

New Aerosol Delivery Devices for Cystic Fibrosis

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Summary

Cystic fibrosis (CF) patients use several therapies to treat chronic inflammation and infection in the lungs and to improve airway clearance. Inhaled therapies in CF typically include bronchodilators, airway wetting agents, mucus-active agents, and antibiotics, among others. There are many variables to take into account when prescribing aerosolized therapies to CF patients, including aerosol factors, patient variables (eg, age, disease severity, and breathing patterns), and the limitations of current aerosol delivery systems. The greatest challenge for patients is dealing with the time burden placed on them to try to fit all the treatments into their day—a burden that is likely to be even greater in the near future due to the exciting pipeline of novel therapies that target the genetic defect of CF as well as the pathophysiologic consequences. Fortunately, novel aerosol delivery systems and drug formulations are being developed to tackle the many challenges of aerosol delivery in CF. If successful, these systems will reduce the time burden and improve the clinical outcomes for the CF community. Key words: cystic fibrosis, aerosol delivery, slow mist device, vibrating mesh, breath-control nebulizers, dry-powder inhaler. [Respir Care 2009;54(6):754–767. © 2009 Daedalus Enterprises]

Introduction

The lung disease in cystic fibrosis (CF) is characterized by insufficient periciliary fluid, impaired clearance of airway secretions, an overactive inflammatory response, and chronic respiratory infections. As in many other chronic

respiratory diseases, inhalation of therapeutic agents is an appealing way to treat the lung disease topically, trying to maximize the dose at the site of disease while minimizing exposure to the rest of the body. Until recently, the number of medications available for CF treatment were limited

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and could easily be delivered by the aerosol devices available, including pressurized metered-dose inhalers (pMDIs), dry-powder inhalers (DPIs), and pneumatic jet or ultrasonic nebulizers. But with the explosion of CF-related research into disease mechanisms and potential treatments of the pathophysiologic cascade,^{1,2} those devices are no longer as appealing. Fortunately, we have coincidentally seen several advances in aerosol delivery technology that can be paired with new drugs to optimize inhaled drug delivery for CF patients.

This paper will review the rationale for the need for new delivery devices, including some of the specific challenges in CF. The limitations of current devices will be discussed, as well as how novel devices are designed to overcome them.

Why Do We Need New Aerosol Devices?

There have been many driving forces over the past few years to develop novel aerosol devices. Most of these factors are not directly related to CF therapies, but are nonetheless applicable to them. The United Nations ban on chlorofluorocarbons in the Montreal Protocol extended to the pMDI, such that after the end of 2008, almost no pMDIs contain chlorofluorocarbons. This led to the development of hydrofluoroalkane propellants for pMDIs, and to novel delivery systems that do not require chemical propellants.³

Another driver of technologic innovation was the systemic delivery of inhaled drugs, using the large surface area of the lung as a sponge to soak up drugs into the circulation. The prime example is inhaled insulin for the treatment of diabetes mellitus. Drugs such as insulin need to be delivered to the lung periphery for better absorption, and often have a very narrow therapeutic index requiring precise dosing. Inhaled insulin has not been a commercial success, but its development helped to spawn new technologies in dry-powder and wet aerosol delivery. Even though topical airway delivery is the goal in CF lung disease (not systemic delivery), there may be substantial advantages to using the targeting precision offered by these novel devices with CF drugs.

Other technology drivers include reducing the time of aerosol administration, overcoming some of the challenges in aerosol delivery efficiency, reducing drug waste (especially for expensive drugs), and the ability to deliver fragile large molecules (proteins, genes) and drugs complexed with carriers (viral vectors, liposomes).⁴

Time Burden

Several aerosol therapies are currently used for CF, and recent evidence-based guidelines were published regarding chronic therapies for CF lung disease.⁵ Aerosolized

drugs are used almost universally in CF patients, regardless of age or disease severity. Bronchodilators are useful in those patients with airway hyperreactivity, and are also used for pretreatment prior to other inhaled drugs that may cause bronchial irritation. Inhaled corticosteroids may be useful in those who also have asthma, but the current guidelines advise against universal inhaled corticosteroids use in CF.⁵ Mucus-active agents and airway-wetting agents such as dornase alfa and hypertonic saline are used to improve the rheology and transport of airway secretions.⁶ Inhaled antimicrobial drugs are used for early eradication or chronic suppressive therapy of organisms such as *Pseudomonas aeruginosa*.⁷ CF patients are asked to use several of these therapies that may take up to 3 hours per day to administer, and then to clean and sanitize the aerosol equipment. The CF drug pipeline is large and exciting, but many of the new treatments will also require inhalation, including new antimicrobials, chloride-channel activators, sodium-channel inhibitors, anti-proteases, anti-oxidants, and gene therapy.² CF patients may have mixed emotions about these advances, since they may face a greater treatment burden as more therapies and aerosol delivery devices are added to their regimens. There is a clear need to shorten treatment times for CF medications.

Dealing With Aerosol and Host Factors in Cystic Fibrosis

The effectiveness of an inhaled therapeutic depends on how much of the drug is able to navigate through the upper airway and into the lung, and how well the distribution of the drug matches the location of the target. The deposition efficiency of aerosols in the lungs is related to numerous variables, including aerosol characteristics, drug formulation, patient variables, and the interface between the delivery device and the patient. Designing aerosol therapies for CF is particularly challenging, since the disease affects a wide age range, from newborns to adults, and the spectrum of disease severity from normal lung function to severe airway obstruction.⁸ Delivery of aerosol drugs has historically been a “sloppy” business, with huge variability in lung dose for inhaled drugs. This imprecision has been tolerated because most inhaled drugs (ie, bronchodilators and inhaled corticosteroids) are inexpensive and have a high therapeutic index. That is not necessarily the case with some of the inhaled drugs for CF; therefore, it is important that we understand the basic principles of aerosol delivery and how delivery systems function, so that inhaled therapies can be optimized. The physiology of aerosol delivery has been thoroughly discussed recently.⁸⁻¹¹ We will review some of the key points here as background for why certain features are included in new device technology.

The most important aerosol characteristics are the size and size distribution of the particles, and the velocity at which they travel. The upper airway is a very effective filter for particulates. Particles less than 5 μm in size have the highest probability of bypassing the upper airway and entering the lower airways. Large particles and those with higher velocity will likely impact on the upper airway and not be able to make the bend around the throat. This principle was nicely demonstrated by Laube et al, who studied 9 CF adults and showed higher lung deposition with radiolabeled 1.01- μm particles than with 3.68- μm particles.¹² Deposition further increased when the subjects were guided to inhale more slowly. Regional distribution may also change by manipulating particle size, with improved homogeneity of deposition with smaller particles.¹³ Two clinical studies of dornase alfa support these deposition studies, showing a trend toward improved lung function in those receiving a smaller-particle aerosol with a jet nebulizer.^{14,15}

Patient-related factors are just as important as aerosol characteristics in determining aerosol deposition and distribution in the lung. Patient factors are responsible for the huge intra-subject and inter-subject variability that has been observed in clinical trials. Some of the variables include age, upper-airway size, breathing pattern, inspiratory flow, and degree of airway obstruction. The device-patient interface is also important, including cognitive ability and coordination necessary to operate the device, as well as how easy it is to clean and sanitize.^{8,9}

Age affects many of the other variables. Infants and young children, for example, have small-caliber upper and lower airways, small tidal volumes, fast respiratory rates, and the inability to perform special breathing maneuvers. These children are limited to tidal breathing and mask interfaces, though the use of smaller particles improves lung deposition.¹⁶ As patients age, there is less upper-airway impaction and greater lung deposition.^{17,18} However, as patients get older, they tend to have worsening airway obstruction that causes aerosol particles to deposit more centrally and at sites of obstruction.^{13,18,19} Poor aerosol distribution in sicker patients means that poorly ventilated areas may get no drug at all, which may reduce the clinical effectiveness of some drugs.²⁰ Attempts have been made to solve that problem. Homogeneity of drug distribution has been shown to improve modestly in patients who are pretreated with bronchodilators or given positive expiratory pressure.^{21,22} Using very slow inspiratory flow may also allow particles to pass areas of partial obstruction and reach more peripheral regions.^{12,23} If novel aerosol delivery systems can overcome some of the challenges related to aerosol physiology, it would be possible to have more precision and less variability in targeting the lungs in CF.

Waste Reduction

Improving the delivery efficiency of aerosols often means addressing the inefficiencies of current devices and techniques, including reducing the amount of wasted drug (that portion that doesn't reach the target in the lung). There are many potential sources of waste, including drug left in the delivery device at the end of a treatment (residual dose), and drug that is delivered during the expiratory phase of the breathing cycle. Of course, poor technique and non-adherence will also result in wasted drug or ineffective therapy, so the delivery devices should be as intuitive to use as possible. Most of the novel aerosol devices have at least one feature that reduces drug waste.

Current Devices: Advantages and Limitations

A number of aerosol delivery systems have been in use for decades, including pMDIs, DPIs, and jet and ultrasonic nebulizers. These devices have been extensively reviewed,^{8,24,25} so we will focus on the advantages and limitations of current devices as they relate to CF therapies.

The pMDI is the most popular delivery device for asthma-related drugs such as β agonists, anticholinergic agents, and inhaled corticosteroids. They are small, portable, and the treatment time is very short. The dose-to-dose consistency is excellent when tested in vitro. The transition from chlorofluorocarbons to hydrofluoroalkane propellants is almost complete, and recently many of the pMDIs have incorporated dose counters so that patients can tell when the canisters are empty. The main disadvantage of pMDIs is that the press-and-breathe technique is difficult to master (up to 75% of patients make errors when using them).²⁶ Also, the particle exit velocity is high, resulting in a large amount of throat impaction. Using a valved holding chamber with a pMDI can improve coordination and reduce upper-airway deposition, but there are many different brands of valved holding chamber, with different design features; therefore, there is large variability in drug output between them. The most limiting factor for using a pMDI for CF-related drugs is that it is designed to deliver very small quantities of drug (less than a milligram per puff), making it impractical for most CF drugs. The other technical limitations are that the drug must be stable in a multi-dose canister, and must be compatible with the propellant.

DPIs are also small, portable, and quick to use. There is no need for coordination of actuation and inhalation, because the patient's inspiratory force deaggregates the powder and generates the aerosol. DPIs come in a variety of types, including single-dose capsule-based designs, multi-dose units containing bulk drug, and multi-dose units containing unit-doses in individual blisters. The plethora of DPI types may confuse some patients who use more than

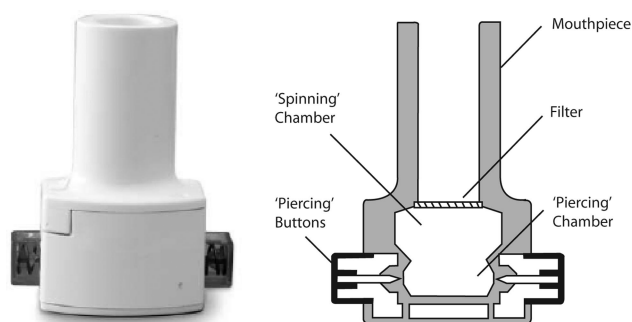


Fig. 1. A simple, capsule-based dry-powder inhaler used for mannitol delivery. (Courtesy of Pharmaxis.)

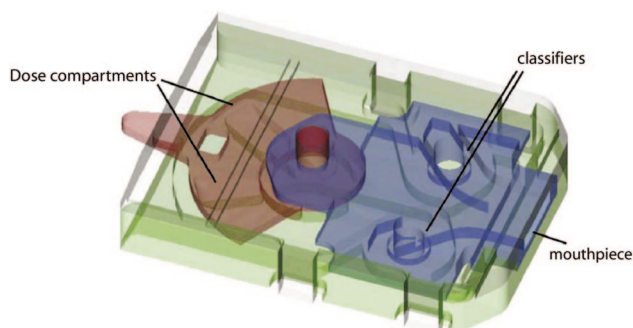


Fig. 2. The Twincer dry-powder inhaler, with 2 parallel air classifiers, used in a trial of inhaled colistimethate in cystic fibrosis. (From Reference 29, with permission.)

one type. Most CF subjects 6 years and older have the cognitive skills and inspiratory capacity to operate current commercial DPIs effectively.²⁷

Unlike pMDIs, DPIs have the capacity to deliver higher payloads of drug to the airways, which means that DPIs are a potential option for many current and novel CF drugs. For example, high-dose mannitol powder is being studied in CF and other airway diseases, to enhance airway clearance.²⁸ The powder is made by a milling process, and the inhaler is a simple, capsule-based system that resembles the Aerolizer device for formoterol (Fig. 1). Also, a pilot study in CF demonstrated that milled colistin powder mixed with lactose compared favorably with nebulized delivery when delivered by a novel Twincer DPI (Fig. 2).²⁹

DPIs may solve some of the problems of convenience, portability, and cleaning, but there are some disadvantages also. For example, if the therapeutic dose of a drug is high (like mannitol), the delivery would be limited to a capsule-based or blister-based system that requires manual loading and unloading of several individual units per dose. The large amounts of powder are also more likely to provoke upper-airway irritation, coughing, and bronchospasm in susceptible individuals.²⁸ Inter-patient dose variability is still likely to be high. Finally, not all drugs can be formu-

lated by milling of powders, but an alternate spray-drying technique is available that will be discussed later.

Liquid formulations delivered by nebulization have been favored for most inhaled CF drugs. The classic types of nebulizers are ultrasonic nebulizers and jet nebulizers. Nebulizers have been extensively reviewed elsewhere, and vibrating-mesh nebulizers will be discussed in the new technology section. Ultrasonic nebulizers historically were larger and more expensive than jet nebulizers, and though they can nebulize solutions more quickly, they are not effective for aerosolizing suspensions or high-viscosity liquids.^{9,30} The piezoelectric crystal can heat and inactivate protein drugs such as dornase alfa. Therefore, pneumatic jet nebulizers are favored, as they can be used in patients of all ages and disease severities with tidal breathing technique. The drawbacks for nebulizer/compressor systems include that they are noisy, less portable than pMDIs and DPIs, time-consuming, require a power source, and they need routine cleaning and disinfection.³¹ There are also different types of jet nebulizer (unvented, vented, breath-enhanced, breath-actuated) and many different manufacturers of nebulizers and compressors, with widely variable performance characteristics. These differences in nebulizer performance led the Food and Drug Administration (FDA) to limit pharmaceutical companies to the drug-device combinations that were tested in clinical trials, including dornase alfa (Pulmozyme, Genentech, South San Francisco, California) and tobramycin solution for inhalation (TSI, TOBI, Novartis Pharmaceuticals, East Hanover, New Jersey). Even though aerosol technology has advanced substantially since those drugs were launched, the FDA has not approved newer devices for those drugs unless a clinical trial program has shown safety and effectiveness of the new drug-device combination. Thus, the use of new, more efficient nebulizers (perhaps based on bench testing or limited pharmacokinetic studies) remains off-label, and any liability associated with recommending them lies with the prescriber.

The biotechnology and pharmaceutical industries often choose jet nebulizers for new drug development because of the ability to deliver high doses of medication and the lower development costs, compared to other systems. However, in recent years many companies have recognized the time burden that this places on patients, so they have been initiating preclinical development with newer, more efficient technologies to help tackle that problem.

Novel Aerosol Delivery Devices

The development of new aerosol technologies that address several of the current device limitations is an ongoing process. We will now focus on new device technologies, and how they are being applied to CF drugs.



Fig. 3. The Respimat slow-mist inhaler. (Courtesy of Boehringer Ingelheim.)

Slow-Mist Devices

The Respimat (Boehringer Ingelheim, Ingelheim, Germany) is a small, propellant-free, multi-dose device that retains the convenience of a pMDI but improves the particle characteristics and ease of use.³² The device employs a spring mechanism to push liquid through nozzles to generate a “slow mist” aerosol over 1–1.5 seconds (Fig. 3). The qualities of the aerosol produced are not dependent on propellants or inspiratory effort (unlike pMDIs and DPIs respectively). The Respimat does not require a spacer, battery, or electric power source. The drug contained in the cartridge is in solution form rather than suspension, so no shaking is required. The user has to push a button to actuate the dose, so the coordination of actuation and inspiration (press and breathe) is still necessary. That probably precludes the use of the Respimat in young children. However, the aerosol velocity is much slower than that of a pMDI, so it is easier to inhale and there is less impaction of particles in the upper airway. The resulting deposition fraction is approximately 40% in adults.³³ The Respimat is currently available in some countries outside the United States for asthma and chronic-obstructive-pulmonary-disease drugs (bronchodilators and inhaled corticosteroids). It has a very small dosing chamber (15 μL), so it is only useful for low-dose drugs, and is unlikely to be used for CF-specific drugs. However, it is worth mentioning here because it is currently being tested in phase-2 studies in CF patients with tiotropium bromide, a long-acting anticholinergic bronchodilator.

The other slow-mist devices are the AERx and AERx Essence platforms (Aradigm, Hayward, California).³² The first-generation AERx is an electronic microprocessor-controlled device designed to provide precise dosing of liquid formulations to the lung (Fig. 4A). To

achieve the high level of precision and drug targeting to the lung, the AERx controls all aspects of the dosing, including the generation of the aerosol and the patient's inhalation pattern. It is a hand-held, battery-powered, unit-dose system. The electronics function in several ways, by heating the entrained air to reduce the influence of ambient conditions, by providing dose-titration capability, by giving feedback to the patient for proper inhalation technique and breath-holding time, and by releasing a dose during a preset portion of inspiration only if the patient's inspiratory flow and volume fit chosen parameters. The AERx can also monitor dose times and frequency, download the information to the clinician, and provide safeguards against unauthorized use. The AERx has so many features that improve dose precision that it is considered as one of the “smart” aerosol devices. It has been tested with several drugs for both systemic and topical lung delivery.

The drug is contained in a single-use, multi-layer, laminated dose blister that consists of a drug reservoir and a layer with a slot that directs drug through a nozzle array (Fig. 4B). The nozzle consists of a number of small, micron-size, laser-drilled holes. There are no clogging issues because each dose blister is used only once.

The AERx addresses several limitations of older devices. First, the time it takes to load a dose blister and take a dose is similar to that of a unit-dose DPI. Second, the AERx overcomes many of the patient factors by encouraging a slow inspiration with a breath-hold. In fact, no drug is released unless the patient inhales correctly, and the slow release of drug and slow inspiratory flow minimize the upper-airway impaction and maximize the lung deposition, which can be as high as 80% of the delivered dose.³⁴ Finally, there is very little residual dose in the blister, so drug waste is minimized. The drawback of the AERx is the small capacity of the drug blister, which holds only about 45 μL of liquid, limiting its use to low-dose drugs, or those that can be concentrated to high levels, as long as the lung-dose requirement is less than about 10 mg.³⁵ The AERx also cannot be used in young children because of cognitive difficulties and small lung volumes, with a lower age limit of about 8 years.

In a small proof-of-concept trial, the AERx was used in a group of CF patients to administer dornase alfa for 14 days. The drug used for the study was 10 times the concentration of the commercial preparation, Pulmozyme, and was given in 3 dose blisters, each containing 0.45 mg. There was a significant increase in lung function after 2 weeks, showing the potential of giving lower-dose CF drugs with the AERx.³⁶

The first-generation AERx is highly sophisticated and expensive, so an alternative design was developed to satisfy more general needs. The AERx Essence (Fig. 4C) uses the same dose blisters as the original AERx, but it is

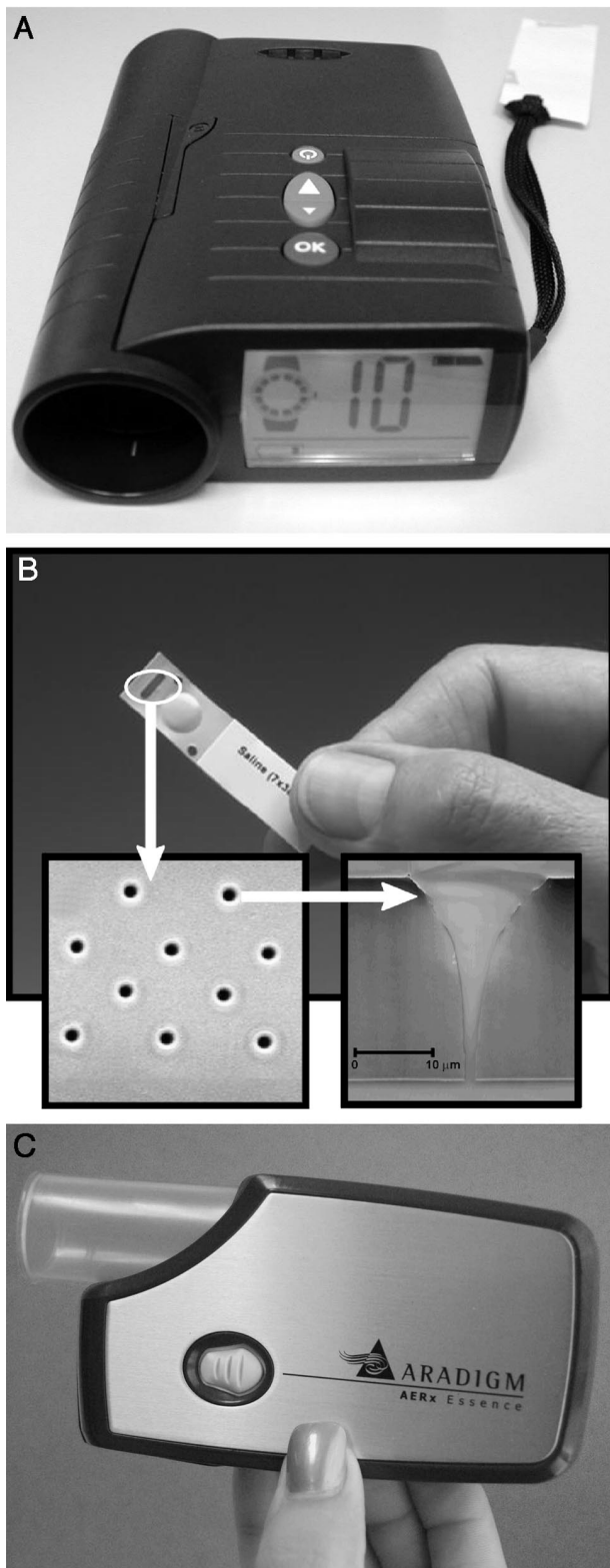


Fig. 4. A: Electronic version of the AERx "smart" slow-mist device. (Courtesy of Aradigm.) B: The AERx dose blister incorporates a nozzle array through which the drug is forced, creating the aerosol. (Courtesy of Aradigm.) C: Mechanical version of the AERx. (Courtesy of Aradigm.)



Fig. 5. Omron MicroAir portable, vibrating horn/mesh nebulizer. (From Reference 25.)

a mechanical device rather than electronic. There is no heat conditioning of entrained air, and no electronic feedback for air flow, breath-holding, or dose compliance. The dose is released by pressing a button (similar to the RespiMat), and during inhalation a built-in flow resistor prevents the patient from inhaling too quickly, thus reducing upper-airway impaction and improving particle dispersion. The dose is released as a slow mist, and lung deposition is almost as high as with the electronic AERx. Therefore, there are many advantages over the pMDI, but patients must still be educated about how to properly use this press-and-breathe device. A video of the AERx Essence can be found at <http://www.aradigm.com/technologies.html> (accessed March 1, 2009).

Vibrating-Mesh Devices

A new generation of aerosol delivery systems has been developed that use a vibrating, perforated mesh to generate the droplets.^{37,38} Three technologies are currently being used for vibrating-mesh devices. The Omron NE-U22V MicroAir nebulizer (Omron, Vernon Hills, Illinois) has a piezoelectric element that vibrates a transducer horn that pulses fluid through a mesh, creating the aerosol droplets (Fig. 5). Aerogen's OnQ aerosol generator (Nektar Therapeutics, San Carlos, California, now part of Novartis) and Pari's eFlow TouchSpray technologies (Pari, Starnberg, Germany) produce a controlled distribution of low-velocity droplets from a thin, perforated mesh actuated by an annular piezoelectric element. The actuator encircles the dome-shaped mesh and causes it to vibrate at high frequency, causing a micro-pump action at the fluid-mesh interface (Fig. 6). Aerogen meshes are created with an

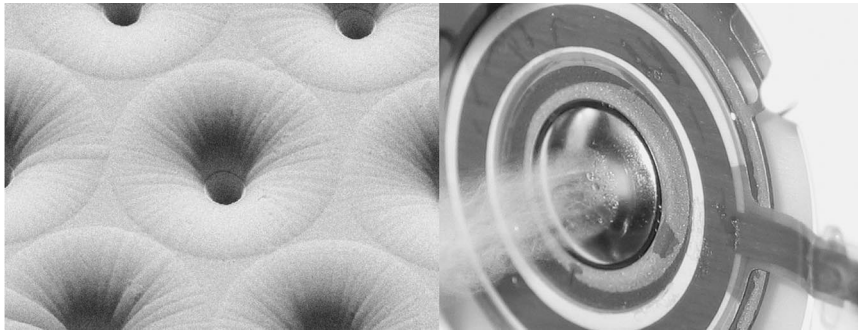


Fig. 6. Aerogen mesh formed by electroplating method creates tapered holes (left). The eFlow nebulizing head (right) has a stainless steel, laser-drilled mesh surrounded by a piezo element to create a rapid to-and-fro motion. (From Reference 8, with permission.)

electroplating technique to form tapered holes, whereas the eFlow meshes are precision, laser-drilled, stainless steel membranes.

Vibrating-mesh nebulizers are electronic devices that have several advantages over jet nebulizers. They are portable, silent, fast, do not require compressed air, and can operate with batteries or alternating-current power. There is no recirculation of drug from baffles, so there is little evaporative loss or cooling of the drug. The mesh can aerosolize almost all of the fluid, so there is the potential to significantly reduce residual dose and drug waste. However, the efficiency of delivery depends on the device housing that holds the mesh, which can be adapted to specific needs. The particle size of the aerosol produced is dependent on the size of the holes in the mesh and the physicochemical properties of the drug formulation. Because of the low shear stresses on the fluid, several fragile molecules (eg, proteins or genes) may be aerosolized with this technology.³⁸ One of the drawbacks to the vibrating-mesh devices is the potential to clog the tiny holes of the mesh. Suspension-type drugs may get caught in the mesh holes, and some solutions may be too viscous to pass through a mesh system. With repeated use the nebulization time can gradually increase, and thorough cleaning methods are necessary to maintain the efficient function of the mesh. Replacement of the meshes is usually required periodically to maintain optimal operation.

For the past few years the Omron MicroAir NE-U22V and the Aerogen AeroNeb Go have been available as open devices for general-use purposes. These devices were designed to have similar performance efficiencies as the breath-enhanced jet nebulizers already on the market. The Omron device has a very low residual volume, but the particle-size distribution is larger, reducing the overall efficiency to that of a jet nebulizer.³⁹ In the case of the AeroNeb Go, the mesh nebulizes most of the fluid, but because the aerosol stream is directed downward and not toward the patient, there is a high residual dose in the device housing.³⁹ These devices are commonly used for

bronchodilators, but are off-label for CF drugs such as dornase alfa and TSI.

The Aerogen OnQ aerosol generator has been customized for a variety of specific uses, including mechanical ventilation, noninvasive ventilation, and ambulatory uses (Fig. 7).⁴⁰ A small, breath-actuated, electronic, prototype device called the AeroDose was used in a pharmacokinetics study in CF.⁴¹ The AeroDose charged with 90 mg of tobramycin delivered almost the same amount of drug to the lung as a 300-mg dose using the Pari LC Plus, and in less than half the time. Though there were other issues with the AeroDose performance, this study showed the potential to deliver high drug doses more quickly and efficiently with mesh technology. The AeroNeb Pro and Solo devices were developed to improve delivery efficiency of aerosols to intubated patients. A conical, vertical, valved spacer called Idehaler (La Diffusion Technique Française, Saint-Étienne, France) has been coupled with these devices to dramatically improve delivery efficiency to ambulatory patients (as high as 70% of inhaled dose, Fig. 7).⁴⁰ This system has not been studied with CF drugs yet, but *in vitro* data suggest that there is potential for the AeroNeb/Idehaler combination to be an efficient, relatively low-cost system. Aerogen mesh devices have been studied with antibiotics, proteins, inhaled vaccines, and gene vectors, and do not seem to disrupt the activities of these agents.

The eFlow electronic nebulizer (Pari, Starnberg, Germany) (Fig. 8) is a device platform that can be customized for a particular drug formulation.³⁸ The medication cup has an internal slope that guides the fluid to the metal mesh, minimizing the residual dose. The direction of the aerosol stream is toward the patient, and the aerosol chamber conserves drug during the exhalation phase. Even though the device operates continuously, these factors dramatically improve the performance over jet nebulizers. The eFlow can be optimized for a particular formulation by changing the following parameters: hole size, hole number and distribution, power input to the piezo element,



Fig. 7. Aerogen family of products includes (left) the AeroNeb Go for ambulatory use, (middle) AeroNeb Pro for mechanical ventilators, and (right) the AeroNeb Pro coupled with the experimental Idehaler chamber to improve delivery efficiency. (left, from Reference 25; middle, courtesy of Nektar Therapeutics; right, from Reference 40, with permission.)

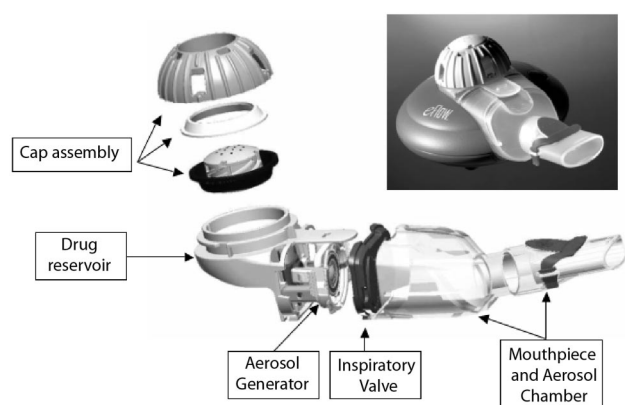


Fig. 8. A configuration of the eFlow platform, showing components that can be customized for a particular formulation. (From Reference 8, with permission.)

aerosol chamber dimensions, and valve design. Further enhancements could include breath-actuation and proprietary, liquid-feed, closed systems. There is even a version with a face-mask for infants and toddlers.⁴²

In addition to the attributes of vibrating-mesh devices noted above, the eFlow platform has other possible advantages. Because of the precision laser-drilling process, the distribution of particles sizes is narrow for a particular mesh configuration, which aids in drug targeting and improves the respirable fraction. The high efficiency of nebulization reduces drug waste, which may be of critical importance with drugs that are expensive to manufacture.

The eFlow was chosen and optimized for the delivery of aztreonam lysine inhalation solution (AZLI, Gilead Sciences, Foster City, California),⁴³ having completed three phase-3 trials in CF.⁴⁴ The eFlow-AZLI combination has been reviewed by the FDA, but another clinical trial was requested before they would approve it. Also, the eFlow platform has been studied with many other drugs in development for CF: inhaled antibiotics (including liposome-antibiotic complexes), hypertonic saline, L-arginine, cy-

closporine, and alpha-1 antitrypsin. Thus, many CF patients in clinical trials have had exposure to the eFlow and have expressed positive feelings about the portability and rapid drug delivery with the device. It is also important to note that these agents have not had their biologic activity affected significantly by the vibrating mesh.³⁸ Even dornase alfa, which is denatured by ultrasonic nebulizers, is not damaged by the eFlow.⁴⁵

Two versions of the eFlow have been recently made available as “open” nebulizers for existing drugs. The eFlow Rapid was developed for some markets (Europe, Israel, and Australia) in response to the long treatment times for CF drugs, and was designed to have similar delivery efficiency as the Pari LC jet nebulizers. The medication reservoir was designed to have a larger residual volume, and the aerosol chamber is smaller, so it conserves less drug during exhalation (ie, less efficient vs investigational eFlow devices). Thus in theory, unit doses of drugs such as dornase alfa or TSI are aerosolized with the same respirable dose but much more quickly than with the Pari LC jet nebulizers.⁴⁶ In the United States the eFlow SCF is an open device available through a limited number of specialty compounding pharmacies for CF patients. In vitro testing of the eFlow SCF shows 2–4-fold higher delivery efficiency, compared with other approved devices for such drugs as albuterol, dornase alfa, and antibiotics.^{39,45,47} The benefits and risks of having high-efficiency devices available as “open” systems for patients and caregivers will be discussed later.

Smart Devices

Some newer aerosol systems incorporate ways of timing the dose to a specific portion of inhalation, or of guiding the patient to inhale in an optimal way to maximize lung targeting. Some also have systems that can monitor treatment adherence. One so-called smart device, the electronic version of the AERx, was described in the soft-mist device

section. Two other classes of devices can be considered in this category.

Adaptive Aerosol Delivery. Over half the drug from continuously operating nebulizers is wasted while the patient exhales. Breath-actuated jet nebulizers such as the AeroEclipse (Trudell Medical International, London, Ontario, Canada) emit aerosol only during inhalation, reducing drug waste and environmental contamination during exhalation. Adaptive aerosol delivery systems (Respironics, Cedar Grove, New Jersey, now part of Philips) use electronic means to adapt the timing of aerosol delivery to the patient's breathing pattern and to improve the precision and reproducibility of dosing. The HaloLite and ProDose devices were the first- and second-generation adaptive aerosol delivery systems developed.⁴⁸ Adaptive aerosol delivery devices continually monitor the patient's breathing pattern, adapt to any changes based on a rolling average of the prior 3 breaths, and then release aerosol during the first 50–80% of inspiration. The ProDose utilizes a microchip disc for each drug that tells the device about the dose, administration frequency, drug-lot number, and expiration date. Patient usage patterns can be recorded to monitor adherence with therapy. The ProDose is used in Europe for colistimethate in CF and is licensed in the United States and Europe with iloprost for treatment of pulmonary hypertension. These early adaptive aerosol delivery devices helped to solve some of the challenges of aerosol delivery, but not all of them. They reduce drug waste during exhalation, environmental (caregiver) exposure, and dosing variability. However, the HaloLite and ProDose are still compressor-driven jet nebulizer systems, and have some of the same limitations (noisy, high residual dose, long duration of nebulization, require power source and cleaning).

The I-neb (Respironics/Philips) is a third-generation device using adaptive aerosol delivery technology, and it addresses some of the limitations of its predecessors (Fig. 9).^{8,48} The I-neb incorporates the Omron vibrating-mesh technology and the advantages associated with it (small, portable, silent, battery operated). The I-neb has minimal residual dose, so a smaller nominal dose can be used (important for drugs and genes that are expensive to make). The power to the vibrating horn that governs the aerosol output is determined by the microchip disc and can be optimized for each drug. Dose-metering chambers are made in various sizes to accommodate dose requirements for different drugs. The device gives continuous feedback on the device functions through a liquid-crystal-display screen, along with tactile patient feedback at the end of a completed treatment. The I-neb Insight is an accessory that downloads information about how the device was used. A year-long study in 28 children with CF in the United Kingdom that used this technology to monitor the use of in-



Fig. 9. I-neb with the liquid-crystal-display screen and memory disc (by the thumb). (Courtesy of Respironics/Philips.)

haled antibiotics showed that overall adherence ranged between 60% and 70%; adherence to the evening dose tended to be better than to the morning dose, and there was considerable variation between and within subjects.⁴⁹

The I-neb can operate in 2 different modes. The tidal-breathing mode uses similar adaptive aerosol delivery algorithms as the ProDose to deliver drug during the first portion of an inhalation during spontaneous tidal breathing. With this mode there is no control over how fast a patient inhales. However, we know that by significantly slowing and controlling the inspiratory flow rate there should be less upper-airway impaction, improved dispersion of aerosol particles in the lungs, and less variability of lung dose.^{12,21,23,50}

The targeted-inhalation mode was developed to reduce the high variability of dosing associated with tidal breathing. By incorporating a high-resistance mouthpiece into the I-neb, the patient's inspiratory flow is limited to about 20 L/min. The patient is coached to perform slow, deep inhalations by a tactile indicator that tells them when to exhale. Targeted-inhalation mode guides the patient to inhale slowly according to their capability (as long as 9 s), and aerosolizes drug during all but the last 2 seconds, to allow for particle deposition. Figure 10 shows the difference between the tidal-breathing mode and targeted-inhalation-mode settings, and how the targeted-inhalation mode coaches the patient to inhale longer with each successive breath until the targeted inhalation time is reached.⁸ In a scintigraphy study of healthy controls, the I-neb operated with targeted-inhalation mode resulted in lung deposition of 73.3% of the emitted dose, versus 62.8% using tidal-breathing mode.⁵¹ Also, in our laboratory we showed sig-

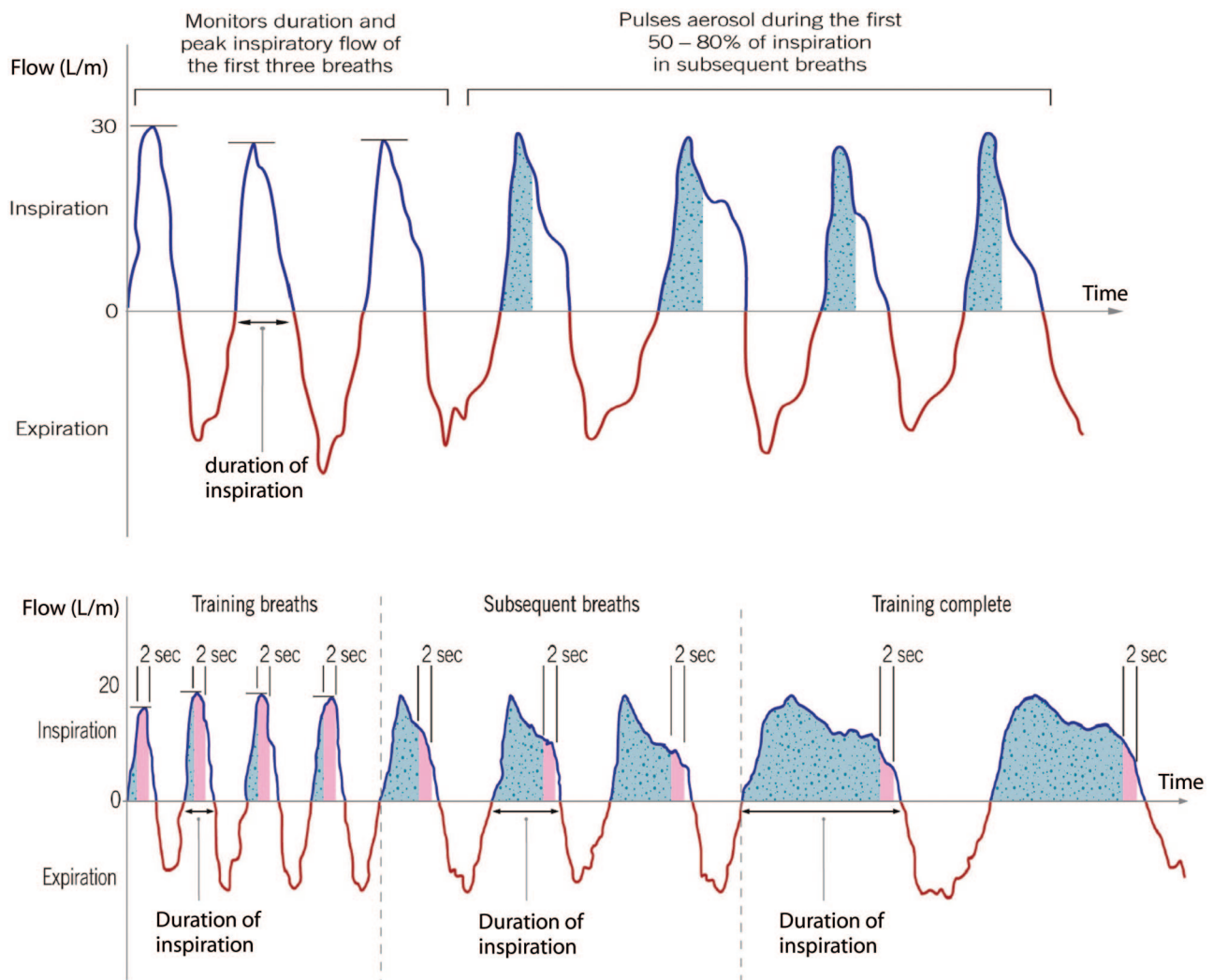


Fig. 10. Adaptive aerosol delivery breathing modes. Tidal breathing mode is used in the Halolite, ProNeb, and I-neb devices (above). The device monitors timing of breathing and begins to time the aerosol with the first portion of inspiration after the third breath. Targeted inhalation mode trains the subject to take longer, slower inhalations, and delivers aerosol in all but the last 2 seconds of inhalation (below). (From Reference 8, with permission.)

nificant reduction in treatment times using the I-neb with targeted-inhalation mode.⁵² The I-neb solves many of the issues and challenges of aerosol delivery mentioned above. Its limitations are the same as those of the other vibrating-mesh technologies (performs poorly with suspensions or viscous solutions; may have to replace mesh periodically; requires careful cleaning).

Akita Breath Control. Since it is such an important variable in particle impaction and deposition, it should not be surprising that more than one technology addresses inspiratory flow rate. The Akita (Activaero, Gemünden, Germany) device allows individualized controlled inhalations in combination with either a Pari jet nebulizer or an eFlow vibrating mesh (Fig. 11).⁵³ The Akita stores a patient's pulmonary function on a "smart card" that is in-

serted into the device. The smart card is programmed to tell the device when to pulse the aerosol during inspiration, depending on the drug target (early inspiration for distal airway deposition or late inspiration for large-airway targeting). When the patient starts to inhale on the mouthpiece, the Akita supplies air from a compressor at a constant, slow flow of 12–15 L/min.

In a scintigraphy study in CF subjects, a mean of 86% of the emitted dose was deposited in the lungs using the Akita—a striking improvement over devices that do not control the inspiratory maneuver.⁵⁴ A recent study used the Akita to deliver alpha-1 antitrypsin aerosol to either the peripheral airways or central bronchi in CF subjects.⁵⁵ The outcome variables were not different between central and peripheral deposition modes, showing that we don't always understand the exact lung targets for CF drugs.

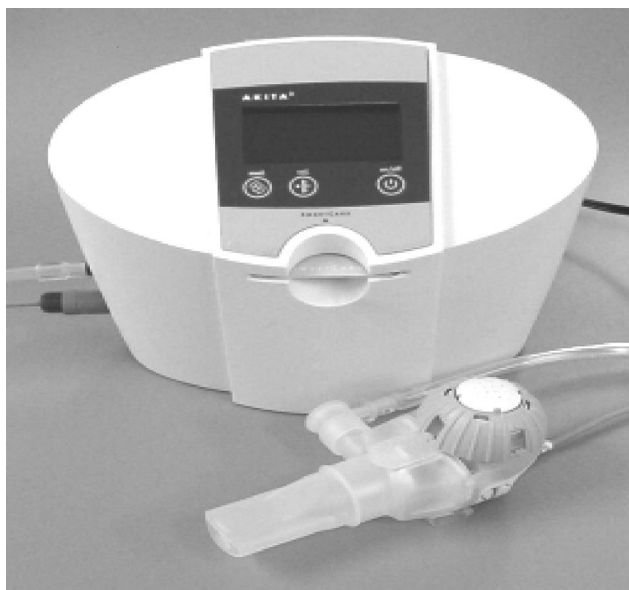


Fig. 11. The Akita device coupled with an efficient vibrating-mesh nebulizer. A programmed smart card tells the device how much drug to dose and how to time dosing with inhalation. Inspiratory flow is limited by the device, which provides low flow via a compressor. (From Reference 8, with permission.)

However, the ability to control targeting and delivery precision with devices like this can enable better study of specific drug targets in the future. The Akita uses a compressor and needs an alternating-current power source, so lack of portability is an issue. The Akita has been studied in CF with antibiotics, glutathione, and alpha-1 antitrypsin.

By controlling the breathing pattern with devices such as the I-neb and Akita, aerosol deposition in the lung is greater, distribution is more uniform, variability is reduced, and treatment time is shorter. Currently, the high expense of these devices limits them to high-cost drugs, so that the device costs are buried in the expense of a drug-device combination. But the breath-control technique holds great promise for many drugs in development for CF.

Novel Dry-Powder Formulations

DPIs are one of the most convenient of the inhaled drug delivery systems. However, many drugs for CF require several milligrams of drug to be deposited in the lungs, and require a more efficient system than simple milled powders delivered with a typical DPI. The small, milled particles of most compounds tend to adhere to one another, which requires either mixing with larger lactose particles or using high inspiratory force to deaggregate the powder. Either technique is impractical with most high-payload drugs. A newer generation of engineered powder particles was developed originally to target the distal lung for sys-

temic drug delivery. Spray-drying emulsions that contain the drug results in a light, porous-particle powder (Fig. 12) that can reach the deep lung for systemic delivery of drugs, or can be delivered topically to the airways for lung disease.^{8,24} These low-density porous particles behave aerodynamically as very small particles, resulting in enhanced delivery efficiency, even when using simple capsule-based or blister-based inhalers.

Nektar Therapeutics (San Carlos, California, now part of Novartis Pharmaceuticals) used this technology for the development of inhaled insulin (Exubera), and also formulated several other compounds this way, including antibiotics, peptides, and proteins. A study of tobramycin inhalation powder showed the delivery efficiency to the lung was almost triple that of a jet nebulizer, and the time of administration was reduced from 16 min (TSI) to under 5 min (tobramycin inhalation powder).⁵⁶ Tobramycin and ciprofloxacin are currently in clinical trials as light, porous-particle powders for CF subjects who harbor *P. aeruginosa* in their respiratory tracts. Besides the advantages of portability, no power source, and no cleaning issues, this technology holds tremendous promise for solving the time-burden issue in CF patients. The disadvantage is that many patients may not be able to tolerate inhaling large amounts of powder. Excessive coughing or bronchospasm from high-payload powder inhalers may preclude some patients from taking advantage of this technology.

Cautions About New Efficient Technologies

The reader may have noticed that many of the new technologies will not benefit infants and young children who have neither the cognitive skill set nor the lung capacity to use DPIs, soft mist, or smart devices. Caregivers should also be aware that popping an aerosol mask on a new technology device does not necessarily mean it will function as well as in adults. There is still a lot of work to be done to improve aerosol delivery to young children.

Also as mentioned, the FDA began approving inhaled CF drugs such as dornase alfa and TSI only with the nebulizers that they were tested with in clinical trials. However, even as the clinical trials of those drugs were in progress, there were advances in aerosol delivery technology that would allow faster and more efficient delivery of inhaled drugs. Since there are differences in delivery characteristics between nebulizers, the decision to designate the nebulizers in the package inserts of these products was to make sure that the patients using these drugs would have similar outcomes as those in the clinical trials, given the known risks of those drug-nebulizer combinations. A meeting of experts at the 2008 European CF Society consensus meeting on inhaled drugs and devices stated, "Every drug-device combination should be tested in clinical studies for efficacy and safety, which is especially relevant

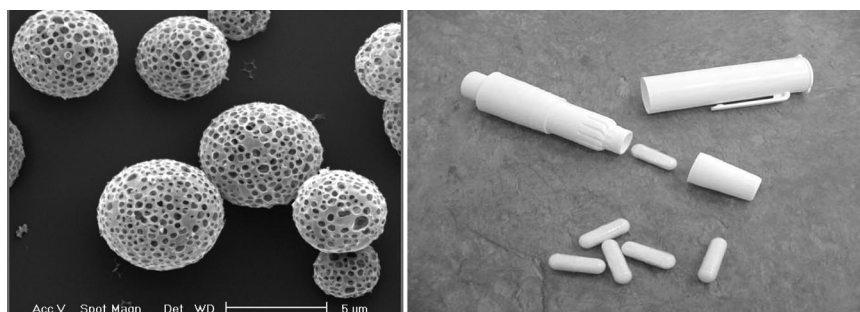


Fig. 12. Light, porous powder particles behave aerodynamically like small particles, and can be delivered by a simple dry-powder inhaler. (From Reference 8, with permission.)

for drugs with a small therapeutic window. Old and new drugs should only be used with new devices after clinical testing.⁵⁷

An example of widespread, off-label use occurred when the Sidestream nebulizer coupled with a powerful Mobilair compressor was shown to deliver dornase alfa in about 2 min.¹⁵ When patients use the Sidestream with dornase alfa, many of them also use it for their TSI, to reduce the administration time. That creates a potential problem, since the original Sidestream wasted considerable drug during exhalation, and pharmacokinetic studies demonstrated that the lung dose of tobramycin was about half as much with the Sidestream (off-label) versus the Pari LC Plus (on-label).⁵⁸ Therefore, those patients may not have received the full benefit of their inhaled antibiotic.

On the other hand, we now have efficient systems that can be used as open systems by patients for any drug they wish to place in them. The eFlow SCF, for example, is faster than jet nebulizers, but also far more efficient for lung delivery.^{39,45,47} With this scenario, delivering a unit dose of a commercial preparation with the eFlow SCF results in a much higher dose to the patient than the doses given in clinical trials. With some drugs (such as dornase alfa) the risk of toxicity is low with higher doses, but for other common drugs there are risks. Though it is desirable to have a fast, efficient aerosol system available for our patients, we must recognize that there may be bad consequences if the system is used without forethought. Patients and clinicians must recognize that there are no clinical data for existing CF drugs in super-efficient devices to support dosing recommendations. In order to compensate for the device efficiency, dose-splitting and compounding have been tried. However, dividing a unit-dose ampule is not simple, and it may contaminate the remaining drug. The FDA does not regulate compounding pharmacies, so there is no quality-control over product purity, dose accuracy, sterility, or safety. To compensate for the high device efficiency, doses of compounded drugs are usually lower

than a typical dose, based on in vitro experiments or limited pharmacokinetic studies (which may not correlate with the clinical effect). Also, patients tempted to use all of their nebulized drugs in a faster device may risk adverse effects if they ignore caregiver warnings (ie, tachyarrhythmia with unit-dose albuterol).

These issues are likely to amplify when these devices are approved as drug-device combinations if there are no lock-out mechanisms for other drugs. New aerosol devices are very promising for improving patient adherence and increasing the number of therapies that can be given in a day. We must learn how to minimize the potential risks and temptations associated with them so that patients can achieve the most benefit from these technologies. A collaborative effort between CF clinicians, pharmaceutical and device companies, and the CF Foundation would help to guide the proper handling and use of these devices and educate patients and caregivers about the risks of off-label use.

Summary

There are many challenges associated with treating CF lung disease with inhaled drugs, with time burden leading the pack. Numerous novel therapies are in development to treat CF lung disease, but these may increase the burden on CF patients. Fortunately, new devices and drug formulation technologies are being developed to address these challenges and improve clinical outcomes.

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Discussion

Geller: You've had a lot of hands-on experience with these devices. From a patient's point of view, or from a respiratory therapist's [RT's] point of view in trying to teach these things, which do you think are the easiest to handle, to clean, and to keep a regimen going in day-to-day use—forgetting about the delivery efficiencies and so forth?

Kesser: If I had to pick the device I like the best, that I thought was most efficient, I'd pick the iNeb, because it's extraordinarily efficient with both medication and time. Its residual volume is negligible. In targeted-inhalation mode, by prolonging the inspiratory time and reducing the inspiratory flow, it is possible to deliver a very high percentage of the dose. But a prolonged inspiratory phase, of 9 seconds or so, could be difficult at best for some patients. The iNeb is very easy to clean, however, and has few parts, which makes it very attractive.

The eFlow is very nice, very easy, and very convenient. It nebulizes very

rapidly, but there are several pieces to it, and some are fairly fragile. Clogging of the mesh alters the performance, which remains a problem and requires periodic mesh replacement.

Rubin: That was very nice and I'm very impressed with all the whiz-bang technology that's coming out. It's truly remarkable. There are two things that bother me that must absolutely be addressed: the RT is the person who teaches the patients how to use these. That teaching has to be clear, and so it's important with all of these new technologies that there will be training of the RT, making sure they know how to use it, they know how to teach it, and they know how to evaluate if the patient is using it properly and getting the medication, is going to be essential. As essential as the fancy equipment.

Kesser: Absolutely.

Rubin: The other thing that bothers me enormously: in asthma therapy there are no short-acting β -agonist bronchodilators in North America currently available as a DPI. Someone

has referred to the term "device delirium," where people are using their DPI for their steroids and then have to switch over to a pMDI or a nebulizer.

Geller: That's actually my term.

Rubin: I sit corrected. It's a great term, David, great term, but more important here because you've got the Akita that's going to be used for gene therapy, because you can put in these big protein particles and it's going to front-end load; then they're going to be taking their aztreonam using a vibrating mesh, using the eFlow; and they're going to be using a junk nebulizer when they have to take their albuterol and their hypertonic saline, because it's cheap; and then you've got your dornase, and of course dornase has only been approved for a couple nebulizers and they don't include any of those.

They're going to go crazy. They're going to have a closet full of nebulizers, they're all going to have to be cleaned; the burden is not just the amount of time inhaling. How can we rationalize this? So if we're going to

give medication, can we perhaps put more than one together and use them all in the same nebulizer, get some of these drugs approved, since now it's not only the drug being approved but the drug/nebulizer combination. This is impossible, for the RT and for the patient.

Kesser: That's an excellent point. Certainly knowing the application and limitations of all of the available devices well enough to teach them to patients and their parents is a challenge, especially with these newer technologies. The number of devices is growing yearly, and I don't know what the answer to that is. Until we can come to some consensus on how that's best accomplished, drug/device combinations are going to exist, and we must continue to follow label guidelines. We'll have to work on improving that, but that's certainly an issue.

Newton: I can imagine that we might see RTs use the eFlow to blow aerosol toward a child's face. We have these nice high-technology devices, yet they're still just blowing it in their face.

Kesser: I've never seen or heard of anyone using an eFlow for blow-by. I certainly wouldn't recommend that.

Newton: Blow-by is being phased out, and we're trying to use more mouthpieces and masks, but I still see use of blow-by. I've put a mask in the child's room and used it, but the next RT removes the mask and uses blow-by.

Geller: The eFlow is not being studied with any medication for kids that young. And the eFlow's aerosol chamber slows the aerosol so much that it doesn't come out with any velocity, so you can't aim the aerosol, so I don't think that's going to be a problem with the eFlow.

Kesser: The aerosol cloud has no driving force behind it, so it remains mainly within the chamber; it doesn't come out like it does from a conventional pneumatic nebulizer.

Newton: We had a physician order an eFlow for a small infant, because of the time.

Geller: Physicians may do things that are not always correct.

Kesser: Without a tight-fitting mask it's not a good idea with the eFlow.

O'Malley: When these devices are approved for use with CF patients, it's

one thing for the home environment, but in the hospital how do we care for those devices? Which ones do I have to worry about?

Kesser: The eFlow is primarily the one you need to worry about. Cleaning the eFlow is an issue. The cleaning guidelines include steam sterilization, which is accomplished in the home with a baby-bottle sterilizer, which is an electric steamer. It's an important issue if you're going to use it in the hospital, and what you're going to do with it.

O'Malley: We've had patients hospitalized on aztreonam, and because it's a study drug, the research pharmacy allowed more nebulizers, so we used the reprocessing department to clean, disinfect, dry, and package the nebulizer, and get it back up to the same patient. But that was one patient admitted at any given time.

Kesser: The sponsor, Gilead, was OK with the sterilizing and processing procedures?

O'Malley: Actually, I was in conversation with Pari about the appropriateness of the process, so that it didn't interfere with the function of the equipment.