Year in Review 2014: Aerosol Delivery Devices

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After centuries of discoveries and technological growth, aerosol therapy remains a cornerstone of care in the management of both acute and chronic respiratory conditions. Aerosol therapy embraces the concept that medicine is both an art and a science, where an explicit understanding of the science of aerosol therapy, the nuances of the different delivery devices, and the ability to provide accurate and reliable education to patients become increasingly important. The purpose of this article is to review recent literature regarding aerosol delivery devices in a style that readers of RESPIRATORY CARE may use as a key topic resource. *Key words: aerosol; delivery device; MDI; DPI; nebulizer; valved holding chamber; pediatrics; positive expiratory pressure; aerosol mask; high-flow cannula; noninvasive ventilation; mechanical ventilation.* [Respir Care 2015;60(8):1190–1196. © 2015 Daedalus Enterprises]

Introduction

The prevalence of respiratory conditions continues to grow with each passing year. Regardless of the specific disease etiology, acute and chronic respiratory conditions require medical treatment either in the short term or on a continual, ongoing basis. One of the therapeutic similarities for all acute and chronic diseases is the necessity for treatment/management with medication. The vast majority of these medications are provided by inhalation. Respiratory medications delivered through the inhalational route require specialized delivery systems to ensure delivery, deposition, and accurate dosage.[1]

History and Rationale

Aerosol delivery devices consist largely of small-volume nebulizers, pressurized metered-dose inhalers, and dry power inhalers.[1] Aerosolized medications for respiratory conditions have been around for almost 70 years, with the ultrasonic nebulizer first introduced in the late 1940s. The nebulizer was quickly followed by the invention of the pressurized metered-dose inhaler about 8 years later in the late 1950s. These 2 delivery systems served as the main vehicles for aerosolized medications until the advent of dry power inhalers in the late 1970s. Even with numerous advances in medical technologies in the past 7 decades, these delivery systems continue to provide acute and chronic relief to millions of patients with respiratory conditions despite the frequent investigation of other delivery sys-

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Table 1. Rationale and Benefits of Aerosolized Respiratory Medications

Progress in aerosol drug delivery has been spurred by significant benefits, including:
Ease of use
Patient comfort
Greater selectivity of effect
Potential to decrease adverse effects

From Reference 2.

tems. The rationale and perceived benefits of aerosolized medications in treatment of respiratory conditions are summarized in Table 1.[2]

Patient-Related Variables

In an editorial published in 2013, Niven[3] stated, "The goal of an inhalation delivery system should be to ensure that the patient will consistently receive the prescribed medication and adhere to therapy." Delivery errors frequently transpire with various aerosol devices, as each device requires precise instructions and specific patient efforts to obtain correct and maximum drug delivery.[1] As management of chronic airway disease is 10% medication and 90% education, the proliferation of inhaler types may be disadvantageous for quality of care.[4] Dekhuijzen et al[5] identified a lack of attention and detail in COPD and asthma guidelines with regard to aerosol delivery devices.

Although delivery errors are common, in a paper published in RESPIRATORY CARE, Yildiz and the Asthma Inhaler Treatment Study Group[6] stated, "Close follow-up with repeated checking of the patient's inhaler technique and correction of errors each time by a physician seem to be associated with a significant decrease in the percentage of patients who make basic errors in inhalation maneuvers and device-independent errors" (Table 2). In a similar study, Arora et al[7] assessed the inhaler techniques of subjects with asthma and COPD. The authors found that the majority of subjects (> 82%) used their inhalation devices incorrectly prior to the intervention. Both studies found that proper education of subjects improved technique and symptom control, which might allow long-term dose reduction.

Table 3. Subject Rationale for Preferred Aerosol Delivery Devices

Factor	Value (%)
Physical characteristics	30
Practical and fast to use	26
Easy to use	26
Subject familiarity	18

From Reference 9.

Whereas the previous studies[6,7] focused on physician-directed education and instruction, Basheti et al[8] focused on a variety of health-care practitioners' knowledge and abilities in Jordan. The authors concluded that with the exception of specialists, most health-care practitioners need updates on inhaler techniques, especially for dry powder inhalers, but health-care practitioner can also improve with education and training.

In a slightly different approach, Chorão et al[9] assessed not only subject technique but also subject device preference. This study also demonstrated that subjects often had difficulty in performing the correct device technique (< 20% of multiple devices assessed). The areas

Table 2. Asthma Control Status in Relation to Inhaler Type Assessed by Physicians

Inhaler	Visit 1 (Month 0)			Visit 4 (Month 6)			*P**
	Total (*N* = 572)	Asthma Control Status		Total (*n* = 308)	Asthma Control Status		
		Controlled (*n* = 352)	Uncontrolled (*n* = 220)		Controlled (*n* = 269)	Uncontrolled (*n* = 39)	
Fixed-dose combination inhalers, *n* (%)							
Diskus (fluticasone propionate/salmeterol)	152 (26.6)	94 (61.8)	58 (38.2)	79 (25.6)	70 (88.6)	9 (110.4)	<.001
Solution spray (beclomethasone dipropionate/formoterol)	107 (18.7)	72 (67.3)	35 (32.7)	60 (19.5)	54 (90)	6 (10.0)	<.001
Turbuhaler (budesonide/formoterol)	156 (27.3)	91 (58.3)	65 (41.7)	87 (28.2)	74 (85.1)	13 (14.9)	<.001
Separate inhalers, *n* (%)							
Aerolizer (budesonide/formoterol)	84 (14.7)	48 (57.1)	36 (42.9)	51 (16.6)	39 (76.5)	12 (23.5)	.13
Easyhaler (budesonide/formoterol)	21 (3.8)	14 (66.7)	7 (33.3)	8 (2.6)	8 (100)	0 (0)	†

From Reference 6.
* *P* via chi-square test for rate of uncontrolled asthma at visit 1 versus visit 4.
† No statistical analysis because of the small number of subjects.
Controlled = Asthma Control Test score of > 20
Uncontrolled = Asthma Control Test score of < 20

that subjects highlighted for device preferences are summarized in Table 3.

Although Chorão et al[9] did not study inhaler adherence factors, Chrystyn et al[10] focused on this in a COPD population. The authors examined the relationship between inhaler satisfaction, treatment adherence, and health status in subjects with COPD. The main findings of the study were that inhaler durability, ergonomics, and ease of use were key features associated with overall satisfaction, and inhaler satisfaction and treatment adherence had a direct positive relationship. In addition, a modest relationship between greater treatment adherence and improved health status was found, including fewer exacerbations and better health-related quality of life.

Pediatrics

Nuances in aerosol delivery[11,12] to infants and children always generate considerable interest and frequent research, and 2014 publications were no different. Aerosol delivery to sleeping pediatric subjects is often a leading topic. Amirav et al[13] investigated the feasibility of administering inhaled medications during sleep using a new delivery system, the SootherMask (InspiRx, Somerset, New Jersey), and assessed both acceptability and lung deposition. This pilot study of 13 infants demonstrated that the Respimat (Boehringer Ingelheim, Ingelheim, Germany), InspiraChamber (InspiRx), and SootherMask together administered aerosol therapy to all sleeping infants who were regular pacifier users with good lung deposition.

Patient Interfaces

Patient interfaces and their impact on aerosolized medications are another area of high interest among the respiratory care community and specialists. Although drug delivery systems often have their own nuances and challenges, the introduction of interfaces and aerosol adjuncts provides an entirely different set of challenges and circumstances. In 2014, there were a number of studies that investigated the impact of positive expiratory pressure (PEP) devices, mask design and utilization, nebulizer/compressor combinations, and valved holding chambers.

The combination of therapies for aerosol delivery and airway clearance, secretion mobilization, and hyperinflation has been an area of interest and debate at the bedside and in lecture symposiums for several years. Two papers published in RESPIRATORY CARE in 2014 sought to provide some evidence for these frequently implemented bedside practices.

Berlinski[14] conducted a study to determine the impact of aerosol deposition in subjects with cystic fibrosis delivered with 2 types of nebulizer devices in combination with PEP and oscillatory PEP devices. Figure 1 shows the mass median aerodynamic diameters of aerosols from the nebulizers alone and connected to PEP devices. Berlinski concluded that concomitant use of nebulizers and PEP or oscillatory PEP devices that obstruct the aerosol pathway significantly decreases the aerosol particle size and subject dose.

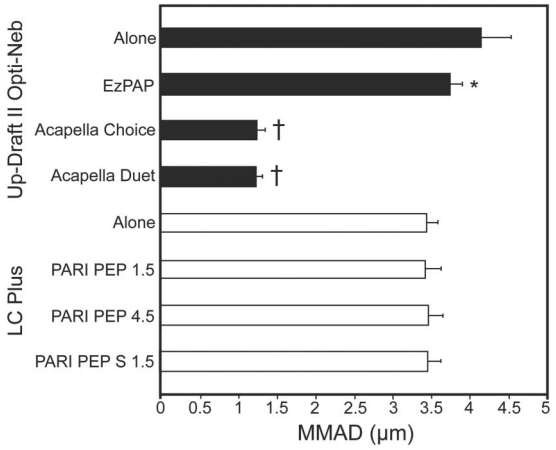

Fig. 1. Mass median aerodynamic diameter (MMAD) of aerosols from the Up-Draft II Opti-Neb (Teleflex, Morrisville, North Carolina) and LC Plus (PARI Respiratory Equipment, Midlothian, Virginia) nebulizers alone and connected to PEP devices: Acapella Duet, Acapella Choice, EzPAP (all from Smiths Medical Dublin, Ohio), PARI PEP, and PARI PEP S, with the resistance set at 1.5 or 4.5. Bars represent the means from 6 experiments. Error bars denote the SD. * $P = .02$ compared with nebulizer alone. † $P < .001$ compared with nebulizer alone. From Reference 14.

Mesquita et al[15] conducted a study to assess lung deposition provided by a variety of nebulizers in combination with the Acapella (Smiths Medical, Watford, United Kingdom) in healthy subjects. The authors hypothesized that placement of the nebulizer distal to the Acapella, as recommended by the manufacturer, would reduce aerosol lung delivery compared with more proximal placement (between the device and mouthpiece) or compared with the nebulizer alone (Fig. 2). They concluded that placing the nebulizer distal to the oscillatory PEP device decreased intrapulmonary deposition compared with proximal placement or the nebulizer alone.

Use of a nebulizer with a mask interface has been reported to provide less aerosol deposition compared with a mouthpiece.[1] Still, there are a number of patients who need to receive nebulized treatments with a mask interface for a variety of reasons. Berlinski[16] compared the effect of different degrees of occlusion of mask holes and different mask dead spaces on the amount of nebulized albuterol available at the mouth opening in a model of a spontaneously breathing child. The amounts of albuterol captured at the mouth opening (expressed in micrograms) for the mean of 3 measurements are provided in Figure 3. These data led Berlinski to conclude that neither decreasing the

Fig. 2. Test configurations. A: Nebulizer attached to the distal end of the Acapella. B: Nebulizer attached via a T-piece to the proximal end of the Acapella. C: Control setup (nebulizer and mouthpiece without Acapella). From Reference 15.

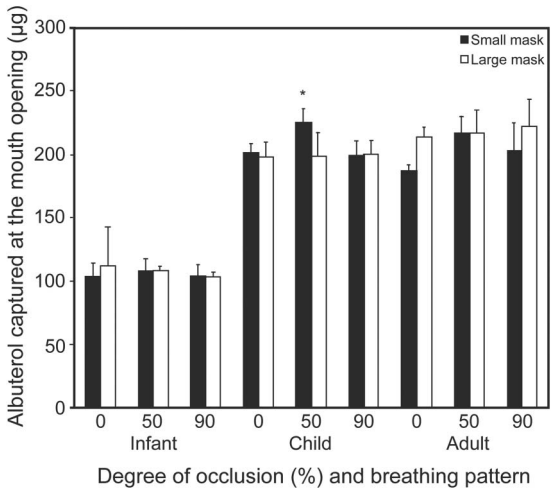

Fig. 3. Amount of albuterol captured at the mouth opening. Bars represent the mean of 3 measurements, and error bars denote the SD. * $P = .02$. From Reference 16.

dead space of the mask nor occluding the mask holes increased the amount of nebulized albuterol captured at the mouth opening, and this practice should be abandoned.

In a study in an out-patient/home care setting, Awad et al[17] examined nebulizer and compressor function over a 24-week period in a treatment regimen similar to that used by patients with cystic fibrosis. The results demonstrated that the long-term use of a compressor and nebulizers in a regimen similar to that of patients with cystic fibrosis affected pressure delivery and mass median aerodynamic diameter output.

Nikander et al[18] provided an excellent review of the scientific history of spacer devices and valved holding chambers, informed by a full patent search, an extensive review of scientific literature, and first-hand experience in this evolving field. However, Slator et al[19] conducted a clinical trial on valved holding chambers in the same publication. The investigators sought to build on previous trials and to determine the impact of inhalation delay and flow on the in vitro delivery of aerosol from 3 different valved holding chamber brands. This bench study looked at a series of automated controlled inhalation delays (0, 5, or 10 s) and a variety of air flows set at 5, 15, and 30 L/min in the delivery of albuterol (ProAir HFA, 90 µg, Teva Pharmaceutical Industries, Petach Tikva, Israel) to a filter (emitted dose) to assess 3 commercially available valved holding chamber brands (one conventional, 2 antistatic). The authors concluded that different inhalation delays and flows had similar effects on drug delivery via the 3 valved holding chambers. The 2 antistatic valved holding chambers were shown to be equivalent in vitro in terms of emitted albuterol dose.

Table 4. Summary of Findings on Delivery Efficiencies Based on Nebulizer and Subject Interfaces

Nebulizer type/interface affects delivery efficiency in simulated spontaneously breathing adult and pediatric models.
Drug delivery was greatest with a valved mouthpiece and mask with both nebulizer types.
Standard aerosol masks were least efficient.
Delivery efficiency of jet nebulizers was lower compared with mesh nebulizers.
Lung deposition in adult lung models was higher than in pediatrics.

From Reference 20.

In a bench study, Ari et al[20] looked at different types of nebulizers and interfaces used for treatment of adults and children with pulmonary diseases. The intent of the study was to determine whether the nebulizer (jet and mesh) and/or patient interfaces (mouthpieces and a variety of aerosol and valved masks) impacted the delivery efficiency of aerosolized medications. A summary of their findings is provided in Table 4.

Delivery to Patients Requiring Mechanical Support

Frequently, patients with respiratory conditions require respiratory support during exacerbations. The ability to provide aerosol therapy for both chronic maintenance and exacerbation relief continues to be an area of high interest to the respiratory care community. Papers published in 2014 on 3 distinct areas (high-flow nasal cannula, noninvasive ventilation, and invasive mechanical ventilation) are discussed.

The ability to deliver aerosols through the nasal passages to a variety of patients has been a prominent topic in the literature. With the increasing number of patients re-

ceiving respiratory support via high-flow nasal cannula in today's hospitals, the ability to deliver aerosol medications to these patients has increased. Tradition has taught us that the nose and its smaller-diameter channels act as a filter of aerosol particles, estimated to be as high as 40% of the emitted dose.[1]

In a bench study, Walenga et al[21] attempted to determine the variability in aerosol delivery through the nose to the lungs with a nasal cannula interface for conventional and excipient-enhanced growth delivery techniques. The models were selected to represent a broad range of nasal cavity constriction. The authors found that the excipient-enhanced growth approach improved the lung penetration of aerosols by a factor of 4 compared with conventional aerosol administration with a nasal cannula interface across a range of nasal anatomies. For a 5-μm initial aerosol size, conventional methods resulted in delivery device and nasal losses of ~80%, whereas a 0.9-μm initial aerosol size under excipient-enhanced growth conditions resulted in ~20% total drug loss, with only 6% depositing in the device and nasal airways.

In an article published in RESPIRATORY CARE, Golshahi et al[22] evaluated in vitro aerosol drug delivery using condensational growth techniques during high-flow nasal cannula therapy with realistic breathing profiles and incorporating intermittent aerosol delivery techniques. This bench trial demonstrated significant improvement in the dose delivered to the exit of the nose-mouth-throat model for both condensational growth methods using intermittent aerosol delivery compared with continuous delivery. Increasing the tidal volume (V_T) was also found to be useful. The combination of the largest V_T with the shortest intermittent delivery time resulted in the lowest respiration losses and the highest dose delivered to the exit of the nose-mouth-throat model.

In a slightly different mode of delivery, 2 other studies published in RESPIRATORY CARE[23,24] investigated noninvasive ventilation techniques to administer aerosol therapy. Farney et al[23] hypothesized that aerosol delivery to the lungs via variable-flow nasal CPAP in an in vitro model would be unreliable and would depend on the position of the aerosol generator within the nasal CPAP circuit. The results of this bench study showed that the relative aerosol delivery to the infant test lung with the nebulizer close to the humidifier was extremely low, whereas placing the nebulizer close to the nasal prongs resulted in significantly improved delivery (Fig. 4). The authors concluded that lung aerosol deposition was substantially improved by moving the nebulizer closer to the model.

Maccari et al[24] investigated the ability to deliver and measure aerosol deposition in 13 healthy volunteers receiving 2 types of noninvasive ventilation (CPAP and bi-level). The 3 breathing methods showed comparable lung deposition. There was no difference between the means of

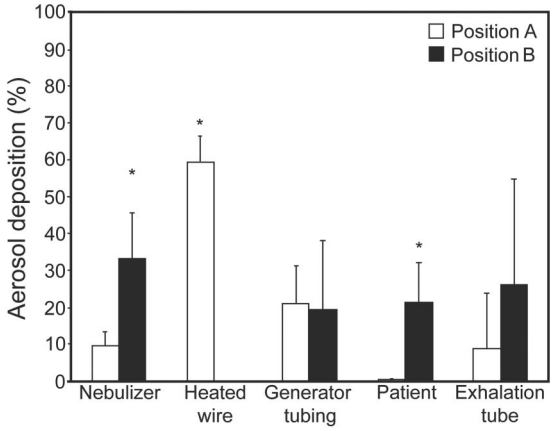

Fig. 4. Aerosol deposition in the 5 components of the test setup. Position A: with nebulizer placed at the humidifier. Position B: with nebulizer placed 32 cm from the nasal prongs. Error bars denote SD. * $P < .001$. From Reference 23.

radioaerosol deposition in either lung or the trachea, and the lung calculated ratio was similar comparing ventilatory strategies. The authors concluded that there was equivalent deposition of inhaled substances in individuals with healthy lungs when comparing spontaneous breathing, CPAP, and bi-level ventilation.

The final 4 papers discussed in this section examined various aspects of integrating aerosol therapy into invasive mechanical ventilation. In a bench study, Ehrmann et al[25] measured changes in V_T to assess inspiratory synchrony when operating integrated jet nebulization systems. The results demonstrated that synchronization was good at the beginning of insufflation, but prolonged nebulization was observed with all ventilators at the end of insufflation, until up to 1 s during expiration. Five to 80% of nebulization occurred during expiration with significant aerosol loss in the expiratory limb. The authors concluded that streamlined components could significantly improve the delivery of pharmaceutical aerosols during mechanical ventilation based on analysis of multiple aerosol-generation devices, endotracheal tube sizes, and flows.

In another bench study, Mazela et al[26] characterized the delivery of aerosolized albuterol sulfate in vitro under simulated neonatal ventilatory conditions using a novel ventilator circuit/patient interface connector (AFECTAIR, Discovery Laboratories, Warrington, Pennsylvania). The results demonstrated that compared with traditional methods, the amount of albuterol delivered using the ventilator circuit/patient interface connector was significantly greater ($P < .001$) under simulated neonatal ventilatory conditions.

In a similar bench study geared at adult subjects, Longest et al[27] sought to improve the delivery of aerosol through an invasive mechanical ventilation system by redesigning circuit components using a streamlining approach. The

components that were redesigned were the T-connector interface between the nebulizer and ventilator line and the Y-connector leading to the endotracheal tube. The goal of the streamlining approach was to minimize aerosol deposition and loss by eliminating sharp changes in flow direction and tubing diameter that lead to flow disruption. The experimental results demonstrated that the streamlined components improved delivery through the circuit by factors ranging from 1.3 to 1.5 compared with a commercial system with adult 8- and 9-mm endotracheal tubes.

Finally, Wan et al[28] determined the efficiency of 3 pneumatic nebulization modes (inspiratory intermittent, continuous, and expiratory intermittent) provided by a ventilator with adult and pediatric in vitro lung models. The nebulizer was placed proximal to the ventilator, 15 cm from the inlet of the heated humidifier chamber with a T-piece and corrugated aerosol tubing, and powered by gas from the ventilator in each of the 3 modes. The investigators concluded that aerosol drug delivery with a jet nebulizer placed proximal to the ventilator was not dependent on nebulization mode during simulated pediatric and adult conventional mechanical ventilation. Use of the expiratory intermittent mode and continuous nebulization should be considered to reduce treatment time.

Emerging Technologies

What does the future of aerosol therapy hold? If anyone had a crystal ball and could predict that future, it would quite possibly lead to both fame and fortune. Although current technologies and medications are quite effective, patients with chronic respiratory disorders continue to suffer with symptoms and exacerbations. New medication formularies for a variety of diseases create ongoing developments in technologies and delivery.[22-32]

Sirsi and Borden[33] authored a paper that examined emerging technologies for new formularies of aerosolized cancer medications with the original delivery system, ultrasonic nebulizers. Although there are both opportunities and challenges involved, the authors concluded, "Ultrasonic drug targeting of chemotherapeutic agents has the potential to alter current clinical paradigms of cancer treatment to significantly improve therapeutic outcomes and the quality of life of patients undergoing chemotherapeutic treatment."

A comprehensive overview of the future of aerosol therapy in both a traditional and futuristic sense is provided in an article written by Rubin and Williams.[34] The review stated that new medicines and novel aerosol formulations have enhanced our ability to treat lung disease and are opening the doors for therapy to treat diseases such as diabetes, pulmonary hypertension, and cancer. Progress in the aerosol drug delivery has been spurred by significant benefits, including ease of use, patient comfort, greater selectivity of effect, and potential to decrease adverse effects.

Summary

This 2014 year in review of aerosol delivery devices provides a comprehensive and diverse look at a variety of innovations and studies in existing and new technologies that have been published over the past year. Perhaps the best concluding statement is provided by Rubin and Williams[34]:

> The benefits of inhalation therapy continue to spur innovation and development to broaden its role in clinical medicine. Progress has been steady, and the pace is increasing. The unprecedented levels of sharing among disciplines possible today may be shortening the time between milestones. Though we hope that most of the steps to progress are forward, there is likely to be great opportunity from the unexpected turns, as the line between bench and bedside blurs.

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