less efficient for use by patients with small tidal volumes.

5.2.4 Lung Deposition

Zar *et al* [2000] measured lung deposition of radio-labelled aerosol from the *AeroChamber** VHC and GSK's Babyhaler[†] in a study of 40 children with asthma (aged 3-7 years). Although the *AeroChamber** VHC is less than half the volume of the Babyhaler[†], equivalent aerosol deposition was obtained from both devices.

6 References

Agertoft L, Pedersen S. Lung deposition and systemic bioavailability of fluticasone Diskus and budesonide Turbuhaler. *Am J Respiratory Critical Care Med.* 2003;168: 779-782.

Amirav I, Newhouse MT. Aerosol therapy with valved holding chambers in young children: importance of facemask seal. *Pediatrics* 2001; 108(2): 389-394.

Asmus MJ, Liang J, Coowanitwong I, Vafadari R, Hochhaus G. In vitro deposition of fluticasone aerosol from a metered-dose inhaler with and without two common valved holding chambers. *Ann Allergy Asthma Immunol* 2002; 88: 204-208.

Barry PW, O'Callaghan C. Inhalational drug delivery from seven different spacer devices. *Thorax* 1996a; 51: 835-840.

Barry PW, O'Callaghan C. The effect of delay on the delivery of fluticasone propionate and salmeterol from spacer devices. *Eur Respir J* 1996b; 9 (Suppl 123): 432s

Barry PW, O'Callaghan C. The effect of breathing pattern on clearance of aerosol from spacers. *Eur Respir J* 1996c; 9 (Suppl 123): 432s

Barry PW, O'Callaghan C. In vitro comparison of the amount of salbutamol available for inhalation from different formulations used with different spacer devices. *Eur Respir J* 1997; 10: 1345-1348.

Barry PW, O'Callaghan C. A comparative analysis of the particle size output of beclomethasone dipropionate, salmeterol xinafoate and fluticasone propionate metered dose inhalers used with the Babyhaler, Volumatic and AeroChamber spacer devices. *Br J Clin Pharmacol* 1999; 47: 357-360.

Berlinski A, Waldrep JC. Metering performance of several metered-dose inhalers with different spacers/holding chambers. *J Aerosol Med* 2001; 14(4): 427-432.

Bisgaard H. A metal aerosol holding chamber devised for young children with asthma. *Eur Respir J* 1995; 8: 856-860.

Bisgaard H, Price MJ, Maden C, Olsen NA. Cost-effectiveness of fluticasone propionate administered via metered dose inhaler plus Babyhaler spacer in the treatment of asthma in pre-school children. *Chest* 2001; 120(6): 1835-1842.

British Guideline on the Management of Asthma, A national clinical guideline. British Thoracic Society (BTS). Revised April 2004.

Brown PH, Blundell G, Greening AP, Crompton GK. Do large volume spacers reduce the systemic effects of high dose inhaled corticosteroids? *Thorax* 1990; 45: 736-739.

Brutsche MH, Brutsche IC, Munavvar M, Langley SJ, Masterson CM, Daley-Yates PT, Brown R, Custovic A, Woodcock A (2000). Comparison of pharmacokinetics and systemic effects of inhaled fluticasone propionate in subjects with asthma and healthy volunteers: a randomised crossover study. *Lancet.* 2000;356: 556-561.

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

Chapman KR. The choice of inhalers in adults and children over six. *J Aerosol Med* 1995; 8: S27-S36.

- Chou KJ, Cunningham, SJ, Crain, Ellen. Metered-Dose inhalers with spacers vs nebulizers for pediatric asthma. *Arch Pediatr Adolesc Med*. 1995;149:201-205.
- Closa RM, Ceballos JM, Gomez-Papi A, Galiana AS, Gutierrez C, Marti-Henneber C. Efficacy of bronchodilators administered by nebulisers versus spacer devices in infants with acute wheezing. *Pediatric Pulmonology*, 1998; 26: 344-348.
- Connolly M. Inhaler technique of elderly patients: a comparison of metered dose inhalers and large volume spacer devices. *Age Ageing* 1995; 24: 190-192.
- Corr D, Dolovich MB, McCormack D et al. Design and characteristics of a portable breath-actuated particle size selective medical aerosol inhaler. *J Aerosol Sci* 1982; 13:1-7.
- Crim C, Lee B, Lincourt W, Holmes M, Cavanaugh R. In vitro comparison of the performance of valved holding chambers (VHC) for delivery of Ventolin HFA inhalational aerosol. *Am J Resp Crit Care Med* 2003; 167 (No 7): A497.
- Cripps A, Munro AJ, Boles MG et al. Pharmaceutical development studies on a new non-CFC metered dose inhaler. *Drug Deliv Lungs* 1997; VIII: 43-46.
- Cripps A, Riebe M, Sculze M, Woodhouse R. Pharmaceutical transition to non-CFC pressurized metered dose inhalers. *Respir Med* 2000; 94 (Suppl B): S3-S9.
- Crompton GK. Problems patients have using pressurized metered dose inhalers. *Eur J Respir Dis* 1982; 63: 101-104.
- Daley-Yates P, Tournant J, Kunka RL. Comparison of the systemic availability of fluticasone propionate in healthy volunteers and patients with asthma. *Clin Pharmacokinet* 2000; 39 Suppl 1: 39-45.
- Delgado A, Chou KJ, Silver EJ, Crain EF. Nebulisers 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.
- Demirkan K, Tolley E, Mastin T, Soberman J, Burbeck J, Self T. Salmeterol administered by metered dose inhaler plus valved holding chamber. *Chest* 2000; 117: 1314-1318.
- Devadason SG, Walker SL, Owen J. The effect of inhalation technique, spacer volume and training on aerosol delivery from spacers in children. *Proceedings of the American Thoracic Society* 2005; Vol. 2, Abstracts Issue, A376.
- Dewsbury NJ, Kenyon CJ, Newman SP. The effect of handling techniques on electrostatic charge on spacer devices: a correlation with in vitro particle size analysis. *Int J Pharm* 1996; 137: 261-264.
- Dolovich M, Ruffin RE, Corr D, Newhouse MT. Optimal delivery of aerosol from metered dose inhalers. *Chest* 1981; 80S: 911-915.
- Dolovich MB. Physical principles underlying aerosol therapy. *J Aerosol Med* 1989; 2: 171-185.
- Dolovich MB, Ruffin M, Corr D, Newhouse MT. Clinical evaluation of a simple demand inhalation MDI aerosol delivery device. *Chest* 1983; 84(1): 36-41.
- Dolovich MB, Clelland L, Rhem R, Coates G. Salmeterol administration by MDI alone versus MDI plus AeroChamber. *Eur Respir J* 1999
- 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.
- Freigang B. New method of delivering beclomethasone aerosol administration to children under 4 years of age. *Can Med Assoc J* 1977; 17: 1308-1309.
- Giraud V, Roche N. Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability. *Eur Respir J* 2002; 19: 246-251.
- Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention, NHLBI/WHO workshop report March 1993. Bethesda: National Institutes of Health, National Heart, Lung and Blood Institute 1995. Publication number 96-3659B. Revised, 2003.
- Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of Chronic Obstructive Pulmonary Disease. NHLBI/WHO workshop report. Updated 2003. National Institutes of Health, National Heart, Lung and Blood Institute. Publication 2701.
- Gunawardena KA, Sohal T, Jones T et al. The Spacehaler for delivery of salbutamol: a comparison with standard metered dose inhaler plus Volumatic spacer device. *Respir Med* 1997; 91: 311-316.

- Janssens HM, Devadason SG, Hop WCJ, LeSouef PN, De Jongste JC, Tiddens HAWM. Variability of aerosol delivery via spacer devices in young asthmatic children in daily life. *Eur Respir J* 1999; 13: 787-791.
- Jones V, Fernandez C, Diggory P. A comparison of large volume spacer, breath-activated and dry powder inhaler in older people. *Age Ageing* 1999; 28: 481-484.
- Kelly HW, Ahrens RC, Holmes M, Stevens AL, Vandermeer AK, Garris T, Reisner C. Evaluation of particle size distribution of salmeterol administered via metered dose inhaler with and without valved holding chambers. *Ann Allergy Asthma Immunol* 2001; 87(6): 482-487.
- Kim CS, Eldridge MA, Sackner MA. Oropharyngeal deposition and delivery aspects of metered dose inhaler aerosols. *Am Rev Respir Dis* 1987; 135: 157-164.
- König P. Spacer devices used with metered dose inhalers, breakthrough or gimmick? *Chest* 1985; 88: 276-284.
- Kraemer R, Frey U, Sommer CW, Russi E. Short term effect of albuterol delivered via a new auxiliary device in wheezy infants. *Am Rev Respir Dis* 1991; 144: 347-351.
- Leversha AM, Campanella SG, Aickin RP, Asber MI. Costs and effectiveness of spacer versus nebulizer in young children with moderate and severe acute asthma. *The Journal of Pediatrics* 2000. 136: 497-502.
- Levison H, Reilly PA, Worsley GH. Spacing devices and metered dose inhalers in childhood asthma. *J Paediatr* 1985; 107: 662-668.
- Liang J, Asmus MJ, Hochhaus G, Chesrown S, Hendeles L. Differences in inhaled fluticasone bioavailability between holding chambers in children with asthma. *Pharmacotherapy* 2002; 22(8): 947-953.
- Lin Y-Z, Hsieh K-H. Metered dose inhaler and nebuliser in acute asthma. *Archives of Disease in Childhood*, 1995; 72: 214-218.
- Lippmann M, Yeates DB, Albert RE. Deposition, retention and clearance of inhaled particles. *Br J Ind Med* 1980; 37: 337-362.
- Mitchell JP, Nagel MW, Rau JL. Performance of large volume versus small volume holding chambers with chlorofluorocarbon-albuterol and hydrofluoroalkane-albuterol sulfate. *Respir Care* 1999; 44: 38-44.
- Mitchell J, Morton R, Schmidt J, Snyder S, Doyle C, Nagel M. Overcoming electrostatic charge retention in a new valved holding chamber (VHC): In vitro performance comparison with current devices. *Respiratory Drug Delivery* 2004; In press.
- Mitchell J, Nagel M, Dolovich M. Delivery of Beclomethasone Dipropionate (BDP) as a Function of Number of Breaths at Low Tidal Volume in Two Small Volume Holding Chambers for Pediatric Use, *Eur. Resp. J.*, 9S23, 433, 1996
- National Institutes of Health (NIH), National Heart, Lung and Blood Institute. Expert Panel Report: Guidelines for the diagnosis and management of asthma. Revised 2002.
- O'Callaghan C, Barry P. How to choose delivery devices for asthma. *Arch Dis Child* 2000; 82: 185-191.
- Parkin PC, Saunders NR, Diamon SA, Winders PM, Macarthur C. Randomised trial spacer v nebuliser for acute asthma. *Archives of Disease in Childhood*, 1995; 72: 239-240.
- Pierart, F., Wildhaber, J.H., Vrancken, I., Devadason, S.G., LeSouef, P. Washing plastic spacers in household detergent reduces electrostatic charge and greatly improves delivery. *Eur. Respir J*, 13, 673-678 (1999)
- Ross DL, Gabbrio BJ. Advances in metered dose inhaler technology with the development of a chlorofluorocarbon-free delivery system. *J Aerosol Med* 1999; 12 (3): 151-160.
- Salzman GA, Pyszczynski DR. Oropharyngeal candidiasis in patients treated with beclomethasone dipropionate delivered via metered dose inhaler alone and with AeroChamber. *J Allergy Clin Immunol* 1988; 81: 424-428.
- Toogood JH. Complications of topical steroid therapy for asthma. *Am Rev Respir Dis* 1990; 141: S89-S96.
- Wildhaber JH, Devadason SG, Hayden MJ, James R, Dufty AP, Fox RA, Summers QA, LeSouef PN. Electrostatic charge on a plastic spacer device influences the delivery of salbutamol. *Eur Respir J* 1996; 9: 1943-1946.
- Williams JR, Bothner JP, Swanton RD. Delivery of albuterol in a pediatric emergency department. 1996; Vol. 12, No. 4, 263-267.
- Zar HJ, Weinberg EG, Binns HJ, Mann MD. Lung deposition of aerosol – a comparison of different spacers. *Arch Dis Child* 2000;82:495-498.



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