



# A Guide To Aerosol Delivery Devices for Respiratory Therapists

4th Edition



Douglas S. Gardenhire, EdD, RRT-NPS, FAARC

Dave Burnett, PhD, RRT, AE-C

Shawna Strickland, PhD, RRT-NPS, RRT-ACCS, AE-C, FAARC

Timothy R. Myers, MBA, RRT-NPS, FAARC

# A Guide to Aerosol Delivery Devices for Respiratory Therapists,

4th Edition

Douglas S. Gardenhire, EdD, RRT-NPS, FAARC

Dave Burnett, PhD, RRT, AE-C

Shawna Strickland, PhD, RRT-NPS, RRT-ACCS, AE-C, FAARC

Timothy R. Myers, MBA, RRT-NPS, FAARC

With a Foreword by

Timothy R. Myers, MBA, RRT-NPS, FAARC

Chief Business Officer

American Association for Respiratory Care

## DISCLOSURE

Douglas S. Gardenhire, EdD, RRT-NPS, FAARC has served as a consultant for the following companies: Westmed, Inc. and Boehringer Ingelheim.



Produced by the  
American Association  
for Respiratory Care



**PHILIPS**

# Foreward

Aerosol therapy is considered to be one of the cornerstones of respiratory therapy that exemplifies the nuances of both the art and science of 21st century medicine. As respiratory therapists are the only health care providers who receive extensive formal education and who are tested for competency in aerosol therapy, the ability to manage patients with both acute and chronic respiratory disease as the experts in aerosol therapy allows the concept of “art” and “science” to take on a practical reality.

Respiratory therapists continue to be the experts when it comes to the art and science of aerosol therapy. With the rapidly changing field of aerosol medications and delivery systems, it is imperative that we not only share this expertise with patients but also other members of the health care delivery team across the continuum of care. With a renewed focus on wellness and prevention within the U.S. health care system and a determined focus to minimize cost and waste, the choice of appropriate respiratory medications and delivery devices makes selection of both the drug and optimum delivery device even more critical.

How does a therapeutic intervention around for centuries still combine the art with science in the context of aerosol therapy? The “science” component includes many different aspects such as pharmacology, cardiopulmonary anatomy and physiology, physics, and a thorough understanding of the different aerosol delivery technologies on the market today. In order to claim expertise in the science of aerosol therapy and optimize it for patients, the respiratory therapist must have concrete knowledge and understanding of the numerous drug formulations, their mode of action, and an understanding of the respiratory conditions where the drug and delivery is recommended and supported by the scientific evidence.

While the “art” of aerosol delivery is much more abstract than the science, it is as equally important to the appropriate delivery of respiratory medications for optimal outcomes. For aerosol therapy, the interaction between technology and human behavior is where “art” comes into play. There is ample scientific evidence of sub-optimal or ineffective use of aerosols when self-administered in large part due to lack of knowledge about proper technique by patients. All too often, patients do not receive optimum (or sometimes

any) benefit from their prescribed metered-dose inhalers, dry-powder inhalers, and nebulizers simply because they are not adequately trained or evaluated on their proper use.

The combination of the right medication and the most optimal delivery device with the patient’s cognitive and physical abilities is the critical juncture where science intersects with art. For aerosol therapy to be effective, the appropriate delivery system for the medication must be matched to the patient’s ability to use it correctly. The art of aerosol therapy does indeed arise from the science. When these two different, but synergistic components of medicine do not properly align, patient adherence decreases. Medication is wasted. Minimal patient benefit is derived.

Because aerosol therapy is integral to our scope of practice and because we are considered the experts in this area, we have a professional obligation to our patients to continue our learning and competencies in the delivery of aerosolized medicines. Respiratory therapists must take advantage of this opportunity to reinforce their value by updating their knowledge of aerosol delivery systems and combining that knowledge with effective assessment of patients requiring this therapy. Recommending an appropriate delivery system tailored specifically to the patient’s abilities is part of that assessment.

This guide will provide you the opportunity to advance your knowledge and expertise in aerosol delivery. Mastery of both the art and science of aerosol delivery can have a profound impact on appropriately matching medications and delivery devices to optimize your patients’ clinical outcomes. You will also contribute to more cost-effective use of health care system resources.

The fourth edition of this Aerosol Guide delivers detailed and comprehensive information that, when combined with your dedication and commitment to be the professional experts in this important area, will empower you to provide guidance to your physician, nurse, and pharmacist colleagues — but, most importantly, to your patients.

**Timothy R. Myers, MBA, RRT-NPS, FAARC**  
Chief Business Officer  
American Association for Respiratory Care

# Continuing Respiratory Care Education (CRCE)

As part of your membership benefits in the American Association for Respiratory Care® (AARC), the Association:

- provides you with continuing education opportunities;
- keeps track of all the CRCE® hours you earn from CRCE-approved programs; and
- allows you to print online a transcript of your CRCE records.

These services are available to you 24 hours a day, seven days a week, on the AARC web site ([www.AARC.org](http://www.AARC.org)).

The contents of this book are approved for six CRCE contact hours; and as an AARC member, there is no charge to you. To earn those CRCE contact hours, please go to the AARC web site at:

<http://c.aarc.org/go/adu>

Further instructions will be given on that web site, including:

- how to register to take an examination to assess your mastery of course objectives;
- how to update your e-mail address so that registration confirmation can be sent to you.

## Learning Objectives

As you read this book, you will be able to:

1. Identify the terminology used in aerosol medicine.
2. State approximate amount of aerosol deposited in the lower respiratory tract for nebulizers, pressurized metered-dose inhalers (pMDIs), and dry-powder inhalers (DPIs).
3. List advantages and disadvantages of inhalation compared to other routes of drug administration.
4. Identify hazards of aerosol therapy that can impact the patient receiving therapy as well as care providers and bystanders.
5. List advantages and disadvantages of nebulizers for aerosol delivery.
6. Compare the principle of operation of a jet nebulizer, mesh nebulizer, and ultrasonic nebulizer.
7. Describe types of pneumatic jet nebulizer designs and methods that are used to decrease aerosol loss from a jet nebulizer during exhalation.
8. Learn steps for correct use of jet, ultrasonic, and mesh nebulizers.
9. Describe the basic components of a metered-dose inhaler.
10. List advantages and disadvantages of metered-dose inhalers.
11. Compare and contrast performance of pMDIs with HFA and CFC propellants.
12. Discuss factors affecting the pMDI performance and drug delivery.
13. Explain the importance of priming and tracking the number of doses for a metered-dose inhaler.
14. Compare and contrast the design of holding chambers and spacers.
15. Identify factors that affect dose delivery from a holding chamber/spacer.
16. List advantages and disadvantages of dry-powder inhalers.
17. Describe the principle of operation of various commercially available dry-powder inhalers.
18. Identify factors affecting the DPI performance and drug delivery.
19. Explain how you know that each DPI is empty.
20. List the correct steps for use of a nebulizer, metered-dose inhaler, metered-dose inhaler with holding chamber/spacer, and dry-powder inhaler.
21. Describe causes and solutions of problems seen with nebulizers, pMDIs, and DPIs.
22. Discuss criteria to assist clinicians in selecting an aerosol delivery device.
23. Identify special considerations for neonatal and pediatric drug delivery.
24. Explain how to establish an infection control management system in aerosol drug delivery.
25. Describe the proper technique of cleaning aerosol delivery devices.
26. Discuss the importance of occupational health and safety for respiratory therapists.
27. List common problems and errors with each type of inhaler.
28. Describe how to instruct and evaluate patients in the use of inhaler devices.

# Table of Contents

Foreword .....	i
Acronyms .....	iv
The Science of Aerosol Drug Delivery .....	1
Terminology	
Mechanisms of Aerosol Deposition and Particle Sizes	
Types of Aerosol Generators	
Where Does an Inhaled Aerosol Drug Go?	
Equivalence of Aerosol Device Types	
Advantages and Disadvantages of Inhaled Aerosol Drugs	
Hazards of Aerosol Therapy	
Currently Available Aerosol Drug Formulations	
Small-Volume Nebulizers .....	9
Advantages and Disadvantages of SVNs	
Types of SVNs	
Factors Affecting Jet Nebulizer Performance and Drug Delivery	
Nebulizers for Specific Applications	
Continuous Aerosol Therapy	
Drug-Delivery Technique	
Inhalers .....	19
Pressurized Metered-Dose Inhalers .....	21
Advantages and Disadvantages of pMDIs	
Types of pMDIs	
Currently Available pMDI Formulations	
Factors Affecting pMDI Performance and Drug Delivery	
Drug-Delivery Technique	
Metered-Dose Inhaler Accessory Devices .....	29
Advantages and Disadvantages of pMDI Inhaler Accessory Devices	
Spacers	
Valved Holding Chambers	
Drug-Delivery Technique	
Dry-Powder Inhalers .....	32
Advantages and Disadvantages of DPIs	
Types of DPIs	
Currently Available DPI Formulations	
Factors Affecting the DPI Performance and Drug Delivery	
Drug-Delivery Technique	
Criteria to Select an Aerosol Generator .....	40
Patient-Related Factors	
Drug-Related Factors	
Device-Related Factors	
Environmental and Clinical Factors	
Neonatal and Pediatric Aerosol Drug Delivery .....	42
Age and Physical Ability	
Age and Cognitive Ability	
Aerosol Drug Delivery in Distressed or Crying Infants	
Patient-Device Interface	
Parent and Patient Education	
Infection Control .....	44
IC Management System in Aerosol Drug Delivery	
Preventing Infection and Malfunction of Aerosol Generators at Hospitals or Clinics	
Occupational Health and Safety of Respiratory Therapists	
Educating Patients in Correct Use of Aerosol Devices .....	48
Patient Adherence	
Common Patient Errors with pMDIs	
Common Patient Errors with Holding Chambers/Spacers	
Common Patient Errors with DPIs	
Common Patient Errors with SVNs	
Instructing and Evaluating Patients in the Use of Inhaler Devices	
References .....	52

# Acronyms

CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CF	cystic fibrosis
DPI	dry-powder inhaler
FDA	U.S. Food and Drug Administration
FPF	fine-particle fraction
GSD	Geometric Standard Deviation
HFA	hydrofluoroalkane
IC	infection control
MMAD	mass median aerodynamic diameter
MMD	mass median diameter
pMDI	pressurized metered-dose inhaler
SPAG	small particle aerosol generator
SVN	small-volume nebulizer
VHC	valved holding chamber

# The Science of Aerosol Drug Delivery

Aerosols exist everywhere there is gas to breathe. From pollen and spores, to smoke and pollution, to man-made chemicals, the aerosol category includes any fine liquid or solid particles. A “medical aerosol” is any suspension of liquid (nebulizer or pMDI) or solid drug particles (pMDI or DPI) in a carrier gas.<sup>1</sup> Our respiratory systems evolved to have filtration and elimination systems that must be overcome or bypassed in the process of providing local delivery of medications to the lung. Methods for generating aerosols, formulating drugs, and administering medications effectively to the desired site of action constitute the science of aerosol drug delivery. As is the case in any scientific discipline, one must first understand the terms and definitions used to describe the principles of aerosol medicine in order to subsequently master its methods.

## Terminology

Definitions of key terms used in aerosol drug delivery are listed in alphabetical order below.

- aerosol:** a suspension of liquid and solid particles produced by an aerosol generator such as the small-volume nebulizer (SVN), the pressurized metered-dose inhaler (pMDI), or the dry-powder inhaler (DPI)
- aerosol deposition:** process of aerosol particles depositing on absorbing surfaces
- aerosol generator:** a device used for producing aerosol particles
- aerosol output:** mass of medication exiting an aerosol generator
- aerosol therapy:** delivery of solid or liquid aerosol particles to the respiratory tract for therapeutic purposes
- dead volume (or residual volume):** the amount of medication that remains in the nebulizer after a treatment is complete
- diffusion:** the mechanism of aerosol deposition for small particles less than 3  $\mu\text{m}$  (Diffusion is also called Brownian motion.)
- dry-powder inhaler:** an aerosol device that delivers the drug in a powdered form, typically with a breath-actuated dosing system
- emitted dose:** the mass of medication leaving an aerosol generator as aerosol
- fine-particle fraction (FPF):** percentage of the aerosol between 1–5  $\mu\text{m}$  that deposits in the lung
- heterodisperse:** aerosol particles of different sizes
- hydrofluoroalkane (HFA):** a nontoxic liquefied gas propellant developed to be more environmentally friendly than CFCs and used to administer the drug from a pMDI
- inhaled dose:** the proportion of nominal or emitted dose that is inhaled
- inhaled mass:** the amount of medication inhaled
- inhaler:** device used to generate an aerosolized drug for a single inhalation
- inertial impaction:** the mechanism of aerosol deposition for particles larger than 5  $\mu\text{m}$
- gravitational sedimentation (gravitational settling):** the settling rate of an aerosol particle due to gravity, particle size, and time
- geometric standard deviation (GSD):** one standard deviation above and below the median particle sizes in an aerosol distribution that indicates the variability in aerosol particle size
- mass median aerodynamic diameter (MMAD):** average aerosol particle size as measured by a cascade impactor
- monodisperse:** aerosol particles of same or similar sizes
- nebulizer:** an aerosol generator producing aerosol particles from liquid-based formulations
- nominal dose:** the total drug dose placed in the nebulizer
- plume:** a bolus of aerosol leaving the pMDI or other aerosol devices
- pressurized metered-dose inhaler (pMDI):** a drug device combination that dispenses multiple doses by means of a metered value; used interchangeably with pMDI
- respirable mass:** the product of the fine particle fraction multiplied by the inhaled mass
- residual volume (or dead volume):** the amount of medication that remains in the nebulizer at the end of a treatment
- spacer:** a valveless extension device that adds distance between the pMDI outlet and the patient’s mouth
- valved holding chamber:** a spacer with a one-way valve used to contain aerosol particles until inspiration occurs



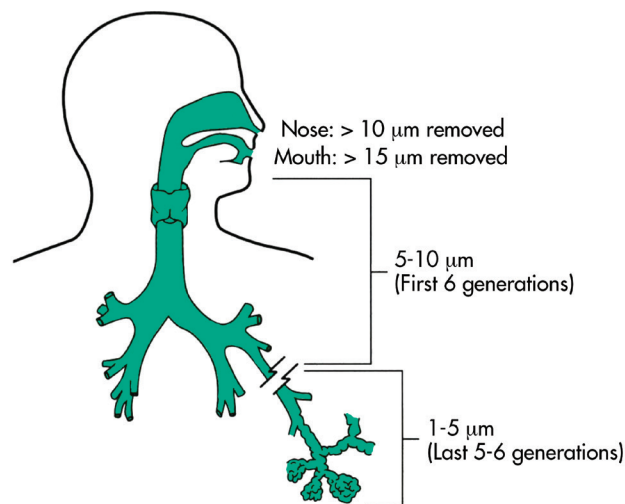
## Mechanisms of Aerosol Deposition and Particle Sizes

The major mechanisms of aerosol deposition include inertial impaction, gravitational sedimentation (settling), and diffusion. *Inertial impaction* occurs with larger ( $>3\ \mu\text{m}$ ), fast-moving particles. *Gravitational settling* is a function of particle mass and time, with the rate of settling proportional to particle size and mass. *Diffusion* occurs with particles smaller than  $1\ \mu\text{m}$ . These mechanisms come into play as aerosol particles are inhaled orally or through the nose. Larger particles ( $>10\ \mu\text{m}$ ) are filtered in the nose and/or the oropharynx, largely by inertial impaction; particles of  $5\text{--}10\ \mu\text{m}$  generally reach the proximal generations of the lower respiratory tract, and particles of  $1\text{--}5\ \mu\text{m}$  reach to the lung periphery.

Particle size plays an important role in lung deposition, along with particle velocity and settling time. As particle size increases above  $3\ \mu\text{m}$ , aerosol deposition shifts from the periphery of the lung to the conducting airways. Oropharyngeal deposition increases as particle size increases above  $6\ \mu\text{m}$ . Exhaled loss is high with very small particles of  $1\ \mu\text{m}$  or less. Consequently, particle sizes of  $1\text{--}5\ \mu\text{m}$  are best for reaching the lung periphery, whereas  $5\text{--}10\ \mu\text{m}$  particles deposit mostly in the conducting airways, and  $10\text{--}100\ \mu\text{m}$  particles deposit mostly in the nose.

Aerosol devices in clinical use produce *heterodisperse* (also termed *polydisperse*) particle sizes, meaning that there is a mix of sizes in the aerosol. *Monodisperse* aerosols, which consist of a single particle size, are rare in nature and medicine. A measure that quantifies a polydisperse aerosol is the *mass median diameter* (MMD). This measure determines the particle size (in  $\mu\text{m}$ ) above and below which 50% of the mass of the particles is contained. This is the particle size that evenly divides the *mass*, or amount of the drug in the particle size distribution. This is usually given as the *mass median aerodynamic diameter*, or MMAD, due to the way sizes are measured. The higher the MMAD, the more particle sizes are of larger diameters.

As seen in Figure 1, larger particles between  $10\text{--}15\ \mu\text{m}$  deposit mostly in the upper airways, particles within the  $5\text{--}10\ \mu\text{m}$  range reach the large bronchi, and particles of  $1\text{--}5\ \mu\text{m}$  penetrate to the lower airways and lung periphery.<sup>2</sup>



**Figure 1.** A simplified view of the effect of aerosol particle size on the site of preferential deposition in the airways (From Reference 2, with permission)

## Types of Aerosol Generators

Three common types of aerosol generators are used for inhaled drug delivery: the small-volume nebulizer (SVN), the pressurized metered-dose inhaler (pMDI), and the dry-powder inhaler (DPI). Each device type is described below.

- **Small-Volume Nebulizer:** The SVN is an aerosol generator that converts liquid drug solutions or suspensions into aerosol and is powered by compressed air, oxygen, a compressor, or an electrically powered device.
- **Pressurized Metered-Dose Inhaler:** The pMDI is a small, portable self-contained drug device combination that dispenses multiple doses by a metered value. Because of high medication loss in the oropharynx and hand-held coordination difficulty with pMDIs, holding chambers and spacers are often used as ancillary devices with the pMDI.
- **Dry-Powder Inhaler:** The DPI is an aerosol device that delivers drug in a powdered form, typically with a breath-actuated dosing system.

## Where Does an Inhaled Aerosol Drug Go?

Lung deposition may range from  $1\text{--}50\%$  with clinical aerosol delivery systems.<sup>3-7</sup> Deposition is dependent on a variety of factors such as the device, the patient, the drug, and the disease. For example, out of  $200\ \mu\text{g}$  of albuterol in two actuations or puffs from a pMDI, only about  $20\text{--}40\ \mu\text{g}$  reach the lungs with correct technique. The remaining drug is lost in the oropharynx, in the device, or in the exhaled breath. Figure 2 indicates the percentages of drug deposition for different aerosol systems, showing that oropharyngeal loss, device loss, and exhalation/ambient loss differ among aerosol device types, as do lung doses.



**Table 1. Differences in nominal (total) dose between a pMDI and an SVN for different drug formulations** (Modified, with permission, from Reference 1)

Drug	pMDI Nominal Dose	SVN Nominal Dose
Albuterol	0.2 mg (200 µg)	2.5 mg
Ipratropium	0.04 mg (40 µg)	0.5 mg
Levalbuterol	0.045 mg – 0.09 mg	0.31 mg – 1.25 mg

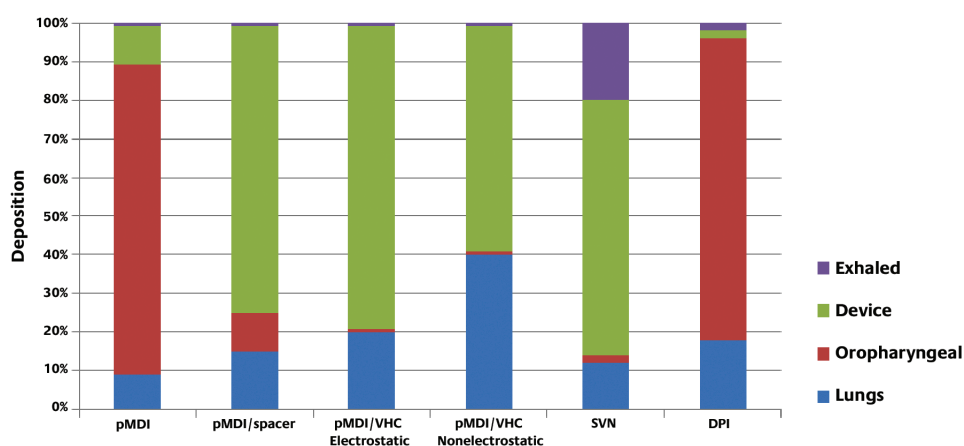
It is important to realize that different types of aerosol devices deposit a different fraction of the total dose of a given drug (also termed “nominal” dose) in the lungs. In addition, different types of aerosol devices such as nebulizers and pMDIs do not have the same nominal dose. Using albuterol as an example, the typical pMDI nominal dose is two actuations, or about 200 µg, while the typical nebulizer nominal dose is 2.5 mg, or 12 times more drug. Table 1 lists both the pMDI and nebulizer nominal doses for several drugs, showing this difference.

### Equivalence of Aerosol Device Types

Historically, nebulizers were thought to be more effective than pMDIs, especially for short-acting bronchodilators in acute exacerbations of airflow obstruction. Contrarily, evidence has shown equivalent clinical results whether a pMDI, a nebulizer, or a DPI is used, *provided that the patient can use the device correctly*.<sup>8</sup> For bronchodilators, the same clinical response is often achieved with

the labeled dose from the pMDI or nebulizer, despite the higher nominal dose for the nebulizer. Because any of these aerosol generators, *if used properly*, can be effective with their label dose, dosage should be device specific and based on the label claim.

Newer aerosol devices and drug formulations are increasing the efficiency of lung deposition when compared to the traditional devices commonly used. For example, lung deposition for HFA-beclomethasone dipropionate (QVAR™, Teva Pharmaceuticals, North Wales, PA) is in the range of 40–50% of the nominal dose using a pMDI formulation with hydrofluoroalkane propellant, which replaces the older chlorofluorocarbon (CFC) propellants.<sup>9</sup> New devices such as the Respimat® inhaler (Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT) have shown lung depositions of 40%.<sup>10</sup> Although lung dose efficiency varies between devices, inhalers with relatively low lung deposition fraction have been clinically proven to achieve the desired therapeutic effect in the target audience.

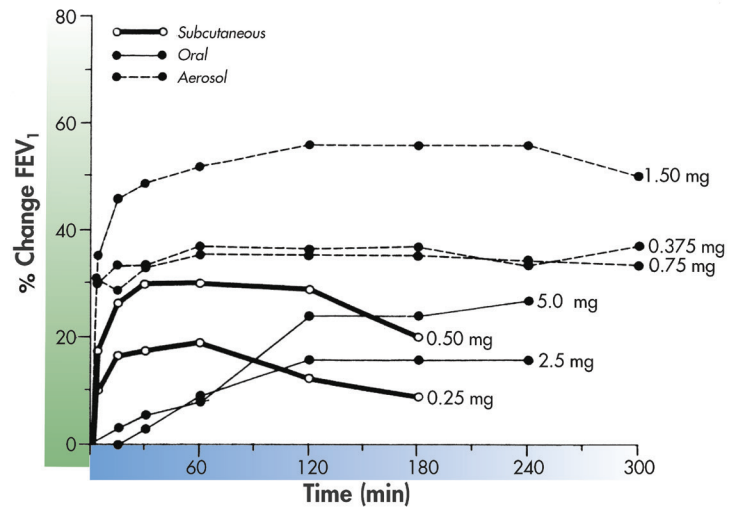


**Figure 2.** Drug deposition with common aerosol inhaler devices. Shown by color are the varying percentages of drug lung deposition and drug loss in the oropharynx, device, and exhaled breath.

pMDI = pressurized metered-dose inhaler; VHC = valved holding chamber; SVN = small-volume nebulizer; DPI = dry-powder inhaler  
(Modified, with permission, from Reference 1 and Reference 7)

## Advantages and Disadvantages of Inhaled Aerosol Drugs

There are a number of advantages and disadvantages that go along with the inhalation of drugs to treat pulmonary disease (Table 2). The primary advantage of inhaled aerosol therapy is treating the lung directly with smaller doses, resulting in fewer side effects than with oral delivery.<sup>11</sup> As seen in Figure 3, inhalation of terbutaline, a short-acting beta-2 agonist, from a pMDI resulted in better airflow than with a much larger oral dose or even with a subcutaneous injection of drug.



**Figure 3.** Changes in FEV<sub>1</sub> for three different routes of administration with terbutaline. Greater clinical effect was seen with drug delivered as inhaled aerosol from a pMDI, compared to similar or larger doses delivered orally or by subcutaneous injection. (From Reference 6, with permission)

## Hazards of Aerosol Therapy

Hazards associated with aerosol drug therapy may occur as a result of inhaled medication, an aerosol generator being used, the aerosol administration technique, and the environment. Hazards of aerosol therapy can impact the patient receiving therapy, as well as care providers and bystanders.

### Hazards for Patients

**Adverse Reaction:** Most hazards associated with aerosol therapy are attributed to adverse reactions to the drug being used. Therefore, inhaled medications should be administered with caution. Types of adverse reactions

**Table 2. Advantages and disadvantages of the inhaled aerosolized drugs**

(Modified, with permission, from Reference 1)

### Advantages

Aerosol doses are generally smaller than systemic doses.

Onset of effect with inhaled drugs is faster than with oral dosing.

Drug is delivered directly to the lungs, with minimal systemic exposure.

Systemic side effects are less frequent and severe with inhalation when compared to systemic delivery.

Inhaled drug therapy is less painful than injection and is relatively comfortable.

### Disadvantages

Lung deposition is a relatively low fraction of the total dose.

A number of variables (correct breathing pattern, use of device) can affect lung deposition and dose reproducibility.

The difficulty of coordinating hand action and inhalation with the pMDIs reduces effectiveness.

The lack of knowledge of correct or optimal use of aerosol devices by patients and clinicians decreases effectiveness.

The number and variability of device types confuses patients and clinicians.

The lack of standardized technical information on inhalers for clinicians reduces effectiveness.

include headache, insomnia, and nervousness with adrenergic agents, local topical effects with anticholinergics, and systemic/local effects of corticosteroids.<sup>12,13</sup> If any of these adverse reactions are seen during aerosol drug therapy, the treatment should be ended and the physician should be notified.

**Bronchospasm:** Administering a cold and high-density aerosol may induce bronchospasm in patients with asthma or other respiratory diseases.<sup>13-15</sup> If bronchospasm occurs during aerosol therapy, the therapy should be immediately discontinued for 15-20 minutes. If it persists, the physician should be notified.

**Drug Concentration:** In both jet and ultrasonic nebulizers, drug concentration may increase significantly during aerosol therapy.<sup>16-18</sup> An increase in drug concentration may be due to evaporation, heating, or the inability to efficiently nebulize suspensions.<sup>13,16,18,19</sup> As a result of changes in drug concentration, the amount of the drug remaining in the nebulizer at the end of aerosol therapy is increased and the patient is exposed to higher concentrations of inhaled medications. This is a great problem with continuous-feed nebulization.

**Infection:** It has been well documented that aerosol generators can become contaminated with bacteria and increase the risk of infection in patients with respiratory diseases.<sup>20-25</sup> The risk of transmission of an infection is dependent upon duration of exposure of drugs with pathogens and the procedures taken by respiratory therapists to avoid pathogen exposure. Proper practices of medication handling, device cleaning, and sterilization can greatly reduce this risk.

**Eye Irritation:** Inhaled medications delivered with a face mask may inadvertently deposit in the eyes and result in eye irritation. Improving the interface between the face mask and patient may eliminate this problem and increase the amount of drug delivered to the distal airways. Therefore, caution should be exercised when using a face mask during aerosol drug administration.

### Hazards for Care Providers and Bystanders

**Exposure to Secondhand Aerosol Drugs:** Care providers and bystanders have the risk of exposure to inhaled medications during routine monitoring and care of patients. While workplace exposure to aerosol may be detectable in the plasma,<sup>26</sup> it may also increase the risk of asthma-like symptoms and cause occupational asthma.<sup>27-29</sup> The development and implementation of an occupational health and safety policy in respiratory therapy departments can minimize exposure to secondhand aerosol drugs.

**Infection:** Care providers, bystanders, and even other patients have the risk of inhaling pathogens during aerosol therapy. The risk of infection can be minimized with the development and implementation of an infection control management system including use of masks, filters, and ventilation systems.<sup>30-32</sup>

### Currently Available Aerosol Drug Formulations

Some aerosol drugs are available in more than one formulation. Others (often newer drugs) are available only in a single formulation. Table 3 provides currently available aerosol drug formulations, their brand names, their FDA-approved aerosol delivery devices, and their costs.

**Table 3. Currently available aerosol drug formulations with corresponding inhaler devices and costs for use in the United States.**

HFA = hydrofluoroalkane; pMDI = pressurized metered-dose inhaler; SVN = small-volume nebulizer; DPI = dry-powder inhaler  
 Cost information from www. goodrx.com. Prices used were from WalMart in 2017.

**Short-Acting Bronchodilator**

Drug	Brand	Device	Strength	Doses	Cost	Cost/Dose			
Albuterol Sulfate	AccuNeb®	SVN	0.63	25	\$50.20	\$2.01			
			1.25	25	\$50.20	\$2.01			
	Albuterol Sulfate	SVN	2.5	25	\$15.30	\$0.61			
					ProAir® HFA	pMDI	200	\$58.99	\$0.30
					ProAir RespiClick®	DPI	200	\$55.73	\$0.28
					Proventil® HFA	pMDI	200	\$73.74	\$0.37
Ventolin® HFA	pMDI	200	\$56.42	\$0.28					
Levalbuterol	Xopenex® Inhalation Solution	SVN	0.31/3ml	24	\$39.16	\$1.63			
			0.63/3ml	24	\$39.16	\$1.63			
			1.25/3ml	24	\$39.16	\$1.63			
			1.25/0.5ml	24	\$23.08	\$0.96			
	Xopenex HFATM	pMDI	200	\$61.61	\$0.31				
Ipratropium Bromide	Ipratropium Bromide	SVN	vial	25	\$4.57	\$0.18			
	Atrovent HFA®	pMDI		200	\$331.32	\$1.66			
Ipratropium Bromide and Albuterol Sulfate	Ipratropium Bromide and Albuterol Sulfate	SVN		120	\$59.57	\$0.25			
				DuoNeb®	SVN	120	\$284.54	\$2.37	
				Combivent® Respimat®	pMDI	120	\$336.97	\$2.81	

**Long-Acting Bronchodilator**

Drug	Brand	Device	Strength	Doses	Cost	Cost/Dose
Aclidinium Bromide	Tudorza Pressair®	DPI	400 mcg	60	\$318.10	\$5.30
Arformoterol	Brovana®	SVN	15 mcg/2ml	30	\$457.06	\$15.24
				60	\$907.12	\$15.12
Formoterol	Perforomist®	SVN	20 mcg/2ml	60	\$873.92	\$9.57
Indacaterol	Arcapta®	DPI	75 mcg	30	\$227.70	\$7.59
Salmeterol	Serevent®	DPI	50 mcg	60	\$340.31	\$5.67
Tiotropium	Spiriva®	DPI	18 mcg	30	\$359.25	\$11.98
	Spiriva Respimat®	pMDI	1.5 mcg	30	\$359.25	\$11.98
	Spiriva Respimat®	pMDI	2.5 mcg	30	\$359.25	\$11.98
Olodaterol	Stiverdi Respimat®	pMDI	2.5 mcg	60	\$180.74	\$3.01
Umeclidinium	Incruse® Ellipta®	DPI	62.5 mcg	30	\$314.17	\$10.47
Glycopyrrolate	Seebri Neohaler	DPI	15.6 mcg	60	\$313.67	\$5.23

**Table 3. (continued)**

<b>Corticosteroids</b>						
<b>Drug</b>	<b>Brand</b>	<b>Device</b>	<b>Strength</b>	<b>Doses</b>	<b>Cost</b>	<b>Cost/Dose</b>
Beclomethasone	QVAR™ 40	pMDI	40 mcg	120	\$162.14	\$1.35
	QVAR™ 80	pMDI	80 mcg	120	\$211.57	\$1.76
Budesonide	Pulmicort Respules	SVN	0.25 mg	30	\$277.14	\$9.24
			0.5 mg	30	\$324.93	\$10.83
			1.0 mg	30	\$642.92	\$21.43
	Generic	SVN	0.25 mg	30	\$63.48	\$2.12
			0.5 mg	30	\$73.47	\$2.45
			1.0 mg	30	\$145.49	\$4.85
Pulmicort® Flexhaler®	DPI	90 mcg	120	\$164.14	\$1.37	
		180 mcg	120	\$214.12	\$1.79	
Ciclesonide	Alvesco®	pMDI	80 mcg	60	\$243.51	\$4.06
			160 mcg	60	\$243.51	\$4.06
Flunisolide	Aerospan®	pMDI	80 mcg	120	\$214.56	\$1.79
Fluticasone propionate	Flovent Diskus®	DPI	50 mcg	60	\$165.03	\$2.75
			100 mcg	60	\$173.96	\$2.90
			250 mcg	60	\$226.57	\$3.78
	Flovent HFA®	pMDI	44 mcg	120	\$173.96	\$1.45
			110 mcg	120	\$226.57	\$1.89
			220 mcg	120	\$348.05	\$2.90
ArmonAir® RespiClick®	DPI	55 mcg	60	Newly approved No pricing available		
		113 mcg	60			
		232 mcg	60			
Fluticasone furoate	Arnuity® Ellipta®	DPI	100 mcg	30	\$164.41	\$4.48
			200 mcg	30	\$214.43	\$7.15
Mometasone furoate	Asmanex® HFA	pMDI	100 mcg	120	\$191.68	\$1.60
			200 mcg	120	\$224.06	\$1.87
	Asmanex®	DPI	110 mcg	30	\$190.00	\$6.33
			220 mcg	30	\$205.00	\$6.83

<b>Mucoactive Drugs</b>						
<b>Drug</b>	<b>Brand</b>	<b>Device</b>	<b>Strength</b>	<b>Doses</b>	<b>Cost</b>	<b>Cost/Dose</b>
Dornase Alpha N-Acetylcysteine	Pulmozyme®	SVN	2.5mg/2.5ml	30	\$3173.13	\$105.77
			4ml/10%	1	\$2.46	\$2.46
			10ml/10%	1	\$4.16	\$1.64
			30ml/10%	1	\$9.81	\$1.31
			4ml/20%	1	\$3.21	\$3.21
			10ml/20%	1	\$6.02	\$2.41
			30ml/20%	1	\$12.00	\$1.60
			Hyperosmolar Saline	HyperSal®	SVN	3.5%
PulmoSal™ (ph 7.4)	SVN	7%		60	\$91.94	\$1.03
		7%		60	\$51.94	\$0.87

**Table 3. (continued)**

**Combination Drugs**

Drug	Brand	Device	Strength	Doses	Cost	Cost/Dose
Fluticasone and Salmeterol	Advair HFA®	pMDI	45/21 mcg	120	\$285.26	\$2.38
			115/21 mcg	120	\$352.74	\$2.94
			230/21 mcg	120	\$461.72	\$3.85
	Advair Diskus®	DPI	100/50 mcg	60	\$285.26	\$4.75
			250/50 mcg	60	\$352.74	\$5.88
			500/50 mcg	60	\$461.72	\$7.70
	AirDuo RespiClick®	DPI	55/14 mcg	60	Newly approved No pricing available	
			113/14 mcg	60		
			232/14 mcg	60		
Budesonide and Formoterol	Symbicort®	pMDI	80/4.5 mcg	120	\$270.22	\$2.25
			160/4.5 mcg	120	\$307.87	\$2.57
Mometasone/ Formoterol	Dulera®	pMDI	100/4 mcg	120	\$290.54	\$2.42
			200	120	\$290.54	\$2.42
Fluticasone furate/ Vilanterol	Breo® Ellipta®	DPI	100/25 mcg	60	\$314.80	\$5.25
			200/25 mcg	60	\$314.80	\$5.25
Tiotropium/ Olodaterol	Stiolto® Respimat®	pMDI	2.5/2.5 mcg	60	\$333.16	\$5.55
Umeclidinium/ Vilanterol	Anoro® Ellipta®	DPI	62.5/25 mcg	60	\$333.16	\$5.55
Indacaterol/ Glycopyrrolate	Utibron Neohaler®	DPI	27.5/15.6 mcg	60	\$313.67	\$5.23
Formoterol/ Glycopyrrolate	Bevespi Aerosphere®	pMDI	9/4.8 mcg	120	\$333.16	\$2.78

**Other Drugs**

Drug	Brand	Device	Strength	Doses	Cost	Cost/Dose
Zanamivir	Relenza®	DPI	5 mg	20	\$65.49	\$3.28
Tobramycin generic Bethkis Tobi Podhaler	TOBI®	SVN	300mg/5ml	56	\$7,578.95	\$135.33
		SVN	300mg/5ml	56	\$1590.21	\$28.40
		DPI	300mg/4ml 28 mg	56 224	\$5862.93 \$9152.54	\$209.40 \$40.85
Aztreonam	Cayston®	SVN	75 mg	84	\$8254.28	\$98.27
Cromolyn Sodium		SVN	20mg/2ml	60	\$211.63	\$3.53
Ribavirin	Virazole®	SPAG	6g	1	\$25766.30	\$25766.30
Mannitol	Aridol®	DP	Bronchial Challenge Test Kit, No pricing available			



# Small-Volume Nebulizers

Small-volume nebulizers (SVNs) are popular aerosol generators in acute care settings with clinicians and patients as they convert drug solutions or suspensions into aerosols that deposit into the patient's lower respiratory tract while requiring minimal patient cooperation.

## Advantages and Disadvantages of SVNs

Nebulizers have long been the cornerstone of medical aerosol therapy in the acute and critical care setting. Also, they are frequently the device selected for patients such as infants, small children, and the elderly who are unable to operate, coordinate, or cooperate with the use of various inhalers that require active participation and hand-eye-breath coordination. This functionality offsets the issues of portability, weight, noise, cost, and time of administration associated with nebulizers. Table 4 lists the advantages and disadvantages of small-volume nebulizers.

Nebulizers are regulated as medical devices by the U.S. Food and Drug Administration (FDA) Center for Devices and

Radiological Health (CDRH). They are tested in accordance with applicable standards for medical device electrical safety, electromagnetic compatibility, environmental temperature and humidity, shock and vibration, as well as for their biocompatibility of materials.

Nebulizers are designed to be used with a broad range of liquid formulations. Drugs for use with nebulizers are approved by the FDA and the Center for Drug Evaluation and Research (CDER). Historically, drug solutions for inhalation were approved based on studies using standard jet nebulizers (the first type of SVN) ranging in efficiency from 6–12%. The use of more efficient nebulizers created the risk of delivering inhaled dose above the upper threshold of the therapeutic window, increasing the risk of side effects and toxicity. Consequently, the FDA requires that the drug label of new liquid formulations identify the nebulizers used in the clinical studies (Table 5). Because drug delivery varies with different nebulizer types, it is important to use the nebulizer cited on the drug "label" when possible. At the

**Table 4. Advantages and disadvantages of SVNS** (Modified, with permission, from Reference 1)

Advantages	Disadvantages
Ability to aerosolize many drug solutions	Treatment times may range from 5–25 minutes.
Ability to aerosolize drug mixtures (>1 drug), if drugs are compatible	Equipment required may be large and cumbersome.
Minimal patient cooperation or coordination is needed.	Need for power source (electricity, battery, or compressed gas)
Useful in very young, very old, debilitated, or distressed patients	Potential for drug delivery into the eyes with face mask delivery
Drug concentrations and dose can be modified.	Potential for drug delivery exposure to clinicians and caregivers
Variability in performance characteristics among different types, brands, and models	Assembly and cleaning are required.
Normal breathing pattern can be used, and an inspiratory pause (breath-hold) is not required for efficacy.	Contamination is possible with improper handling of drug and inadequate cleaning.

very least, clinicians should be aware of the relative performance of the “label” nebulizer.

Pneumatic jet nebulizers most commonly used in the hospital or clinic are low-cost, mass-produced, single-patient-use disposable devices. Newer, more efficient nebulizers that operate at a higher efficiency and require shorter

treatment durations tend to be more expensive (Table 6). Nebulizer systems may include a nebulizer hand set, compressor or power pack, tubing, and accessories. In general, the compressor or electronics are durable and long-lasting, whereas handsets and accessories require more frequent replacement. Replacement costs are shown in Table 7.

**Table 5. Drug formulations and approved nebulizers for that formulation**

(Modified, with permission, from Reference 1)

Drug Formulation	Approved Nebulizer
Bronchodilator	Nebulizer type not specified
Acetylcysteine	Nebulizer type not specified
Arformoterol	Nebulizer type not specified
Formoterol	Nebulizer type not specified
Budesonide (Pulmicort Respules®)	Should not be used with ultrasonic nebulizer
Tobramycin (TOBI®)	Pari LC®, Sidestream Plus
Dornase alfa (Pulmozyme®)	Hudson T Up-draft II, Marquest Acorn® II, Pari LC®, Durable Sidestream®, Pari Baby™
Pentamidine (NebuPent)	Marquest Respirgard II
Ribavirin (Virazole®)	Small Particle Aerosol Generator
Iloprost (Ventavis®)	I-neb Adaptive Aerosol (AAD) System
Aztreonam (Cayston®)	Altera™ Nebulizer System
Treprostinil (Tyvaso®)	Tyvaso® Inhalation System

**Table 6. Relative costs of different nebulizer systems**

(Modified, with permission, from Reference 1)

Nebulizer Type	Approximate Cost Range
Pneumatic compressor nebulizer	\$30–\$200
Ultrasonic nebulizer	\$70–\$250
Vibrating mesh/horn nebulizer	\$200–\$1,200
Microprocessor-controlled breath-actuated nebulizer	\$750–\$2,000

**Table 7. Replacement costs of nebulizer components**

(Modified, with permission, from Reference 1)

Nebulizer Components (Interval)	Approximate Cost Range
Disposable jet nebulizer (1–7 days in acute care, longer use at home)	\$1–3
Jet nebulizer with bag reservoir (1–3 days)	\$4–15
Jet nebulizer with filter (1–3 days)	\$10–12
Breath-enhanced nebulizer	\$4–20
Breath-actuated jet nebulizer	\$4–6
Ultrasonic nebulizer medication chamber (daily or weekly)	\$1–5
USN handset replacement (3–12 months)	\$100–250
Vibrating mesh replacement (3–12 months)	\$40–150

## Types of SVNs

### Jet Nebulizers

Jet nebulizers are operated by compressed air or oxygen in order to aerosolize liquid medications. They are commonly used because they are the least expensive kind of nebulizer. A jet nebulizer delivers

compressed gas through a jet, causing a region of negative pressure. The solution to be aerosolized is entrained into the gas stream and is sheared into a liquid film. This film is unstable and breaks into droplets due to surface tension forces. A baffle located in the aerosol stream impacts these droplets producing smaller particles. The operating performance of jet nebulizers is affected by both the technical and patient-related factors described in Table 8.

### Factors Affecting Jet Nebulizer Performance and Drug Delivery

There are many factors for respiratory therapists to keep in mind during aerosol therapy. Nebulizer design holds a key determining factor in the size of particles and output performance produced, which results in the ultimate efficiency of medication according to the factors discussed below. Various types of nebulizers are available on the market, and several studies have indicated that performance varies between manufacturers and also between nebulizers from the same manufacturer.<sup>1,33,34</sup>

- **Gas Flow and Pressure:** Jet nebulizers are designed to operate by means of varied levels of compressed gas flow and pressure. Each model of jet nebulizer is designed to work best at a specific flow, ranging from 2–8 L/min, which should be listed on the device label. Operating any jet nebulizer at a lower flow or pressure will increase particle size. For example, a jet nebulizer designed to operate at 6–8 L/min at 50 psi will produce larger particles if driven by a compressor producing 13 psi. Consequently, jet nebulizers should be matched with a compressor or gas source that matches their intended design. Gas flow is also inversely related to nebulization time. Using a higher gas flow rate in aerosol therapy will decrease the amount of treatment time needed to deliver the set amount of drug.

**Table 8. Factors affecting penetration and deposition of therapeutic aerosols delivered by jet nebulizers** (Modified, with permission, from Reference 1)

#### Technical Factors

Design and model of nebulizer  
Flow used to power nebulizer  
Fill volume of nebulizer  
Solution characteristics  
Composition of driving gas  
Designs to enhance nebulizer output  
Continuous vs. breath-actuated

#### Patient Factors

Breathing pattern  
Nose vs. mouth breathing  
Composition of inspired gas  
Airway obstruction  
Positive pressure delivery  
Artificial airway and mechanical ventilation

- **Fill and Dead Volumes:** Altering the fill volume is another factor that impacts the efficiency of jet nebulizers. Studies report increased efficiency with this due to nebulizers with a fixed dead volume, and thus an increase in fill volume reduces the proportion of dead volume within the nebulizer. Although efficiency increases with a greater fill volume, there is also an increase in nebulization time.<sup>34</sup> Likewise, these nebulizers do not function well with small fill volumes like 2 mL or less because this is close to dead volume (also termed residual volume). Jet nebulizers do not aerosolize below dead volume; therefore, it is recommended to use a fill volume of 4–5 mL unless the nebulizer is specifically designed for a smaller fill volume.<sup>1,34</sup> This precaution dilutes the medication, allowing for a greater proportion to be nebulized, though it increases the treatment time. Dead volume, the amount of medication remaining in the jet nebulizer at the end of a treatment, can range from 0.5 to 2.0 mL. The greater the dead volume, the less drug is nebulized.
- **Gas Density:** By a similar offsetting, the density of gas used to run a jet nebulizer can impact aerosol deposition by affecting aerosol output and particle size. For example, delivering aerosol with helium-oxygen (heliox) gas mixtures can increase lung deposition by as much as 50%. Using heliox at the same flow rate as with air or oxygen reduces particle size and aerosol output, ultimately increasing treatment times. Consequently, the flow with heliox should be increased by 1.5–2 times to bring particle size and output back to levels achieved with air or oxygen.
- **Humidity and Temperature:** Humidity and temperature can also affect particle size and residual volume.

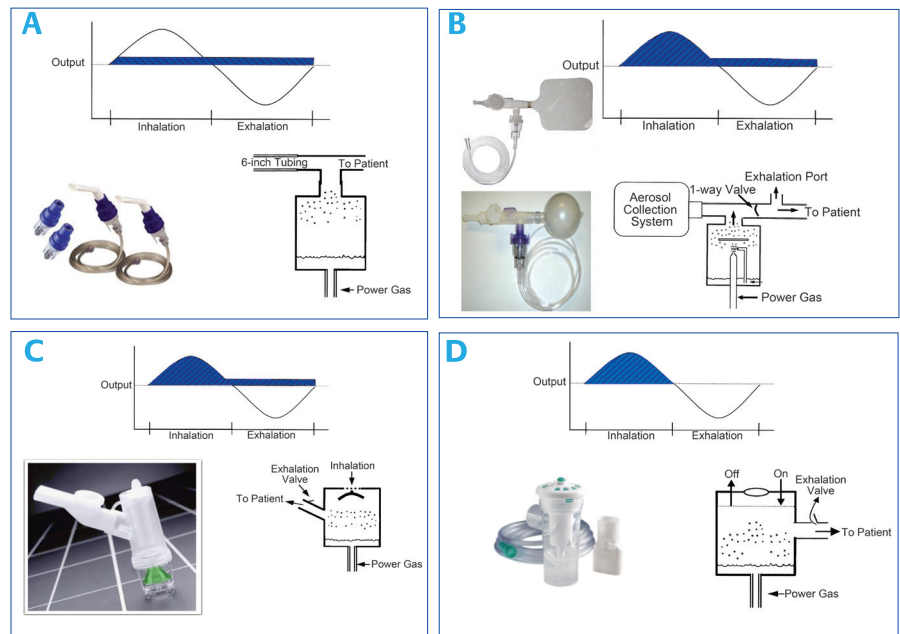
Specifically, water evaporation during aerosol therapy can reduce the temperature of an aerosol, which results in an increase in solution viscosity and a decrease in the nebulizer output of drug.

- Breathing Pattern:** Breathing pattern influences aerosol deposition in the lower respiratory tract. The patient should be instructed to do tidal breathing with periodic deep breaths during aerosol therapy.
- Device Interface:** Medical aerosols can be administered using either a mouthpiece or a face mask. Ideally, a mouthpiece should be used. The nose tends to filter more aerosol than the mouth, so use of a mouthpiece should be encouraged, when appropriate. Mouthpieces cannot be used for infants and small children. In addition, the use of a mouthpiece may be uncomfortable for longer aerosol therapy. Use of a mask increases the amount of aerosol deposited on the face, in the eyes, and into the nose. Whether a mouthpiece or a face mask is used, it is important to instruct the patient to inhale through the mouth during aerosol therapy. Proper mask fit and design can optimize the inhaled dose and reduce deposition to the eyes. The respiratory therapist must keep all of these factors in mind when practicing or equipping patients.

### Types of Pneumatic Jet Nebulizer Designs

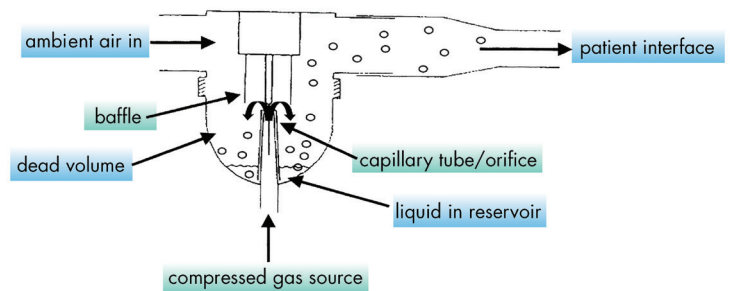
Nebulizer design changes over the past decade have created different nebulizer categories.<sup>35,36</sup> There are four different designs of the pneumatic jet nebulizer: jet nebulizer with reservoir tube, jet nebulizer with collection bag or elastomeric reservoir ball, breath-enhanced jet nebulizer, and breath-actuated jet nebulizer. All four of these are depicted in Figure 4 and described below.

**A. Jet Nebulizer with a Reservoir Tube:** This is the least expensive and most widely used nebulizer. It provides



**Figure 4.** Different types of pneumatic jet nebulizer designs and their aerosol output indicated by the shaded area: **A.** pneumatic jet nebulizer with reservoir tube; **B.** jet nebulizer with collection bag; **C.** breath-enhanced jet nebulizer; **D.** breath-actuated jet nebulizer. (From Reference 1, with permission)

continuous aerosol during inhalation, exhalation, and breath-hold, causing the release of aerosol to ambient air during exhalation and anytime when the patient is not breathing (Figure 4-A).<sup>36-37</sup> Consequently, only 8-15% of the emitted aerosol is inhaled. In order to decrease drug loss and increase inhaled mass, a t-piece and large bore tubing are attached to the expiratory side of the nebulizer. These types of nebulizers have been considered to be inefficient due to their providing a low percentage of the dose to the patient.<sup>38</sup> Figure 5 illustrates the functioning of a jet nebulizer. Examples of a jet nebulizer with a reservoir tube model include the Sidestream Nebulizers™ (Philips, Murrysville, PA) and the Micro Mist® (Teleflex Medical, Research Triangle Park, NC).



**Figure 5.** Schematic illustration of the function of a jet nebulizer (From Reference 1, with permission)

### B. Jet Nebulizer with Collection Bag or Elastomeric Reservoir Ball:

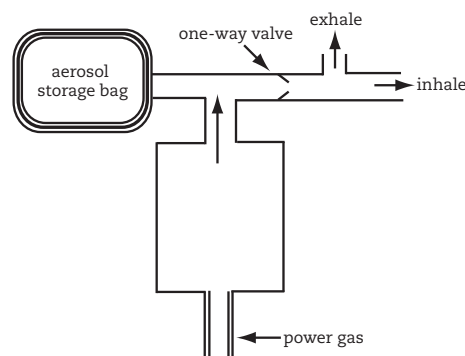
These types of nebulizers generate aerosol by continuously filling a reservoir (Figure 4-B). The patient inhales aerosol from the reservoir through a one-way inspiratory valve and exhales to the atmosphere through an exhalation port between the one-way inspiratory valve and the mouthpiece.<sup>35,37</sup> Figure 6 illustrates the principle of operation and patterns of gas flow during inhalation and exhalation with the Circulaire® II (Westmed, Tucson, AZ) which is one model of the nebulizer with a collection bag or elastomeric reservoir ball.

**C. Breath-Enhanced Jet Nebulizer:** Breath-enhanced nebulizers use two one-way valves to prevent the loss of aerosol to environment (Figure 4-C). When the patient inhales, the inspiratory valve opens and gas vents through the nebulizer. Exhaled gas passes through an expiratory valve in the mouthpiece. Figure 7 illustrates the operation principle of the breath-enhanced nebulizer. PARI LC® Sprint (PARI, Midlothian, VA), NebuTech HDN® (Salter Labs, Arvin, CA), and SideStream Plus® (Philips, Murrysville, PA) are the breath-enhanced nebulizers available on the market.

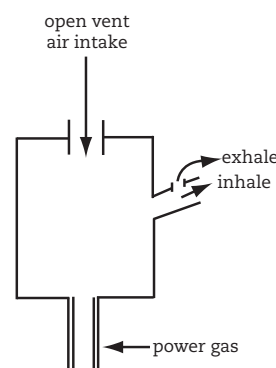
**D. Breath-Actuated Jet Nebulizer:** Breath-actuated nebulizers are designed to increase aerosol drug delivery to patients by generating aerosol only during active inspiration. Consequently, loss of medication during expiration phase is greatly reduced, as shown in Figure 4-D.<sup>37</sup> Whereas breath actuation can increase the inhaled dose by more than three-fold, this efficiency is achieved only by an increase in dosing time. Breath-actuation mechanisms can be classified as manual, mechanical, and electronic:

**1. Manual Breath-Actuated:** The first generation of breath-actuated nebulizers uses a thumb control to regulate aerosol production during inspiration and expiration. Blocking the patient-controlled thumb port directs gas to the nebulizer only during inspiration; releasing the thumb at the port pauses the nebulization (Figure 8). The thumb control breath-actuated nebulizer wastes less of the medication being aerosolized, but it significantly increases the treatment time and requires good hand-breath coordination.

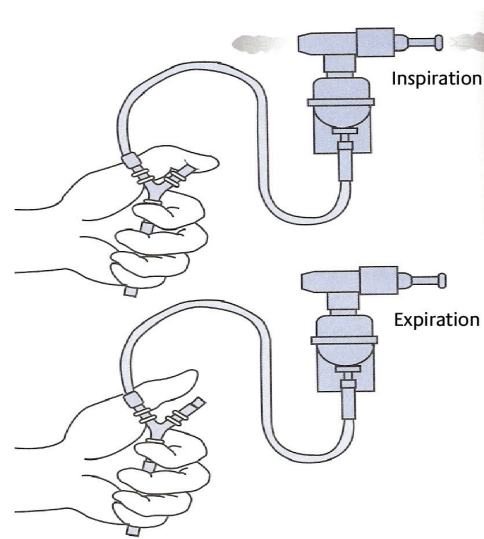
**2. Mechanical Breath-Actuated:** The AeroEclipse® II BAN



**Figure 6.** Schematic illustration of the function of a jet nebulizer with collecting bag (From Reference 37, with permission)



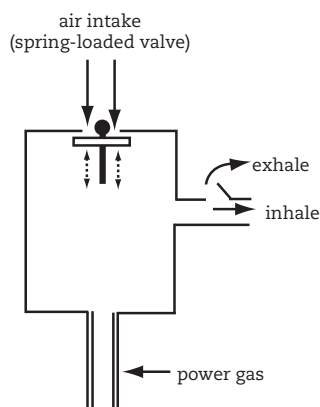
**Figure 7.** Schematic illustration of the function of a breath-enhanced jet nebulizer (From Reference 37, with permission)



**Figure 8.** Schematic illustration of the function of a manual breath-actuated jet nebulizer (From Reference 7, with permission)

(Monaghan Medical Corporation, Plattsburgh, NY) is an example of mechanical breath-actuated nebulizers. As shown in Figure 9, the mechanical breath-actuated nebulizer has a breath-actuated valve that triggers aerosol generation only during active inspiration and eliminates the need for a storage bag or reservoir. Patients must be able to generate a sufficient inspiratory flow to trigger the nebulizer. Therefore, the sensitivity of this mechanism makes it suitable only for some children and adults.

**3. Microprocessor Breath-Actuated:** The final type of breath-actuated jet nebulizer is more complex but more appropriate to a wider range of users. In this type, compressor-driven jet nebulizers are actuated by an electronic circuit, commonly triggered by a pressure transducer sensing inspiratory effort. For several decades these devices have been used in pulmonary function and research labs to administer precise boluses of aerosol for methacholine challenge. A newer generation of “smart” microprocessor-controlled breath-actuated nebulizers uses computer programs and sensing technology to control the pattern of aerosol generation and even to calculate and track the delivered dose. The I-neb AAD® system (Philips) is one model of the microprocessor, breath-actuated that uses vibrating mesh nebulization.



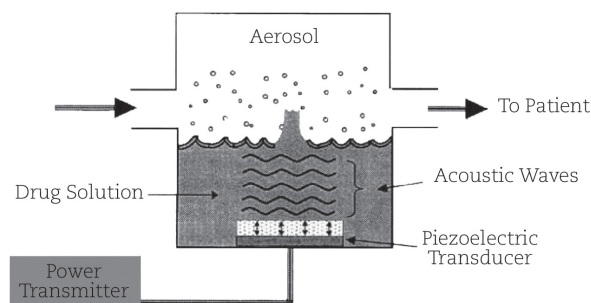
**Figure 9.** Schematic illustration of the function of a mechanical breath-actuated nebulizer (From Reference 37, with permission)

### Ultrasonic Nebulizers

Ultrasonic nebulizers convert electrical energy to high-frequency vibrations using a transducer. These vibrations are transferred to the surface of the solution, creating a standing wave that generates aerosol (Figure 10). Ultrasonic nebulizers were initially introduced as large-volume nebulizers most commonly used to deliver hypertonic saline for sputum inductions. Small-volume ultrasonic nebulizers are now commercially available for delivery of inhaled bronchodilators but should not be used with suspensions such as budesonide. Ultrasonic nebulizers tend to heat medication. This raises concerns about disrupting proteins, but that does not affect commonly inhaled medications. The MicroAir® Ultrasonic Model (Omron Healthcare, Bannockburn, IL) and MABIS® NebPak™ and MiniBreeze™ Ultrasonic Nebulizers (Mabis Healthcare, Waukegan, IL) are different models of the ultrasonic nebulizer.

### Mesh Nebulizers

Mesh nebulizers use electricity to vibrate a piezo (at approximately ~128 KHz) element that moves liquid formulations through a fine mesh to generate aerosol. The diameter of the mesh or aperture determines the size of the particle generated. Mesh nebulizers are very efficient and result in minimal residual volume (0.1–0.5 mL). As seen in Figure 11, mesh nebulizers utilize two basic mechanisms of action: active vibrating mesh and passive mesh.

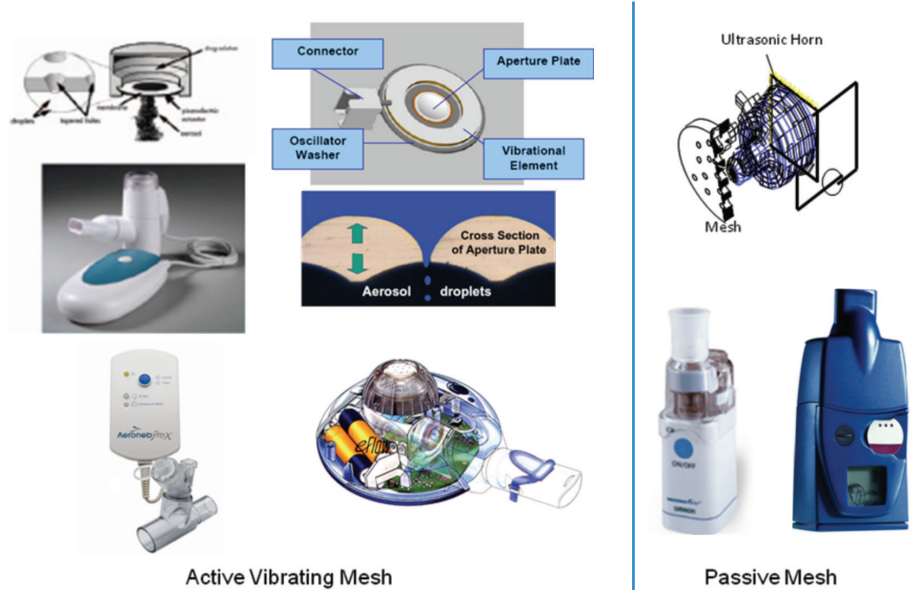


**Figure 10.** Components and operation principle of an ultrasonic nebulizer (From Reference 1, with permission)

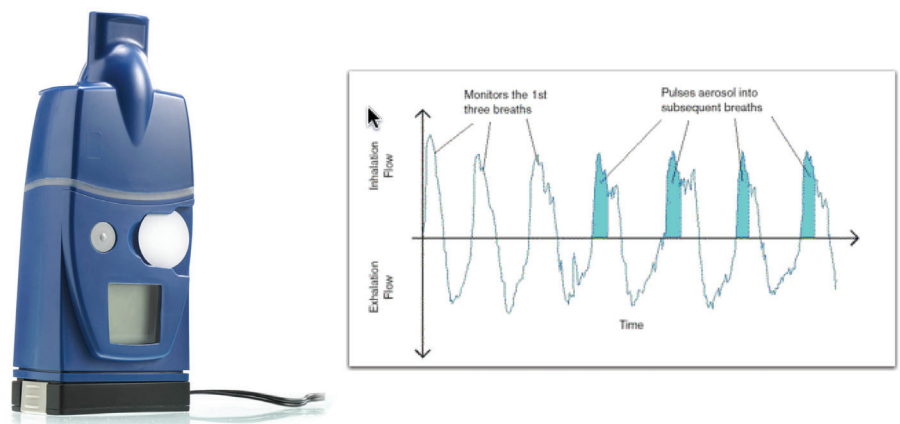


**Active Vibrating Mesh:** Active vibrating mesh nebulizers have an aperture plate with 1,000–4,000 funnel-shaped holes vibrated by a piezo-ceramic element that surrounds the aperture plate. The Aeroneb® Ultra and Solo (Aerogen, Galway, Ireland), Akita® Jet (Inamed, Germany) and eRapid® (PARI, Midlothian, VA) are models of the active vibrating mesh nebulizers (Figure 11, left).

**Passive Mesh:** These types of nebulizers utilize an ultrasonic horn to push fluid through a mesh (Figure 11, right). I-neb® AAD System® (Philips) and MicroAir™ U22 (Omron Healthcare) are models of the passive mesh nebulizer. A third-generation adaptive aerosol delivery (AAD) system such as the I-neb® has a small, battery-powered, lightweight, and silent drug delivery device designed to deliver a precise, reproducible dose of drug. The aerosol is created by a passive mesh, and aerosol is injected into the breath at the beginning of inhalation (Figure 12). The dosage of the drug is controlled through specific metering chambers. The metering chambers can deliver a pre-set volume ranging from 0.25 to 1.7 mL with a residual volume of about 0.1 mL. The I-neb® model incorporates an AAD algorithm that pulses medication delivery into 50–80% of each inspiration, based on a rolling average of the last three breaths. Throughout the treatment, the I-neb® provides continuous feedback to the patient through a liquid crystal display; and upon successful delivery of the treatment, the patient receives audible and tactile feedback.



**Figure 11.** Basic configurations of mesh nebulizers



**Figure 12.** Adaptive aerosol delivery as provided by the Philips I-neb®. As illustrated, aerosol is injected into the breath at the beginning of inhalation. (With permission of Philips)

## Nebulizers for Specific Applications

### Nebulizer for Ribavirin Administration

The small-particle aerosol generator (SPAG) is a large-volume nebulizer designed solely to deliver

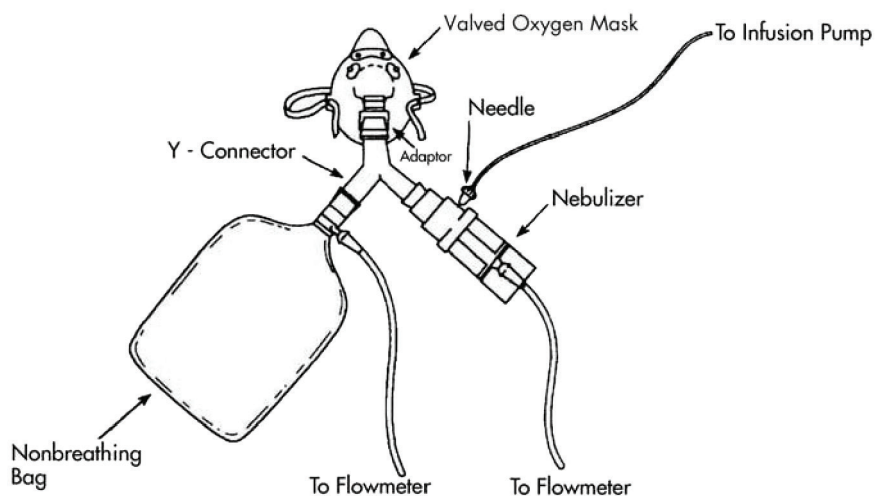
aerosolized ribavirin (Virazole®, Valeant Pharmaceuticals, Aliso Viejo, CA) for prolonged periods of nebulization. It consists of a nebulizer and a drying chamber that reduces the MMAD to about 1.3  $\mu\text{m}$ . Because of teratogenic characteristics of ribavirin, a scavenging system is strongly recommended for use during its administration.

### Nebulizer for Aerosolized Pentamidine Administration

When administering aerosolized pentamidine, an SVN fitted with inspiratory and expiratory one-way valves and with expiratory filter is used. These valves prevent exposure of secondhand pentamidine aerosol and contamination of the ambient environment with exhaled aerosol. In 2014, the National Institute for Occupational Safety and Health (NIOSH) removed pentamidine from its hazardous drug list indicating it no longer requires these devices or aerosol treatments to be delivered in a negative pressure room.

### Continuous Aerosol Therapy

Continuous aerosol drug administration is a safe treatment modality and is used to treat patients suffering acute asthma exacerbations. Researchers reported that it may be as effective as intermittent aerosol therapy or may, in fact, be superior to intermittent nebulization in patients with severe pulmonary dysfunction.<sup>39</sup> Figure 13 illustrates a basic setup for continuous aerosol therapy that includes an infusion pump, a one-way valved oxygen mask, and a reservoir bag. Commercial nebulizers used in continuous nebulization commonly have luer lock ports designed for use with infusion pumps. The nebulization is most commonly administered using standard aerosol masks.



**Figure 13.** Setup for continuous aerosol therapy (From Reference 1, with permission)

### Drug-Delivery Technique

Because different types of nebulizers are available on the market, the respiratory therapist should carefully review operation instructions prior to giving aerosol therapy and certainly prior to instructing patients in at-home aerosol delivery. Proper technique is provided in Technique Box 1.

## Technique Box 1. Steps for Correct Use of Nebulizers

### Technique for Jet Nebulizers: When a jet nebulizer is used, the patient should:

1. Assemble tubing, nebulizer cup, and mouthpiece (or mask).
2. Place medicine into the nebulizer cup.
3. Sit in an upright position.
4. Connect the nebulizer to a power source.
5. Breathe normally with occasional deep breaths until sputter occurs or until the end of nebulization.
6. Keep the nebulizer vertical during treatment.
7. Rinse the nebulizer with sterile or distilled water and allow to air dry.

### Technique for Mesh and Ultrasonic Nebulizers: When a mesh or ultrasonic nebulizer is used, the patient should:

1. Correctly assemble the nebulizer per manufacturer's specifications.
2. If applicable, follow manufacturer's instructions in performing a functionality test prior to the first use of a new nebulizer as well as after each disinfection to verify proper operation.
3. Pour the solution into the medication reservoir. Do not exceed the volume recommended by the manufacturer.
4. Sit in an upright position.
5. Turn on the power.
6. Hold the nebulizer in the position recommended by the manufacturer.
7. Follow the instructions for breathing technique that is recommended by the manufacturer for these uniquely designed mesh and ultrasonic nebulizers.
8. If the treatment must be interrupted, turn off the unit to avoid waste.
9. At the completion of the treatment, disassemble and clean as recommended by the manufacturer.
10. When using a mesh nebulizer, do not touch the mesh during cleaning. This will damage the unit.
11. Once or twice a week, disinfect the nebulizer following the manufacturer's instructions.

### General Steps To Avoid Reduced or No Dosing for All Nebulizers: When using nebulizers, the following steps should be used in order to avoid reduced or no dosing during aerosol treatment. The patient should:

1. Read and follow the instructions.
2. Make sure that the nebulizer is properly assembled and all connections are secured tightly.
3. Make sure that the nebulizer is cleaned and dried between uses.
4. Make sure that the nebulizer operated in its proper orientation.

## Technique Box 1. Steps for Correct Use of Nebulizers (continued)

### Troubleshooting

#### Problem with Jet Nebulizers: Absent or Low Aerosol

Causes	Solutions
Loose or unattached connections	Check the connections and make sure that they are properly attached.
Inappropriate flowmeter setting	Check the flowmeter setting and adjust the flow if it is not appropriate.
Obstruction in the orifice of the jet nebulizer	Check the orifice of the jet nebulizer and clear obstructions when needed.

#### Problems with Mesh and Ultrasonic Nebulizers: The Unit Does Not Operate

Causes	Solutions
Incorrect battery installation (seen in both mesh and ultrasonic nebulizers)	Check the battery installation and reinstall if needed.
External power source connection (seen in both mesh and ultrasonic nebulizers)	Check the connections with the AC adapter and the electrical output.
Overheated unit (seen in ultrasonic nebulizers)	Turn off the unit, wait until it cools down, and restart the unit.
Incorrect connection of the control module cable (seen in mesh nebulizers)	Check the connections with the control module cable and attach them properly, if needed.
Malfunctioning electronics (seen in both mesh nebulizers and ultrasonic nebulizers)	Replace the unit.

#### When Does the Treatment Need To Be Ended?

Nebulizers are commonly used for intermittent short-duration treatments and typically have a set volume of drug formulation placed in the medication reservoirs. The drug remaining in a nebulizer after therapy ranges from 0.1 to 2 mL.<sup>18</sup> Whereas some respiratory therapists and patients tap the nebulizer in order to reduce dead volume and increase nebulizer output,<sup>40</sup> others continue aerosol therapy past the point of sputtering in an effort to decrease dead volume.<sup>18</sup> Some nebulizers will sputter for extended periods of time

after the majority of the inhaled dose has been administered. Evidence suggests that after the onset of sputter, very little additional drug is inhaled.<sup>18,41</sup> Because the time it takes to administer the drug is a critical factor for patient adherence to therapy, some clinicians have adopted recommendations to stop nebulizer therapy at, or one minute after, the onset of sputter. Newer nebulizers may use microprocessors to monitor how much dose has been administered and automatically turn off the nebulizer at the end of each dose.

**\*Cleaning:** Please refer to the Infection Control section on pages 44–47 for the cleaning instructions of small-volume nebulizers.

# Inhalers

The pressurized metered-dose inhaler and dry-powder inhaler are medical aerosol delivery devices that combine a device with a specific formulation and dose of drug. Each actuation of the inhaler is associated with a single inspiration of the patient. These are typically single-patient-use devices dispensed from the pharmacy with a specific quantity of medication and disposed of when the medication has been depleted.

Inhalers are approved by the FDA Center for Drug Evaluation Research (CDER) as drug and device combinations. They typically are required to go through the complete drug development process from pre-clinical to pivotal trials in hundreds to thousands of patients. Inhaler-based drugs must have reproducible doses ( $\pm 20$ ) from first to last dose and have a shelf life with drug of at least 12–24 months. Once an inhaler enters the Phase III trials, the

design and materials are set and cannot be changed without additional expensive clinical trials.

There is a large variety of inhaler designs, and many drugs are available only in a single inhaler form (Figure 14). Patients are commonly prescribed several types of inhalers with different instructions for operation. Confusion between device operation can result in suboptimal therapy. For example, pMDIs typically require slow inspiratory flow ( $<30$  L/min) with a breath-hold, while a DPI may require significantly high flows (30–90 L/min) based on their resistive properties to disperse a full dose. Patients may confuse which inspiratory flow to use with which device and may get much less drug from both devices. Therefore, education and repetitive return demonstration is the key to proper inhaler use.



**Figure 14.** Common Inhalers Available in the United States

## Anticholinergics/ $\beta_2$ -Agonist Combination

**Combivent®  
Respimat®**  
(ipratropium  
bromide and  
albuterol sulfate)  
Inhalation Spray



Boehringer Ingelheim Pharmaceuticals, Inc.

**Stiolto®  
Respimat®**  
(tiotropium  
bromide  
and olodaterol)  
Inhalation Spray



Boehringer Ingelheim Pharmaceuticals, Inc.

**Utibron™  
Neohaler®**  
(indacaterol  
and  
glycopyrrolate)  
Inhalation Powder



Sunovion Pharmaceuticals Inc.

**Anoro®  
Ellipta®**  
(umeclidinium  
and vilanterol)  
Inhalation  
Powder



GlaxoSmithKline

**Bevespi  
Aerosphere™**  
(glycopyrrolate  
and formoterol  
fumarate)  
Inhalation Aerosol



AstraZeneca Pharmaceuticals

## Anticholinergics

**Spiriva®  
Handihaler®**  
(tiotropium  
bromide)  
Inhalation Powder



Boehringer Ingelheim  
Pharmaceuticals, Inc.

**Atrovent® HFA**  
(ipratropium  
bromide HFA)  
Inhalation  
Aerosol



Boehringer Ingelheim  
Pharmaceuticals, Inc.

**Tudorza™  
Pressair™**  
(aclidinium  
bromide)  
Inhalation Powder



Forest Pharmaceuticals, Inc.

**Incruse®  
Ellipta®**  
(umeclidinium)  
Inhalation  
Powder



GlaxoSmithKline

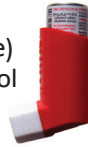
**Seebri™  
Neohaler®**  
(glycopyrrolate)  
Inhalation  
Powder



Sunovion Pharmaceuticals Inc.

## $\beta_2$ -Agonists

**ProAir® HFA**  
(albuterol sulfate)  
Inhalation Aerosol



Teva Specialty  
Pharmaceuticals

**ProAir® RespiClick®**  
(albuterol sulfate)  
Inhalation Powder



Teva Specialty  
Pharmaceuticals

**Proventil® HFA**  
(albuterol sulfate)  
Inhalation Aerosol



3M Pharmaceuticals Inc.

**Arcapta™  
Neohaler™**  
(indacaterol)  
Inhalation Powder



Novartis Pharmaceuticals

**Striverdi®  
Respimat®**  
(olodaterol)  
Inhalation Spray



Boehringer Ingelheim  
Pharmaceuticals, Inc.

**Xopenex® HFA**  
(levalbuterol tartare)  
Inhalation Aerosol



Sunovion Pharmaceuticals Inc.

**Ventolin® HFA**  
(albuterol sulfate HFA)  
Inhalation Aerosol



GlaxoSmithKline

**Serevent® Diskus®**  
(salmeterol xinafoate)  
Inhalation Powder



GlaxoSmithKline

**Serevent® HFA**  
(salmeterol xinafoate)  
Inhalation Aerosol



GlaxoSmithKline

## Corticosteroids

**Alvesco®**  
(ciclesonide)  
Inhalation  
Aerosol



Nycomed

**Asmanex  
Twisthaler®**  
(mometasone)  
Inhalation  
Powder



Schering Corporation

**Flovent® Diskus®**  
(fluticasone  
propionate)  
Inhalation  
Powder



GlaxoSmithKline

**ArmonAir™ RespiClick®**  
(fluticasone propionate)  
Inhalation Powder



Teva Specialty Pharmaceuticals

**Arnuity®  
Ellipta®**  
(fluticasone  
furoate)  
Inhalation  
Powder



GlaxoSmithKline

**Flovent® HFA**  
(fluticasone  
propionate)  
Inhalation  
Aerosol



GlaxoSmithKline

**Pulmicort®  
Flexhaler®**  
(budesonide)  
Inhalation Powder



AstraZeneca LP

**QVAR®**  
(beclomethasone  
dipropionate)  
Inhalation  
Aerosol



Teva Specialty Pharmaceuticals

**Aerospan®**  
(flunisolide)  
Inhalation  
Aerosol



Mylan Pharmaceuticals

## $\beta_2$ -Agonist/Corticosteroid Combination

**Advair® Diskus®**  
(fluticasone  
propionate and  
salmeterol)  
Inhalation Powder



GlaxoSmithKline

**Advair® HFA**  
(fluticasone propionate  
and salmeterol  
xinafoate)  
Inhalation Aerosol



GlaxoSmithKline

**Breo® Ellipta®**  
(fluticasone furoate  
and vilanterol)  
Inhalation Powder



GlaxoSmithKline

**Dulera®**  
(mometasone  
furoate/  
formoterol  
fumarate  
dihydrate)  
Inhalation Aerosol



Merck

**Symbicort®**  
(budesonide and  
formoterol fumarate  
dihydrate)  
Inhalation Aerosol



AstraZeneca

**AirDuo  
RespiClick®**  
(fluticasone  
propionate  
and salmeterol)  
Inhalation Powder



Teva Specialty Pharmaceuticals

## Other

**Relenza®**  
(zanamivir)  
Inhalation Powder



GlaxoSmithKline

**TOBI® Podhaler®**  
(tobramycin)  
Inhalation  
Powder



Novartis Pharmaceuticals



# Pressurized Metered-Dose Inhalers

Since its development by Dr. George Mason in 1955, the pMDI has been the most common aerosol generator prescribed for patients with asthma and COPD. This is because it is compact, portable, easy to use, and provides multi-dose convenience in a single device.

## Advantages and Disadvantages of pMDIs

The pMDI was designed and developed as a drug and device combination that delivers precise doses of specific drug formulations. Unlike nebulizers, drug preparation and handling is not required with pMDIs, and the internal components of pMDIs are difficult to contaminate. Table 9 gives the advantages and disadvantages associated with the use of pMDIs.

## Types of pMDIs

There are two major types of pMDIs: conventional pMDIs and soft-mist inhalers. Regardless of manufacturer or active ingredient, the basic components of the pMDI include the canister, propellants, drug formulary, metering valve, and actuator. The characteristics of each pMDI component are described in Table 10.

## Conventional pMDI

As seen in Figure 15, the pMDI consists of a canister, the medication, the propellant/excipient, a metering valve, the mouthpiece, and actuator.<sup>42</sup> The medication represents only 1–2% of the mixture emitted from the pMDI and is either suspended or dissolved in the propellant/excipient mixture. The propellant of the pMDI makes up 80% of the mixture. These agents prevent aggregation of the drug particles and lubricate the metering valve. They also ensure that the drug is well suspended in the canister. The metering valve acts to prepare a pre-measured dose of medication along with the propellant. The volume of the metering valve changes from 25–100  $\mu\text{L}$  and provides 50  $\mu\text{g}$  to 5 mg of drug per actuation, depending on the drug formulation.

The conventional pMDI has a press-and-breathe design. Depressing the canister into the actuator releases the drug-propellant mixture, which then expands and vaporizes to convert the liquid medication into an aerosol. The initial vaporization of the propellant cools the aerosol suspension. The canister aligns the hole in the metering valve with the metering chamber when it is pressed down. Then, the high propellant vapor pressure forces a pre-measured dose of

**Table 9. Advantages and disadvantages of pMDIs** (Modified, with permission, from Reference 1)

### Advantages

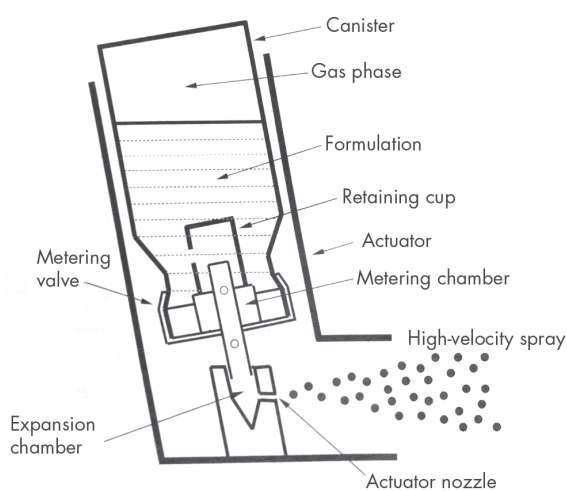
- Portable, light, and compact
- Multiple dose convenience
- Short treatment time
- Reproducible emitted doses
- No drug preparation required
- Difficult to contaminate

### Disadvantages

- Hand-breath coordination required
- Patient activation, proper inhalation pattern, and breath-hold required
- Fixed drug concentrations and doses
- Reaction to propellants in some patients
- Foreign body aspiration from debris-filled mouthpiece
- High oropharyngeal deposition
- Difficult to determine the dose remaining in the canister without dose counter

**Table 10. Basic components of the pMDI (From Reference 1 with permission)**

Component	Particulars
<b>Canister</b>	Inert, able to withstand high internal pressures and utilize a coating to prevent drug adherence
<b>Propellants</b>	Liquefied compressed gases in which the drug is dissolved or suspended
<b>Drug Formulary</b>	Particulate suspensions or solutions in the presence of surfactants or alcohol that allocate the drug dose and the specific particle size
<b>Metering Valve</b>	Most critical component that is crimped onto the container and is responsible for metering a reproducible volume or dose  Elastomeric valves for sealing and preventing drug loss or leakage
<b>Actuator</b>	Frequently referred to as the “boot,” partially responsible for particle size based on the length and diameter of the nozzle for the various pMDIs (Each boot is unique to a specific pMDI/drug.)
<b>Dose Counter</b>	This component provides a visual tracking of the number of doses remaining in the pMDI

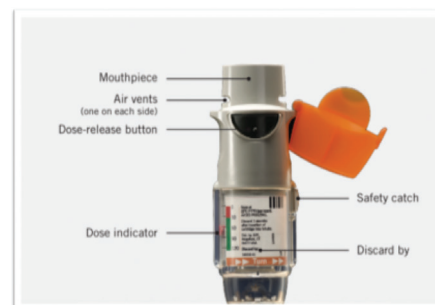


**Figure 15.** Standard components of pMDI (Modified with permission from Reference 42)

medication out of this hole and through the actuator nozzle. Last, releasing the metering valve refills the chambers with another dose of the drug-propellant mixture. The propellants used with pMDIs are HFAs. HFAs are pharmacologically inert and do not contain surfactant or use alcohol for this purpose.

#### **Soft-Mist pMDI**

The Respimat® (Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT) is a propellant-free soft-mist inhaler. The Respimat® utilizes mechanical energy in the form of a tensioned spring to generate the soft aerosol plume. The energy from turning the transparent base to the right one-half turn draws a predetermined metered volume of solution from the medication cartridge through a capillary tube into a micro-pump. When the dose release button is depressed, the energy from the spring forces the solution to the mouthpiece, creating a soft aerosol plume that lasts approximately 1.5 seconds. Similar to pMDIs, the Respimat® will need to be primed before use and at times when the device has had no use. If not used for more than 3 days, actuate the inhaler once. After more than 21 days of no use, it is



**Figure 16.** Soft-mist inhaler

recommended to actuate the device until aerosol is seen, then actuate 3 more times. Since the device is propellant free, there is no need to shake it. The Respimat® has a dose indicator and will lock once all medication is used. Figure 16 shows the standard components of the Respimat®.

### Currently Available pMDI Formulations

A number of aerosol formulations are available for use in pMDIs today (Figure 14). Pressurized metered-dose inhalers are presently used to administer beta-2 agonists, anticholinergics, anticholinergic/beta-2 agonist combinations, corticosteroids, and anti-asthmatic drugs.

### Factors Affecting pMDI Performance and Drug Delivery

Most pMDIs are designed to deliver a drug dose of 100 µm per actuation. Just like other aerosol generators, drug delivery with the pMDIs is approximately 10–20% of the nominal dose per actuation. The particle size of aerosols produced by the pMDI is in the fine particle fraction range in which the aerodynamic diameter of aerosols is less than 5 µm. Several factors influence the pMDI performance and aerosol drug delivery. Understanding the effects of these factors will improve the efficacy of pMDIs when used for patients with pulmonary diseases. Therefore, both respiratory therapists and patients must actively control the following effects:

- **Shaking the Canister:** Not shaking a pMDI canister that has been standing overnight decreases total and respirable dose by 25% and 35%, respectively, because the drugs in pMDI formulations are usually separated from the propellants when standing.<sup>43</sup> Therefore, pMDIs must be shaken before the first actuation after standing in order to refill the metering valve with adequately mixed suspension from the canister.<sup>12</sup>

- **Storage Temperature:** Outdoor use of pMDIs in very cold weather may significantly decrease aerosol drug delivery. Dose delivery was constant with HFA pMDIs over the range of -20° to 20°C.
- **Nozzle Size and Cleanliness:** The amount of medication delivered to the patient is dependent upon nozzle size, cleanliness, and lack of moisture. Actuator nozzle is pMDI specific, and the coordination of the nozzle with the medication will influence both inhaled dose and particle size. In general, there is an inverse relationship between the inner diameter of the nozzle extension and the amount of drug delivered to the patient.<sup>44</sup> A nozzle extension with an inner diameter < 1 mm increases drug delivery.<sup>44</sup> White and crusty residue due to crystallization of medication may influence drug delivery. Therefore, the nozzle should be cleaned periodically based on the manufacturer's recommendations.
- **Timing of Actuation Intervals:** The rapid actuation of more than two puffs with the pMDI may reduce drug delivery because of turbulence and the coalescence of particles.<sup>43</sup> A pause between puffs may improve bronchodilation, especially during asthma exacerbations with episodes of wheezing and poor control of symptoms.<sup>45</sup> In other cases, such as in the day-to-day management of pre-adolescents with a beta agonist (terbutaline) and a corticosteroid (budesonide), pauses between puffs have not been found to be beneficial.<sup>46</sup> Although early research was mixed regarding the importance of a pause between the two actuations, recent literature suggests a pause of one minute between actuations for effective aerosol therapy.<sup>1,7,13</sup>
- **Priming:** Priming is releasing one or more sprays into the air. Initial and frequent priming of pMDIs is required in order to provide an adequate dose. The drug may be

**Table 11. Priming requirements for commercially available pMDIs** (Modified, with permission, from Reference 1)

**Short-Acting Bronchodilators**

Generic Name	Brand Name	Time to Prime	No. of Sprays
Albuterol Sulfate HFA	Proventil® HFA	New and when not used for 2 weeks	4
	Ventolin® HFA	New and when not used for 14 days	4
Levalbuterol HCl	Xopenex® HFA	New and when not used for 3 days	4
Ipratropium Bromide HFA	Atrovent® HFA	New and when not used for 3 days	2
Ipratropium Bromide/ Albuterol Sulfate Combination	Combivent® HFA	New and when not used for 24 hours	3

**Inhaled Corticosteroids**

Generic Name	Brand Name	Time to Prime	No. of Sprays
Beclomethasone Propionate HFA	QVAR™	New and when not used for 10 days	2
Ciclesonide	Alvesco®	New and when not used for 10 days	3
Fluticasone Propionate	Flovent® HFA	New	4
		Not used more than 7 days or if dropped	1

**Combination Drugs**

Generic Name	Brand Name	Time to Prime	No. of Sprays
Budesonide combined with Formoterol	Symbicort® HFA	New and not used more than 7 days or if dropped	2

separated from the propellant and other ingredients in the canister and metering valve when the pMDI is new or has not been used for awhile. Because shaking the pMDI will mix the suspension in the canister but not the metering chamber, priming of the pMDI is required. Table 11 provides the recommended guidelines for priming the various pMDIs available on the market.

- Characteristics of the Patient:** Characteristics of the patient using the pMDI will result in a variability of aerosol deposition. For example, aerosol deposition will be lower in infants and children due to differences in their anatomy and their physical and cognitive abilities.
- Breathing Techniques:** There are two primary techniques for using a pMDI without a spacer: the open-mouth technique and the closed-mouth technique. The manufacturers of pMDIs universally recommend the closed-mouth technique for using a pMDI. In this method, the mouthpiece of the boot is placed between the sealed lips of the patient during drug administration. On the other hand, some researchers and clinicians have advocated an open-mouth technique in an attempt to reduce oropharyngeal deposition and increase lung dose.<sup>47,48</sup>

When using the open-mouth technique, the inhaler is placed two finger widths away from the lips of an open mouth and aimed at the center of the opening of the mouth. Studies suggest that the open-mouth technique reduces unwanted oropharyngeal deposition by allowing aerosol plume more distance to slow down before reaching the back of the mouth and up to two-fold more drug deposition to the lung than with use of the closed-mouth technique.<sup>47,49</sup> In contrast, other researchers suggest that the open-mouth technique does not offer any advantage over the closed-mouth technique,<sup>50,51</sup> but that it does create additional hazards such as the aerosol plume being misdirected from the mouth and into the eye or elsewhere.<sup>52</sup> Therefore, the best technique should be determined based on the patient's physical abilities, coordination, and preference. If the patient is well coordinated and can master the open-mouth technique better, it can be used by following the directions below. Also, the patient's aerosol administration technique should be observed continuously and corrected when appropriate. Proper technique is provided in Technique Box 2.

### Drug-Delivery Technique

Because different types of pMDIs are available on the market, the respiratory therapist should carefully review operation instructions prior to giving aerosol therapy and certainly prior to instructing patients in at-home use. Proper technique is provided in Technique Box 2.

**How To Know the pMDI Is Empty:** Since their introduction in the 1950s, pMDIs have not been packaged with dose counters that allow patients to determine when a pMDI should be discarded.<sup>53-55</sup> After the pMDI delivers the number of puffs stated on their label, it may look, taste, and feel like it is still working, but the dose delivered may be very low. This “tailing off effect” may last long after the pMDI is “empty of drug.”<sup>13,56</sup> Also, the pMDI without a dose counter could lead to waste if the inhaler is discarded prematurely. Indirect methods such as floating the canister in water are misleading and can reduce the ability of the pMDI to work properly.<sup>55,57,58</sup> Therefore, they should not be used to

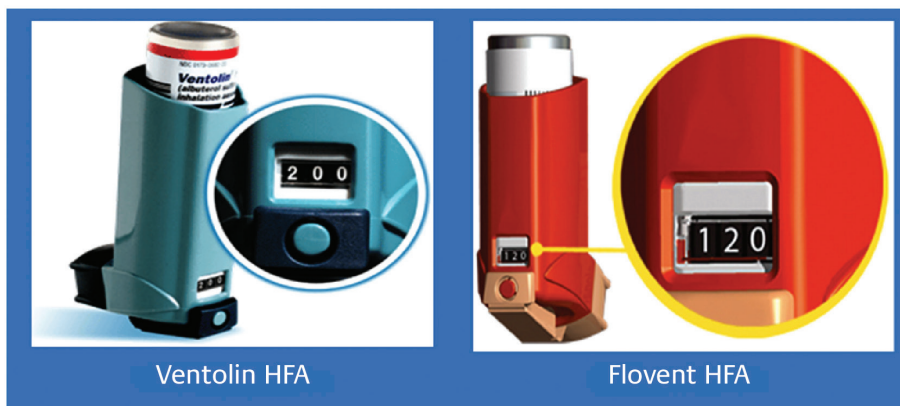
determine the amount of medication remaining in the canister.

The only reliable method to determine the number of doses remaining in a pMDI is counting the doses given either manually or with a dose counter. Manual methods include reading the label to determine the total number of doses available in the pMDI and using a log to indicate every individual actuation given (including both priming and therapy doses). This tally is subtracted from the number of actuations on the label until all have been used. At that time, the pMDI should be properly discarded. Unfortunately, manually counting doses may be impractical and undependable, especially in patients who use reliever medications on the go.

Therefore, the U.S. Department of Health and Human Services FDA requires new pMDIs to have integrated dose counters and recommends that all pMDIs have dose counting devices that indicate when the pMDI is approaching its last dose.<sup>59</sup> The dose counter is a counting device attached to the top of the pMDI canister or to the boot of the device. When the pMDI is actuated, it counts down the number of actuations from the total remaining in the canister. The Ventolin<sup>®</sup> HFA (GlaxoSmithKline, Research Triangle Park, NC) and Flovent<sup>®</sup> HFA (GlaxoSmithKline) have built-in dose counters (Figure 17).

Also, mechanical or electronic dose counters have been available from third parties for use by attachment to a range of pMDIs. Although research has confirmed acceptable performance and patient satisfaction by pMDIs with

(continued on page 28)



**Figure 17.** Counter on Ventolin<sup>®</sup> HFA and Flovent<sup>®</sup> HFA pMDIs

## Technique Box 2. Steps for Correct Use of pMDIs

### Technique for pMDIs

#### Open-Mouth Technique: The patient should be instructed to:

1. Remove the mouthpiece cover and shake the pMDI thoroughly.
2. Prime the pMDI into the air if it is new or has not been used for several days.
3. Sit up straight or stand up.
4. Breathe all the way out.
5. Place the pMDI two finger widths away from their lips.
6. With mouth open and tongue flat (tip of tongue touching inside of their lower front teeth), tilt outlet of the pMDI so that it is pointed toward the upper back of the mouth.
7. Actuate the pMDI as she/he begins to breathe in slowly.
8. Breathe slowly and deeply through the mouth and hold their breath for 10 seconds. If she/he cannot hold their breath for 10 seconds, then for as long as possible.
9. Wait one minute if another puff of medicine is needed.
10. Repeat Steps 2–10 until the dosage prescribed by the physician is reached.
11. If taking a corticosteroid, she/he should rinse their mouth after the last puff of medicine, spit out the water, and not swallow it.
12. Replace the mouthpiece cover on the pMDI after each use.

#### Closed-Mouth Technique: The patient should be instructed to:

1. Remove the mouthpiece cover and shake the inhaler thoroughly.
2. Prime the pMDI into the air if it is new or has not been used for several days.
3. Sit up straight or stand up.
4. Breathe all the way out.
5. Place the pMDI between their teeth; make sure that their tongue is flat under the mouthpiece and does not block the pMDI.
6. Seal their lips.
7. Actuate the pMDI as they begin to breathe in slowly.
8. Hold their breath for 10 seconds. If they cannot hold their breath for 10 seconds, then for as long as possible.
9. Wait one minute if another puff of medicine is needed.
10. Repeat Steps 2–10 until the dosage prescribed by the patient's physician is reached.
11. If taking a corticosteroid, she/he should rinse the mouth after the last puff of medicine, spit out the water and not swallow it.
12. Replace the mouthpiece cover on the pMDI after each use.

#### Breath-Actuated pMDI (Autohaler™) Technique: When using the Autohaler™, the patient should be instructed to:

1. Remove the mouthpiece cover and check for foreign objects.
2. Keep the Autohaler™ in a vertical position while the arrow points up, and do not block the air vents.
3. Prime the Autohaler™ into the air if it is new or has not been used recently.
4. Push the lever up.
5. Push the white test fire slide on the bottom of the mouthpiece for priming the Autohaler™.
6. Push the lever down in order to release the second priming spray.
7. Return the lever to its down position and raise the lever so that it snaps into place.
8. Sit up straight or stand up.
9. Shake the Autohaler™ three or four times.
10. Breathe out normally, away from the Autohaler™.
11. Place the pMDI between their teeth. Make sure that their tongue is flat under the mouthpiece and does not block the pMDI.
12. Seal their lips around the mouthpiece.
13. Inhale deeply through the mouthpiece with steady moderate force,
14. Pay attention to the click sound and the feel of a soft puff when the Autohaler™ triggers the release of medicine.
15. Continue to inhale until the lungs are full.
16. Remove the mouthpiece from the mouth.
17. Hold breath for 10 seconds or as long as possible.
18. Repeat steps above until the dosage prescribed by the patient's physician is reached.
19. Replace the mouthpiece cover and make sure the lever is down.



## Technique Box 2. Steps for Correct Use of pMDIs (continued)

### Technique for pMDIs

**Soft Mist pMDI (Respimat™) Technique: When using the Respimat™, the patient should be instructed to:**

#### Preparation:

1. With the cap closed, press the safety catch while pulling off the clear base. Be careful not to touch the piercing element located inside the bottom of the clear base.
2. Push the narrow end of the cartridge into the inhaler. The base of the cartridge will not sit flush with the inhaler. About 1/8 of an inch will remain visible when the cartridge is correctly inserted.
3. The cartridge can be pushed against a firm surface to ensure it is correctly inserted.
4. Do not remove the cartridge once it has been inserted into the inhaler.
5. Write the discard by date on the label of the inhaler. The discard by date is 3 months from the date the cartridge is inserted.
6. Put the clear base back into place. Do not remove the clear base again. The inhaler should not be taken apart after they have inserted the cartridge and put the clear base back.

#### Priming:

7. Hold the inhaler upright with the cap closed to avoid accidental release of dose.
8. Turn the clear base in the direction of the white arrows on the label until it clicks (half a turn).
9. Flip the cap until it snaps fully open.
10. Point the inhaler toward the ground. Press the dose-release button. Close the cap.
11. Repeat steps 7–10 until a spray is visible.
12. Once the spray is visible, repeat steps 7–10 three more times to make sure the inhaler is ready for use.

#### Patient-Use Instructions:

1. Hold the inhaler upright with the cap closed to avoid accidental release of dose.
2. Turn the clear base in the direction of the white arrows on the label until it clicks (half turn).
3. Flip the cap until it snaps fully open.
4. Breathe out slowly and fully, and then close lips around the end of the mouthpiece without covering the air vents.
5. Point inhaler toward the back of mouth.
6. While taking in a slow, deep breath through the mouth, press the dose-release button and continue to breathe in slowly for as long as possible.
7. Hold breath for 10 seconds or for as long as comfortable.
8. Close the cap until next prescribed dose.

**General Steps To Avoid Reduced or No Dosing for pMDIs: The patient should:**

1. Remove the cap of the pMDI from the boot.
2. Prime as directed (Table 11 on page 24).
3. Clean and dry the boot of the pMDI based on the manufacturer's guidelines.
4. Track remaining doses.

### Troubleshooting

#### Problem with Jet Nebulizers: Absent or Low Aerosol

##### Causes

Incorrect pMDI assembly

Incorrect pMDI and spacer assembly

Empty the pMDI

##### Solutions

Check the assembly and reassemble when needed.

Check the assembly of the pMDI/spacer and reassemble if needed.

Check the dose counter or daily log sheet to ensure there is enough medicine in the canister. Otherwise, replace the pMDI.

(continued from page 25)  
 dose counters,<sup>60-62</sup> care must be taken to assure that a third-party dose counter works with the specific pMDI being used.<sup>18,63</sup> Some of the built-in counters may not fit the spacer, and improper fit to the canister may interfere with proper actuation, resulting in no or partial drug being emitted and in a miscalculation of remaining doses.<sup>63</sup> Using a third-party dose-counting device increases the cost of aerosol therapy, which may limit their wide acceptance. Figure 18 shows currently available pMDI dose counters in the United States.



**Figure 18.** Currently available pMDI dose counters on the market

With any third-party counter, read the product label and accompanying package information for each pMDI before use and follow the manufacturer's recommended doses. When attempting to keep track of the number of doses remaining in the pMDI, Table 12 outlines monitoring recommendations with and without integrated dose counters.

**Cleaning:** Please refer to the Infection Control section on page 44 for the cleaning instructions for inhalers.

## Table 12. Monitoring remaining pMDI doses

### Without Dose Counter: The user should:

1. Determine the number of puffs that the pMDI has when it is full.
2. Calculate how long the pMDI will last by dividing the total number of puffs in the pMDI by the total puffs used. Also remember that the medication will run out sooner if the pMDI is used more often than planned.
3. Identify the date that the medication will run out and mark it on the canister or on the calendar.
4. Keep track of how many puffs of medicine administered on a daily log sheet and subtract them to determine the amount of medication left in the pMDI.
5. Keep the daily log sheet in a convenient place such as bathroom mirror.
6. Replace the pMDI when all of the puffs have been administered.

### With Dose Counter: The user should:

1. Determine how many puffs of medicine that the pMDI has when it is full.
2. Track the pMDI actuations used and determine the amount of medication left in the pMDI by checking the counter display.
3. Learn to read the counter display. Each dose counter has a specific way of displaying doses remaining in the canister. For example, turning red indicates that the number of actuations is less than 20 puffs and it is time to refill the pMDI. Reading the manufacturer's guidelines to interpret the counter display is recommended before its use.
4. When the last dose is dispensed, properly dispose of the pMDI.

# Metered-Dose Inhaler Accessory Devices

Metered-dose inhaler accessory devices were designed to overcome the difficulties experienced when using a pMDI and are available in different forms and sizes.

## Advantages and Disadvantages of pMDI Inhaler Accessory Devices

The use of these devices improves the effectiveness of aerosol therapy and reduces oropharyngeal deposition by adding volume and space between the metering valve and the patient's mouth. They overcome problems with hand-breath coordination. Table 13 lists both advantages and disadvantages seen with valved holding chambers (VHCs) and spacers used in conjunction with pMDIs.

While the term *spacer* is used in clinical practice to refer to all types of extension add-on devices, these devices are categorized into *spacers* or *holding chambers* (or *valved holding chambers*) based on their design. A spacer is a simple tube or extension device which adds space and volume between the pMDI and mouth with no one-way valves to contain the aerosol plume after pMDI actuation. A holding chamber (valved holding chamber) is an extension spacer device with one-way valve(s) to contain the aerosol until inhaled and direct exhalation away from the aerosol in the

chamber, reducing aerosol losses with poor hand-breath coordination. In addition to the major design difference that defines spacers versus (valved) holding chambers, there are other design differences among brands of holding chambers and spacers. *Volume* may vary, although in the United States most holding chambers/spacers are less than 200 mL. *Direction of spray* may vary between forward (toward the mouth) and reverse (away from the mouth). The AeroChamber® (Monaghan Medical Corporation), OptiChamber Diamond® and the OptiChamber® Advantage (Philips) are examples of forward sprays. The ACE® Aerosol Cloud Enhancer (Smiths Medical, Dublin, OH) is an example of reverse spray. Some holding chambers/spacers accept the manufacturer's mouthpiece-actuator (the boot), while others have a nozzle receptacle for accepting only the canister. As an example, the ACE® has a canister nozzle receptacle, while the AeroChamber®, OptiChamber Advantage® and OptiChamber Diamond® have malleable openings to accept the pMDI mouthpiece. While boots are designed specific to each pMDI, the canister nozzles vary and may not fit any one specific nozzle receptacle, reducing drug efficacy. Figure 19 shows examples of spacers and holding chambers.

**Table 13. Advantages and disadvantages of holding chambers or spacers (“add-on” devices) used with pMDIs** (Modified, with permission, from Reference 64)

Advantages	Disadvantages
Reduced oropharyngeal drug impaction and loss	Large and cumbersome compared to the pMDI alone
Increased inhaled drug by two to four times than the pMDI alone	More expensive and bulky than a pMDI alone
Allows use of the pMDI during acute airflow obstruction with dyspnea	Some assembly may be needed
No drug preparation required	Patient errors in firing multiple puffs into chamber prior to inhaling or there is a delay between actuation and inhalation
Simplifies coordination of pMDI actuation and inhalation	Possible contamination with inadequate cleaning
Helps reduce local and systemic side effects. <sup>64</sup>	

## Spacers

The use of a spacer with pMDIs should produce at least an equivalent inhaled dose and clinical effect to that of a correctly used pMDI alone. A spacer provides additional volume that slows the aerosol velocity from a pMDI, allowing a reduction in particle size. Aerosol retention and discharged dose depends on the size and shape of the spacer, and electrostatic charge on the inner walls of plastic spacers. Spacers decrease oral deposition, but they only provide limited protection against poor hand-breath coordination. When using a spacer, it is important for the patient

to coordinate their inhalation to occur slightly before actuating the inhaler. Some spacers require removal of the inhaler canister from the manufacturer's actuator and incorporation into a special orifice on the spacer. It is important to understand that dose delivery can be affected in some spacer designs if the device does not fit the pMDI properly or if the design uses a special orifice or actuator incorporated into the spacer itself. Occasionally, clinicians or patients construct homemade holding chambers from plastic containers (e.g., soda bottle) or other devices (e.g., toilet paper roll). These may function as a spacer and provide protection against reduced dose with pMDI actuation before inhalation, but they do not protect against actuation during exhalation. Also, their performance is variable, so they should not be considered as suitable replacements for a commercially available spacer.

## Valved Holding Chambers

A valved holding chamber (VHC) has a low-resistance one-way valve that allows aerosol particles to be contained within the chamber for a short time until an inspiratory effort opens the valve. Although the presence of a one-way valve prevents aerosol particles from exiting the chamber until inhalation begins, *optimal* aerosol dosing still depends on inhaling as close to or simultaneously with pMDI actua-



Figure 19. Examples of VHCs and spacers

tion into the chamber. Time delays can significantly reduce the available dose for inhalation from a VHC. The one-way valve should have a low resistance so that it opens easily with minimal inspiratory effort. Valves placed between the chamber and the patient also act as an impaction point, further reducing oropharyngeal deposition. It's important to assure the valve works properly, as dysfunctional valves can cause ineffective delivery of medication.<sup>65</sup> Ideally, there should be a signal to provide feedback if inspiratory flow is too high. Children with low tidal volumes (less than device dead space) may need to take several breaths from a VHC through a face mask for a single pMDI actuation. In this case, the VHC should incorporate one-way valves for both inhalation and exhalation to decrease rebreathing and avoid blowing aerosol from the chamber. A VHC with mouthpiece costs as little as \$15–\$20, and a static-free device with mask can cost as much as \$50–\$60.

## Drug-Delivery Technique

While spacers and VHCs provide many benefits for optimal drug delivery with pMDIs, there are also potential problems with their use (Table 13). Improper technique may decrease drug delivery or, in some cases, cause the dose to be lost. Possible causes of decreased drug delivery include multiple actuations into the device, electrostatic charge, inhaling before actuating the pMDI, delay between

actuation and inhaling the dose, or improper insertion of actuator into spacer and/or VHC.<sup>66</sup> It has been shown that improper insertion of the actuator can contribute to a spray of medication that does not follow the optimal axis of the chamber and a good proportion of medicine ends up deposited on the inside of the chamber.<sup>67</sup> Also, it has been suggested that spacer size and shape may provide better deposition of specific particle sizes.<sup>66</sup> More research is needed on length, shape, and volume of spacers. In

children, lack of a proper mask fit, a spacer volume that is greater than tidal volume (mechanical dead space), and crying are problematic. Proper technique is provided in Technique Box 3.

**Cleaning:** Please refer to the Infection Control section on page 44 for cleaning instructions for the pMDI chamber and collapsible bag device.

### Technique Box 3. Steps for Correct Use of pMDI with Spacer/VHC

#### Technique for pMDIs with Spacer/VHC: The patient should be instructed to:

1. Remove the mouthpiece cover and shake the inhaler thoroughly.
2. Prime the pMDI into the air if it is new or has not been used for several days.
3. Assemble the apparatus and check for foreign objects.
4. Keep the canister in a vertical position.
5. Sit up straight or stand up.
6. Breathe all the way out.
7. Follow the instructions below based on the type of device interface used:  
**With the mouthpiece:**
  - a. Place the mouthpiece of the spacer between their teeth and seal their lips. Make sure that their tongue is flat under the mouthpiece and does not block the pMDI.
  - b. Actuate the pMDI as they begin to breathe in slowly. Also make sure to inhale slowly if the device produces a “whistle” indicating that inspiration is too rapid.
  - c. Move the mouthpiece away from the mouth and hold their breath for 10 seconds. If they cannot hold their breath for 10 seconds, then hold for as long as possible.**With the mask:**
  - d. Place the mask completely over the nose and mouth and make sure it fits firmly against the face.
  - e. Hold the mask in place and actuate the pMDI as they begin to breathe in slowly. Also make sure to inhale slowly if the device produces a “whistle” indicating that inspiration is too rapid.
  - f. Hold the mask in place while the child takes six normal breaths (including inhalation and exhalation), then remove the mask from the child’s face.
8. Wait 15–30 seconds if another puff of medicine is needed.
9. Repeat steps above until the dosage prescribed by the patient’s physician is reached.
10. If taking a corticosteroid, rinse the mouth after the last puff of medicine, spit out the water, and do not swallow it.
11. Replace the mouthpiece cover on the pMDI after each use.

#### General Steps To Avoid Reduced or No Dosing for pMDIs with Spacer/VHC: The patient should:

1. Assure proper fit of the pMDI to the spacer or VHC.
2. Remove cap from the pMDI boot.
3. Clean and reassemble the pMDI spacers and VHCs based on the manufacturers’ instructions.

# Dry-Powder Inhalers

Dry-powder inhalers (DPIs) are portable, inspiratory-flow-driven inhalers that administer dry-powder formulations to the lungs. DPIs do not contain propellant and are breath-actuated. The patient's inspiratory effort, both their inspiratory flow rate and the volume inhaled, creates the energy to disaggregate the small drug particles from larger carrier particles and disperse the particles as aerosol emitted from the device. DPIs coordinate release of the drug with the act of inhalation. They have been developed to overcome the difficulties of using metered-dose inhalers and are often prescribed with the intention of providing the patient with an overall more user-friendly and predictable therapy.

## Advantages and Disadvantages of DPIs

Dry-powder inhalers have both advantages and disadvantages as seen in Table 14. Because they do not require hand-held coordination, the patient's inspiratory flow should be adequate enough to draw the drug from the device. It is important that the patient understands how the DPI works and how it should be used. For example, the patient should know that they should not exhale into the device. This will prevent the introduction of ambient

humidity into the mouthpiece and the resulting negative effect to the medication. Such precautions and others, explored in greater detail below, should be considered by clinicians when prescribing a DPI for individual patients and when performing follow-up evaluations of patient success with a DPI.

## Types of DPIs

Currently, DPIs can be classified into three categories based on the design of their dose containers, i.e., single-dose DPIs, multiple unit-dose DPIs, and multiple-dose DPIs (Figure 20). While the single-dose DPIs have individually wrapped capsules that contain a single-dose of medication, multiple unit-dose DPIs disperse individual doses that are premeasured into blisters of medication by the manufacturer. The third type, the multiple-dose DPI, either measures the dose from a powder reservoir or uses blister strips prepared by the manufacturers to deliver repeated doses. Regardless of the type of DPI, they all have the same essential components incorporated within the inhaler. They all have a drug holder, an air inlet, an agglomeration compartment, and a mouthpiece. The design of these components allows DPIs to induce sufficient turbulence and particle-to-particle collision

**Table 14. Advantages and disadvantages of DPIs** (Modified, with permission, from Reference 1)

Advantages	Disadvantages
Small and portable	Dependence on patient's inspiratory flow
Built-in dose counter	Patient less aware of delivered dose
Propellant free	Relatively high oropharyngeal impaction
Breath-actuated	Vulnerable to ambient humidity or exhaled humidity into mouthpiece
Short preparation and administration time	Limited range of drugs
	Different DPIs with different drugs
	Easy for patient to confuse directions for use with other devices



that detaches particles from their carrier surface and deagglomerates larger particles into smaller particles.

### Single-Dose DPIs

Single-dose DPIs operate by evacuating powder medication from a punctured capsule. The HandiHaler® (Boehringer Ingelheim), The TOBI Podhaler® (Novartis), and the Neohaler (Sunovion) are examples of single-dose DPIs (Figure 20). While the HandiHaler® is used for the delivery of tiotropium bromide, the TOBI Podhaler is utilized for the administration of tobramycin. The Neohaler® is used for the delivery of glycopyrrolate as well as Utibron®, the combination of indacaterol and glycopyrrolate. Although the HandiHaler®, Podhaler, and Neohaler® have different configurations, their principle of operation is similar. When using a single-dose DPI, the user places each capsule into the drug holder. Then, the user must prime the device by piercing the single-dose capsule and allowing entrainment of air into the device for dispersion with inhalation. The primary disadvantage of single-dose DPIs is the time needed to load a dose for each use. Also, patients should be instructed not to swallow the capsules.

### Multiple Unit-Dose DPIs

The Diskhaler® (GlaxoSmithKline) is an example of the multiple unit-dose DPI. It is used for the administration of zanamivir through a rotating wheel that contains a case with four or eight blisters of medication. Each blister is mechanically punctured when the cover is lifted, allowing the medication to be inhaled through the mouth. When using the Diskhaler®, the inspiratory flow rate should be greater than 60 L/min to achieve an adequate drug deposition into the lungs.

### Multiple-Dose DPIs

Multiple-dose DPIs measure doses from a powder reservoir or disperse individual doses through pre-metered



**Figure 20.** Currently available dry-powder aerosol formulations in the United States categorized by design features (see text description of design features)

blister strips. The most common types of multi-dose DPIs include the RespiClick®, the Flexhaler® and the Pressair® (AstraZeneca, Wilmington, DE), and the Diskus® and Ellipta® (GlaxoSmithKline). The Twisthaler® is a multi-dose DPI used to deliver mometasone furoate. The Flexhaler® delivers budesonide, and the Diskus® administers salmeterol, fluticasone, or a combination of salmeterol and fluticasone.

In the Twisthaler® and the Flexhaler®, the DPI nozzle is comprised of two parts: a lower swirl chamber and an upper chimney in the mouthpiece. Their fluted chimney designs produce a stronger vortex with an increased number of particle collisions with the chimney for deagglomeration. When using a new Flexhaler®, it should be primed by holding it upright and then twisting and clicking the brown grip at the bottom twice. The Twisthaler® does not require priming before use.

The Diskus® is a multi-dose DPI that contains 60 doses of dry-powder medication individually wrapped in blisters. The wrapping in blisters protects the drug from humidity and other environmental factors. Sliding the dose-release lever punctures the wrapped blister on a foil strip and prepares the dose for inhalation. When the Diskus® cover is closed, the dose release lever is automatically returned to its starting position. As with the Twisthaler®, no priming is necessary with the Diskus®.



The Ellipta® is similar to the Diskus® and is used in the delivery of various long-acting beta agonists and combination medications such as Brea® and Anoro® as well as other drugs such as Incruse®, an ultra-long-acting anticholinergic, and Arnuity®, a corticosteroid. Similar to the Diskus®, this multi-dose DPI utilizes two coiled blister strips containing individually wrapped doses of dry-powder medication. Opening the mouthpiece cover peels the foil to expose the medication dosage. After inhaling the medication, the mouthpiece cover is returned to its closed position. It is important to note that, if the mouthpiece cover is opened and the dose is prepared, closing the mouthpiece cover without inhalation of the medication will result in a lost dose.

The Pressair® is multi-dose dry power inhaler that administers acclidinium bromide in 30 or 60 doses. The device utilizes a button that once depressed loads the medication. This can be confirmed visually by checking the control window that changes from red to green once a new dose is ready. Once the patient inhales a click can be heard, noting the dose was inhaled. The individual may confirm by looking at the control window that changes from green to red to indicate a dose has been taken. Patients will need to have a minimum peak inspiratory flow of 35 L/min to effectively use this device.

### Currently Available DPI Formulations

As seen in Figure 20, the device design largely determines whether a DPI model is single dose (loading a single dose prior to each use), multiple unit-dose (loading four or eight blisters of medication), or multiple-dose (containing an entire month's prescription).

### Factors Affecting DPI Performance and Drug Delivery

Respiratory therapists and patients must actively control the following effects:

- **Intrinsic Resistance and Inspiratory Flow:** Each type of DPI has a different intrinsic resistance to airflow that determines how much inspiratory flow needs to be created in the device to release the correct amount of drug. For example, the HandiHaler® has a higher resistance than the Diskus® and therefore requires a greater inspiratory effort. When the patient inhales through the DPI, she/he creates an airflow with a pressure drop

between the intake and exit of the mouthpiece. Thus, the patient can lift the powder from the drug reservoir, blister, or capsule depending on the model being used. The patient's inspiratory effort is also important in its deaggregating of the powder into finer particles. Whereas higher inspiratory flows improve drug deaggregation, fine-particle production, and lung delivery, excessive inspiratory flow can increase impaction on the oral cavity and thus decrease total lung deposition.

- **The Patient's Inspiratory Flow Ability:** DPIs depend on the patient's ability to create adequate inspiratory flows. Very young children and patients with acute airflow obstruction due to asthma or COPD may not be able to generate an adequate inspiratory flow when using the DPI. Because very low inspiratory flows result in reduced drug delivery, especially fine-particle delivery, potential DPI patients should be evaluated for the ability to generate a minimal inspiratory flow.
- **Exposure to Humidity and Moisture:** Because all DPIs are affected by humidity and moisture, which can cause powder clumping and reduce deaggregation and fine-particle development during inhalation, they must be kept dry. Capsules and drug blisters generally offer more protection from ambient humidity than a reservoir chamber containing multiple doses for dispensing. Therefore, designs with a reservoir chamber such as the Twisthaler® and Pressair® should be protected from humidity and moisture as much as possible. Whereas it is easy to keep the Twisthaler® and Pressair® out of the bathroom, avoiding use in ambient humidity is difficult if it is carried to the beach, kept in a house with no air conditioning, or left in a car. An alternative DPI design or availability of the drug in a different aerosol system, such as a pMDI, might be considered for such situations. All DPIs are also affected by exhaled air introduced into the mouthpiece, especially after the device is cocked and loaded and when the powder is exposed. Therefore, patients must be instructed to exhale away from the DPI prior to inhalation.

### Drug-Delivery Technique

Because different types of DPIs are available on the market, respiratory therapists should carefully review operation instructions prior to giving aerosol therapy and certainly prior to instructing patients in at-home use. Proper technique is provided in Technique Box 4.

## Technique Box 4. Steps for Correct Use of Each Model of DPIs

### Technique for Single-Dose DPIs

#### HandiHaler®: The patient should be instructed to:

1. Peel back the aluminum foil and remove a capsule immediately before using the HandiHaler®.
2. Open the dust cap by pulling it upward.
3. Open the mouthpiece.
4. Place the capsule in the center chamber; it does not matter which end is placed in the chamber.
5. Close the mouthpiece firmly until they hear a click; leave the dust cap open.
6. Hold the HandiHaler® with the mouthpiece up.
7. Press the piercing button once and release; this makes holes in the capsule and allows the medication to be released during inhalation.
8. Exhale away from the HandiHaler®.
9. Place the mouthpiece into the mouth and close lips tightly around the mouthpiece.
10. Keep head in an upright position.
11. Breathe in at a rate sufficient to hear the capsule vibrate, until the lungs are full.
12. Remove the mouthpiece from the mouth and hold breath for 10 seconds or as long as comfortable.
13. Exhale away from the HandiHaler®.
14. Repeat the inhalation from the HandiHaler®.
15. Open the mouthpiece, remove the used capsule, and dispose of it. Do not store capsules in the HandiHaler®.
16. Close the mouthpiece and dust cap for storage of the HandiHaler®.
17. Store the device in a cool, dry place.

#### Neohaler®: The patient should be instructed to:

1. Remove the mouthpiece cover.
2. Hold the base of the inhaler and tilt the mouthpiece to open the Neohaler®.
3. Remove the capsule from the blister pack immediately before use.
4. Place the capsule into the chamber in the base of the Neohaler®.
5. Close the inhaler; a click will sound to indicate the inhaler is closed.
6. Simultaneously press both buttons on the side of the Neohaler® to pierce the capsule and then release.
7. Keep the head in a neutral, upright position.
8. Do not exhale into the device.
9. Hold the device horizontal, with the buttons on the left and right.
10. Place the mouthpiece into the mouth and close lips tightly around the mouthpiece.
11. Breathe in a full breath rapidly and deeply; the capsule should be heard vibrating in the device.
12. Remove the mouthpiece from the mouth and perform a 10-second breath hold (or as long as comfortable).
13. Do not exhale into the device.
14. Open the chamber and examine the capsule; if there is powder remaining, repeat the inhalation process.
15. After use, remove and discard the capsule. Do not store the capsule in the Neohaler®.
16. Close the mouthpiece and replace the cover.
17. Store in a cool, dry place.

#### Podhaler: The patient should be instructed to:

1. Hold base of Podhaler and unscrew lid in a counter-clockwise direction, setting aside lid once complete.
2. Stand Podhaler upright in the base of the case.
3. Hold body of Podhaler and unscrew mouthpiece in a counter-clockwise direction, setting aside mouthpiece on a clean, dry surface.
4. Take blister card and tear the pre-cut lines along the length and width.
5. Peel foil that covers one Podhaler capsule on blister card.
6. Remove capsule one at a time and place in capsule chamber at the top of Podhaler.
7. Place mouthpiece back on Podhaler and screw mouthpiece in a clockwise direction until tight.
8. Hold Podhaler pointing mouthpiece down.
9. Placing the thumb on the blue button, pressing the blue button all the way down once.
10. Exhale as completely as possible away from the inhaler.
11. Place the mouthpiece into the mouth and close lips tightly around mouthpiece.
12. Breathe in a full breath deeply and slowly and perform a 10-second breath hold (or as long as comfortable).
13. Exhale away from the device.
14. To ensure the entire dose has been inhaled, repeat steps 10 through 12.
15. Unscrew the mouthpiece and remove capsule from chamber and throw away.
16. Repeat steps 4 to 15 three more times until all four doses (4 capsules) have been used.

## Technique Box 4. Steps for Correct Use of Each Model of DPIs (continued)

### Technique for the Multiple Unit-Dose DPI

**Diskhaler®:** The patient should be instructed to:

1. Remove the cover and check that the device and mouthpiece are clean.
2. Extend tray and push ridges to remove tray.
3. Load medication disk on the rotating wheel.
4. Pull the cartridge all the way out and then push it all the way in until the medication disk is seen in the dose indicator. This will be the first dose that will be given.
5. Keep the device flat and lift the back of the lid until it is lifted all the way up to pierce the medication blister.
6. Click back into place.
7. Move the Diskhaler® away from the mouth and breathe out as much as possible.
8. Place the mouthpiece between the teeth and lips and make sure the air hole on the mouthpiece is not covered.
9. Inhale as quickly and deeply as possible.
10. Move the Diskhaler® away from the mouth and perform a 10-second breath hold or as long as comfortable.
11. Breathe out slowly.
12. If another dose is needed, pull the cartridge out all the way and then push it back in all the way in order to move the next blister into place. Then repeat Steps 4 through 12.
13. Place the mouthpiece cover back on after the treatment. Make sure the blisters remain sealed until inspiration in order to protect them from humidity and loss.

### Technique for Multiple-Dose DPIs

**Diskus®:** The patient should be instructed to:

1. Open the device.
2. Slide the lever from left to right.
3. Breathe out normally; do not exhale into the device.
4. Place the mouthpiece into the mouth and close lips tightly around the mouthpiece.
5. Keep device horizontal while inhaling dose with a rapid and steady flow.
6. Remove the mouthpiece from the mouth and perform a 10-second breath hold or as long as comfortable.
7. Be sure not to exhale into the device.
8. Store the device in a cool dry place.
9. Observe the counter for the number of doses remaining and replace when appropriate.

**Twisthaler®:** The patient should be instructed to:

1. Hold the inhaler straight up with the pink portion (the base) on the bottom.
2. Remove the cap while it is in the upright position to ensure the right dose is dispensed.
3. Hold the pink base and twist the cap in a counter-clockwise direction to remove it.
4. As the cap is lifted off, the dose counter on the base will count down by one. This action loads the dose.
5. Make sure the indented arrow located on the white portion (directly above the pink base) is pointing to the dose counter.
6. Breathe out normally; do not exhale into the device.
7. Place the mouthpiece into the mouth and close the lips tightly around the mouthpiece.
8. Inhale the dose with a rapid and steady flow while holding the Twisthaler® horizontal.
9. Remove the mouthpiece from the mouth and perform a five to 10-second breath hold or as long as comfortable.
10. Do not exhale into the device.
11. Immediately replace the cap, turn in a clockwise direction, and gently press down until a click is heard.
12. Firmly close the Twisthaler® to assure that the next dose is properly loaded.
13. Be sure that the arrow is in line with the dose-counter window.
14. Store device in cool, dry place.

## Technique Box 4. Steps for Correct Use of Each Model of DPIs (continued)

### Technique for Multiple-Dose DPIs (continued)

#### Flexhaler®: The patient should be instructed to:

1. Twist the cover and lift it off.
2. Hold the Flexhaler® in the upright position (mouthpiece up) while loading a dose.
3. Do not hold the mouthpiece when the inhaler is loaded.
4. Twist the brown grip fully in one direction as far as it goes. It does not matter which way is turned first.
5. Twist it full back in the other direction as far as it goes.
6. Make sure to hear a click during each of the twisting movements.
7. Do not exhale into the device.
8. Place the mouthpiece into the mouth, close the lips tightly around the mouthpiece, and inhale deeply and forcefully through the inhaler.
9. Remove the inhaler from the mouth and exhale.
10. Do not exhale into the device.
11. If more than one dose is required, repeat the steps above.
12. Put the cover back on the inhaler and twist it shut.
13. Rinse the mouth with water after each dose to reduce the risk of developing thrush. Do not swallow the rinse water.

#### Tudorza Pressair: The patient should be instructed to:

1. Wash and dry hands thoroughly.
2. Remove the protective cap by gently squeezing the marked arrows on each side of the cap and pulling outward.
3. Hold the inhaler with the mouthpiece facing toward the patient and the green button on top. DO NOT place in the mouth yet.
4. Press the green button all the way down and release it. DO NOT hold the button down.
5. Check the control window on the device (above the mouthpiece) to ensure the color has changed from red to green, indicating the dose and device are ready for use.
6. Exhale away from the device before placing the mouthpiece into the mouth.
7. Place the mouthpiece into the mouth and breathe in quickly and deeply.
8. A click is heard when the dose is delivered, but continue the deep breath until at full capacity.
9. Remove the device from the mouth and breathe out.
10. Check the control window on the device (above the mouthpiece) to ensure the color has changed from green to red. IF NOT, repeat Step 7.
11. Replace the protective cap on the mouthpiece.

#### RespiClick®: The patient should be instructed to:

1. Hold the inhaler upright with the red mouthpiece cover facing the patient.
2. Remove the red mouthpiece cover in the upright position until a click is heard. This exposes the mouthpiece as well as loads the medication. The dose counter on the back of the device will count down one number each time the medication is delivered.
3. Exhale away from the device.
4. Place the mouthpiece into the mouth and close lips tightly around the mouthpiece.
5. Do not block the air vent above the mouthpiece.
6. Inhale deeply through the RespiClick®.
7. Remove the mouthpiece from the mouth and perform a 10-second breath hold or as long as comfortable.
8. Check the dose counter on the back of the device to make sure the dose was delivered.
9. Firmly close the cap over the mouthpiece.
10. Store the device in a cool dry place.
11. Observe the counter for the number of doses remaining and replace when appropriate.

## Technique Box 4. Steps for Correct Use of Each Model of DPIs (continued)

### Technique for Multiple-Dose DPIs (continued)

**Ellipta®:** The patient should be instructed to:

1. Open the device by sliding the mouthpiece cover down until a click is heard. This exposes the mouthpiece as well as loads the medication. The center dose counter will count down one number each time the mouthpiece cover is opened.
2. Hold the Ellipta® in an upright position.
3. Exhale away from the Ellipta®.
4. Place the mouthpiece into the mouth and close lips tightly around the mouthpiece. Do not block the air vent on the device.
5. Keep the device horizontal while inhaling the dose with a rapid and steady breath.
6. Remove the mouthpiece from the mouth and perform a 10-second breath hold or as long as comfortable.
7. Do not exhale into the device.
8. Close the mouthpiece cover.
9. Store the device in a cool dry place.
10. Observe the counter for the number of doses remaining and replace when appropriate.

### General Steps To Avoid Reduced or No Dosing for DPIs: The patient should:

1. Read and follow the instructions for proper assembly.
2. Make sure to keep the DPI clean and dry.
3. Keep the DPI in proper orientation during the treatment.
4. Be sure to puncture the capsule or blister pack.
5. Do not exhale into the DPI.
6. Make sure to generate adequate inspiratory flow.
7. Track the doses remaining in the DPI.

## Troubleshooting

### Problem with DPIs: Malfunctioning DPIs

Causes	Solutions
Incorrect DPI assembly	Check the assembly and reassemble, when needed.
Failure to discharge medicine	Replace the unit.
Empty DPI	Check the dose counter to ensure that it is not empty. Otherwise, replace the DPI.

### How To Know the DPI Is Empty

**Single-Dose DPI:** Single-dose DPIs such as the HandiHaler® use a single capsule for each dose, and only full capsules should be used when each dose is given. The capsule should be inspected to assure that the patient took the full dose. If there is powder remaining, the capsule should be returned to the inhaler and inhalation should be repeated.<sup>68</sup> Then, the capsule should be disposed of after treat-

ment. Prescription renewal should be based on the remaining capsules.

**Multiple Unit-Dose DPI:** The Diskhaler® is a multiple unit-dose DPI with a refill disk that contains 4- or 8-unit-dose blisters.<sup>69</sup> Because there is not a dose counter on the DPI, doses must be tracked manually. Therefore, visual inspection will confirm use of all packets. The disk is disposed of when all the doses have been used.

**Multiple-Dose DPIs:** Multiple-dose DPIs historically come with integrated mechanical devices that indicate the number of doses remaining in the inhaler.<sup>68</sup> The devices give a particular display when the doses are coming to an end so that a new DPI can be ordered from the pharmacist. The dose counter of each type of multiple-dose DPI is explained in Table 15.

**Cleaning:** Please refer to the Infection Control section on page 44 for the cleaning instructions for DPIs.

**Table 15. Monitoring remaining doses of multiple-dose DPI**

	Dose Container	No. of Doses	Type of Indicator	Meaning of Dose Indicator
<b>Flexhaler®</b>	Reservoir	60 or 120	“0”	Although the indicator counts down every time a dose is loaded, it will not move with each individual dose but intervals of five or so doses.  The indicator is marked in intervals of 10 doses, alternating numbers and dashes. When it is down to “0,” it must be thrown away.
<b>Twisthaler®</b>	Reservoir	30	“01”	The dose display showing “01” indicates the last dose of medicine in the Twisthaler®, and the medicine must be refilled.
<b>Diskus®</b>	Blister Strip	60	Red numbers	The numbers turning red in the dose display indicates that there are five doses left.  When the dose window shows “0,” there is no medicine left, and the discus should be disposed.
<b>RespiClick®</b>	Reservoir	60 or 200	“0”	When the dose counter displays “0,” there is no medicine left and the device should be disposed.
<b>Ellipta®</b>	Blister strip	30	“0”	When the dose counter displays “0”, this is the last dose. Discard the device after inhalation.
<b>Pressair®</b>	Reservoir	30 or 60	“0”	When dose counter displays “0,” there is no medicine left and the device should be disposed.



# Criteria To Select an Aerosol Generator

The selection of the delivery device is very important for optimizing the results of aerosol drug therapy. Evidence indicates that all three types of aerosol generators can be equally effective if they are used correctly by the patient.<sup>8</sup> The criteria to select an aerosol generator can be divided into four categories: patient-related, drug-related, device-related, and environmental and clinical factors.

## Patient-Related Factors

### Age, Physical, and Cognitive Ability of Patients

An aerosol generator should be selected in accord with the patient's age, physical, and cognitive ability. Age changes anatomic and physiologic factors such as airway size, respiratory rate, and lung volume.<sup>13,69-76</sup> The patient's cognitive ability to understand how and when to use a device and drug as well as his/her physical ability and coordination in using an aerosol generator should guide the selection of an aerosol generator.<sup>8,13,18,69,75,77-79</sup> Aerosol devices have different requirements for proper use. For guidance about the device selection in infants and pediatrics, see "Neonatal and Pediatric Aerosol Drug Delivery" on pages 42-43.

As for adults and the elderly who cannot manage hand-held coordination or proper inhalation technique,<sup>77,80-82</sup> pMDIs may not be a good option. Also, the inability to generate sufficient inspiratory flow (>40–60 L/min) eliminates the use of aerosol generators such as DPIs.<sup>77,83</sup>

### Preference of Patients

Patient preference is a critical factor in the selection of an aerosol generator and the effectiveness of aerosol therapy. Patients tend to use devices they prefer more regularly than devices they dislike.<sup>84-87</sup> Therefore, the selection of an aerosol generator should be tailored according to the patient's needs and preferences.

## Drug-Related Factors

### Availability of Drug

Some drug formulations are available with only one type of aerosol generator. If a drug can be administered with the three types of aerosol generators, the clinician should select an aerosol generator based on the patient's needs and preference.<sup>8,18,79,87</sup> Otherwise, a drug formulation that can be used with only a single aerosol generator dictates which aerosol generator to choose.

### Combination of Aerosol Treatments

Many patients are prescribed more than one inhaled drug. In that case, using the same type of aerosol generator may increase the patient's adherence to therapy while minimizing the patient's confusion caused by the use of different aerosol devices.<sup>8,18,87-88</sup>

## Device-Related Factors

### Convenience of Aerosol Generator

Selecting the most convenient aerosol generator for the patient is very important to adherence. Ease of use, treatment time, portability, cleaning, and maintenance required for each device should guide the selection process. For example, a rescue medication needs to be small, light, and portable so the patient can easily have it available when needed.<sup>69,79</sup> Also, nebulizers may be less preferable to deliver inhaled medications as they are more expensive, require a power source, and need regular maintenance.<sup>69,87,89-90</sup> When all other factors are equal, the most convenient device should be chosen for patients.

### Durability of Aerosol Generator

A selected aerosol generator should have good durability so that it can withstand rigorous treatment and cleaning procedures every day. Devices that require extensive cleaning are not a good choice for patients unwilling to routinely clean and maintain the device.

### **Cost and Reimbursement of Aerosol Generator**

It is very important to select an aerosol generator that is the least out-of-pocket expense for the patient. Patients do not use drugs and devices they cannot afford.<sup>91-93</sup> As shown in Table 3, Table 6, and Table 7, costs of aerosol generators and drug formulations vary widely. The cost to the patient will depend on the presence and type of medical insurance they have.<sup>79</sup> If the “best” device/drug is not one that the patient can afford, the least costly aerosol generator and drug combination should be identified in order to meet the patient’s needs. Therefore, it is important to work with the patient to identify strategies to access affordable drug/device options in order to meet their clinical needs. If all the other factors are constant, the least costly aerosol generator and drug combination should be selected.

### **Environmental and Clinical Factors**

When and where the aerosol therapy is required can impact device selection. For example, therapy that is given routinely, once or twice a day, before or after bedtime does not need to be as portable as rescue medications that may be required at anytime. Also, noisy compressors may not be good in small homes where a late-night treatment might awaken other members of the family. In environments where patients are in close proximity to other people, secondhand exposure to aerosols may be a factor, and devices that limit or filter exhaled aerosol should be selected.

# Neonatal and Pediatric Aerosol Drug Delivery

Infants are not simply anatomically scaled-down adults. Therefore, aerosol drug administration differs fundamentally in infants and children. Cognitive ability (i.e., understanding how and when to use a device and drug) and physical ability (i.e., coordination to use that device) as well as age-related anatomic and physiologic factors (i.e., airway size, respiratory rate, lung volumes) create substantial challenges for effective aerosol delivery at each stage of development.<sup>70-73,94-95</sup> When respiratory therapists gain a clear understanding of these challenges, they can optimize aerosol drug delivery and its therapeutic outcomes in less developed patients. This section explores the challenges and solutions that may optimize aerosol drug delivery in infants and pediatrics.

## Age and Physical Ability

Selection of an aerosol device is critical to successful aerosol therapy in infants and children.<sup>70,78,95</sup> Children under the age of three may not reliably use a mouthpiece, making delivery via mask necessary for both nebulizers and pMDIs.<sup>95-99</sup> Especially at low tidal volumes, VHCs are the preferred method for pMDI delivery in infants and small children.<sup>97-98</sup> Breathing patterns, inspiratory flow rates, and tidal volumes change with age. Even healthy children below four years of age cannot reliably generate sustained inspiratory flow rates of 60–90 L/min required for optimal use of many DPIs. Thus, the use of breath-actuated nebu-

lizers or DPIs may not be reliable in children younger than four years.<sup>73,100</sup>

## Age and Cognitive Ability

The choice of aerosol device should be tailored to the patient's age and to cognitive ability to use the device correctly. Table 16 presents the recommended ages for introducing different types of aerosol generators to children.<sup>69-71,100-103</sup> Small-volume nebulizers and pMDIs with VHCs are recommended for use with infants and children up to five years of age.<sup>70-71,100</sup> Since children up to three years of age typically cannot use a mouthpiece, both nebulizers and pMDIs with holding chambers should be administered via masks.<sup>70,97-98</sup> Independent of age, a face mask should be used until the child can comfortably use a mouthpiece. A child below five years of age may not be able to master specific breathing techniques.<sup>70-71,100</sup> With low tidal volumes and short inspiratory times, breath-actuated nebulizers may increase inhaled dose compared to continuous nebulization.<sup>104</sup> However, it may take three-fold more time to administer that dose. Also, time constraints and portability of compressor nebulizers make them less desirable for preschool children.<sup>70</sup> It is generally accepted that the cognitive ability to control breathing and hand/breath coordination develops by age five or six.<sup>69,70,101</sup> Once children reach age four and above, they may have a sufficient understanding of how to use a pMDI or DPI successfully.<sup>73,100</sup>

**Table 16. Age guidelines for use of aerosol delivery device types**

Aerosol Generator	Age
SVN with mask or hood	Infant <sup>94</sup>
SVN with mask	≤ 3 years
SVN with mouthpiece	≥ 3 years
pMDI with valved holding chamber/spacer and mask	< 4 years
pMDI with valved holding chamber/spacer	≥ 4 years
Dry-powder inhaler	≥ 4 years
Metered-dose inhaler	≥ 5 years
Breath-actuated MDI (e.g., Autohaler®)	≥ 5 years
Breath-actuated nebulizer	≥ 5 years

## Aerosol Drug Delivery in Distressed or Crying Infants

Inhaled drugs should be given to infants when they are settled and breathing quietly. Crying children receive virtually no aerosol drug to the lungs,<sup>94,96,102,105-106</sup> with most of the inhaled dose depositing in the upper airways or pharynx, which is then swallowed.<sup>71-72,94,106-107</sup> Therefore, it is essential to develop approaches that minimize distress before administering aerosol drugs. These approaches include, but are not limited to, playing games, comforting babies, and providing other effective forms of distraction. Also, aerosol drugs can be administered while the infant is asleep as long as administration does not wake up or agitate the infant. Although sleep breathing patterns indicated a higher lung dose in an infant-model study,<sup>108</sup> an in-vivo study showed that 69% of the children woke up during aerosol administration and 75% of them were distressed.<sup>109</sup>

## Patient-Device Interface

Even infants and small children can make known their preferences for specific devices. This should be a consideration in device selection. Using a device that is preferred by the child and parent can increase adherence, inhaled dose, and desired clinical response.

## Mouthpiece or Face Mask?

Mouthpieces and face masks are commonly used for aerosol drug delivery in children above three years of age. Studies suggest that the mouthpiece provides greater lung dose than a standard pediatric aerosol mask<sup>104,110</sup> and is effective in the clinical treatment of children.<sup>104,111-112</sup> Consequently, the use of mouthpieces should be encouraged, but a mask that is consistently used is better than a mouthpiece that is not.

## Importance of a Closely Fitting Face Mask

A good face mask seal is a critical factor in achieving optimal drug deposition and avoiding getting aerosol into eyes. Even small leaks of 0.5 cm around the face mask decrease drug inhaled by children and infants by more than 50%.<sup>113-117</sup> Initially, a small child may refuse to use a face mask when feeling sick or irritable. However, parental education, play activities, encouragement to hold the mask firmly against the child's face, and close supervision can reduce poor tolerance of face masks and improve aerosol drug delivery.

## Face Mask or Blow-by?

Blow-by is the administration of aerosolized drug through the nebulization port of a nebulizer that is directed toward the patient's face. Although blow-by is a technique commonly used for crying babies or uncooperative children, it has been documented that it is less efficient compared with a face mask as aerosol drug deposition decreases significantly as the distance from the device to the child's face is increased. Therefore, evidence suggests blow-by to be ineffective and use should be discouraged.<sup>97,113,118-119</sup>

## Parent and Patient Education

As children grow and their aerosol device needs to be changed, they and their care providers should be taught the best techniques for the use and maintenance of aerosol devices. Also, children may demonstrate poor adherence to aerosol drug delivery because they lack the ability to use a device correctly or contrive to use it ineffectively.<sup>120-121</sup> Therefore, respiratory therapists should explain the effects of medications prescribed, the importance of aerosol therapy, and the proper use of aerosol generators to the patient and the parent. After initial training is provided, frequent follow-up demonstration is essential to optimize aerosol drug delivery and adherence to prescribed therapy in infants and children.

# Infection Control

Aerosol generators can become contaminated with pathogens from the patient, the care provider, and the environment. The contamination of nebulizers has been documented in patients with cystic fibrosis (CF),<sup>20-22</sup> asthma,<sup>23-24</sup> and immunodeficiency.<sup>122</sup> A survey of respiratory therapists and cystic fibrosis patients found a wide disparity of nebulizer cleaning methods.<sup>123</sup> In another survey, it was shown that only 60% of cystic fibrosis caregivers were aware of infection control guidelines.<sup>124</sup> In the absence of infection control (IC), an aerosol generator will be contaminated and may cause bacterial colonization in the respiratory tract.<sup>20-22,25,125</sup> Therefore, it is essential to establish an IC management system that will reduce nosocomial infections, length of stay in the hospital, and costs associated with hospitalization.<sup>24,125-126</sup>

## IC Management System in Aerosol Drug Delivery

### Patient Education and Awareness

**Patient Education:** It has been documented that aerosol generators used at home are frequently contaminated with bacteria.<sup>23-24,127-128</sup> Therefore, the importance of cleaning and maintaining aerosol equipment should be emphasized in IC education programs<sup>129</sup> with patients and caregivers through repeated oral and written instructions.

**Patient Adherence:** Approximately 85% of patients with CF fail to disinfect their nebulizers at home.<sup>130</sup> It has been

determined that, in addition to the constraints of cleaning and disinfecting instructions provided by the manufacturers, adherence can be influenced by personal, socio-cultural, and psychological factors.<sup>131</sup> Furthermore, a majority of cystic fibrosis health care workers reported a low self-efficacy with using infection control guidelines, which can be linked to poor adherence.<sup>124</sup> Changing aerosol generators every 24 hours, using disposable equipment with health insurance approval, and partnering with patients to increase adherence<sup>85</sup> can increase patient compliance to IC and minimize the risk of infection.

### Cleaning and Maintenance of Aerosol Generators

**Cleaning:** The cleaning instructions for the different types of aerosol generators are given below.

- *Pressurized Metered-Dose Inhalers:* The plastic container of pMDIs should be cleaned at least once a week<sup>132-133</sup> as shown in Table 17.
- *Metered-Dose Inhalers Accessory Devices:* When a spacer is used with a pMDI, it should be cleaned before first use and then periodically cleaned based on the manufacturer's suggestions. Table 18 provides the steps for cleaning the pMDI accessory devices.
- *Dry-Powder Inhaler:* It is important to note that DPIs should not be submerged in water. Also, they should be kept dry as moisture will decrease drug delivery. Although there is no clear evidence about the DPI cleaning practice, each manufacturing company has

**Table 17. Cleaning instructions for the pMDI**

#### Cleaning the pMDI

Clean once a week and as needed. Look at the hole where the drug sprays out from the inhaler.

Clean the inhaler if you see powder in or around the hole.

Remove the pMDI canister from the plastic container so it does not get wet.

Rinse the plastic container with warm water and shake out to remove excess water.

Dry overnight.

Replace the canister back inside the mouthpiece and recap the mouthpiece.

recommendations for periodic cleaning and suggests wiping the mouthpiece of the DPI with a clean dry cloth.

- **Nebulizers:** In the home, nebulizers should be cleaned after every treatment. A study showed that 73% of nebulizers were contaminated with microorganisms and 30% had potentially pathogenic bacteria.<sup>134</sup> Moreover, there was a significant increased risk of COPD exacerbation in COPD patients that had nebulizers with pathogens versus those with non-pathogenic bacteria. However, nebulizer contamination can be significantly improved with proper instruction on infection control.<sup>135</sup> The longer a dirty nebulizer sits and is allowed to dry, the harder it is to thoroughly clean. Rinsing and washing the nebulizer immediately after each treatment can go a long way in reducing infection risk. According to the Cystic Fibrosis Foundation guidelines,<sup>136</sup> parts of aerosol generators should be washed with soap and hot water after each treatment, with care taken not to damage any parts of the aerosol generator. Table 19 provides the cleaning instructions for the jet nebulizer. Mesh and ultrasonic nebulizers should be cleaned and disinfected based on the manufacturer's recommendations. Also, it is important to remember not to touch the mesh during the cleaning of mesh nebulizers because this will damage the unit.

**Disinfection:** Periodic disinfection and nebulizer replacement is highly recommended to minimize contamination.

Each manufacturer suggests a different method of disinfection for its product. Therefore, the manufacturer's specific instructions on disinfecting aerosol generators should be followed. It is also important to note that all solutions should be discarded after disinfection. The varied methods for disinfection include having the patient:

Heat methods:

1. Boil or microwave<sup>137</sup> the nebulizer parts for five minutes. This disinfection process does not require a final rinse.
2. Wash in a dishwasher if the dishwasher achieves a temperature of > 158°F or 70°C for 30 min.<sup>137</sup>

Cold Methods:

1. Soak them in solution of one-part household bleach and 50-parts water for three minutes.
2. Soak the parts in 70% isopropyl alcohol for five minutes.
3. Soak them in 3% hydrogen peroxide for 30 minutes.
4. Soak them in one-part distilled white vinegar in three-parts hot water for one hour (not recommended for CF patients).

The patient should disinfect the nebulizer once or twice a week by using one of the methods for disinfection listed above. Evidence suggests that a quaternary ammonium compound can also be used for disinfecting jet nebulizers as it has comparable effectiveness with the combined disinfection procedure of a detergent pre-wash and 1.25% acetic acid soak. Also, a quaternary ammonium compound

**Table 18. Cleaning instructions for the pMDI chamber**

### Cleaning the Chamber Device

Clean every two weeks and as needed.

Disassemble the device for cleaning.

Soak the spacer parts in warm water with liquid detergent and gently shake both pieces back and forth.

Shake out to remove excess water.

Air dry spacer parts in the vertical position overnight.

Do not towel dry the spacer as this will reduce dose delivery because of static charge.

Replace the back piece on the spacer when it is completely dry.



**Table 19. Cleaning instructions for the jet nebulizer**

Cleaning After Each Use	Cleaning Once or Twice a Week
Wash hands before handling equipment.	Wash hands before handling equipment.
Disassemble parts after every treatment.	Disassemble parts after every treatment.
Remove the tubing from the compressor and set it aside. The tubing should not be washed or rinsed.	Remove the tubing from the compressor and set it aside. The tubing should not be washed or rinsed.
Rinse the nebulizer cup and mouthpiece with either sterile water or distilled water.	Wash nebulizer parts in warm water with liquid dish soap.
Shake off excess water.	Disinfect the nebulizer based on the manufacturer's recommendations. The nebulizer parts may be soaked in one of the following solutions:
Air dry on an absorbent towel.	<ol style="list-style-type: none"> <li>1. One-part household bleach and 50-parts water for three minutes</li> <li>2. 70% isopropyl alcohol for five minutes</li> <li>3. 3% hydrogen peroxide for 30 minutes</li> <li>4. One-part distilled white vinegar in three-parts hot water for one hour (not recommended for CF patients).</li> </ol>
Store the nebulizer cup in a zippered plastic bag.	Rinse parts with sterile or distilled water.
	Shake off excess water and place all parts on a clean paper towel.
	Allow them to air dry completely on an absorbent towel.
	Reassemble the nebulizer and store in a clean, dry bag container.

soak need only be 10 minutes, while the acetic acid soak should not be less than one hour. Another advantage of using the quaternary solution is that it can be reused for up to one week, as opposed to the acetic acid solution that cannot be reused.<sup>138</sup>

**Final Rinse:** The patient should use sterile water (not distilled or bottled) for the final rinse.<sup>136</sup> Sterile water can be made by boiling tap water for five minutes.

**Drying and Maintenance:** Because bacteria grow in wet, moist places, nebulizers should be thoroughly dried and stored in a clean dry place between treatments. Drying can be enhanced by attaching gas flow to the nebulizer

for a short time after it is rinsed. It has been reported that nebulizer performance may change in time due to incorrect cleaning, maintenance, and disinfection procedures.<sup>139</sup> Nebulizers must be kept from being contaminated by following the manufacturer's instructions for care and cleaning. This is necessary for all aerosol generators used for inhaled medication.

### Preventing Infection and Malfunction of Aerosol Generators at Hospitals or Clinics

**Aerosol Generators:** Bacterial contamination of nebulizers at the hospital has been associated with nosocomial infections.<sup>140-141</sup> The Centers for Disease Control and Prevention (CDC) recommends that nebulizers be cleaned, rinsed with

sterile water, and air-dried between treatments.<sup>142</sup> Also, each hospital or out-patient clinic should have an infection surveillance program that can determine local IC practices based on the continuous and systematic collection, analysis, and interpretation of infection data. Nebulizers should be changed every 24 hours.<sup>143-144</sup> If an aerosol generator is labeled “For Single Patient Use,” it should be used on a single patient and then discarded.

**MDI – Common Canister Use:** Many hospital pharmacies see a robust number of MDI canisters still containing medication returned, leading to strategies for reducing cost.<sup>10</sup> As a result, some hospitals practice common canister protocol for specific patient populations. A review focusing on common canister protocol and the risk of infection found some evidence of cross-contamination.<sup>145</sup> However, the evidence from the studies in this review is weak since none of the research is in the form of peer-reviewed publications. A recent study indicated a common canister protocol was associated with significant cost savings when compared to single-patient MDI, and reported similar rates of ventilator assisted pneumonia, mortality, and length of stay.<sup>146</sup> Hospital decision makers must perform a full risk-benefit evaluation before incorporating a common canister protocol in their institution, as more work needs to be done in this area before best-practices can be suggested with a high degree of confidence.

**Inhaled Drugs:** Multi-dose drug containers have been associated with contaminated nebulizers and are a potential source of spreading nosocomial infections.<sup>149-151</sup> Therefore, unit-dose medications are recommended when possible.<sup>142</sup> Also, it is important to avoid contaminating drug solutions.

**Infection Transmission:** The transmission of infection from therapist to patient can be reduced by therapists washing their hands with water and soap or cleaning hands with hand sanitizers before and after treatment.<sup>151-152</sup> The use of gloves should be considered an adjunct to hand hygiene. A respiratory therapist must change gloves between patients and clean hands *after* gloves are removed due to the fact that gloves create a warm and moist environment that supports the growth of microbial contamination and, thereby, the transmission of infection.<sup>30,153</sup> Goggles, face masks, and face shields should be used alone or in combination to seal out airborne pathogens that therapists may inhale with aerosol drug therapy.

**Compliance to IC Management System:** The IC management system can be effective only with the practice of the dedicated and knowledgeable respiratory therapists who implement it. Therefore, respiratory therapists should be trained appropriately in using set protocols established by the IC management system in aerosol drug delivery.

**Infection Surveillance:** It is essential for hospitals to establish simple and sensible infection surveillance measures to periodically evaluate the IC activities used by respiratory therapists.

## Occupational Health and Safety of Respiratory Therapists

Respiratory therapists undergo not only the risk of exposure to inhaled medications but are also faced with the risk of inhaling pathogens during aerosol therapy. The elements of occupational health and safety for the respiratory therapist are shown below.

**Health Assessment and Immunization:** Screening respiratory therapists for infection and immunization must occur from the beginning to the end of employment.

**Hand Hygiene:** It has been documented that hand hygiene is effective in decreasing the transmission of respiratory viruses.<sup>31,152,154-156</sup> Also, the World Health Organization’s guidelines suggest that inadequate hand hygiene is the leading cause of nosocomial infection and spread of multi-drug resistant organisms.<sup>157</sup> Health care workers who self-reported handwashing during patient care had a lower risk of having respiratory infections.<sup>31,154-156</sup>

**Protective Equipment:** Respiratory therapists must have access to the appropriate personal protective equipment, such as masks and eye protectors, when needed.<sup>30</sup>

**Ventilation System:** These systems exchange room air six to 10 times per hour<sup>31</sup> and create a negative-pressure environment in patient rooms that is effective in removing 99.9% of airborne contaminants in 69 minutes.<sup>32</sup>

**Filtered Nebulizers:** Placing a filter on the exhalation part of a nebulizer may protect respiratory therapists from infection and reduce secondhand aerosol breathing in hospitals and out-patient clinics.

# Educating Patients in Correct Use of Aerosol Devices

A number of problems occur with patient use of aerosol devices. Knowledge of these problems can help the respiratory therapist better instruct patients. Understanding there are problems with use of aerosol devices can also direct the therapist in evaluating a patient who has poor management of airways disease. Either poor patient adherence to prescribed aerosol therapy or errors in the use of aerosol devices can reduce the effectiveness of inhaled drug therapy. Both of these problem areas should be evaluated and, if possible, ruled out in a patient who presents with poor control of their airway disease before other changes in their disease management are initiated.

## Patient Adherence

A general problem with the use of inhaled medications is patient adherence with prescribed use, although this problem is not unique to inhaled drugs. “Adherence” refers to a patient’s choice to follow prescribed therapy, whereas “compliance” implies following of orders and passivity on the patient’s part. Lack of adherence can result in

poor health outcomes and increased healthcare costs.<sup>158</sup> Both long- and short-term adherence may be influenced by patient and social factors.<sup>158-159</sup> There are a number of ways to monitor patient adherence with prescribed aerosol therapy such as provider interview, patient self-report, dose counting, and electronic monitoring devices attached to the inhaler. Monitoring devices attached to inhaler devices are considered the most accurate and objective. In one study, diary reports from patients showed a median use of beta agonists of 78%, while data from an electronic pMDI monitor reported only 48%.<sup>160</sup> Therapists should be aware that patients tend to over-report use of inhaled drugs compared to data obtained from device monitors. Failure to adhere to prescribed therapy is categorized as “unintentional” or “intentional.” Table 20 lists both types of non-adherence with definitions and examples.<sup>131</sup> Upon assessing poor patient adherence, a strategy incorporating patient-centered care may help the caregiver understand patient beliefs, views, and concerns about their treatment. Goal setting and action plans are two motivational tools

**Table 20. General types of non-adherence to prescribed aerosol therapy and potential factors that can predispose to each type** (Modified, with permission, from Reference 1 and Reference 131)

### Unintentional Factors: Not Understanding Therapy Correctly

#### Misunderstanding prescribed drug regimen:

- Poor physician-patient communication
- Poor therapist-patient communication

#### Language barriers

### Intentional Factors: Understanding Therapy But Not Adhering Correctly

#### Patient beliefs:

- Do not really require regular medication
- Are not really sick
- Gain attention from parents and kept at home (children)
- Medication too expensive
- Concern about side effects
- Perceived lack of effect from medication

#### Patient forgetfulness

#### Patient stress and busy lifestyle

#### Complex and demanding aerosol regimens

#### Psychological factors (e.g., depression)

that may improve patient adherence and can be discussed in a supportive bi-directional conversation with the patient during the patient-centered approach.

Note that one example of unintentional non-adherence is incorrect aerosol device technique due to misunderstanding prescribed drug regimen, which can be corrected through patient training. There is no perfect, fail-safe, error-proof inhaler on the market today. The pMDI is rec-

ognized as a difficult inhaler for patients to use without proper training. Even holding chambers and spacers introduced to address these issues present additional problems (Table 21). DPIs were also introduced, in part, with the rationale that their use would be simpler than with a pMDI.<sup>161-162</sup> Nebulizers are probably the simplest inhaler type for a patient to use if we assume that assembly, proper cleaning, and maintenance is not a problem. However,

**Table 21. Common problems, disadvantages, and errors with each type of aerosol generator**

(Modified, with permission, from References 1 and 132)

### Pressurized Metered-Dose Inhalers

Errors in technique

- Failure to coordinate pMDI actuation on inhalation
- Too short a period of breath hold after inhalation
- Too rapid an inspiratory flow rate
- Inadequate priming/shaking/mixing before use
- Abrupt discontinuation of inspiration as aerosol hits throat
- Actuating pMDI at total lung capacity
- Actuating pMDI prior to inhalation
- Firing pMDI multiple times during single inhalation
- Firing pMDI into mouth but inhaling through nose
- Exhaling during actuation
- Putting wrong end of inhaler in mouth
- Holding canister in the wrong position
- Failing to remove cap before use
- Excessive use of pMDI beyond rated capacity (loss of dose count)
- Failure to clean boot
- Wasting remaining doses

Lack of adequate patient training in use of pMDI

Cognitive impairment of users

Lack of adequate hand strength or flexibility to activate pMDI

Ideomotor dyspraxia

### Valved Holding Chambers/Spacers

Incorrect assembly of add-on device

Failure to remove electrostatic charge in non-electrostatic holding chambers/spacers can decrease emitted dose in new holding chamber/spacer

Lengthy delay between pMDI actuation and inhalation from holding chamber/spacer

Inhaling too rapidly

Firing multiple puffs into holding chamber/spacer before inhaling

Lack of patient instruction in assembly or use

### Dry-Powder Inhalers

Errors in technique

- Not holding device correctly while loading dose
- Failure to pierce or open drug package
- Using the inhaler in wrong orientation
- Failure to prime
- Exhaling through the mouthpiece
- Not exhaling to residual volume before inhaling
- Not inhaling forcefully enough
- Inadequate or no breath hold
- Exhaling into mouthpiece after inhaling

Use of multi-dose reservoir designs in high ambient humidity, which can reduce fine-particle dose

Lack of patient instruction in assembly or use

### Nebulizers

Failure to assemble equipment properly

Spillage of dose by tilting some nebulizers

Failure to keep mouthpiece in mouth during nebulization

Failure to mouth breathe

there can be problems with all types of inhaler devices. Table 20 lists the common errors and mistakes that can occur with each type of device.<sup>131,161-162</sup>

### Common Patient Errors with pMDIs

Although hand-breath coordination with a pMDI has long been recognized as a problem, there are a number of other potential mistakes a patient can make when using a pMDI (Table 21). A large systematic review on errors in inhaler use revealed that incorrect inhaler technique is frequent and has not improved over the last 40 years.<sup>163</sup> Lack of coordination, improper inhalation (speed and/or depth), and no post-inhalation breath hold were the most frequent MDI technique errors.<sup>163</sup> Also, failure to shake a pMDI before each use can interfere with correct drug release. Failure to prime a pMDI can also affect correct drug release. A very practical problem and a real inconvenience for users is the lack of a built-in dose counter to indicate when a pMDI is empty. Dose counters are commercially available, but this involves purchasing an additional item. In one survey, 72% of patients said they continued to use their pMDI until there was no sound when it was actuated.<sup>94</sup> A pMDI can continue to produce a spray with propellant and little or no drug if it is actuated after its rated capacity, whether that is 120 or 200 puffs. Therapists should instruct patients in the importance of tracking the number of doses remaining in the pMDI (see page 39). It has been shown that MDI's without a counter results in significantly poorer adherence (underuse and overuse) when compared to MDI's with a counter.<sup>164</sup> Furthermore, significantly more asthma and COPD patients visited the ED when not using a dose counter when compared to a group using a dose counter.<sup>165</sup>

### Common Patient Errors with Holding Chambers/Spacers

Common errors that can occur with holding chambers/spacers are also listed in Table 21. Incorrect assembly of the holding chamber/spacer is a potential problem. Many patients mistakenly believe that pausing before inhaling from a holding chamber/spacer after the MDI is actuated has no effect on the delivered dose. This technique can cause reduced drug availability. The ideal technique is to place the mouthpiece between the lips and take a slow,

deep inhalation beginning when the pMDI is actuated. Available dose can also be reduced if multiple puffs are fired into a holding chamber/spacer followed by a single inhalation. Electrostatic charge is present on the chamber walls of a new plastic holding chamber/spacer, which can be removed by pre-washing with an ionic detergent or by actuating 10–20 puffs from the pMDI through the chamber.<sup>33,166</sup> An alternative is to purchase a non-electrostatic holding chamber/spacer.

### Common Patient Errors with DPIs

Problems have also been identified with patient use of DPIs (Table 21). Error rates, defined as failure to correctly perform an essential step, have been shown to be similar for pMDIs and DPIs.<sup>167</sup> In contrast, another study revealed that the DPI had a significantly lower rate of improper handling compared to the MDI.<sup>167</sup> A large study on asthma patient errors with a DPI showed that the most common mistakes included failure to exhale prior to inhalation, insufficient breath hold at end of inhalation, and lack of forceful inhalation.<sup>168</sup> Moreover, factors significantly associated with one or more of these major errors included an asthma-related hospitalization or no inhaler technique review during the previous year.<sup>167</sup> One of the unfortunate aspects of DPIs is that the models currently available in the United States all have a somewhat different design. They look different, and there are differences in the details of cocking and loading the DPIs.<sup>161</sup> One of the highest error rates is failing to hold the device correctly, which is an aspect of loading and cocking the device for use.

### Common Patient Errors with SVN's

The usual problems cited with SVN's are not problems of patient use but rather general disadvantages with this type of aerosol device (Table 21). Disadvantages include bulk and size of equipment, need for external power source (compressed gas or electricity), and lengthy treatment times. Also, aerosol generators can function at suboptimal levels for providing adequate medication delivery.<sup>169</sup> Of all the inhaler devices, however, nebulizers are the simplest for patients to use. In addition, newer nebulizer technology is directed at reducing the overall size of devices, eliminating the need for an external power source, providing shorter treatment times, and eliminating drug loss during exhalation.

## Instructing and Evaluating Patients in the Use of Inhaler Devices

There is an increasing variety of aerosol devices and operation, even within the same category of device type (e.g., DPIs). Confusion and errors of use can result. The following general steps are recommended for clinicians to ensure correct patient use:

1. Review device instructions carefully and practice with a placebo device prior to teaching others.
2. Demonstrate assembly and correct use of device to patients using a checklist.
3. Provide the patient with written instructions on how to use the device, and include a written plan for use of the medication (frequency based on symptoms).
  - a. Written instructions should be accompanied by pictures for patients with low literacy.
4. Have the patient practice use of the device while being observed by the clinician.
5. Review patient use of the device at each return visit.
6. Review the patient's understanding of the inhaled medications at each return visit (when to use, purpose of drug, prescribed frequency).
7. Have a high index of suspicion for incorrect use or non-adherence if poor management of airway disease occurs.



# References

1. Hess DR, Myers TR, Rau JL. A guide to aerosol delivery devices for respiratory therapists. American Association for Respiratory Care, Dallas, Texas 2005.
2. Gardenhire, D.S. Rau's Respiratory Care Pharmacology. St. Louis: Elsevier, 2016.
3. Newman S, Hollingworth A, AR C. Effect of different modes of inhalation on drug delivery from a dry powder inhaler. *Int J Pharm* 1994; 102:127-132.
4. Newman SP, Pavia D, Moren F, et al. Deposition of pressurised aerosols in the human respiratory tract. *Thorax* 1981; 36(1):52-55.
5. Newman SP, Woodman G, Clarke SW, Sackner MA. Effect of InspirEase on the deposition of metered-dose aerosols in the human respiratory tract. *Chest* 1986; 89(4):551-556.
6. Lewis RA, Fleming JS. Fractional deposition from a jet nebulizer: how it differs from a metered-dose inhaler. *Br J Dis Chest* 1985; 79(4):361-367.
7. Fink JB. Humidity and aerosol therapy. In: Mosby's respiratory care equipment. St. Louis MO: Mosby-Elsevier Inc; 2010:91-140.
8. Dolovich MB, Ahrens RC, Hess DR, 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.
9. Leach CL, Davidson PJ, Hasselquist BE, Boudreau RJ. Influence of particle size and patient dosing technique on lung deposition of HFA-beclomethasone from a metered dose inhaler. *J Aerosol Med* 2005; 18(4):379-385.
10. Geller DE. New liquid aerosol generation devices: systems that force pressurized liquids through nozzles. *Respir Care* 2002; 47(12):1392-1404.
11. Dulfano MJ, Glass P. The bronchodilator effects of terbutaline: route of administration and patterns of response. *Ann Allergy* 1976; 37(5):357-366.
12. Gardenhire DS. Airway pharmacology. In: Egan's fundamentals of respiratory care. St Louis MO: Mosby Elsevier; 2009:667-692.
13. Fink JB. Aerosol drug therapy. In: Egan's fundamentals of respiratory care. St Louis MO: Mosby Elsevier; 2009:801-842.
14. Babu KS, Marshall BG. Drug-induced airway diseases. *Clin Chest Med* 2004; 25(1):113-122.
15. Leuppi JD, Schnyder P, Hartmann K, et al. Drug-induced bronchospasm: analysis of 187 spontaneously reported cases. *Respiration* 2001; 68(4):345-351.
16. Steckel H, Eskandar F. Factors affecting aerosol performance during nebulization with jet and ultrasonic nebulizers. *Eur J Pharm Sci* 2003; 19(5):443-455.
17. O'Callaghan C, Barry PW. The science of nebulised drug delivery. *Thorax* 1997; 52(Suppl 2):S31-S44.
18. Hess DR. Aerosol delivery devices in the treatment of asthma. *Respir Care* 2008; 53(6):699-723.
19. Ip AY, Niven RW. Prediction and experimental determination of solute output from a Collision nebulizer. *J Pharm Sci* 1994; 83(7):1047-1051.
20. Pitchford K, Corey M, Highsmith A, et al. Pseudomonas species contamination of cystic fibrosis patients' home inhalation equipment. *J Pediatr* 1987; 111(2):212-216.
21. Rosenfeld M, Emerson J, Astley S, et al. Home nebulizer use among patients with cystic fibrosis. *J Pediatr* 1998; 132(1):125-131.
22. Vassal S, Taamma R, Marty N, et al. Microbiologic contamination study of nebulizers after aerosol therapy in patients with cystic fibrosis. *Am J Infect Control* 2000; 28(5):347-351.
23. Barnes KL, Clifford R, Holgate ST, et al. Bacterial contamination of home nebuliser. *Br Med J (Clin Res Ed)* 1987; 295(6602):812.
24. Wexler MR, Rhame FS, Blumenthal MN, et al. Transmission of gram-negative bacilli to asthmatic children via home nebulizers. *Ann Allergy* 1991; 66(3):267-271.
25. Jakobsson BM, Onnered AB, Hjelte L, Nystrom B. Low bacterial contamination of nebulizers in home treatment of cystic fibrosis patients. *J Hosp Infect* 1997; 36(3):201-207.
26. Carnathan B, Martin B, Colice G. Second hand (S)-albuterol: RT exposure risk following racemic albuterol (Abstract). *Respir Care* 2001; 46(10):1084.
27. Dimich-Ward H, Wymer ML, Chan-Yeung M. Respiratory health survey of respiratory therapists. *Chest* 2004; 126(4):1048-1053.
28. Christiani DC, Kern DG. Asthma risk and occupation as a respiratory therapist. *Am Rev Respir Dis* 1993; 148(3):671-674.
29. Kern DG, Frumkin H. Asthma in respiratory therapists. *Ann Intern Med* 1989; 110(10):767-773.
30. Rhinehart E, Friedman MM. Personal protective equipment and staff supplies. In: Infection control in home care (An official APIC publication). Gaithersburg MD: Aspen Publishers, Inc.; 2006:61-69.
31. Gamage B, Moore D, Copes R, et al. Protecting health care workers from SARS and other respiratory pathogens: a review of the infection control literature. *Am J Infect Control* 2005; 33(2):114-121.
32. Segal-Maurer S, Kalkut G. Environmental control of tuberculosis: continuing controversy. *Clin Infect Dis* 1994; 19(2):299-308.
33. Dennis JH. Standardization issues: in vitro assessment of nebulizer performance. *Respir Care* 2002; 47(12):1445-1458.
34. Hess D, Fisher D, Williams P, et al. Medication nebulizer performance. Effects of diluent volume, nebulizer flow, and nebulizer brand. *Chest* 1996; 110(2):498-505.
35. Dennis JH. A review of issues relating to nebulizer standards. *J Aerosol Med* 1998; 11(Suppl 1):S73-S79.
36. Welch MJ. Nebulization therapy for asthma: a practical guide for the busy pediatrician. *Clin Pediatr (Phila)* 2008; 47(8):744-756.
37. Rau JL, Ari A, Restrepo RD. Performance comparison of nebulizer designs: constant-output, breath-enhanced, and dosimetric. *Respir Care* 2004; 49(2):174-179.
38. Alvine GF, Rodgers P, Fitzsimmons KM, Ahrens RC. Disposable jet nebulizers. How reliable are they? *Chest* 1992; 101(2):316-319.
39. Camargo CA Jr, Spooner CH, Rowe BH. Continuous versus intermittent beta-agonists in the treatment of acute asthma. *Cochrane Database Syst Rev* 2003; (4):CD001115.
40. Everard ML, Evans M, Milner AD. Is tapping jet nebulisers worthwhile? *Arch Dis Child* 1994; 70(6):538-539.
41. Malone RA, Hollie MC, Glynn-Barnhart A, Nelson HS. Optimal duration of nebulized albuterol therapy. *Chest* 1993; 104(4):1114-1118.
42. Newman SP. Principles of metered-dose inhaler design. *Respir Care* 2005; 50(9):1177-1190.
43. Everard ML, Devadason SG, Summers QA, Le Souef PN. Factors affecting total and "respirable" dose delivered by a salbutamol metered dose inhaler. *Thorax* 1995; 50(7):746-749.
44. Niven RW, Kacmarek RM, Brain JD, Peterfreund RA. Small bore nozzle extensions to improve the delivery efficiency of drugs from metered dose inhalers: laboratory evaluation. *Am Rev Respir Dis* 1993; 147(6 Pt 1):1590-1594.
45. Pedersen S. The importance of a pause between the inhalation of two puffs of terbutaline from a pressurized aerosol with a tube spacer. *J Allergy Clin Immunol* 1986; 77(3):505-509.
46. Pedersen S, Steffensen G. Simplification of inhalation therapy in asthmatic children. A comparison of two regimes. *Allergy* 1986; 41(4):296-301.

47. Dolovich M, Ruffin RE, Roberts R, Newhouse MT. Optimal delivery of aerosols from metered dose inhalers. *Chest* 1981; 80(6 Suppl):911-915.
48. Lawford P, McKenzie. Pressurized bronchodilator aerosol technique: influence of breath-holding time and relationship of inhaler to the mouth. *Br J Dis Chest* 1982; 76(3):229-233.
49. Thomas P, Williams T, Reilly PA, Bradley D. Modifying delivery technique of fenoterol from a metered dose inhaler. *Ann Allergy* 1984; 52(4):279-281.
50. Unzeitig JC, Richards W, Church JA. Administration of metered-dose inhalers: comparison of open- and closed-mouth techniques in childhood asthmatics. *Ann Allergy* 1983; 51(6):571-573.
51. Chhabra SK. A comparison of "closed" and "open" mouth techniques of inhalation of a salbutamol metered-dose inhaler. *J Asthma* 1994; 31(2):123-125.
52. Newman S, Clark A. Inhalation techniques with aerosol bronchodilators. Does it matter? *Pract Cardiol* 1983; 9:157-164.
53. Holt S, Holt A, Weatherall M, et al. Metered dose inhalers: a need for dose counters. *Respirology* 2005; 10(1):105-106.
54. Ogren R, Baldwin J, Simon R. How patients determine when to replace their metered dose inhalers. *Ann Allergy Asthma Immunol* 1995; 75(6 Pt 1):485-489.
55. Rubin BK, Durotoye L. How do patients determine that their metered-dose inhaler is empty? *Chest* 2004; 126(4):1134-1137.
56. Schultz RK. Drug delivery characteristics of metered-dose inhalers. *J Allergy Clin Immunol* 1995; 96(2):284-287.
57. Cain WT, Oppenheimer JJ. The misconception of using floating patterns as an accurate means of measuring the contents of metered-dose inhaler devices. *Ann Allergy Asthma Immunol* 2001; 87(5):417-419.
58. Brock TP, Wessell AM, Williams DM, Donohue JF. Accuracy of float testing for metered-dose inhaler canisters. *J Am Pharm Assoc (Wash)* 2002; 42(4):582-586.
59. U.S. Department of Health and Human Services, U.S. Food and Drug Administration. Guidance for industry: integration of dose-counting mechanisms into MDI drug products. Rockville MD, 2003.
60. Sheth K, Wasserman RL, Lincourt WR, et al. Fluticasone propionate/salmeterol hydrofluoroalkane via metered-dose inhaler with integrated dose counter: Performance and patient satisfaction. *Int J Clin Pract* 2006; 60(10):1218-1224.
61. Simmons MS, Nides MA, Kleerup EC, et al. Validation of the Doser, a new device for monitoring metered-dose inhaler use. *J Allergy Clin Immunol* 1998; 102(3):409-413.
62. Julius SM, Sherman JM, Hendeles L. Accuracy of three electronic monitors for metered-dose inhalers. *Chest* 2002; 121(3):871-876.
63. Williams DM, Wessell A, Brock TP. The Doser external counting device. *Chest* 1999; 116(5):1499.
64. Momeni S, Nokhodchi A, Ghanbarzadeh S, et al. The effect of spacer morphology on the aerosolization performance of metered-dose inhalers. *Adv Pharm Bull* 2016; 6(2):257-260.
65. Mitchell JP, Nagel MW. Valved holding chambers (VHCs) for use with pressurized metered-dose inhalers (pMDIs): a review of causes of inconsistent medication delivery. *Prim Care Respir J* 2007; 16(4):207-214.
66. Yazdani A, Normandie M, Yousefi M, et al. Transport and deposition of pharmaceutical particles in three commercial spacer-MDI combinations. *Comput Biol Med* 2014; 54:145-155.
67. Ogrodnik N, Azzi V, Sprigge E, et al. Nonuniform deposition of pressurized metered-dose aerosol in spacer devices. *J Aerosol Med Pulm Drug Deliv* 2016; 29(6):490-500.
68. American College of Chest Physicians. Patient instructions for inhaled devices in English and Spanish. Northbrook IL, 2006.
69. Rau JL. The inhalation of drugs: advantages and problems. *Respir Care* 2005; 50(3):367-382.
70. Fink JB, Rubin BK. Aerosol and medication administration. In: Czerviske MP, Barnhart SL, editors. *Perinatal and pediatric respiratory care*. St Louis MO: Elsevier Science; 2003.
71. Everard ML. Aerosol delivery to children. *Pediatr Ann* 2006; 35(9):630-636.
72. Everard ML. Inhalation therapy for infants. *Adv Drug Deliv Rev* 2003; 55(7):869-878.
73. Ahrens RC. The role of the MDI and DPI in pediatric patients: "Children are not just miniature adults". *Respir Care* 2005; 50(10):1323-1328.
74. Pongracic JA. Asthma delivery devices: age-appropriate use. *Pediatr Ann* 2003; 32(1):50-54.
75. Boe J, Dennis JH, O'Driscoll BR, et al. European Respiratory Society Guidelines on the use of nebulizers. *Eur Respir J* 2001; 18(1):228-242.
76. Rubin BK, Fink JB. Optimizing aerosol delivery by pressurized metered-dose inhalers. *Respir Care* 2005; 50(9):1191-1200.
77. Rau JL. Practical problems with aerosol therapy in COPD. *Respir Care* 2006; 51(2):158-172.
78. Rubin BK. Nebulizer therapy for children: the device-patient interface. *Respir Care* 2002; 47(11):1314-1319.
79. Geller DE. Comparing clinical features of the nebulizer, metered-dose inhaler, and dry powder inhaler. *Respir Care* 2005; 50(10):1313-1321.
80. Gray SL, Williams DM, Pulliam CC, et al. Characteristics predicting incorrect metered-dose inhaler technique in older subjects. *Arch Intern Med* 1996; 156(9):984-988.
81. Allen SC, Ragab S. Ability to learn inhaler technique in relation to cognitive scores and tests of praxis in old age. *Postgrad Med J* 2002; 78(915):37-39.
82. McFadden ER Jr. Improper patient techniques with metered-dose inhalers: clinical consequences and solutions to misuse. *J Allergy Clin Immunol* 1995; 96(2):278-283.
83. Atkins PJ. Dry powder inhalers: an overview. *Respir Care* 2005; 50(10):1304-1312.
84. Fink JB, Rubin BK. Problems with inhaler use: a call for improved clinician and patient education. *Respir Care* 2005; 50(10):1360-1375.
85. Lewis RM, Fink JB. Promoting adherence to inhaled therapy: building partnerships through patient education. *Respir Care Clin N Am* 2001; 7(2):277-301, vi.
86. Fink JB. Inhalers in asthma management: is demonstration the key to compliance? *Respir Care* 2005; 50(5):598-600.
87. Berlinski A. Assessing new technologies in aerosol medicine. *Respir Care* 2015;60(6):833-849.
88. van der Palen J, Klein JJ, van Herwaarden CL, et al. Multiple inhalers confuse asthma patients. *Eur Respir J* 1999; 14(5):1034-1037.
89. Castro-Rodriguez JA, Rodrigo GJ. Beta-agonists through metered-dose inhaler with valved holding chamber versus nebulizer for acute exacerbation of wheezing or asthma in children under 5 years of age: a systematic review with meta-analysis. *J Pediatr* 2004; 145(2):172-177.
90. Meadows-Oliver M, Banasiak NC. Asthma medication delivery devices. *J Pediatr Health Care* 2005; 19(2):121-123.
91. Chan PW, DeBruyne JA. Parental concern towards the use of inhaled therapy in children with chronic asthma. *Pediatr Int* 2000; 42(5):547-551.
92. Apter AJ, Reisine ST, Affleck G, et al. Adherence with twice-daily dosing of inhaled steroids. Socioeconomic and health-belief differences. *Am J Respir Crit Care Med* 1998; 157(6 Pt 1):1810-1817.
93. Rubin BK. What does it mean when a patient says, "my asthma medication is not working?" *Chest* 2004; 126(3):972-981.
94. DiBlasi RM. Clinical controversies in aerosol therapy for infants and children. *Respir Care* 2015;60(6):894-916.
95. Everard ML. Inhaler devices in infants and children: challenges and solutions. *J Aerosol Med* 2004; 17(2):186-195.
96. Tal A, Golan H, Grauer N, et al. Deposition pattern of radiolabeled salbutamol inhaled from a metered-dose inhaler by means of a spacer with mask in young children with airway obstruction. *J Pediatr* 1996; 128(4):479-484.
97. Everard ML, Clark AR, Milner AD. Drug delivery from holding chambers with attached facemask. *Arch Dis Child* 1992; 67(5):580-585.
98. Nikander K, Berg E, Smaldone GC. Jet nebulizers versus pressurized metered dose inhalers with valved holding chambers: effects of the facemask on aerosol delivery. *J Aerosol Med* 2007; 20(Suppl 1):S46-S55.

99. Bower L, Barnhart S, Betit P, et al. American Association for Respiratory Care. AARC Clinical Practice Guideline: selection of an aerosol delivery device for neonatal and pediatric patients. *Respir Care* 1995; 4(12):1325-1335.
100. National Asthma Education and Prevention Program. Expert Panel Report III: guidelines for the diagnosis and management of asthma. Bethesda MD: National Institutes of Health; 2007.
101. Everard ML. Guidelines for devices and choices. *J Aerosol Med* 2001; 14(Suppl 1):S59-S64.
102. Ritson S JD, Everard ML. Aerosol delivery systems acceptable to young children improve drug delivery. *Thorax* 1998; 53:A55.
103. Fink JB. Aerosol delivery to ventilated infants and pediatric patients. *Respir Care* 2004; 49(6):653-665.
104. Nikander K, Agertoft L, Pedersen S. Breath-synchronized nebulization diminishes the impact of patient-device interfaces (face mask or mouthpiece) on the inhaled mass of nebulized budesonide. *J Asthma* 2000; 37(5):451-459.
105. Iles R, Lister P, Edmunds AT. Crying significantly reduces absorption of aerosolised drug in infants. *Arch Dis Child* 1999; 81(2):163-165.
106. Everard ML. Trying to deliver aerosols to upset children is a thankless task. *Arch Dis Child* 2000; 82(5):428.
107. Murakami G, Igarashi T, Adachi Y, et al. Measurement of bronchial hyperreactivity in infants and preschool children using a new method. *Ann Allergy* 1990; 64(4):383-387.
108. Janssens HM, van der Wiel EC, Verbraak AF, et al. Aerosol therapy and the fighting toddler: is administration during sleep an alternative? *J Aerosol Med* 2003; 16(4):395-400.
109. Esposito-Festen J, Ijsselstijn H, Hop W, et al. Aerosol therapy by pressured metered-dose inhaler-spacer in sleeping young children: to do or not to do? *Chest* 2006; 130(2):487-492.
110. Restrepo RD, Dickson SK, Rau JL, Gardenhire DS. An investigation of nebulized bronchodilator delivery using a pediatric lung model of spontaneous breathing. *Respiratory Care* 2006; 51(1):56-61.
111. Kishida M, Suzuki I, Kabayama H, et al. Mouthpiece versus facemask for delivery of nebulized salbutamol in exacerbated childhood asthma. *J Asthma* 2002; 39(4):337-339.
112. Lowenthal D, Kattan M. Facemasks versus mouthpieces for aerosol treatment of asthmatic children. *Pediatr Pulmonol* 1992; 14(3):192-196.
113. Smaldone GC, Berg E, Nikander K. Variation in pediatric aerosol delivery: importance of facemask. *J Aerosol Med* 2005; 18(3):354-363.
114. Amirav I, Newhouse MT. Aerosol therapy with valved holding chambers in young children: importance of the facemask seal. *Pediatrics* 2001; 108(2):389-394.
115. Janssens HM, Tiddens HA. Facemasks and aerosol delivery by metered-dose inhaler valved holding chamber in young children: a tight seal makes the difference. *J Aerosol Med* 2007; 20(Suppl 1):S59-S65.
116. Everard ML, Clark AR, Milner AD. Drug delivery from jet nebulisers. *Arch Dis Child* 1992; 67(5):586-591.
117. Esposito-Festen JE, Ates B, van Vliet FJ, et al. Effect of a facemask leak on aerosol delivery from a pMDI-spacer system. *J Aerosol Med* 2004; 17(1):1-6.
118. Kesser B, Geller D, Amirav I, Fink J. Baby don't cry: in vitro comparisons of "baby's breath" aerosol delivery hood vs. face mask or blow-by using the "Saint" infant upper airway model and "Aeroneb Go" vs. T-piece nebulizer (Abstract). *Respir Care* 2003; 48(11):1079.
119. Rubin BK. Bye-bye, Blow-by. *Respir Care* 2007; 52(8):981.
120. Everard ML. Aerosol therapy: regimen and device compliance in daily practice. *Paediatr Respir Rev* 2006; 7(Suppl 1):S80-S82.
121. Everard ML. Regimen and device compliance: key factors in determining therapeutic outcomes. *J Aerosol Med* 2006; 19(1):67-73.
122. Craven DE, Lichtenberg DA, Goularte TA, et al. Contaminated medication nebulizers in mechanical ventilator circuits. Source of bacterial aerosols. *Am J Med* 1984; 77(5):834-838.
123. Lester MK, Flume PA, Gray SL, et al. Nebulizer use and maintenance by cystic fibrosis patients: a survey study. *Respir Care* 2004; 49(12):1504-1508.
124. Garber E, Desai M, Zhou J, et al. Barriers to adherence to cystic fibrosis infection control guidelines. *Pediatr Pulmonol* 2008; 43(9):900-907.
125. Hutchinson GR, Parker S, Pryor JA, et al. Home-use nebulizers: a potential primary source of Burkholderia cepacia and other colistin-resistant, gram-negative bacteria in patients with cystic fibrosis. *J Clin Microbiol* 1996; 34(3):584-587.
126. Saiman L, Siegel J. Infection control recommendations for patients with cystic fibrosis: microbiology, important pathogens, and infection control practices to prevent patient-to-patient transmission. *Infect Control Hosp Epidemiol* 2003; 24(5 Suppl):S6-S52.
127. Cohen HA, Kahan E, Cohen Z, et al. Microbial colonization of nebulizers used by asthmatic children. *Pediatr Int* 2006; 48(5):454-458.
128. Blau H, Mussaffi H, Mei Zahav M, et al. Microbial contamination of nebulizers in the home treatment of cystic fibrosis. *Child Care Health Dev* 2007; 33(4):491-495.
129. Saiman L, Siegel J. Infection control in cystic fibrosis. *Clin Microbiol Rev* 2004; 17(1):57-71.
130. Lester MK, Flume PA, Gray SL, et al. Nebulizer use and maintenance by cystic fibrosis patients: A survey study. *Respir Care* 2004; 49(12):1504-1508.
131. Rau JL. Determinants of patient adherence to an aerosol regimen. *Respir Care* 2005; 50(10):1346-1359.
132. Chew NY, Reddel HK, Bosnic-Anticevich SZ, Chan HK. Effect of mouthpiece washing on aerosol performance of CFC-free Ventolin. *J Asthma* 2004; 41(7):721-727.
133. American College of Chest Physicians. Priming and cleaning your MDI and spacer, 2006.
134. Jarvis S, Ind PW, Thomas C, et al. Microbial contamination of domiciliary nebulisers and clinical implications in chronic obstructive pulmonary disease. *BMJ Open Respir Res* 2014; 1(1):e000018.
135. Della Zuana A, Garcia Dde O, Juliani RC, et al. Effect that an educational program for cystic fibrosis patients and caregivers has on the contamination of home nebulizers. *J Bras Pneumol* 2014; 40(2):119-127.
136. The Cystic Fibrosis Foundation. Stopping the spread of germs, 2009.
137. Saiman L, Siegel JD, LiPuma JJ, et al. Infection prevention and control guideline for cystic fibrosis: 2013 update. *Infect Control Hosp Epidemiol* 2014; 35 Suppl 1:S1-S67.
138. Chatburn RL, Kallstrom TJ, Bajaksouzian S. A comparison of acetic acid with a quaternary ammonium compound for disinfection of hand-held nebulizers. *Respir Care* 1988; 33(3):179-187.
139. Le Brun PP, de Boer AH, Heijerman HG, Frijlink HW. A review of the technical aspects of drug nebulization. *Pharm World Sci* 2000; 22(3):75-81.
140. Griebler HG, Colton FR, Bird TJ, et al. Fine-particle humidifiers. Source of Pseudomonas aeruginosa infections in a respiratory-disease unit. *N Engl J Med* 1970; 282(10):531-535.
141. Mertz JJ, Scharer L, McClement JH. A hospital outbreak of Klebsiella pneumonia from inhalation therapy with contaminated aerosol solutions. *Am Rev Respir Dis* 1967; 95(3):454-460.
142. Tablan OC, Anderson LJ, Besser R, et al. Guidelines for preventing health care-associated pneumonia, 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. *MMWR Recomm Rep* 2004; 53(RR-3):1-36.
143. O'Malley CA, VandenBranden SL, Zheng XT, et al. A day in the life of a nebulizer: surveillance for bacterial growth in nebulizer equipment of children with cystic fibrosis in the hospital setting. *Respir Care* 2007; 52(3):258-262.
144. American Association for Respiratory Care. AARC Clinical Practice Guideline: selection of an aerosol delivery device. *Respir Care* 1992; 37(8):891-897 (retired August 2006).
145. Larson T, Gudavalli R, Prater D, et al. Critical analysis of common canister programs: a review of cross-functional considerations and health system economics. *Curr Med Res Opin*; 2015; 31(4):853-860.
146. Gowan M, Bushwitz J, Watts P, et al. Use of a shared canister protocol for the delivery of metered-dose inhalers in mechanically ventilated subjects. *Respir Care* 2016; 61(10):1285-1292.
147. Estivariz CF, Bhatti LI, Pati R, et al. An outbreak of Burkholderia cepacia associated with contamination of albuterol and nasal spray. *Chest* 2006; 130(5):1346-1353.

148. Hamill RJ, Houston ED, Georgiou P, et al. An outbreak of *Burkholderia* (formerly *Pseudomonas*) cepacia respiratory tract colonization and infection associated with nebulized albuterol therapy. *Ann Intern Med* 1995; 122(10):762-766.
149. Rau JL, Restrepo RD. Nebulized bronchodilator formulations: unit-dose or multi-dose? *Respir Care* 2003; 48(10):926-939.
150. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Public health advisory: contamination of multi-dose bottles of Albuterol Sulfate Solution for Inhalation (0.5%), 2002.
151. Center for Disease Control and Prevention. Clean hands save lives, 2008.
152. Center for Disease Control and Prevention. Guideline for hand hygiene in healthcare settings, 2008.
153. Larson EL. APIC guideline for handwashing and hand antisepsis in health care settings. *Am J Infect Control* 1995; 23(4):251-269.
154. Paes BA. Current strategies in the prevention of respiratory syncytial virus disease. *Pediatr Respir Rev* 2003; 4(1):21-27.
155. Purssell E. Preventing nosocomial infection in paediatric wards. *J Clin Nurs* 1996; 5(5):313-318.
156. Hall CB. Nosocomial respiratory syncytial virus infections: the "Cold War" has not ended. *Clin Infect Dis* 2000; 31(2):590-596.
157. World Health Organization (WHO). WHO Guidelines on Hand Hygiene in Health Care: First Global Patient Safety Challenge Clean Care Is Safer Care. World Health Organization: Geneva; 2009.
158. Braido F, Baiardini I, Blasi F, et al. Adherence to asthma treatments: 'we know, we intend, we advocate'. *Curr Opin Allergy Clin Immunol* 2015; 15(1):49-55.
159. Bourbeau J, Bartlett SJ. Patient adherence in COPD. *Thorax* 2008; 63(9):831-838.
160. Milgrom H, Bender B, Ackerson L, et al. Noncompliance and treatment failure in children with asthma. *J Allergy Clin Immunol* 1996; 98(6 Pt 1):1051-1057.
161. Melani AS, Zanchetta D, Barbato N, et al. Inhalation technique and variables associated with misuse of conventional metered-dose inhalers and newer dry powder inhalers in experienced adults. *Ann Allergy Asthma Immunol* 2004; 93(5):439-446.
162. McFadden ER Jr. Improper patient techniques with metered-dose inhalers: clinical consequences and solutions to misuse. *J Allergy Clin Immunol* 1995; 96(2):278-283.
163. Sanchis, J., I. Gich, and S. Pedersen, Systematic Review of Errors in Inhaler Use: Has Patient Technique Improved Over Time? *Chest*, 2016. 150(2): p. 394-406.
164. Koehorst-ter Huurne K, Moviq K, van der Valk P, et al. The influence of type of inhalation device on adherence of COPD patients to inhaled medication. *Expert Opin Drug Deliv* 2016; 13(4):469-475.
165. Price DB, Rigazio A, Buatti Small M, et al. Historical cohort study examining comparative effectiveness of albuterol inhalers with and without integrated dose counter for patients with asthma or chronic obstructive pulmonary disease. *J Asthma Allergy* 2016; 9:145-154.
166. Wildhaber JH, Devadason SG, Eber E, et al. Effect of electrostatic charge, flow, delay and multiple actuations on the in vitro delivery of salbutamol from different small volume spacers for infants. *Thorax* 1996; 51(10):985-988.
167. Khassawneh BY, Al-Ali MK, Alzoubi KH, et al. Handling of inhaler devices in actual pulmonary practice: metered-dose inhaler versus dry powder inhalers. *Respir Care* 2008; 53(3):324-328.
168. Westerik JA, Carter V, Chrystyn H, et al. Characteristics of patients making serious inhaler errors with a dry powder inhaler and association with asthma-related events in a primary care setting. *J Asthma* 2016; 53(3):321-329.
169. Rau JL. Practical problems with aerosol therapy in COPD. *Respir Care* 2006; 51(2):158-172.