

Aerosol Delivery Devices in the Treatment of Asthma

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Nebulizers convert solutions or suspensions into aerosols with a particle size that can be inhaled into the lower respiratory tract. There are pneumatic jet nebulizers, ultrasonic nebulizers, and mesh nebulizers. Newer nebulizer designs are breath-enhanced, breath-actuated, or have aerosol-storage bags to minimize aerosol loss during exhalation. Nebulizers can be used with helium-oxygen mixture and can be used for continuous aerosol delivery. Increased attention has recently been paid to issues related to the use of a facemask with a nebulizer. The pressurized metered-dose inhaler (pMDI) is a very commonly used device for aerosol delivery. There are press-and-breathe and breath-actuated pMDI designs. Issues related to pMDIs that have received increasing attention are the conversion to hydrofluoroalkane propellant and the use of dose counters. Many patients have poor pMDI technique. Valved holding chambers and spacers are used to improve pMDI technique and to decrease aerosol deposition in the upper airway. In recent years increasing attention has been paid to the issues of electrostatic charge and facemasks related to valved holding chambers. Many newer formulations for inhalation have been released in dry-powder inhalers, which are either unit-dose or multi-dose inhalers. Systematic reviews and meta-analyses have suggested that each of these aerosol delivery devices can work equally well in patients who can use them correctly. However, many patients use these devices incorrectly, so proper patient education in their use is critical. *Key words: aerosol, asthma, dry-powder inhaler, metered-dose inhaler, nebulizer, spacer, valved holding chamber.* [Respir Care 2008;53(6):699–723. © 2008 Daedalus Enterprises]

Introduction

An aerosol is a suspension of liquid or solid particles in a carrier gas. Inhaled drug delivery is an important part of the armamentarium of clinicians caring for patients with asthma. Delivering aerosolized drugs directly into the lungs has the advantages of a higher drug concentration delivered more effectively to the airways, and reduced systemic adverse effects. Some drugs are therapeutically active only when inhaled (eg, most inhaled corticosteroids, cromolyn, salmeterol).¹ The use of inhaled aerosols allows selective treatment of the lungs by achieving a high drug concentration in the airway while reducing systemic adverse effects. Aerosol drug delivery is painless and convenient. One of the most important disadvantages of aerosol therapy is that specific inhalation techniques are necessary for the proper use of the available inhalers. A less-than-optimal technique can result in decreased drug delivery and potentially reduced efficacy. The proliferation of inhalation devices has resulted in a confusing number of choices for the health-care provider and in confusion for both clinicians and patients trying to use these devices correctly.²

Mass median aerodynamic diameter is used to describe a polydisperse aerosol such as that produced by most aerosol-generating devices used in clinical practice. Mass median aerodynamic diameter is the particle size above and below which 50% of the mass of the particles is contained. The higher the mass median aerodynamic diameter, the more particles are of larger diameters. Aerosol particles of 1–5 μm reach the lung periphery. With particle sizes greater than 3 μm there is a shift in aerosol deposition from the lung periphery to the conducting airways. Oropharyngeal deposition increases as particle size increases above 6 μm . Exhaled loss is high with particles less than 1 μm .^{3–5}

Aerosol generators used in asthma management can be categorized as nebulizers, pressurized metered-dose inhalers (pMDIs), pMDI with spacer or valved holding chamber (VHC), and dry-powder inhalers (DPIs). In this paper I will discuss clinically relevant issues related to the performance of each of these categories of aerosol generator.

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I will then address the issue of selection of an aerosol delivery device for an individual patient.

Nebulizers

Pneumatic Jet Nebulizers

A pneumatic nebulizer delivers compressed gas through a jet, which causes a region of negative pressure (Fig. 1).^{6–10} The solution or suspension to be aerosolized is entrained into the gas stream and is sheared into a liquid film. This film is unstable and breaks into droplets because of surface tension forces. A baffle in the aerosol stream produces smaller particles. The aerosol is further conditioned by environmental factors, such as the relative humidity of the carrier gas. Chatburn and McPeck¹¹ developed a conceptual and mathematical model for nebulizer performance that provides a unifying theoretical framework. They created a lexicon to describe the effects of a standardized breathing pattern for evaluating small-volume jet nebulizers (Figs. 2 and 3).

Dead volume, typically in the range 0.5–1 mL, is the solution that is trapped inside the nebulizer. To reduce dead volume, clinicians and patients commonly tap the nebulizer periodically during therapy in an effort to increase nebulizer output.¹² Therapy may also be continued past the point of sputtering, in an attempt to decrease the dead volume, but this is unproductive and not recommended.¹³ Because of evaporative loss within the nebulizer, the solution becomes increasingly concentrated and cools during nebulization.

The most important characteristic of nebulizer performance is the respirable dose, which is the output of droplets in the respirable range, 1–5 μm . Other important characteristics of nebulizer performance include nebulization time, ease of use, ease of cleaning and sterilization, and cost. Nebulization time is important for patient adherence to therapy in the out-patient setting, and clinician super-

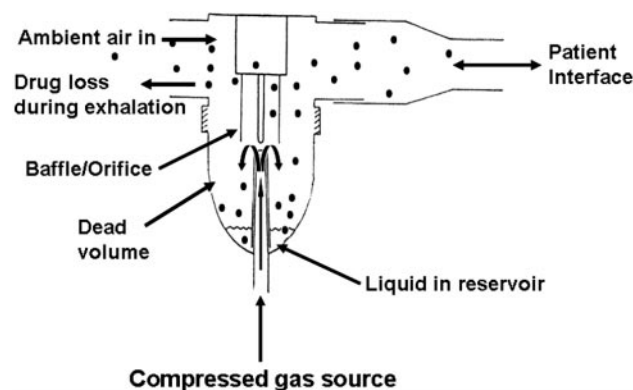


Fig. 1. Functioning of a pneumatic jet nebulizer.

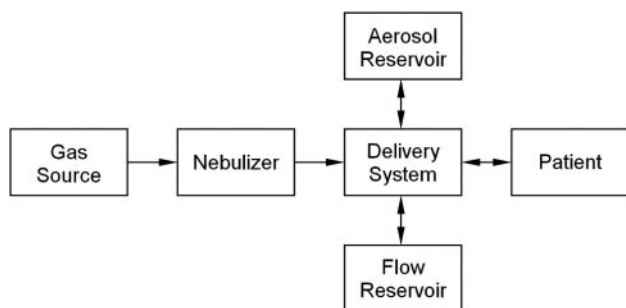


Fig. 2. Schematic of a typical nebulizer system. The gas source powers the nebulizer. The nebulizer is attached to a mouthpiece or facemask. The nebulizer and delivery system act as the reservoir for the generated aerosol, and there may be additional volume devoted to aerosol storage (eg, a reservoir bag or reservoir tubing). The delivery system is also in communication with a reservoir for flow to accommodate the patient's inspiratory flow when it exceeds the source gas flow. The flow reservoir may be a part of the delivery system (eg, reservoir bag) or may simply be a communication to the atmosphere. (From Reference 11)

vision for hospitalized patients. A short nebulization time that delivers an effective dose is desirable.

A fill volume of 4–5 mL is recommended, unless the nebulizer is specifically designed for a smaller or larger fill volume.¹⁴ The volume of some unit-dose medications is suboptimal. Ideally, saline should be added to the nebulizer to bring the fill volume to 4–5 mL, but this might not be practical. The longer nebulization time with a greater fill volume can be reduced by increasing the flow used to power the nebulizer. Increased flow also decreases the droplet size produced by nebulizers; 6–8 L/min is recommended unless the nebulizer is designed specifically for a flow other than that.¹⁴ The flow from many compressors is, unfortunately, too low for optimal nebulizer performance.^{15–21} Several studies have reported performance differences between nebulizers from different manufacturers

and between nebulizers from the same manufacturer.^{14,15,22} Solution temperature also affects nebulizer output; output and droplet size vary directly with temperature.²³

Facemask Versus Mouthpiece

Nebulizer-generated aerosols can be administered via either mouthpiece or facemask. Bronchodilator response occurs with either technique, and some have argued that the selection of patient interface should be based on patient preference.^{24–26} In a retrospective analysis, Mellon et al²⁷ reported that nebulized budesonide inhalation suspension can be administered effectively via either facemask or mouthpiece to young children with persistent asthma. However, it should be appreciated that the nasal passages effectively filter droplets delivered from the nebulizer. Everard et al²⁸ reported a nearly 50% reduction in aerosol delivery to the lungs with nasal inhalation. Kishida et al²⁹ reported that aerosol delivery via mouthpiece resulted in significantly better increase in forced expiratory volume in the first second (FEV₁) than did delivery via facemask. With a nebulizer and mouthpiece, Nikander et al³⁰ reported a mean inhaled mass range of 8.9–12.2%, whereas with a nonsealed facemask the mean inhaled mass range was 5.0–6.9%. The available evidence thus suggests that mouthpiece is preferable to facemask for aerosol delivery. Use of a nose clip is not recommended because of inconvenience, discomfort, and lack of strong evidence to support its use.^{31,32}

Although it is better to use a mouthpiece, nebulizers are often used with facemasks when the patient is sick or uncooperative. Although tight-fitting masks are thought to improve drug delivery, recent studies indicate that facemask seal can impact facial and eye deposition of aerosol.^{33–35} Passage of aerosol around or through a facemask can result in deposition on the face

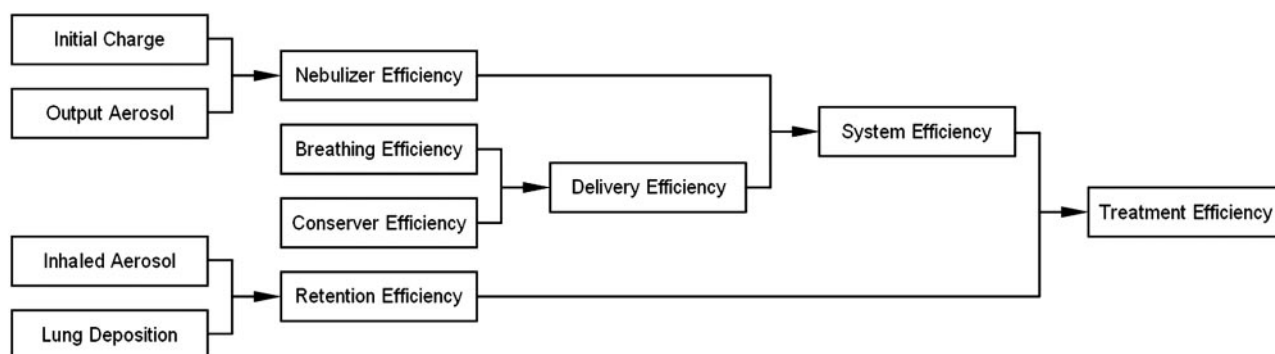


Fig. 3. Schematic of nebulizer performance efficiencies. Treatment efficiency (TE) depends on system efficiency (SE) and retention efficiency (RE): $TE = RE \times SE$. System efficiency depends on delivery efficiency (DE) and nebulizer efficiency (NE): $SE = DE \times NE$. Delivery efficiency depends on conserver efficiency (CE) and breathing efficiency (BE): $DE = CE + BE$. Nebulizer efficiency is the ratio of output aerosol (OE) to initial charge (IC): $NE = OA/IC$. Retention efficiency is the ratio of lung deposition (LD) to inhaled aerosol (IA): $RE = LD/IA$. (From Reference 11.)

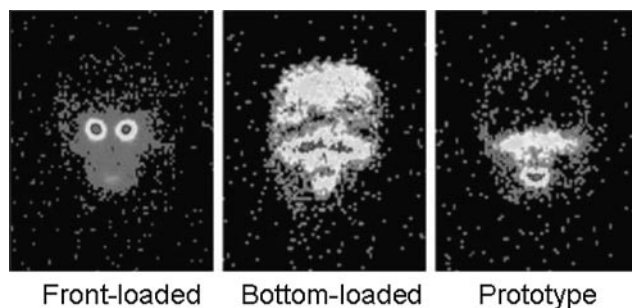


Fig. 4. Scintigraphic images of a face model following a nebulizer treatment with a tight-fitting front-loaded facemask with predominant eye deposition (left), bottom-loaded mask with deposition all over the face (middle), and a prototype mask with eye deposition virtually eliminated (right). (From Reference 42, with permission.)

and in the eyes³⁶⁻⁴¹ The nebulizer aerosol can be inserted straight into the mask (top-loaded), or vertically from below (bottom-loaded). Smaldone et al⁴² used a pediatric face facsimile and radiolabeled saline aerosols with front-loaded and bottom-loaded masks to test aerosol delivery with a pediatric breathing pattern (Fig. 4). Aerosol deposition on the face and eye regions varied widely. With some commercial masks facial deposition was nearly equal to inhaled aerosol mass. Tight-sealing masks increased inhaled aerosol mass but also increased deposition in the eyes. Leaks along the nasal-labial fold resulted in high local linear velocities directed into the eyes. Front-loaded masks were more efficient than bottom-loaded masks with respect to inhaled mass, but favored eye deposition (Fig. 5). When the mask was modified with vents and specialized cutouts in the eye regions, facial and eye deposition was minimized.

An alternative technique for aerosol delivery to the pediatric patient is “blow-by,” in which the clinician aims the aerosol flow toward the patient’s face instead of applying a mask. The rationale is that children do not cooperate with a mouthpiece or mask, so if the aerosol is blown toward the child’s face, perhaps enough of the dose will be inhaled for a therapeutic effect. However, *in vitro* studies have reported that the inhaled mass of albuterol is significantly reduced when the mask is moved away from the face.^{43,44} As stated in a recent editorial, “blow-by is a waste of time, a waste of money, and an unnecessary irritation for the distressed child.”⁴⁵ It should also be noted that aerosol delivery to a distressed child is minimal if the child is crying.⁴⁶

Effect of Formulation

It is not commonly appreciated that the drug formulation can affect nebulizer performance. MacNeish et al⁴⁷ reported that nebulizer output was significantly greater with a formulation that contained a preservative, probably



Fig. 5. Unilateral left dilated pupil, which did not react to light, caused by the inadvertent aerosolization of ipratropium bromide into the eye. (From Reference 37, with permission.)

due to the preservative’s surface activity. Large droplets adhered to the walls of the nebulizer with the preservative-free formulation, whereas foaming was seen with the preservative-containing formulation. Berlinski and Waldrep⁴⁸ reported that co-nebulization of albuterol with other drugs can affect aerosol output and aerosol characteristics. Others have also reported effects of drug formulation on nebulizer output.^{49,50} It is interesting to note that, unlike nebulizers, pMDIs have always been tested and approved as a drug-delivery system combination.

Newer drug solutions (eg, pentamidine, ribavirin, recombinant human deoxyribonuclease, tobramycin) have also been approved for specific nebulizers. The package insert for the recently released nebulizer solution formulation of formoterol states that, “Perforomist inhalation solution should be administered by the orally inhaled route via a standard jet nebulizer connected to an air compressor.” (http://perforomist.com/consumer/documents/perforomist_prescribing_information.pdf) However, that same package insert states, “Perforomist. . . was evaluated in a 12-week. . . trial. . . administered twice daily via a Pari LC Plus nebulizer with a Proneb Ultra compressor.” Although the label does not specify a nebulizer or compressor, the clinician is left to wonder whether the same clinical results will occur if a nebulizer or compressor other than those used in the clinical trials is used.

Another issue is the compatibility of formulations that can be mixed together in the nebulizer. Clinicians and patients prefer to mix formulations to decrease the time required for the treatment. Before mixing solutions of various formulations in the nebulizer cup, however, the clinician must be certain that the combination is compatible.⁵¹⁻⁵⁴

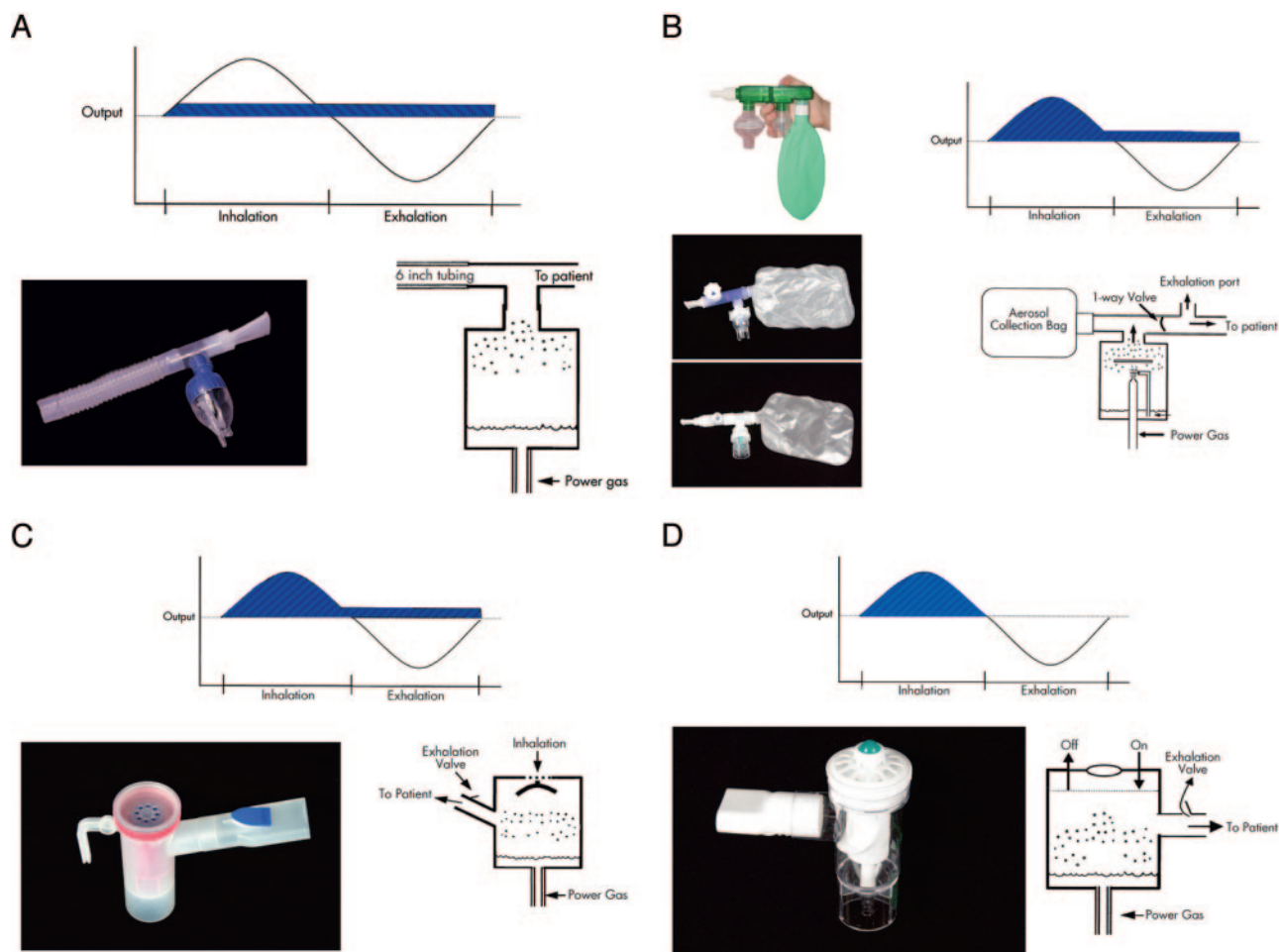


Fig. 6. Nebulizer designs. A: Jet nebulizer with reservoir tube. B: Nebulizer with aerosol collection bag. C: Breath-enhanced nebulizer. D: Breath-actuated nebulizer. In each diagram, the device's aerosol output is indicated by the striped area. From: Hess DR, Myers TR, Rau JL. A guide to aerosol delivery devices. Irving TX: American Association for Respiratory Care; 2007. Available from http://www.aarc.org/education/aerosol_devices/aerosol_delivery_guide.pdf.

Designs to Decrease Aerosol Waste During Exhalation

For many years it has been a common practice to use a T-piece and corrugated tubing as an aerosol reservoir for a small-volume nebulizer.⁵⁵ An extension of this design uses a bag to store aerosol during exhalation (Fig. 6).⁵⁶ In an *in vitro* study, Rau et al⁵⁷ reported a large amount of drug trapped in the storage bag. Corcoran et al⁵⁸ reported that the inhaled dose increased approximately 28%, when compared to a standard nebulizer, despite significant deposition in the storage bag. Mason et al⁵⁹ compared a conventional nebulizer to one with a storage bag in 9 normal subjects and reported better lung deposition, less deposition in the gastrointestinal tract, and less drug loss to the environment with the nebulizer that used a storage bag. In another study by Mason et al,⁶⁰ a nebulizer that used a storage bag was compared to a conventional nebulizer for

bronchodilator delivery in patients with chronic obstructive pulmonary disease (COPD). In that study the pulmonary deposition and therapeutic effect were similar with the nebulizer that had a storage bag and the conventional nebulizer. Hoffman and Smithline⁶¹ compared a nebulizer with a storage bag to a conventional nebulizer for bronchodilator delivery in patients with acute bronchospasm presenting to an emergency department. They reported a greater improvement in peak flow with the nebulizer that had the storage bag.

The traditional nebulizer design incorporates the nebulizer sidestream to the airflow of the patient. Breath-enhanced nebulizers use a mainstream design with valves. In this valved open-vent design, the patient breathes through the nebulizer during inhalation, which enhances the nebulizer output. During exhalation, a one-way valve directs patient flow away from the nebulizer chamber. Several studies reported greater pulmonary deposition with this

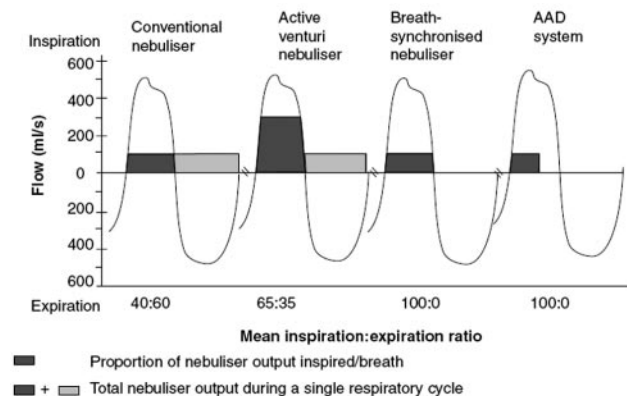


Fig. 7. Schematic of the flow and inspiration/expiration ratios with 4 types of jet nebulizer. The drug available for inhalation is indicated by the darker shaded areas. The lighter shaded areas indicate the aerosol loss to the ambient air. These 2 areas are used to calculate the mean inspiration/expiration ratios for the aerosol output of the various types of nebulizer. AAD = adaptive aerosol delivery system. (From Reference 69, with permission.)

design than with a conventional nebulizer.⁶²⁻⁶⁵ Leung et al⁶⁶ reported that, compared to breath-actuated designs, a breath enhanced nebulizer had the shortest treatment time.

Aerosol waste during the expiratory phase can be eliminated if the nebulizer is active only during the inspiratory

phase; this principle is used in the breath-actuated (ie, breath-synchronized) dosimetric nebulizer design.⁸ Several studies have reported reduced drug waste with this nebulizer design.^{30,57,66-68} A variation on this method is adaptive aerosol delivery,⁶⁹⁻⁷² which was developed to reduce the variability of the delivered dose, reduce the waste of aerosol to the environment during exhalation, and improve patient adherence to treatment and use of the device. The device analyzes the patient's breathing pattern, which determines the timing of the aerosol pulse during inhalation (Fig. 7). The airflow pressure changes of the first 3 breaths are used to determine the correct starting point for aerosol delivery during inhalation. Monitoring of the preceding 3 breaths continues throughout the treatment, and the device continually adapts to the patient's breathing pattern.

Mesh Nebulizers

Several manufacturers have developed aerosol devices that use a mesh or plate that has multiple apertures to produce an aerosol (Fig. 8).⁷³⁻⁷⁵ These devices use a vibrating mesh or a vibrating horn. In the case of the vibrating mesh (eg, Aerogen Aeroneb, Nektar, San Carlos, California; eFlow, Pari, Richmond, Virginia), contraction and

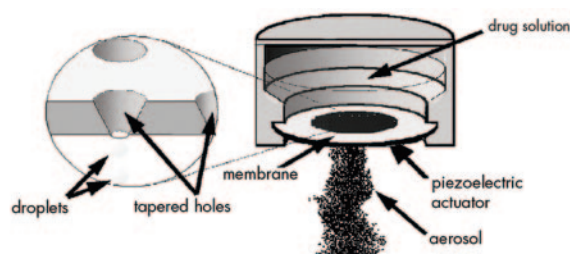


Fig. 8. Mesh nebulizers. Top: Principle of operation. Bottom: Representative commercially available mesh nebulizers. From: Hess DR, Myers TR, Rau JL. A guide to aerosol delivery devices. Irving TX: American Association for Respiratory Care; 2007. Available from http://www.aarc.org/education/aerosol_devices/aerosol_delivery_guide.pdf.

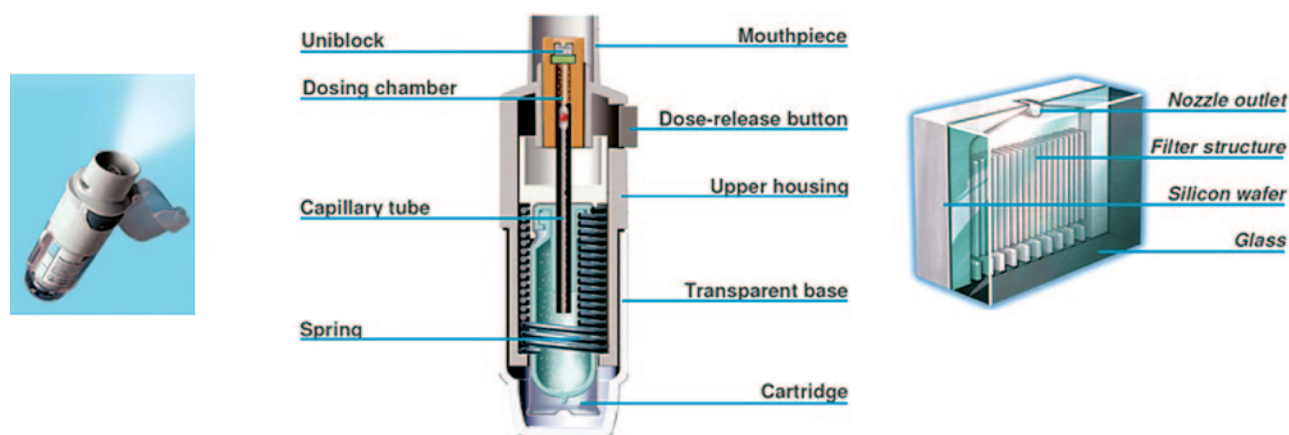


Fig. 9. Left: Respimat Soft Mist Inhaler. Center: Components of Respimat. Right: The uniblock, which is the core element of the Respimat. (Courtesy of Boehringer Ingelheim)

expansion of a vibrational element produces an upward and downward movement of a domed aperture plate. The aperture plate contains up to 1,000 tapered holes. The holes have a tapered shape with a larger cross-section on the liquid side and a smaller cross-section on the side the droplets emerge. The medication is placed in a reservoir above the domed aperture plate. Sound pressure is built up in the vicinity of the membrane, creating a pumping action that extrudes solution through the holes in the plate to produce an aerosol. The aerosol particle size and flow are determined by the exit diameter of the aperture holes. The size of the holes in the plate can be modified for specific clinical applications.

In the vibrating horn system (eg, Omron, Omron Healthcare, Bannockburn, Illinois) a piezoelectric crystal vibrates at a high frequency when electrical current is applied, and the vibration is transmitted to a transducer horn that is in contact with the solution. Vibration of the transducer horn causes upward and downward movement of the mesh plate, and the liquid passes through the apertures in the plate and forms an aerosol. Nebulization with a mesh nebulizer is dependent on fluid characteristics;^{76,77} these nebulizers may be unsuitable for viscous fluids, which suggests that matching the formulation to the device may be important for these aerosol generators. Mesh technology can be coupled with adaptive aerosol delivery, as in the I-neb (Respironics, Murrysville, Pennsylvania).⁷²

Respimat Soft Mist Inhaler

The Respimat Soft Mist Inhaler (Boehringer Ingelheim, Germany), which is not yet available in the United States, delivers a metered dose of medication as a fine mist (Fig. 9).⁷⁸⁻⁸⁰ Medication delivered by the Respimat is stored in a collapsible bag in a sealed plastic container inside the cartridge. With each actuation, the correct dosage is drawn

from the inner reservoir and the flexible bag contracts accordingly. A twist of the inhaler's base compresses a spring. A tube slides into a canal in the cartridge, and the dose is drawn through the tube into a micro-pump. When the dose-release button is pressed, the energy released from the spring forces the solution through the "uniblock" and a slow-moving aerosol is released. The extremely fine nozzle system of the uniblock is the core element of the Respimat. When the medication solution is forced through the nozzle system, 2 jets of liquid emerge and converge at an optimized angle, and the impact of these converging jets generates the aerosol. The aerosol produced by the Respimat moves much slower and has a more prolonged duration than an aerosol cloud from a pMDI.⁸¹ A dose indicator shows how many doses are left. The Respimat, compared to a pMDI with fenoterol plus ipratropium bromide, provides equivalent bronchodilation at half the cumulative dose, compared to a conventional pMDI in asthmatic patients.⁸² Scintigraphy studies have shown that, compared to a pMDI, lung deposition is doubled and oropharyngeal deposition is reduced.⁸³⁻⁸⁵ Low deposition on the face, and especially in the eyes, occurs when the Respimat is fired accidentally outside the body, or is fired at the same time as the patient exhales.⁸⁶ It has been reported that a majority of patients preferred Respimat to pMDI.⁸⁷

Ultrasonic Nebulizers

An ultrasonic nebulizer converts electrical energy to high-frequency ultrasonic waves. Small-volume ultrasonic nebulizers are commercially available for delivery of inhalable bronchodilators. Use of these devices is hampered by their tendency for mechanical malfunction. A potential issue with ultrasonic nebulizers is the possibility of drug inactivation by the ultrasonic waves, although this has not been shown to occur with common aerosol medications.

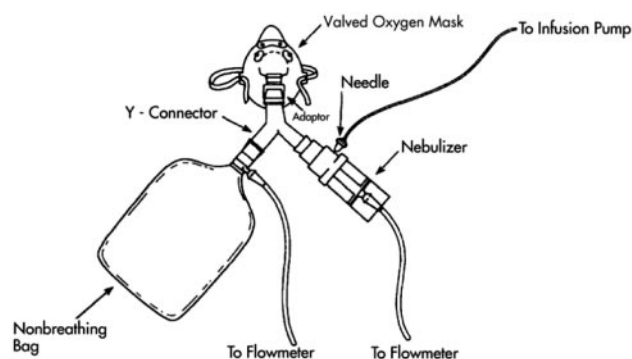


Fig. 10. Setup for continuous aerosol therapy. (From Reference 96, with permission.)

The ultrasonic nebulizer is inefficient in nebulizing a suspension.⁸⁸

Continuous Aerosol Delivery

Continuous aerosolized bronchodilators are occasionally used in the treatment of acute asthma. A typical dose range for continuous albuterol is 5–15 mg/h.⁸⁹ The available evidence suggests that this therapy is safe and at least as effective as intermittent nebulization.^{2,90} Several configurations have been described for continuous nebulization,⁹¹ including frequent refilling of the nebulizer,^{92–95} use of a nebulizer and infusion pump (Fig. 10),^{96–101} and use of a large-volume nebulizer.^{95,102–105} Berlinski and Waldrep¹⁰⁶ reported consistent and adequate aerosol production from a large-volume nebulizer over a 4-hour period. Reisner et al,¹⁰⁷ however, reported more consistent aerosol delivery with a small-volume nebulizer attached to an infusion pump than with a large-volume nebulizer. A commonly used large-volume nebulizer for this therapy is the High-output Extended Aerosol Respiratory Therapy (HEART) nebulizer. Raabe et al¹⁰⁸ and Kelly et al¹⁰⁹ reported that a large-volume HEART nebulizer maintained consistent output up to 8 hours and provides an acceptable method for delivering continuous aerosol through an infant ventilator

circuit. McPeck et al¹¹⁰ reported that albuterol delivery from the HEART nebulizer was significantly less than the target dose from the manufacturer's recommended setup.

Use of Heliox With Nebulizers

Heliox is a gas mixture of helium (60–80%) and oxygen, which is used to improve airflow in patients with partial airway obstruction.¹¹¹ In patients with asthma, heliox has the potential benefit of being able to carry aerosols deeper (than air or oxygen) into the distal airways during severe airway obstruction.^{112–115} Clinical studies of heliox as the nebulizer driving gas for delivery of aerosolized asthma medications have reported conflicting results,¹¹⁶ for which there are several possible explanations. One issue relates to the flow used to power the nebulizer. Hess et al¹¹⁷ found that the flow of heliox with 80% helium and 20% oxygen must be increased by about 50% to generate optimal-size respirable particles. Corcoran and Gamard¹¹⁸ found that, compared to 10 L/min of oxygen, 12 L/min of a heliox with 70% helium and 30% oxygen is needed to generate an equivalent mass of particles < 3 μm . O'Callaghan et al¹¹⁹ reported that, with a vibrating-mesh nebulizer, the total output was significantly higher when heliox (rather than air) was used as the delivery gas. With a breath-enhanced nebulizer, a much higher driving flow of heliox (compared to air) was required to deliver a similar dose of drug.

Another issue is entrainment of room air and the consequent dilution of the heliox. If heliox is used to power the nebulizer but heliox is not provided in the additional gas that is entrained, dilution with air will decrease the inspired helium concentration and reduce the benefit of the heliox. Accordingly, a closed system, or one with sufficiently high flow, should be used to minimize air entrainment. Finally, the studies may have simply been underpowered to detect differences, which makes the case for a meta-analysis.

I conducted a meta-analysis of 4 studies that compared FEV₁ changes with aerosolized bronchodilator delivered

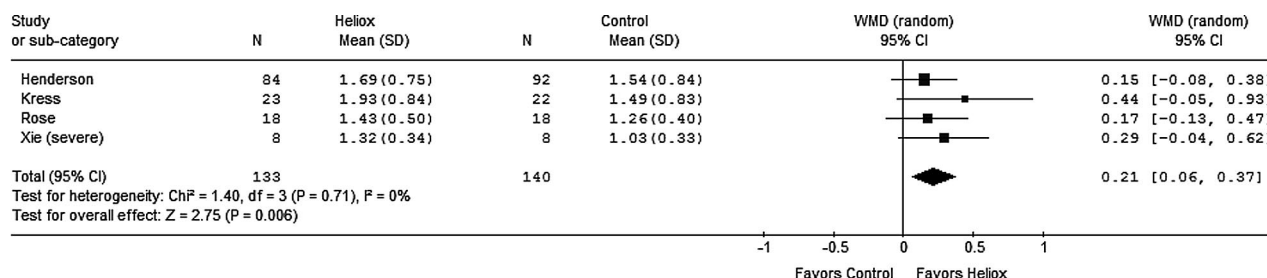


Fig. 11. Meta-analysis of physiologic studies^{120–123} of the effect of bronchodilator delivery with and without helium-oxygen mixture (heliox) on forced expiratory volume in the first second (FEV₁). WMD = weighted mean difference. CI = confidence interval. Chi^2 = chi-square. df = degrees of freedom. I^2 = inconsistency variable, which describes the percentage of total variation among the studies that is due to heterogeneity rather than chance.

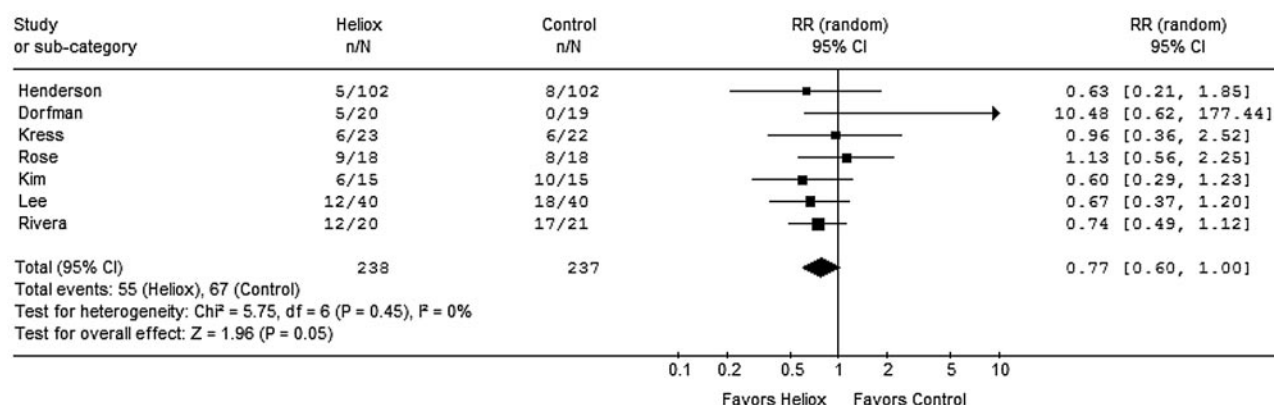


Fig. 12. Meta-analysis of studies^{120-122,124-127} that evaluated the effect of bronchodilator delivery with and without helium-oxygen mixture (heliox) on hospital admission from the emergency department. CI = confidence interval. χ^2 = chi-square. df = degrees of freedom. I^2 = inconsistency variable, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance.

with heliox or air/oxygen.¹²⁰⁻¹²³ There was a significantly greater improvement in FEV₁ with heliox ($p = 0.006$) (Fig. 11). I also conducted a meta-analysis of 7 studies that compared hospital admission rate in patients with asthma who received aerosolized bronchodilator delivered with heliox or air/oxygen in the emergency department.^{120-122,124-127} The admission rate was significantly lower with heliox ($p = 0.05$) (Fig. 12). Although these meta-analyses require confirmation by appropriately designed clinical trials, they suggest that heliox might benefit the delivery of aerosolized bronchodilators in patients with acute asthma.

A systematic review by Ho et al¹²⁸ concluded that there were insufficient data on whether heliox can avert tracheal intubation, or can change intensive care admission rate, hospital admission rate, duration of hospitalization, or mortality. In another systematic review, Rodrigo et al¹²⁹ concluded that there were insufficient data on whether heliox can avert tracheal intubation, or can change intensive care admission rate, hospital admission rate, duration of hospitalization, or mortality. But they also pointed out that their conclusions were based on between-group comparisons and small studies, and these results should be interpreted with caution. Unlike the systematic reviews by Ho et al¹²⁸ and Rodrigo et al,¹²⁹ I looked only at the effects of the use of heliox to deliver aerosolized bronchodilators in the meta-analysis I report above. Moreover, I included studies that were published since the time of these 2 meta-analyses, which increases the power of the analysis. The National Asthma Education and Prevention Program's 2007 Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma¹ recommends that heliox-driven albuterol nebulization be considered for patients who have life-threatening exacerbations and for patients whose exacerbations remain in the severe category after 1 hour of intensive conventional therapy. However, that recommen-

dation received an evidence grade of B (randomized controlled trials with a limited body of data).

Cleaning and Disinfecting Nebulizers

Patients should be taught how to disinfect nebulizers used in the home. After each treatment the patient should shake the remaining solution from the nebulizer cup. The nebulizer cup should be rinsed with either sterile or distilled water and left to air dry on an absorbent towel. Once or twice a week, the nebulizer should be disassembled, washed in soapy tap water, and disinfected with either a 1.25% acetic acid (white vinegar) mixture or a quaternary ammonium compound at a dilution of 1 ounce to one gallon of sterile or distilled water. The acetic acid soak should be at least 1 hour, but a quaternary ammonium compound soak needs only 10 min. Acetic acid should not be reused, but the quaternary ammonium solution can be reused for up to one week.¹³⁰ Pneumatic nebulizers have been reported to function correctly in repeated uses provided that they are cleaned after each use, rinsed, and air dried.¹³¹ Nebulizers for hospital use are disposable, single-patient-use and they should be changed at the conclusion of the dose, every 24 hours, or when visibly soiled. Nebulizers should not be rinsed with tap water, but may be rinsed with sterile water and allowed to dry between treatments.

Metered-Dose Inhalers

The pMDI is a very common device for delivering inhaled drugs.¹³²⁻¹³⁵ Although these devices are often given the acronym MDI, pMDI is preferable to distinguish them from DPIs. The key components of a pMDI are the canister, propellant, drug formulation, metering valve, and actuator (Fig. 13).¹³⁵

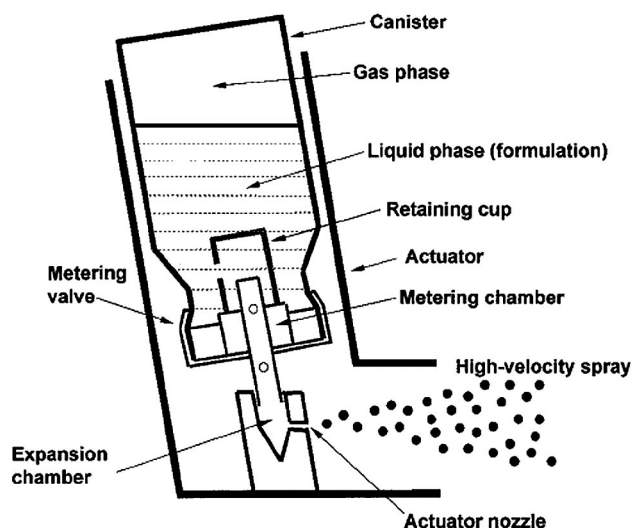


Fig. 13. Components of a pressurized metered-dose inhaler. (From Reference 135.)

Aluminum is the preferred pMDI canister material, and a coating on the canister's inner surface may help prevent adhesion of drug particles and chemical degradation of drug.¹³⁵ The traditional pMDI propellant has been chlorofluorocarbon (CFC), but soon CFC will be replaced by hydrofluoroalkane (HFA), as discussed in detail below. The formulations in pMDIs are either suspensions or solutions.¹³⁵ The metering valve is the most critical component of the pMDI. The pMDI canister is used in the inverted position, with the valve below the container, so it refills from the force of gravity.

It is important to prime the metering chamber before use. When a pMDI is primed, stored valve-down for 3 hours, shaken, and then actuated, the drug content of the first dose may be erratic.^{136,137} Although improvements in valve design have reduced the need for priming, it remains prudent to prime the pMDI if it has not been used recently.^{138,139} For example, the Flovent HFA (GlaxoSmith-Kline, Research Triangle Park, North Carolina) pMDI has the following instructions:

Flovent HFA should be primed before using for the first time, by releasing 4 test sprays into the air, away from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has not been used for more than 7 days, or when it has been dropped, prime the inhaler again by shaking well for 5 seconds before each spray and releasing 1 test spray into the air, away from the face. (http://www.fda.gov/medwatch/safety/2006/oct_pis/floventhfa_ppi.pdf)

Shaking before actuation is also important. Everard et al¹⁴⁰ reported that not shaking a CFC pMDI before use

reduced the delivered dose by 26% and the respirable dose by 36%. They also showed that storing the pMDI stem-down reduced the delivered dose on the first actuation by 25%, despite shaking the pMDI before use.

The actuator nozzle is critical to aerosol formation.^{135,141-143} When the dose leaves the actuator nozzle, the liquid ligaments embedded in the propellant vapor are pulled apart by aerodynamic forces to form a dispersion of liquid droplets. Evaporation of the propellant cools the droplets so that the spray usually feels cold on the back of the throat. As discussed below, however, this effect is less with HFA pMDIs.

The pMDI has the practical benefits of small size, portability, convenience, unobtrusiveness, and relatively low cost.¹³⁵ pMDIs have multi-dose capability and a dose can be delivered quickly. The contents are protected from contamination by pathogens. Drug delivery, however, is highly dependent on patient technique; misuse can result in a suboptimal (even zero) lung deposition. Even with good technique the lung deposition is < 20%. Most of the dose is deposited in the oropharynx.¹⁴⁴ High oropharyngeal deposition of glucocorticosteroids can cause localized adverse effects (dysphonia and candidiasis) and systemic adverse effects.^{145,146} Immediate gargling and rinsing after inhalation is useful for removal of drugs following inhalation of corticosteroids.¹⁴⁷

Breath-Actuated Metered-Dose Inhalers

A breath-actuated pMDI solves the problem of patient coordination of actuation with inhalation. Breath-actuated pMDIs sense the patient's inhalation through the actuator and actuate the inhaler automatically in synchrony.¹³⁵ Some patients find breath-actuated pMDIs easier to use than conventional pMDIs and may prefer them over other devices.^{148,149} The breath-actuated pMDI Autohaler (3M, St Paul, Minnesota) requires a flow of about 27 L/min for actuation.¹⁵⁰ Fergusson et al¹⁵¹ showed that 97% of patients with severe airflow limitation were able to actuate the Autohaler on their first or second attempt. Chapman et al¹⁴⁹ reported that the breath-actuated pMDI was used successfully 64% of the time, compared to 36% with a conventional pMDI by a group of elderly subjects. Newman et al¹⁴⁴ reported a 3-fold increase in lung deposition (21% vs 7%) with the breath-actuated Autohaler, compared to a conventional pMDI, in subjects with poor pMDI coordination. Outside the United States there are newer drug formulations, such as budesonide, for breath-actuated pMDIs.¹⁵²

Hydrofluoroalkane Propellant

The transition from CFC to HFA propellants is due to concern about the detrimental effects of CFCs on the ozone

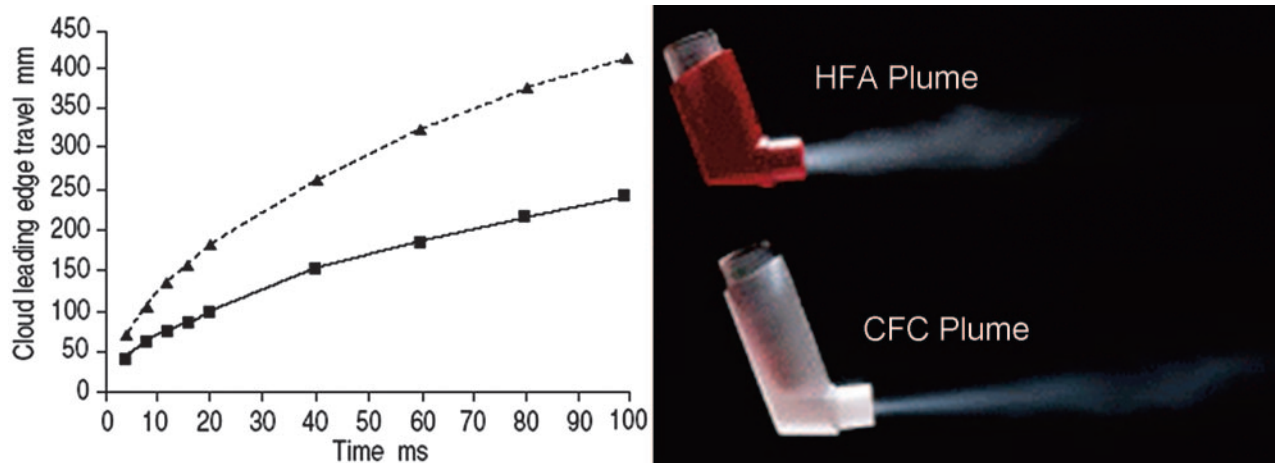


Fig. 14. Left: Distance traveled by the leading edge of the aerosol cloud from a pressurized metered-dose inhaler with hydrofluoroalkane (HFA) propellant (squares) versus chlorofluorocarbon (CFC) propellant (triangles). (From Reference 154, with permission.) Right: CFC and HFA plumes. (Courtesy of Teva Specialty Pharmaceuticals, Jerusalem, Israel.)

layer in the stratosphere, which filters ultraviolet-B radiation. Without the ozone layer, ultraviolet-B radiation would increase the risk of disease, increase global warming, and cause a general disruption of ecological processes. CFCs have been clearly shown to deplete ozone in the stratosphere. The Montreal Protocol, adopted in 1987, requires a complete phase-out of the CFCs. In 2005, the Food and Drug Administration ruled that the sale of CFC albuterol pMDIs would be prohibited in the United States after 2008. HFAs are greenhouse gases, but their greenhouse-gas potential is less than that of CFCs, and the contribution of the HFAs from medical use is negligible.^{139,153}

Some HFA pMDIs resemble their precursor CFC pMDIs, whereas some are quite different from those they replaced. HFA pMDI albuterol formulations are as effective as their CFC counterparts.¹⁵³ Proventil HFA (3M Pharmaceuticals, St Paul, Minnesota), the first CFC-free pMDI, is comparable to the CFC pMDI albuterol in that it has the same emitted dose and same particle-size distribution as the CFC albuterol inhaler. However, because of the redesigned formulation, valve, and actuator, the HFA formulation has a warmer spray temperature and less impact force at the back of the throat. Moreover, Proventil HFA does not suffer a loss of dose when the inhaler is stored inverted, it is not subject to loss of dose in a cold climate, and there is less dose variability at the end of the canister's life.¹³⁹ Because of the differences in the propellant elastomers and excipients, the HFA pMDI has a different taste. The HFA pMDI also has a different feel in the mouth because the spray emitted from the actuator has less force and a smaller plume (Fig. 14).¹⁵⁴ HFA pMDIs may provide greater pulmonary deposition than CFC pMDIs.¹⁵⁵ Although no difference in serum albuterol level is detectable after 2 puffs,¹⁵⁶ the HFA pMDI produces a higher

plasma albuterol level than the CFC pMDI inhaler after 12 puffs.¹⁵⁷ HFA steroid inhalers were engineered to generate aerosol particles with an average size of $1.2 \mu\text{m}$, to more effectively reach the lower respiratory tract and have less oropharyngeal deposition (Fig. 15),^{158,159} which improves clinical outcomes.¹⁴⁶

Each puff of Proventil HFA releases $4 \mu\text{L}$ of ethanol, which may be of concern for patients who abstain from alcohol.¹⁵³ A breath alcohol level of up to $35 \mu\text{g}$ per 100 mL may be detected for up to 5 min after 2 puffs of Proventil HFA.¹⁶⁰ ProAir HFA (Ivax Pharmaceuticals, Miami, Florida) and Xopenex HFA (Sepracor, Marlborough, Massachusetts) also contain ethanol. HFA propellant may cause false positive readings in gas-monitoring systems, because the infrared spectra of HFA overlap with common anesthetic gases.¹⁶¹ Ventolin HFA contains no excipients other than the propellant, but has a greater affinity for moisture than other HFA inhalers and is therefore packaged in a moisture-resistant protective pouch that contains a desiccant and has a limited shelf life once it is removed from the pouch.¹⁵³

Clogging of HFA pMDI albuterol actuators has been reported.¹⁶² They should be cleaned at least once a week by removing the metal canister, running warm water through the plastic actuator for 30 s, shaking the actuator to remove water, and then allowing it to air dry. The actuator should be cleaned more frequently if a reduction in the force of emitted spray is noted.¹⁵³ Most patients and health-care providers are unaware of the need for regular cleaning of HFA pMDIs. In a survey by Slader et al,¹⁶³ 77% of the patients were unaware of the need to clean the actuator, and only 10% actually followed this procedure.

An issue that has received little attention is the cost of HFA pMDIs. HFA pMDI formulations cost about 3 times more than their CFC counterparts. In the United States,

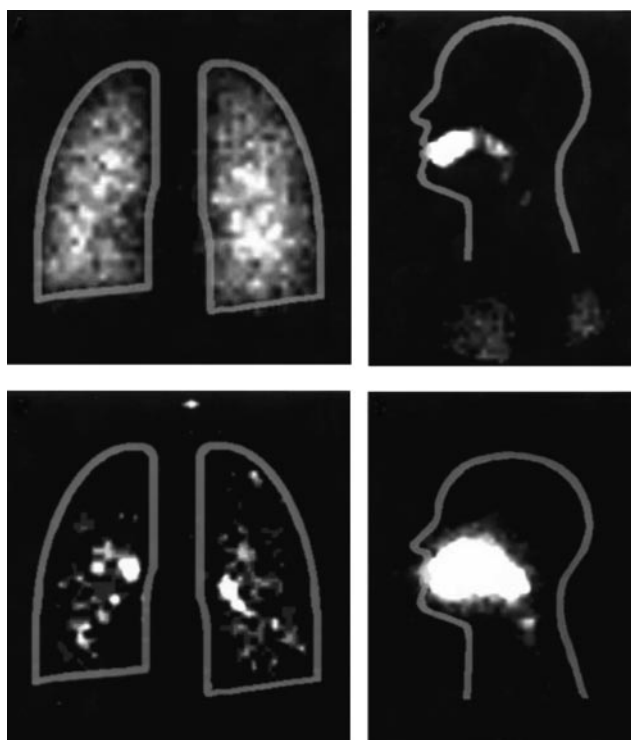


Fig. 15. Top: Lung deposition (left) and oropharyngeal deposition (right) with a beclomethasone pressurized metered-dose inhaler (pMDI) with hydrofluoroalkane (HFA) propellant (top) versus (bottom) a beclomethasone pMDI with chlorofluorocarbon (CFC) propellant (bottom). (From Reference 158, with permission.)

about 52 million prescriptions for albuterol are filled annually.¹⁵³ Others have estimated that approximately 500 million pMDIs are produced annually.¹⁶⁴ The conversion from CFC to HFA is likely to substantially impact health care costs.

Dose-Counting

Although many pMDIs contain more than the labeled number of doses, drug delivery per actuation may be very inconsistent and unpredictable after the labeled number of actuations. Beyond the labeled number of actuations, propellant can release an aerosol plume that contains little or no drug—a phenomenon called tail-off.¹⁶⁵ A practical problem for patients who use pMDIs is the difficulty of determining the number of doses remaining in the device. Ideally the patient knows the number of doses in a full pMDI and keeps track of how many actuations have been used. However, Ogren et al found that 54% of patients were unaware of the number of doses in a full pMDI, and only 8% reported counting the doses used.¹⁶⁶ Rubin and Durotoye¹⁶⁷ asked clinic patients how they determined when their pMDI was empty, and 72% reported that the pMDI was empty if there was no sound when the canister was

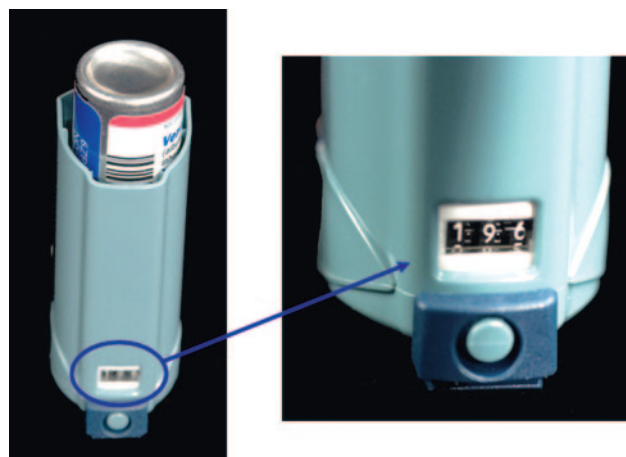


Fig. 16. Dose counter on a hydrofluoroalkane (HFA) pressurized metered-dose inhaler (Ventolin HFA).

actuated. CFC pMDI canisters typically delivered 86% more actuations than the nominal number of doses, and HFA pMDI canisters delivered 52% more. Holt et al¹⁶⁸ reported that, by shaking the canister, patients overestimated the amount remaining in the pMDI by about 40 doses. Floating the canister in water has been suggested as a way to determine when it is depleted, but this method is unreliable and should not be used.^{167,169-171} Sander et al¹⁷² reported that only 36% of bronchodilator users reported ever having been told to keep track of pMDI doses used. Further, 25% reported having found their pMDI empty during an asthma exacerbation (several of those patients had to call 911), and 82% of them considered their pMDI empty when absolutely nothing came out.

In 2003, the Food and Drug Administration released a guidance document that recommended that manufacturers integrate a dose-counting device into new pMDIs (<http://www.fda.gov/cder/guidance/5308fnl.htm#top>). Several pMDIs have integrated dose counters (Ventolin HFA and Flovent HFA) (Fig. 16). The counter does not require batteries, and the overall size, shape, and weight of the pMDI with the counter is similar to the original pMDI. The force needed to actuate the pMDI with the counter is similar to that of the standard pMDI, and no extra steps are required to use or clean it. Seth et al¹⁷³ evaluated the performance and patient satisfaction of a pMDI with an integrated dose counter. Concordance between counter and diary recordings was high (discrepancy rate of 0.94%) and the incidence of the device firing without a change in the counter reading was low (0.13%). Overall, 95% of patients were satisfied with the dose counter and 92% agreed that it would help prevent them from running out of medication.

Add-on devices can be used that count down the number of puffs released from a pMDI. Examples include the Doser (MediTrack Products, Hudson, Massachusetts) and the MD Turbo (Team Pharmaceuticals, Morris-



Fig. 17. Add-on devices to count doses from pressurized metered-dose inhalers. Left: MD Turbo. (Courtesy of Teamm Pharmaceuticals, Morrisville, North Carolina.) Right: Doser. (Courtesy of Medi-Track Products, Hudson, Massachusetts.)

ville, North Carolina) (Fig. 17). The Doser is a small device with a plastic sleeve that allows it to be placed on the end of the pMDI canister. When pressed, an electromechanical switch completes a circuit, recording the actuation. The primary counter is preset to the total number of actuations in the canister and subtracts one with each actuation. A second counter displays the total number of actuations per day and resets at midnight. The history of actuations per day for the prior 45 days can be displayed by scrolling. With the MD Turbo, the pMDI canister is loaded into the device. According to the manufacturer, the MD Turbo is compatible with over 90% of the pMDIs dispensed in the United States. It includes an electronic dose counter that shows the patient how much medication is left in the inhaler. It is breath-actuated at a flow of 30–60 L/min, so it synchronizes the release of medication with the patient's inspiration, to address the problem of poor coordination.

Simmons et al¹⁷⁴ reported that the Doser provides an accurate measure of pMDI use with most commonly prescribed medications and may be useful for monitoring pMDI use. Julius et al¹⁷⁵ evaluated the Doser and concluded that it is sufficiently reliable. However, the Doser occasionally recorded additional actuations. Over time, there was a trend toward decreasing accuracy with the Doser, which may be explained by battery decay. Also, the Doser no longer records actuations after the preset counter reaches zero, which leads to premature arrival of the counter at zero and subsequent inability to record further doses. An issue that has not been adequately addressed with these add-on dose counting devices is patient satisfaction. For example, they add to the cost of therapy and they increase the complexity of therapy because they add a device to the treatment reg-

imen. Some of the devices, such as MD Turbo, are also not compatible with spacers and VHCs.

Spacers and Valved Holding Chambers

These devices are used to overcome some of the limitations of pMDIs.¹⁷⁶ Compared to a pMDI alone, lung deposition with a spacer device is generally either increased or unchanged.¹⁷⁷ Good technique with the pMDI delivered 11% of the total dose to the lungs, whereas the InspirEase spacer increased lung deposition 15%, which was a statistically significant difference, but may not be clinically important.¹⁷⁸ However, the same study showed that the spacer increased lung deposition in patients with poor pMDI technique.¹⁷⁸ By adding space between the pMDI and the patient's mouth, VHCs reduce oropharyngeal deposition,^{179–181} which is particularly important with inhaled corticosteroids.

Although the term “spacer” is often used for all types of extension add-on devices, these devices are properly categorized as either “spacers” or “valved holding chambers” (Fig. 18).¹⁸² A spacer is a simple tube or extension with no valves to contain the aerosol plume after pMDI actuation. A VHC is an extension device, added onto the pMDI mouthpiece or canister, that contains one-way valves to hold the aerosol until inhalation. In the United States, most VHCs are < 200 mL. The direction of spray can be forward (toward the mouth) or reverse (away from the mouth). Some spacers and VHCs accept the pMDI mouthpiece-actuator, whereas others have a nozzle receptacle for the canister only.

There are concerns related to compatibility of newer HFA pMDIs, as the spacers and VHCs on the market today were designed for CFC pMDI, and it is known that the formulation, valve, and actuator have changed with the HFA pMDIs.¹⁸³ VHCs from different manufacturers do not demonstrate equivalent in vitro performance.^{184–188} The respirable dose of beclomethasone dipropionate aerosol from the HFA pMDI was decreased by only 6% when the pMDI was used with an AeroChamber-Plus VHC, and by 56% when used with an OptiChamber VHC.¹⁸⁴ In vitro differences between the highest and lowest respirable doses between devices could lead to clinically relevant differences in dose delivered to the patient.¹⁸⁵

Aerosol drug particles discharged into a VHC or spacer can be lost to the chamber walls by inertial impaction, gravitational sedimentation, and electrostatic attraction to wall of the chamber.¹⁵⁰ Thus, large-volume holding chambers augment lung deposition to a greater degree than do tube spacers or small holding chambers.^{177,189,190} Devices larger than 1 L, however, are impractical, and patients would have difficulty inhaling the complete contents.¹⁸² Delay between actuation and inhalation increases particle loss from sedimentation and electrostatic charge, and can



Fig. 18. Tube spacer, valved holding chambers, and reverse-flow spacers.

reduce the fine-particle mass available for inhalation (Fig. 19).¹⁹¹⁻¹⁹⁴ Multiple actuations of a pMDI into a spacer before inhalation also reduces the proportion of drug inhaled.¹⁹³⁻¹⁹⁸ Five actuations of a corticosteroid inhaler into a large-volume spacer before inhalation delivers a similar

dose to a single actuation into the same spacer inhaled immediately.¹⁹⁷

Because bacterial contamination may be common in spacers and VHCs, it is important that they be cleaned periodically. Cohen et al¹⁹⁹ recommend cleaning after each use, but this may not be necessary or practical. Manufacturers recommend weekly cleaning (http://www.monaghanmed.com/pdfs/copd_aerochamberplus/instruction_adult_76071eng.pdf).

Electrostatic Charge

Electrostatic charge acquired by the aerosol when generated, or present on the surface of the inhaler or add-on device, decreases aerosol delivery from VHCs.^{191,193,200-203} Electrostatic charge may be particularly important with a delay in aerosol inhalation after actuation.^{192,193} Although Dubus et al²⁰⁴ reported that electrostatic charge on the VHC does not affect bronchodilation with albuterol in methacholine-challenged pre-school children, Chuffart et al²⁰⁵ reported a greater bronchodilator response after inhalation of albuterol from a non-static VHC, compared to one with static present.

VHCs made from conducting materials, such as stainless steel or aluminum, avoid this problem.²⁰⁶⁻²⁰⁹ Priming by firing 20 doses into a new spacer coats the inner surface with surfactant and minimizes static charge,²⁰⁸ but this is not practical, because it uses $\geq 10\%$ of the doses in a new pMDI canister.

Washing a nonconducting VHC with detergent is a commonly used method to reduce surface electrostatic charge, and detergent-washing is now incorporated in most manufacturer instructions. Detergent-washing greatly improves drug delivery (Fig. 20) and is easy for the patient to perform.^{191,201,203} After washing, the VHC should not be towel-dried, which could impart electrostatic charge; instead, the device should be allowed to drip-dry in ambient air.²⁰⁰ In a study by Pierart et al,²⁰³ a wide range of detergent concentrations (range 1:125 to 1:10,000) resulted in similar fine-particle mass of albuterol, which suggests that the detergent concentration is not important. In the United States, the Food and Drug Administration requires manufacturers of add-on devices to recommend that patients rinse them in clean water after washing in detergent, to avoid patient contact with detergent-coated surfaces, which could result in contact dermatitis.²⁰⁰ However, Pierart et al²⁰³ reported that rinsed, drip-dried VHCs had substantial electrostatic charge and a lower delivery of fine particles.

VHCs manufactured from transparent, charge-dissipative polymers, as an alternative to opaque conducting materials such as stainless steel or aluminum, have become available in recent years. Rau et al²¹⁰ reported that VHCs made from electrically conductive materials emit signifi-

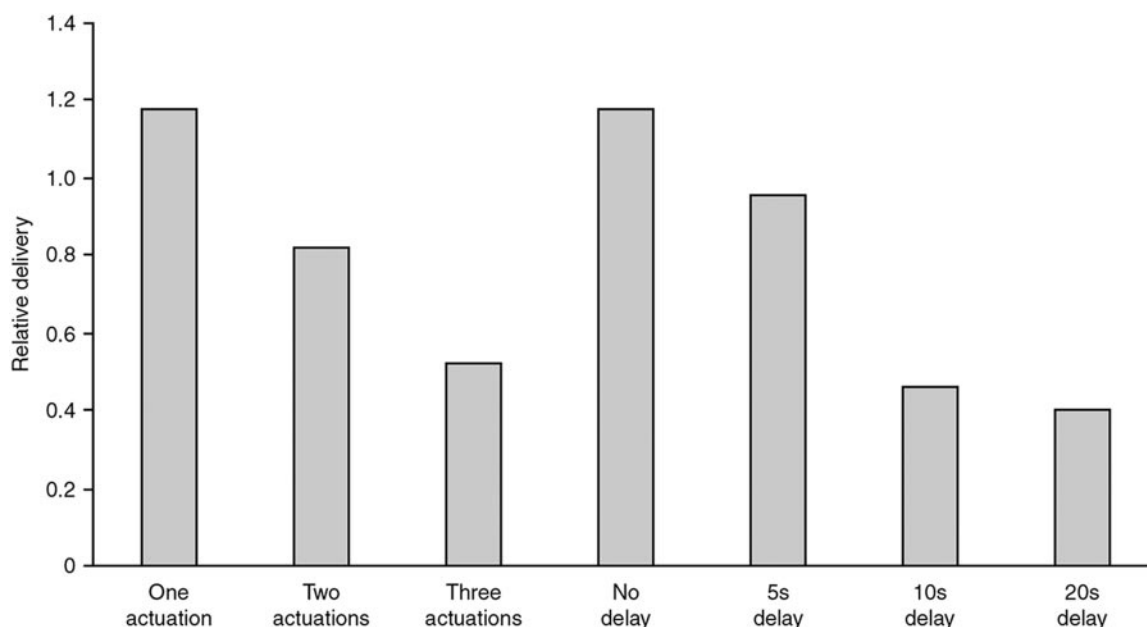


Fig. 19. Dose delivered in respirable ($< 5 \mu\text{m}$) particles from a large-volume spacer, expressed relative to that delivered from a pressurized metered-dose inhaler. The data represent 1, 2, and 3 actuations delivered in a single breath, and delay time of up to 20 s between firing a single dose and starting inhalation. (From Reference 182, with permission.)

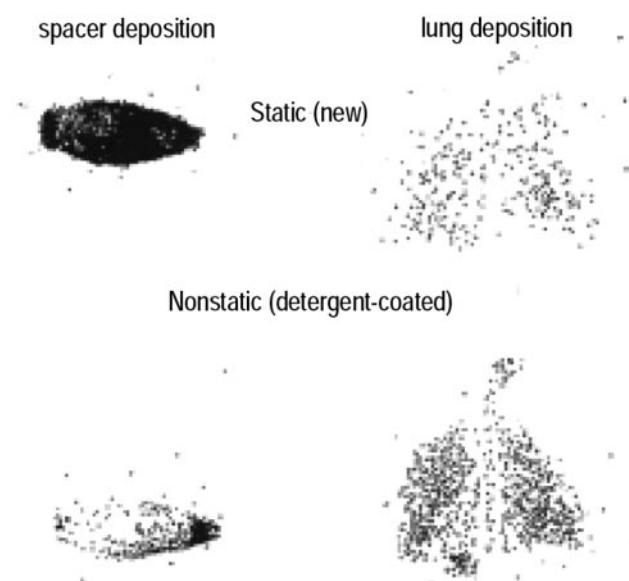


Fig. 20. Typical deposition patterns of radioaerosol in a new, untreated valved holding chamber (VHC) (upper left) and a subject's lung after inhalation from that untreated VHC (upper right), and with a detergent-coated VHC (lower left) and the same subject's lungs after inhalation from that treated VHC (lower right). (From Reference 203, with permission.)

cantly greater fine-particle mass, with either a 2-s or 5-s delay, than do VHCs made from nonconducting materials, even with wash/rinse pretreatment. Coppolo et al²¹¹ in an in vitro investigation, reported that a nonelectrostatic VHC delivers slightly more medication as fine particles than

does a conventional nonconducting VHC that is washed in detergent, rinsed, and drip-dried in air. However, the differences in performance are unlikely to be of clinical importance. The nonelectrostatic VHC had comparable performance whether or not it was prewashed.

Concern has been raised about the potential of improved lung bioavailability of HFA pMDI steroid (eg, fluticasone) in young children who use an antistatic VHC. Khan et al²¹² studied 12 patients, 1–6 years old, with well-controlled asthma. They were treated with an HFA fluticasone pMDI twice daily ($440 \mu\text{g/d}$). The drug was delivered during tidal breathing through conventional VHCs and antistatic VHCs via mask, in a randomized, crossover manner, for 3–7 days. The mean \pm SD fluticasone plasma concentration was $107 \pm 30 \text{ pg/mL}$ after conventional VHC and $186 \pm 134 \text{ pg/mL}$ after the antistatic VHC ($p = 0.03$). In 5 patients (40%), the antistatic VHC increased fluticasone plasma concentration by $\geq 100\%$, and to potentially excessive levels in 4 patients. The antistatic VHC had little effect in 7 patients. Those authors concluded that the antistatic VHC variably increased lung bioavailability, but this could be associated with increased systemic exposure (Fig. 21).

Facemasks and Valved Holding Chambers

Particularly in young children, use of a VHC requires a facemask. When using a facemask, an adequate seal is

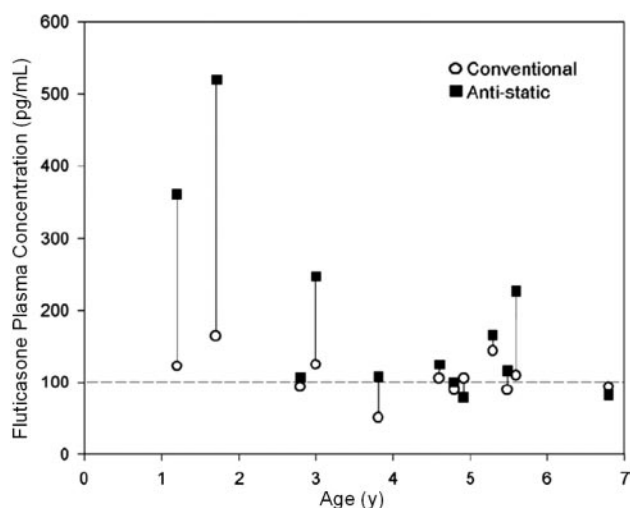


Fig. 21. The relationship of age to steady-state fluticasone plasma concentration 1-hour after delivery of 440 µg of aerosolized fluticasone from a hydrofluoroalkane-propelled pressurized metered-dose inhaler via either a conventional valved holding chamber (circles) or an antistatic valved holding chamber. The dashed line represents the EC₅₀ (median effective concentration, which is the concentration that produces 50% of the maximum possible response) for cortisol suppression in healthy adults. (From Reference 212, with permission.)

necessary, and 5–6 breaths are taken through the chamber to deliver the full dose (http://www.monaghanmed.com/pdfs/copd_aerochambermax/88802_eng.pdf).

In 40 children, 3–7 years old, with stable asthma, Zar et al²¹³ found no difference in lung deposition with a mask or mouthpiece, which suggests that a facemask can be effective in children who cannot use a mouthpiece effectively. The interface between the mask and the child's face is critical. Esposito-Festen et al,²¹⁴ using a model of the upper-airway, found that the dose delivered depends on the size of the face-mask leak. Similar results were found in other studies, which suggests that improving face-mask seal improves drug delivery.^{33,215–217} An inspiratory flow indicator may assist the provider in determining whether the facial seal is adequate. Note that crying significantly reduces drug delivery.^{46,218,219}

Drug delivery is also influenced by mask dead space, VHC dead space, and the opening pressure of the inspiratory and expiratory valves. Drug delivery decreases when dead space increases, and drug delivery increases with smaller VHC volume and lower tidal volume.²²⁰ Mathematical models of aerosol drug delivery suggest that VHC dead space decreases drug delivery when lower tidal volume is used.²²¹ Shah et al²²² conducted an in vitro study of force-dependent static dead space of facemasks used with holding chambers. They reported that mask dead-space volume changes in response to force, and that this change differs significantly among commercially available facemasks attached to VHCs. This relates to the flexibility of the mask and suggests that some of these masks may be

unsuitable for use with infants or small children, due to their relatively large dead-space volume or because of their inability to form an effective seal at the pressures tested.

Dry-Powder Inhalers

DPIs have become very popular in recent years, perhaps related, at least in part, to the impending ban on CFC pMDIs. Powder drug formulations are either in a pure-drug form, such as that with budesonide in the Turbuhaler, or mixed with an inactive excipient such as lactose.²²³ To produce suitably small drug particles, the drug-excipient agglomerate must be de-aggregated by shear forces during inhalation.^{224,225} It is for this reason that DPIs require a relatively high inspiratory flow for drug delivery to the airways. Commercially available DPIs are either unit-dose (the patient loads a single-dose capsule prior to each use) or multi-dose (the device contains a month's prescription).²²⁴ With the unit-dose devices it is important to instruct the patient that the capsules are not to be ingested; they should be administered only via inhalation, with the appropriate delivery device (http://www.fda.gov/cder/drug/mederrors/foradil_spiriva.pdf).

Moreover, the capsules should be used only in the intended device and should not be administered in another device. For example, formoterol capsules should not be administered in the HandiHaler, and the powder should never be dumped from the capsule into a nebulizer for administration. Currently available DPIs are all passive systems, meaning that the patient must provide the energy to disperse the powder from the device.²²⁴ A primary advantage of DPIs is coordination of actuation with inspiration, because they are breath-actuated. A primary disadvantage of unit-dose DPIs is the time needed to load a dose for each use. Another disadvantage of DPIs is that each operates differently from the others in loading and priming.¹⁵⁰

Humidity is a concern with DPIs because of the potential for powder clumping and reduced dispersal of fine particle mass.²²⁶ Humidity can originate from the ambient air or from patient exhalation into the mouthpiece.²²⁷ DPI design influences the effect of humidity. Multi-dose reservoirs (eg, Turbuhaler) are more vulnerable than devices that use blister packs or capsules (eg, Diskus) in which the powder is protected.¹⁵⁰ Another consideration related to humidity is the formulation; some drug particles have greater adhesion and reduced fine-particle mass as humidity increases, whereas other particles are dominated by electrostatic forces and show decreased adhesion with higher humidity.¹⁵⁰

Some DPIs require an inspiratory flow > 60 L/min to effectively de-aggregate the powder,^{228,229} and that flow cannot always be achieved by children and patients with severe airflow obstruction. This has prompted the industry to evaluate ways of providing energy in the inhaler, which

Table 1. Common Patient Errors in the Use of Aerosol Delivery Devices

Nebulizers
Failure to assemble equipment properly
Incorrect flow or fill volume
Spillage of dose by tilting the nebulizer
Failure to keep the mouthpiece in the mouth during nebulization
Leaks around face mask
Failure to mouth-breathe
Pressurized Metered-Dose Inhalers
Failure to prime
Failure to shake
Failure to remove cap
Poor hand-breath coordination
Rapid inspiratory flow
Multiple actuations during inhalation
Inhaling through nose
Wrong end of inhaler in mouth
Holding canister in the wrong position
Breath-hold too short
Use of pMDI beyond rated capacity
Cognitive impairment
Weak hand strength
Valved Holding Chambers
Incorrect assembly of device
Failure to remove electrostatic charge
Delay between actuation and inhalation
Firing multiple puffs into device
Dry-Powder Inhalers
Not holding device correctly while loading dose
Exhaling through the mouthpiece
Not inhaling forcefully
Inadequate breath-hold
Storage in high ambient humidity

is leading to the development of active DPIs, although none are currently available commercially in the United States for delivery of asthma medications.²²⁴ More forceful inhalation generally results in better de-aggregation, more fine particles, and a higher lung deposition. DPIs have inherent but different resistances, so the inspiratory flow needed to create the pressure-drop necessary for optimal drug delivery differs among DPI models. For example, the Turbuhaler has a higher resistance than the Diskus.²³⁰

Selecting an Aerosol Delivery Device

A common clinical question is which aerosol device should be used for a specific patient? There are advantages and disadvantages to each type of device. Recent meta-analyses regarding the selection of aerosol delivery systems for acute asthma concluded that short-acting β agonists delivered via either nebulizer or pMDI with valved holding chamber are essentially equivalent.^{2,231-235}

The most comprehensive evidence-based systematic review was by Dolovich et al.² They reviewed studies that involved nebulizers, pMDIs (with and without valved holding chambers), and DPIs for delivery of β agonists, anticholinergic agents, and inhaled corticosteroids in various clinical settings (emergency department, in-patient, intensive care, and out-patient) and patient populations (pediatric and adult asthma, and COPD). Only randomized controlled trials in which the same drug was delivered via different device types were included in the review. The bottom line of the Dolovich et al² review is that each of the aerosol devices can work equally well in various clinical settings with patients who can use these devices appropriately.

The findings of the Dolovich et al² review should not be interpreted to mean that the device choice for a specific patient does not matter. Rather, the study simply says that each of the devices studied can work equally well in patients who can use them appropriately. This is an important statement because most studies, especially in the out-patient setting, select for patients who are capable of using each of the devices with the appropriate technique or train patients to use the appropriate technique. The randomized controlled trials in the Dolovich et al² review do not provide much information about who is likely to use one device or another properly, nor do they address many other considerations that are important for choosing a delivery device for a specific patient in a specific clinical situation. These include the patient's ability to use the device, patient preference, the availability of equipment, and cost. There are some obvious situations in which device selection clearly does matter. For example, infants and toddlers are unlikely to correctly use a pMDI (without a VHC) or a DPI. Also, there are few randomized controlled trials of pMDI without VHC in the emergency department, since most clinicians believe that the severe dyspnea experienced by many asthma patients in that setting would prevent them from using this device properly.

The Dolovich et al² review did not include studies that compared devices of the same type (ie, nebulizers from different manufacturers or VHCs from different manufacturers). The review also excluded lower levels of evidence, such as the plethora of in vitro studies that have evaluated aerosol delivery devices.

When selecting an aerosol delivery device, Dolovich et al suggest that the following questions should be considered:

1. In what devices is the desired drug available? Some formulations are available only for a single device, which dictates the device used with that formulation.
2. What device is the patient likely to be able to use properly, given the patient's age and the clinical setting? Devices that require manual dexterity will be more difficult for elderly patients. Devices that require considerable

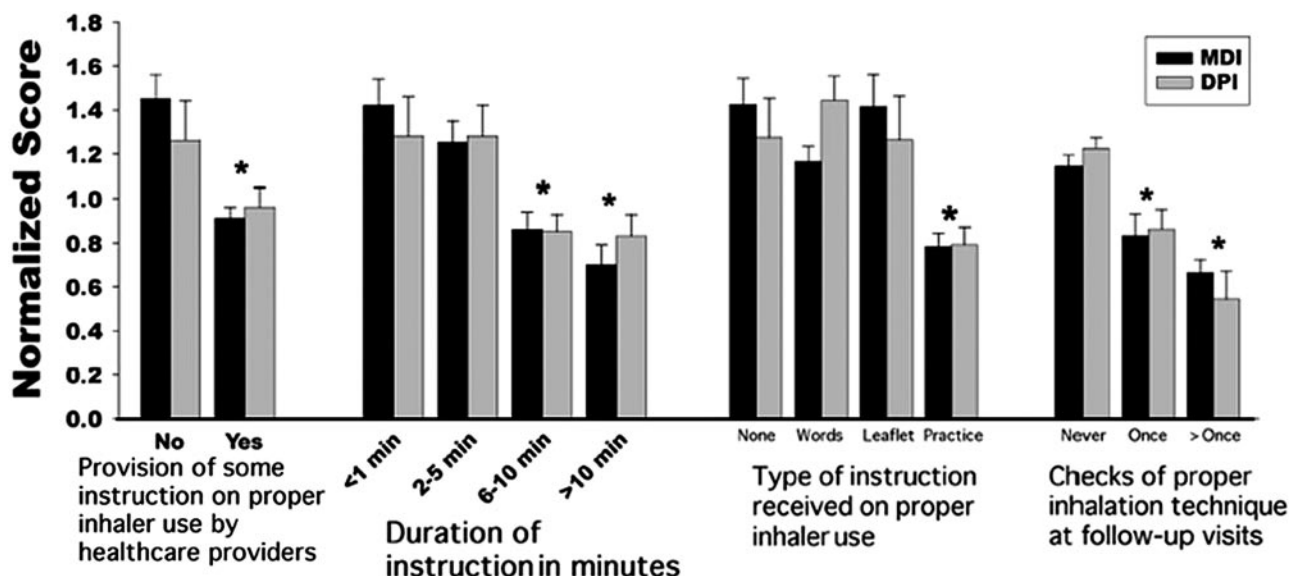


Fig. 22. Normalized score of inhalation technique (lower is better) with pressurized metered-dose inhalers (pMDIs) and dry-powder inhalers (DPIs), relative to: having received any instruction from a health-care provider; the duration of the initial instruction; the type of instruction; and the number of times that a health-care provider re-checked the patient's inhalation technique. * $p < 0.001$. (From Reference 260, with permission.)

patient/device coordination may be difficult for the very young or elderly.^{46,236-242}

3. For which device and drug combination is reimbursement available? This is an important consideration if the cost is not covered by a third-party payer and the patient cannot afford the out-of-pocket expense.²⁴³

4. Which devices are the least costly? This is an important consideration in the hospital.

5. Can all the types of inhaled drugs for asthma and COPD that are prescribed for the patient be delivered with the same type of device? Using the same type of device for all the patient's inhaled drugs may facilitate patient teaching and decrease the chance of confusion among devices that require different inhalation techniques,²⁴⁴ although 1 study reported that concurrent use of pMDI and DPI by children with persistent asthma did not adversely affect technique.²⁴⁵

6. Which devices are the most convenient for the patient, family (out-patient use), or medical staff (acute care setting), given the time required for drug administration and device cleaning, and the portability of the device?

7. How durable is the device?

8. Does the patient or clinician have any specific device preferences?

Patient Education

Whichever device is chosen, proper patient education on its use is critical. Patient errors in the use of aerosol devices are common (Table 1).^{150,227,243,246-252} Misuse of aerosol devices such as the pMDI is associated with decreased asthma control.²⁵³ Physicians, respiratory thera-

pists (RTs), nurses, and pharmacists who care for patients with respiratory diseases should be familiar with issues related to performance and correct use of aerosol devices. It is well documented that health care practitioners' knowledge of the use of aerosol devices is less than adequate.²⁵⁴⁻²⁵⁹ Clinicians who care for patients with asthma must understand how to use, select, and match the best device for the individual patient.²⁴³ Molimard et al reported that primary care physicians check inhalation technique in only 4 of every 10 patients who use these devices.²⁵¹ Sestini et al²⁶⁰ also noted that many physicians are not familiar with the relevant characteristics of currently available inhalers. Respiratory therapists are ideally positioned to instruct patients in the correct use of aerosol devices during hospitalization, as this instruction may occur irregularly in the community. The use of protocols implemented by RTs may be an effective strategy to assure selection of an appropriate device for aerosol delivery in patients with asthma.²⁶¹⁻²⁶⁵

Lack of correct aerosol device use is a particular type of nonadherence to therapy. Factors related to adherence include the complexity of the inhalation regimen (dosing frequency, number of drugs), route of administration (oral vs inhaled), type of inhaled agent (corticosteroid adherence is worse than with short-acting β agonists), patient awareness of monitoring, and various patient beliefs and sociocultural and psychological factors.²⁶⁶ Good communication skills in clinicians and patient education about inhaled medications are central to improving adherence.²⁶⁶

Sestini et al²⁶⁰ conducted an observational study of 1,305 patients on their use of pMDIs and DPIs. With both types of inhalers, misuse was significantly and equally associated with older age, less education, and less instruction by health care personnel. Several findings from that study have important implications for teaching patients how to use their inhalers. More time spent on instruction on proper inhalation technique by health-care providers resulted in better performance (Fig. 22). A practical demonstration of proper inhaler use was associated with better inhalation technique. Evaluation of inhaler use by caregivers at follow-up visits was also strongly associated to better inhalation technique.

Summary

Aerosolized medications can be administered via nebulizer, pMDI, pMDI with spacer or VHC, or DPI. There are advantages and disadvantages to each device. In recent years an increasing array of these devices has become available, resulting in confusion for patients and clinicians. Physicians, RTs, pharmacists, and nurses who care for patients with asthma should be familiar with the performance of these devices and the correct technique for each of these devices. Patient instruction is a key component in determining the device that a patient can use correctly and in teaching the patient how to properly use the device. Instructing patients in correct inhaler use is a unique opportunity for RTs to add value in the care of patients with asthma.

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Discussion

Kallstrom: Dean, what would you say is role of the RT in device selection for patients?

Hess: Certainly in the hospital setting, in many hospitals and many re-

spiratory departments, the RTs, through the use of protocols, are very actively involved in the device selection. Gene wrote a paper on the protocol his group uses.¹

1. Colice GL, Carnathan B, Sung J, Paramore LC. A respiratory therapist-directed protocol for managing in-patients with asthma and

COPD incorporating a long-acting bronchodilator. *J Asthma* 2005;42(1):29-34.

Colice: Yes, in our RT-directed protocol the RTs choose the device. The paper Dean just mentioned was on formoterol, and we are working on a report on tiotropium. The RTs choose

the drug and how to give it, and the protocol works very well.

Kallstrom: How do you determine the competency of the RT to make those decisions?

Colice: We have a very extensive teaching process, and we think that, generally, the RTs are a better choice than the interns or nurses. I would echo Dean's comment that, however the RTs perform, they perform exponentially better than anybody else. I think that's fair, don't you, Dean?

Hess: Absolutely.

Colice: We have a tremendous amount of confidence in our RTs, that they can assess the patient, give the right therapy, observe the response, and make sure they get it all done correctly.

Enright: Do you worry about formoterol solution delivered with nebulizers that it was not tested with? It has quite a dose-response curve and adverse effects, and older people tend to prefer nebulizers.

Hess: The answer is yes. For which nebulizers is formoterol approved?

Enright: It was tested on a Pari nebulizer, which is probably the best and possibly the most expensive, which makes it unlikely to be chosen universally.

Hess: About 10 years ago I published a paper from our laboratory where we looked at the performance of 17 different nebulizers.¹ There was a wide range of performance, so if you started with the best performer and switched to the poorest performer, it could reduce the drug delivery several-fold. How important that is with bronchodilators is yet to be determined. I tend to think that it may be very important with some other types of formulations, such as aerosolized antibiotics; with

those, in my practice, I use the nebulizer that the drug was approved with or with which the clinical trials were done.

1. Hess D, Fisher D, Williams P, Pooler S, Kacmarek RM. Medication nebulizer performance: effects of diluent volume, nebulizer flow, and nebulizer brand. *Chest* 1996;110(2):498-505.

MacIntyre: I was struck by that paper you just mentioned that found such wide variability. It was fascinating that you also found that, regardless of what device you use, and regardless of whether you put 10 times the dose in a nebulizer, versus a pMDI, they all come out the same—provided the device was used properly. One might conclude that it really doesn't matter what dose you put in the lung, as long as you get something in there, but of course that's overly simplified. Further, this conclusion may only apply to bronchodilators. I'm much more concerned about steroids, antibiotics, and other medications, where the dosing implications may be huge. I'm not sure that the assumption that pMDIs and nebulizers are equivalent as long as you use them correctly applies to drugs other than bronchodilators.

Hess: I think part of the reason that we found what we did in our meta-analysis¹ was that the bronchodilator doses tend to be so high that we were just on the flat part of the dose-response curve. There have been very few of these kinds of studies, but if you do a true dose-response study, you may be able to find those differences. Also, in our meta-analysis we excluded studies if they only compared devices of the same type (eg, nebulizers of different brands).

1. Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL, et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. *Chest* 2005;127(1):335-371

Donohue: Both 3-month study papers are available, but I'm first author of 1-year safety data on both of the formoterol aerosol solutions^{1,2}. We've been looking at safety and deaths, and we didn't see any signal. In the slide you showed on HFA-propelled beclomethasone,³ did you cut the dose in half? Whereas in fluticasone, was it a 1-to-1 HFA pMDI to the Diskus device? Were there differences?

1. Donohue JF, Hanania NA, Sciarappa KA, Goodwin E, Grogan DR, Baumgartner RA, Hanrahan JP. Arformoterol and salmeterol in the treatment of chronic obstructive pulmonary disease: a one year evaluation of safety and tolerance. *Therapeutic Advances in Respiratory Disease* 2008;2(2):37-48
2. Donohue JF, Hanania NA, Fogarty C, et al. Long term safety of nebulized formoterol: results of a 12 month, open label clinical trial. *Therapeutic Advances in Respiratory Disease*; 2008; in press.
3. Baumgartner RA, Hanania NA, Calhoun WJ. Nebulized arformoterol in patients with COPD: a 12-week, multicenter, randomized, double-blind, double dummy, placebo-and active-controlled trial. *Clin Ther* 2007;29(2):261-78.

Colice: I'll give you an anecdote, Jim. When they formulated beclomethasone with HFA, the chemists came running in and said, "Oh my God, it's a solution! We screwed it up!" But we said, "Well, maybe a solution will have advantages." And the decision was made to develop it as a solution, which was the first solution aerosol developed for a steroids pMDI. The dosing was 1-to-2 for HFA versus CFC beclomethasone. And it's probably 1-to-1 for HFA beclomethasone and fluticasone. HFA fluticasone was developed as a suspension with the same particle-size distribution, so it's 1-to-1 ratio.

Diette: I was a little worried when you were talking about electrostatic charge and dead space issues, and whether I might be missing something when I'm prescribing different kinds of holding chambers and so forth. Your meta-analysis included different kinds of chambers. Do you think all those

theoretical or potential problems sort of “net out” so that you don’t really have to worry about it if you found no important difference among the different devices? Do you think that integrates those potential problems into the analysis somehow?

Hess: It applies mostly to bronchodilators and steroids. In our meta-analysis we excluded studies that only compared devices of the same type (eg, valved holding chambers of different types and brands).

Diette: Then can you get away without having to deal with some of those potential problems?

Hess: It is pretty easy to deal with the static just by instructing the patient to wash the spacer or chamber periodically in soapy water and let it air dry.

Stoloff: Seventy percent of all asthma is taken care of by primary care physicians, very few of whom have placebo inhalers with which to demonstrate pMDI technique. If you mention the word “nebulizer,” which they prescribe, they have no idea what brand, or what is the nebulizer, or the compressor, or the cleaning technique, or when it should be replaced, or how to put the medication in the nebulizer, or the distance from the mouth that is not acceptable, or the “blow-by” (which is “kiss it goodbye”), or reimbursement. Valved holding chambers are not reimbursable in many of the major health plans.

So the important issue is, how are we going to approach this, which is far more of a barrier to practical application of

these devices, as well as instruction on these devices. If medication education is not a reimbursable item in many health plans—and even though there is a code for them, this becomes as important an issue as the cost of medications—this is a major concern.

The other thing is the importance of “re-instruction.” In my practice, every time a patient with asthma or COPD comes in, they are handed a placebo inhaler and the staff ask, “Show me how you use your inhaler.” And we re-educate them on proper inhaler use. But that’s because it’s my interest. That re-education doesn’t occur in many settings. So that’s another barrier.

Hess: That’s an important point. Where do you get placebo inhalers? I can find placebo powder inhalers but I haven’t found placebo pMDIs.

Stoloff: I’ve got large boxes of Proventil placebo inhalers from Schering-Plough.

Hess: Recently?

Stoloff: Yes. And I put in a request to other companies when one of their representatives comes in. Some companies have them. The issue is that because sampling is becoming an issue all across the country—or the lack of samples, where universities are removing them—the device demonstration is becoming an increasing barrier as time is shortened. I think that, whether the spacer is electrostatically charged or not, we need to come up with better ways of educating people who are providing care for

this population and gain momentum with staff so it’s not left to the primary clinician to do the brunt of the work.

Rubin:* I would say amen to Dr Stoloff, and I would add that additional problems aren’t just in the physician’s office and the physician’s understanding. It’s what happens at home. If you’re discussing adherence, many of the pMDIs and powder inhalers you put in your mouth, inhale, and go. Whereas with nebulization you’re measuring, you’re plugging, you’re sitting, you’re inhaling or blowing it by, and it takes time, it takes a power source, and it takes a lot more effort to do well.

Also, it’s not just the nebulizer one chooses to use for these things, but it’s what you put in the nebulizer. We’ve had people pour all sorts of stuff into a nebulizer cup who are being told to because it doesn’t matter, it doesn’t need to be formulated for the nebulizer. Before budesonide nebulizer solution came out, people were putting all sorts of nasal steroids in there. Today people are taking tiotropium, opening the capsule into water and putting it in their nebulizer, and it’s not formulated for nebulization and they’re probably not getting anything at all into their lungs. So that should also be emphasized.

Hess: Good point.

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