

36th Donald F Egan Scientific Memorial Lecture

Air and Soul: The Science and Application of Aerosol Therapy

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This paper reviews the history of aerosol therapy; discusses patient, drug, and device factors that can influence the success of aerosol therapy; and identifies trends that will drive the science of aerosol therapy in the future. Aerosol medication is generally less expensive, works more rapidly, and produces fewer side effects than the same drug given systemically. Aerosol therapy has been used for thousands of years by steaming and burning plant material. In the 50 years since the invention of the pressurized metered-dose inhaler, advances in drugs and devices have made aerosols the most commonly used way to deliver therapy for asthma and COPD. The requirements for aerosol therapy depend on the target site of action and the underlying disease. Medication to treat airways disease should deposit on the conducting airways. Effective deposition of airway particles generally requires particle size between 0.5 and 5 μm mass median aerodynamic diameter; however, a smaller particle size neither equates to greater side effects nor greater effectiveness. However, medications like peptides intended for systemic absorption, need to deposit on the alveolar capillary bed. Thus ultrafine particles, a slow inhalation, and relatively normal airways that do not hinder aerosol penetration will optimize systemic delivery. Aerosolized antimicrobials are often used for the treatment of cystic fibrosis or bronchiectasis, and mucocactive agents to promote mucus clearance have been delivered by aerosol. As technology improves, a greater variety of novel medications are being developed for aerosol delivery, including for therapy of pulmonary hypertension, as vaccines, for decreasing dyspnea, to treat airway inflammation, for migraine headache, for nicotine and drug addiction, and ultimately for gene therapy. Common reasons for therapeutic failure of aerosol medications include the use of inactive or depleted medications, inappropriate use of the aerosol device, and, most importantly, poor adherence to prescribed therapy. The respiratory therapist plays a key role in patient education, device selection, and outcomes assessment. *Key words: asthma; jet nebulizers; pressurized metered-dose inhalers; dry powder inhalers.* [Respir Care 2010;55(7):911–921. © 2010 Daedalus Enterprises]

Introduction

All things have beginnings. It was 20 years ago when, as a young(er) physician-scientist, I moved to the United States to become Chief of Pulmonary at the Cardinal Glennon Children's Hospital in St Louis and Medical Director of Respiratory Care. My boss was Billy Lamb RRT FAARC, who was respiratory therapy manager and is now speaker-elect of the American Association for Respiratory Care (AARC) House of Delegates and one of my dearest friends. He convinced me that I had to attend the AARC meeting in New Orleans that year. I was hooked. As a mucus scientist and an aerosol scientist, here was an entire Congress of respiratory therapists (RTs) who absolutely "got" my passion. It had only been 10 years since Mike Newhouse handed me his new invention, the AeroChamber, and I became an aerosol clinician and engineer, to the general apathy of my physician colleagues. The RTs, on the other hand, really got it.

Fast forward to September 2009. I have been running without stopping since taking my new job as Chairman in Richmond less than 3 months earlier. I know that I have to prepare the Egan Lecture and that it will be about aerosol medicine, but I have not had the time to sit quietly and think about how I will present this. I finally have the time to sit quietly and contemplate during the services for the Jewish New Year. I flip ahead to the coming holiday when we celebrate the completion of the first 5 books of Moses (the Torah) and begin again with the Creation, where I read that the Lord formed man from dust and blew into his nostrils *neshema*, the breath of life (Genesis 2:7). *Neshema*, meaning both air and soul. Thus began my lecture.

Appropriately, this lecture starts with the history of aerosol therapy. Thus we begin in the 18th Century with the Mudge inhaler and quickly move to the "modern era" starting in the 1950s. We next review the physics and physiology of aerosols, setting the stage for understanding how delivery systems and devices are designed and used

to treat asthma. Other diverse applications of pulmonary aerosol therapy are discussed, including the exciting new field of gene therapy for lung diseases. At the end, we come back to the beginning and the most important role of the RT as an educator teaching patients to use their medications and devices correctly and working to improve adherence. If we can get this right, the rest is relatively easy.

Aerosol History

Aerosol therapy has been used for thousands of years. The smoke from burning compounds has long been inhaled for enjoyment and for therapy. As but one example, asthma cigarettes containing *Datura stramonium*, an anticholinergic, were available for purchase up until the 1970s.¹

The modern era of aerosol therapy began in 1778 with Dr John Mudge and the Mudge inhaler. This device was a tankard with a mouthpiece covering the top and an air passage drilled through the handle, so that by inhaling through the mouthpiece, a patient can draw air through the liquid at the bottom of the vessel and into the handle, to be inhaled. The first pressurized inhaler was the Sales-Giróns Pulverisateur in 1858.² Many other nebulizers were introduced in the late 19th and early 20th century, and attempts were made to administer a number of medications by aerosol.

Just over 50 years ago, Charlie Thiel and colleagues at Riker Laboratories (now 3M) invented the pressurized metered-dose inhaler (pMDI) after Susie Maison, the daughter of a Riker Vice-President asked, "Why can't you make my asthma medicine like mother's hair spray?"³ The pMDI was a huge advance over other aerosol technologies and has continued, with minor modifications, to be the most popular form of aerosol delivery today.⁴

The AARC has its roots in oxygen and aerosol delivery. The forerunner of the AARC, the Inhalation Therapy Association, was founded in 1947.⁵ At that time the principal responsibility of the therapist was delivery of oxygen and of aerosolized medications. Even today RTs are most closely associated with delivering, teaching, and assessing the effects of therapeutic aerosols, and conducting research and development of new aerosols. There are now several societies devoted to medical aerosol therapy, including the International Society of Aerosols in Medicine and the American Association of Aerosol Research. RTs are well represented in these societies.

There is an explosion of knowledge regarding aerosol science. A PubMed search using the term "aerosol therapy" showed 36,875 references of as of 1 December 2009. Over the last decade there has been an average of 1,650 publications each year in this field.

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Physiology and Physics of Aerosol Generation

An aerosol is defined as a group of particles that remain suspended in air because of a low terminal settling velocity. The terminal settling velocity is a factor of both particle size and density.⁶ Particles are sized according to their mass median aerodynamic diameter (MMAD), which, for a spherical particle, is the product of the diameter and the square root of the particle density. Therapeutic particles generated for therapy are rarely spherical and tend to have a heterogeneous size distribution. The distribution of particle size is called the geometric standard deviation (GSD). The more uniform the particle size, the smaller the GSD. By definition, a GSD less than 1.22 is considered a monodisperse aerosol. Most therapeutic aerosols are polydisperse, and the larger the GSD, the smaller the proportion of particles within a specific size range.

In general, we refer to “respirable particles” as those with an MMAD between 0.5 and 5 μm .^{4,6} Extremely small particles may not settle on to the airway after inhalation, and thus are exhaled, while larger particles can be filtered by the upper airway and swallowed. The respirable mass is the volume of particles that falls in the respirable size range and is available for inhalation by the patient. This is one of the key differences between different aerosol devices. Nebulizers and pMDIs or dry powder inhalers (DPIs) may have a mean particle size (MMAD) that is similar, but because the GSD of the aerosol from the jet nebulizer is much greater, a smaller proportion of these particles are an appropriate size for inhalation, and thus the respirable mass output is smaller.⁷

Particles greater than 5 μm MMAD can impact on the oral pharynx, especially when inhaled rapidly. For many medications this can lead to swallowing, with drug loss or greater systemic side effects. This is a reason why albuterol administered by jet nebulization is more likely to produce tachycardia than albuterol given by pMDI.⁸ For medications such as inhaled corticosteroids, oral impaction can lead to candidiasis or hoarseness. Therefore, although it is possible to administer corticosteroids by jet nebulization, this is less efficient than the corticosteroids given by pMDI, and there is greater oral deposition.

Far more important than particle size is how effectively the patient uses the device. The most effective inhalation technique for jet nebulizer and pMDI aerosols is a deep inhalation with a slow inspiratory flow to prevent inertial impaction in the airways, to decrease turbulent flow and to allow deep penetration into the airway. A breath-hold following a deep inhalation allows the medication to settle on the airway.⁹ It is a myth that when children cry they bring medication deeper into their lungs. Crying is a prolonged exhalation with an extremely short and fast inhalation when the child catches his breath. This is the opposite of an effective breathing maneuver, and many studies have shown

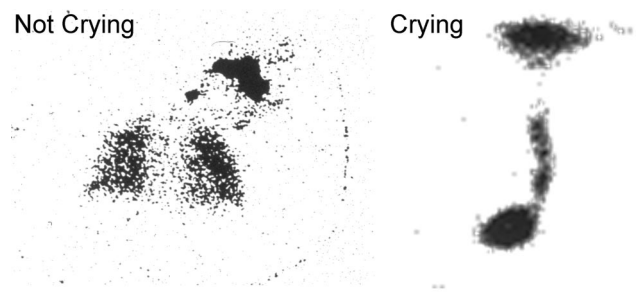


Fig. 1. The effect of crying on lung deposition. Note that when the child is distressed, medication deposits in the mouth and is swallowed, outlining the oral pharynx, esophagus, and stomach. When the same child is breathing quietly on the same aerosol there is excellent pulmonary deposition. (From Reference 11, with permission.)

Table 1. Factors That Can Decrease Aerosol Deposition in Infants and Children

Large tongue in proportion to oral airway
Preferential nose breathing in infants
Narrow airway diameter
Fewer and larger alveoli and fewer generations of airway in infants
More rapid respiratory rate, so relatively greater anatomic dead space
Small tidal volume
Inability to hold breath and coordinate inspiration
High inspiratory flow during respiratory distress and crying

that crying dramatically decreases the amount of medication that is delivered to the child (Fig. 1).^{10,11} This is one of the factors that can dramatically decrease aerosol delivery to the infant and child, as shown in Table 1.

Another common misconception is that medication can be effectively delivered by “blow by”. In blow by delivery, a cloud of medicine is aimed toward the child’s face, generally using a tube or a facemask. The excuse for doing this is the belief that a child is less likely to cry with blow by administration than with a tightly fitting mask. However, there are many studies demonstrating that medication delivery is exponentially decreased as the aerosol source is removed from the child’s face, rendering aerosol blow by delivery all but useless (Fig. 2).^{12,13} When we have objectively assessed patient reactions, it has been our observation that children are just as likely to cry with blow by administration as with a mask on their face. The child is calmer when held and comforted by parents, if they are not in distress or in pain, and if they are familiar with receiving aerosol therapy.

It is also true that using a jet nebulizer with a mouthpiece will more than double the amount of medication delivered to the airway than using a facemask.¹⁴ Most children over the age of 3 years can effectively use a mouthpiece, so using a mask interface would be disadvantageous.

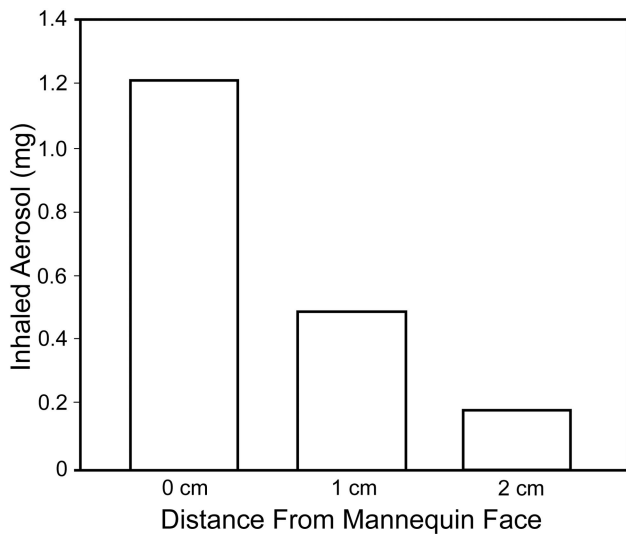


Fig. 2. “Blow-by” aerosol therapy is ineffective. Aerosol was delivered to an infant manikin with mouth held open. Even under these ideal test conditions, when the aerosol mask was just 2 cm from the mouth, deposition on the mouth filter fell by 85%. (Adapted from Reference 13.)

Medication Delivery Systems

Table 2 summarizes the advantages of disadvantages of medication delivery systems.

Jet or Pneumatic Nebulizers

One of the oldest forms of aerosol medication delivery is by jet or pneumatic nebulization. These have evolved from simple “atomizers” to more complex systems, including Venturi systems that increase output on inhalation, and on-demand or breath-activated nebulizers. Jet nebulizers form droplets by using an air compressor to deliver a high-pressure, high-flow stream of air through a narrow opening. This creates a Venturi effect, forcing the liquid drug to be pulled from a reservoir into the jet stream, where it can be inhaled.¹⁵

Nebulizers can be used by very young children breathing with simple tidal respiration, they can be used at any age, and they are relatively easy to use when a child is ill. They can be loaded with higher drug dosages, they contain no propellant, and little teaching is required for use. However, there are important disadvantages to nebulizers. They are less portable than pMDI or DPI, they are more time consuming to use appropriately and to clean after using, the equipment requires maintenance, and most nebulizers require a power source. Because a higher concentration of medication and additional equipment are needed, nebulized therapy is more expensive than the same therapy given by pMDI or DPI (see Table 2). Jet nebulization is a fairly inefficient form of drug delivery, with considerable

variation in the performance characteristics of the different jet nebulizer systems.¹⁶

Jet nebulizer therapy produces a polydisperse aerosol with a greater GSD than pMDI or DPI, leading to medication wastage. Because of the amount of time and effort involved in preparing, administering, and cleaning jet nebulizers, these have the poorest adherence of the aerosol devices.¹⁷ There are also greater differences between jet nebulizer output than there are between pMDIs and DPIs, all of which produce similar respirable masses.^{16,18}

Newer and more efficient nebulizers have been developed.¹⁹ Breath-activated nebulizers deliver medication when triggered by inhalation. Although there is less medication wasted, total treatment time can be extended with this type of nebulizer. Breath-enhanced nebulizers can measure inspiratory flow and volume over a series of breaths and then deliver more of the medication at the start of inhalation, therefore maximizing the amount of medication available to the patient. These are more expensive systems but attractive for delivering expensive medications that are not available as DPI or pMDI. There are also particle-size-enhanced nebulizers like vibrating mesh nebulizers. These nebulizers allow deliver of a much higher respirable mass more quietly, more quickly, and with lower drug volumes, and are becoming an attractive alternative to pMDI or DPI administration.²⁰

Dry Powder Inhalers

DPIs generate aerosol either by scraping a unit dose of medication from a reservoir or by having unit doses of the medicine available as a multi-strip packet or in individual capsules. DPIs are portable and contain no propellants. They are quick and are intrinsically breath-activated. Most DPIs have a dose counter for multi-dose medications. It is relatively easy to teach proper technique for using these devices. Many older children and adults prefer DPIs to either pMDIs or jet nebulizers.

Because dry powders tend to aggregate (stick together), medication given by DPI needs to be de-aggregated to form an appropriate particle size for inhalation. For this to happen there has to be a rapid inspiratory flow (usually between 30 and 60 L/min, depending on the device) and the medication is often brought through a series of baffles with the resistance of the inhaler causing the medication to break apart. The medication powder is often admixed with larger inert particles, usually lactose, to decrease aggregation. The higher-resistance DPIs may be difficult for young children to use, particularly when they are ill.²¹ All DPIs are humidity sensitive. If patients exhale into the device, they risk blowing out the medication, and the humidification from exhaled breath can decrease the efficiency of the inhaler as the particles stick to the orifice.²²

Table 2. Advantages and Disadvantages of Each Type of Aerosol-Generating Device or System Clinically Available

Type	Advantages	Disadvantages
Small-Volume Jet Nebulizer	Patient coordination not required Effective with tidal breathing High dose possible Dose modification possible Can be used with supplemental oxygen Can deliver combination therapies if compatible	Much less portable Pressurized gas source required Longer treatment time Device cleaning required Not all medication available in solution Does not aerosolize suspensions well Device preparation required Performance variability Expensive when compressor added in Poorest adherence
Pressurized Metered-Dose Inhaler (pMDI)	Portable and compact Treatment time is short No drug preparation is required No contamination of contents Dose-dose reproducibility high Some can be used with breath-actuated mouthpiece	Coordination of breathing and actuation needed Device actuation required High pharyngeal deposition Upper limit to unit dose content Remaining doses difficult to determine if no dose counter Not all medications available
Valved Holding Chamber	Reduces need for patient coordination Reduces pharyngeal deposition	More expensive than pMDI alone Less portable than pMDI alone Integral actuator devices may alter aerosol properties, compared with native actuator
Dry-Powder Inhaler	Breath-actuated Less patient coordination required Propellant not required Small and portable Short treatment time Dose counters in most newer designs	Requires moderate to high inspiratory flow Some units are single dose Can result in higher pharyngeal deposition Not all medications available (eg, short-acting beta agonists in the United States)

In North America there is no DPI containing short-acting bronchodilators for use as rescue medication. While it is possible to give maintenance medication for asthma using a DPI and rescue bronchodilator by nebulizer or pMDI, this can lead to confusion, as the techniques of use are quite different.

Pressurized Metered-Dose Inhalers

The pMDI has not changed much in the last 50 years. It is a marvel of engineering science, containing a valve that allows a metering of the drug, an actuator boot to trigger the medication and direct it toward the mouth, and medication formulation, which contains a propellant, excipients, and the medication. In the United States the dose of medication released for actuation is measured as the amount that exits the actuator boot, while in most of the world the amount of medication per dose is measured as that which exits the canister orifice. Because the actuator boot and the canister together represent the drug delivery device, it is more accurate to measure the amount that exits the boot when comparing different devices. The boots are not interchangeable, each being designed for a specific actuator. If the canisters from different actuators are placed in ac-

tuator boots designed for a different canister, the output can dramatically decrease.²³

Pressurized MDIs can be used either alone or with an accessory device such as a spacer or valved holding chamber (VHC). A spacer is a simple tube that permits the patient to direct the aerosol into his or her mouth. The more commonly used VHCs incorporate a valve that holds medication within the chamber until the patient inhales. This allows better coordination of inhalation. Some VHCs with mask also have an exhalation valve so that, when the mask is placed on a child's face, the child can comfortably exhale against a low resistance, and when the child inhales, the medication will flow from the chamber into the mask. When using the mask with a VHC, it is important that the mask seals comfortably and completely on the child's face. Even small leaks can dramatically decrease the amount of medication that can be inhaled.²⁴ Just as there are differences in VHC design, there are also large differences in the masks. Some masks are rigid and do not seal well, making it difficult to achieve a good inhalation. Masks also vary in the amount of dead space, with some masks having a dead-space volume equivalent to or greater than the tidal volume of a one-year-old child.²⁵

VHCs are preferred to simple tube spacers. There are design differences in the VHC that can affect how well medication is delivered. Today most VHCs are made of metal or treated plastics that do not hold an electrostatic charge. These charge-reduced VHCs increase the amount of medication that is delivered to the patient.²⁶ Multiple actuations into the holding chamber before the drug is inhaled causes settling of the medication in the chamber, decreasing the amount of medication available to the patient.

Patients can have a difficult time knowing when their pMDI canister is empty. Although it has been suggested that the flotation pattern of the canister in water can be used to determine the amount of medication that remains, not only is this unreliable but often the valve will clog with water, making it impossible to use the canister.²⁷ Many patients shake the canister to hear or feel how much medication remains; however, if patients rely on this method, they will use the canister for weeks after it is depleted of medication, putting them at risk for an asthma flare.²⁷ The most accurate way to know when the canister is depleted is to use a dose counter, which decrements each time the canister is actuated.

Until recently the principal carriers used in the pMDI have been chlorofluorocarbon (CFC) 11 and 12. Although these propellants are effective and well tolerated in the airway, when CFCs reach the upper atmosphere, they break down the ozone layer. In September 1987 a group of countries met in Canada and developed the Montreal Protocol (treaty) for reducing the release of substances that deplete the protective ozone layer.²⁸ Soon after the Montreal protocol was adopted, CFCs were eliminated from air conditioning and packaging, but they continued to be used for medication aerosol propellants until a suitable substitute was available. The hydrofluoroalkanes (HFAs), in particular HFA 227 and 134A, are effective substitutes for CFC 12.²⁹ All pMDIs now marketed contain only HFA propellants.

The development of HFA propellants has allowed re-design of the valve for the pMDI canisters, which in turn has permitted a much smaller particle size for some inhaled corticosteroids, like beclomethasone (QVAR, Teva) and flunisolide (Aerospan, Forest). These inhaled corticosteroids decreased the particle size from about 4 μm MMAD in the CFC formulation to about 1 μm MMAD in the HFA carrier. Other inhaled corticosteroids, like budesonide (Pulmicort, AstraZeneca) and fluticasone (Flovent, Glaxo-SmithKline), and inhaled bronchodilators have the same particle size in the HFA propellant as in the CFC.³⁰

For the inhaled corticosteroids with a much smaller particle size, this can dramatically increase the amount of medication deposited in the lung. For this reason, the dos-

Table 3. Other Aerosol Drugs Available or Under Development

	Status
Topical treatment of pulmonary diseases	
Anti-bacterials	Available
Anti-virals	Available
Anti-fungals	Under development
Immunosuppressive drugs	Available
Non-steroidal anti-inflammatory drugs	Under development
Surfactants	Available
Prostaglandins	Available
Mucolytics	Available
Anti-tussives	Under development
Gene therapy vectors	Available
Aerosol Drugs for Systemic Therapy	
Insulin	Available
Heparin	Under development
Ergotamine	Under development
Calcitonin	Under development
Human growth hormone	Under development
Sildenafil	Under development
Antiproteases (alpha-1 antitrypsin)	Under development
Vaccines	Available
Gene therapy vectors	Under development
Morphine	Under development
Fentanyl	Under development

age of inhaled corticosteroid per canister actuation has been decreased. With a smaller particle size there were concerns that there could be increased alveolar deposition, thus increased systemic absorption and greater suppression of the hypothalamic pituitary axis. Studies have shown that there is no greater hypothalamic pituitary axis suppression using the HFA propellant formulations than with the CFC propellants.³¹

It had been hoped that these small particles will better deposit in smaller airways, thus improving asthma control. However, there are no data that clearly demonstrate that a smaller particle size leads to better asthma control.

Other Medications for Aerosol Delivery

Although the most common use of aerosol therapy is for using bronchodilators and inhaled corticosteroids, there are a large number of other medications that are being given by aerosol (Table 3).

Mucolytics

A mucolytic medication degrades the polymeric structure of airway secretions. Usually this will reduce viscosity, and this in turn can decrease secretion adherence to the epithelium. A decreased viscosity can improve mucociliary clearance, although it may decrease the cough clear-

ance of secretions.³² The main polymeric components of normal mucus are the mucin glycoproteins. Although more than 20 mucins have been identified in man, the most important gel-forming mucins in the human airway are MUC5AC and MUC5B.³³ These are long, oligomerized glycoproteins, structurally described as a tangled network. The most commonly used classic mucolytics have free sulfhydryl groups that are able to hydrolyze the disulfide bonds connecting mucin oligomers.

The archetype of the classic mucolytics is *N*-acetyl-L-cysteine or NAC, commercially available as an aerosol preparation under the trade name of Mucomyst (Bristol-Myers Squibb, Princeton, New Jersey). Although Mucomyst has been administered for decades as a mucolytic, it has never been shown to improve pulmonary function or clinical outcome in patients with asthma, chronic bronchitis, cystic fibrosis (CF), or other airway diseases.³⁴⁻³⁶ Long-term studies in chronic bronchitis have demonstrated no benefit from the use of oral³⁴ or inhaled NAC. Because there is almost no intact mucin in the CF airway,³⁷ NAC may be dangerous when used to treat CF. NAC has a pH of 2.2 and is irritating to the airway, so benefit may be derived only from its ability to induce a cough. Classic mucolytics are not recommended for treating airway disease.

There is a secondary polymer network in sputum that is derived from the breakdown of inflammatory cells and bacteria. This secondary network is composed of highly polymerized DNA, which co-polymerizes with filamentous (F-) actin.³³ This rigid co-polymer increases sputum tenacity and decreases the ability to expectorate in persons with CF. Aerosolization of dornase alfa (Pulmozyme, Genentech, South San Francisco, California) has been used for more than 15 years for treating CF. Taken once daily, this medication improves pulmonary function and decreases the risk of pulmonary exacerbation.³⁸ Other peptide mucolytics are being developed, such as thymosin beta 4, which can break down the F-actin network and is synergistic with dornase alfa *in vitro*.³⁹

Medications have been developed that draw water into the airway (so called “hydrators”), including 7% hyperosmolar saline⁴⁰ and DPI mannitol (Bronchitol, Pharmaxis, Australia).⁴¹ These also induce mucin secretion,⁴² and promote effective cough. Pilot studies suggest that dornase alfa may be more effective than hyperosmolar saline for the treatment of CF.⁴³ Dornase alfa has been studied for diseases other than CF, but no proven clinical benefit has been shown.⁴⁴

There are other mucoactive agents, including mucolytics and mucokinetic agents, that are in early testing for treating CF and possibly chronic bronchitis.

Antibiotics

Aerosol antibiotics have been used for decades to treat chronic lung infection in bronchiectasis and CF. There are

compelling data that demonstrate that aerosolized aminoglycosides like tobramycin or gentamicin and aerosolized colistin are effective in reducing the bacterial load in CF airways, improving pulmonary function, and decreasing the frequency of pulmonary exacerbation.^{45,46} The first commercially available preparation of antibiotic developed for aerosolization was tobramycin solution for inhalation delivered by jet nebulization at a dose of 300 mg twice daily (TOBI, Novartis). This preservative-free form of tobramycin solution for inhalation is effective for the treatment of patients with CF who are chronically infected with *Pseudomonas*. Aztreonam lysinate for inhalation (Cayston, Gilead Sciences, Seattle, Washington), using the Pari eFlow vibrating-mesh nebulizer, was approved by the FDA for the therapy of CF lung disease in early 2010.⁴⁷ Other aerosol antibiotics under study include tobramycin inhalation powder, ciprofloxacin inhalation powder, levofloxacin, and others.

Data suggest that, although aerosol antibiotics can reduce airway bacterial load in patients with non-CF bronchiectasis, they may not have the same beneficial effect on pulmonary function or frequency of exacerbations as when used for CF. This may be due to irritation from the high dose used, different efficacy in different diseases, or that patients with CF are more accustomed to using airway clearance devices and breathing exercises and thus adherence may be better.⁴⁸

One of the benefits of aerosolized antibiotics is that high concentrations of drug can be achieved in the proximal airway, far exceeding the MIC₉₀ (minimum inhibitory concentration required to inhibit the growth of 90% of the organisms) of the antibiotic. However, there is a concentration gradient of antibiotics in airways after aerosolization. While the concentration may be very high in the proximal airway, moving deeper in the airway, the antibiotic concentration will decrease to below the MIC₉₀. This fosters the development of antimicrobial resistance.

Patients with chronic bronchitis also have persistent lung infection, and those with frequent exacerbations and infection with *Pseudomonas* are at high risk of developing bronchiectasis. It is possible that chronic bronchitis exacerbations might be better treated by the combined use of aerosol and systemic antibiotics. Aerosol antibiotics are also being evaluated as a preventive therapy to decrease the risk of ventilator-associated tracheitis or pneumonia.⁴⁹

Proteins and Peptides for Systemic Delivery

The gas-exchanging surface of the lungs is a conduit to the systemic circulation. The lungs receive the entire cardiac circulation from the right heart, which is then returned to the left side of the heart, making them a potential portal for the systemic delivery of medications. One of the first aerosol medications for systemic administration was insu-

lin.⁵⁰ Although aerosolized insulin could decrease blood sugar, the effect was unpredictable. This was due in part to very low efficiency nebulization. For medication to be absorbed into the circulation it needs to reach the alveolar capillary bed where it can cross the blood-airway barrier. Medication landing on the conducting airways can be trapped in the mucus layer and is less likely to reach the endothelium. Aerosol particles must be ultrafine (MMAD < 2 μm) and have a small GSD to maximize alveolar deposition. Furthermore, the lungs should be healthy so that there is not an excess of secretions impairing delivery.⁵¹

Extensive studies were conducted using an insulin aerosol (Exubera, Pfizer) that has since been withdrawn from market. Other companies are developing inhaled peptides, such as growth hormone that can be administered by aerosol to children with growth hormone deficiency, avoiding the unpleasant use of needles, as well as other proteins for systemic delivery, using the acinus as a portal of entry.⁵²

Therapy for Pulmonary Hypertension

There are a number of medications available to treat pulmonary hypertension, including drugs that increase nitric oxide, inhibit endothelin, or activate phosphodiesterase 5. Among these are the prostacyclin analogs epoprostenol and iloprost, which are well accepted as nebulized medications for treating severe pulmonary hypertension.⁵³

Immunizations

The nasal administration of cold attenuated influenza virus has been well accepted.⁵⁴ Because of difficulties associated with vaccine preservation and with injections, particularly in developing countries, unit dose aerosolized medications are being developed to prevent diseases such as influenza, measles, and tuberculosis.⁵⁵ Many of these are in late stage testing after showing promising results.

Airway Inflammation

A number of medications have been studied to reduce oxidant stress or airway inflammation. Aerosol α -1 proteinase inhibitor has been studied to treat patients with CF.⁵⁶ Studies are under way evaluating if glutathione can be delivered by aerosol to reduce morbidity in patients with CF.⁵⁷ Other aerosol anti-inflammatory medications being evaluated include cyclosporine and tacrolimus to treat severe asthma⁵⁸ and to prevent lung transplant rejection.⁵⁹

Other Medications

Morphine has been administered by nebulization for the treatment of severe dyspnea, although it is not recom-

mended for patients who are hypoventilating and have retained carbon dioxide.⁶⁰

Aerosolized ergotamine has been effectively used in small trials for the treatment of migraine headaches.⁶¹

Replacement therapy for patients who are addicted to nicotine or narcotics has been administered by aerosol, and several nicotine replacement products continue in development.⁶²

Gene transfer therapy for airway diseases could ultimately be delivered by aerosol. This has been most extensively studied in CF, where complementary DNA of the CFTR gene is inserted in a vector, which is then administered by aerosol.⁶³ This form of therapy has been limited by the inflammatory response to viral vectors and by difficulty in packaging of the large complementary DNA. It is very likely that gene therapy for genetic diseases such as CF and alpha-1 antitrypsin deficiency will be administered by aerosol.^{64,65}

Effective Use of Aerosol Therapy

Lung Deposition

Lung deposition increases significantly in older children and adults, compared to infants. But because total lung dose increases with age, deposition for airway surface (roughly correlated with body mass) is similar at all ages (Fig. 3).⁶⁶⁻⁶⁹ Therefore, it is not necessary to increase the dose for very small children because of a relatively ineffective breathing pattern and higher inspiratory flow, nor is it necessary to decrease the dose because they are smaller in size.

Lung deposition using a DPI or pMDI is greater than that of jet nebulizers. In preschool children, deposition is up to 15%, and it is double that in adolescents and adults. The lung deposition using DPIs and pMDIs with holding chambers is almost identical and roughly 6 times greater than deposition using a jet nebulizer.^{7,68,69}

When using a VHC we prefer using a mouthpiece as early as possible in order to maximize the amount of medication that can be delivered and to decrease errors associated with poor mask fit. In general, we are able to use a mouthpiece for children over the age of 3 if they have had some training.

Adherence to Therapy

There have been tremendous advances in the development of drugs and devices used for aerosol therapy. Beta agonist and anticholinergic bronchodilators, and inhaled corticosteroids now on the market are highly effective and generally can be delivered efficiently to treat most patients with asthma. Aerosol devices have become easier to use, and accessory devices allow pMDIs to be used effectively

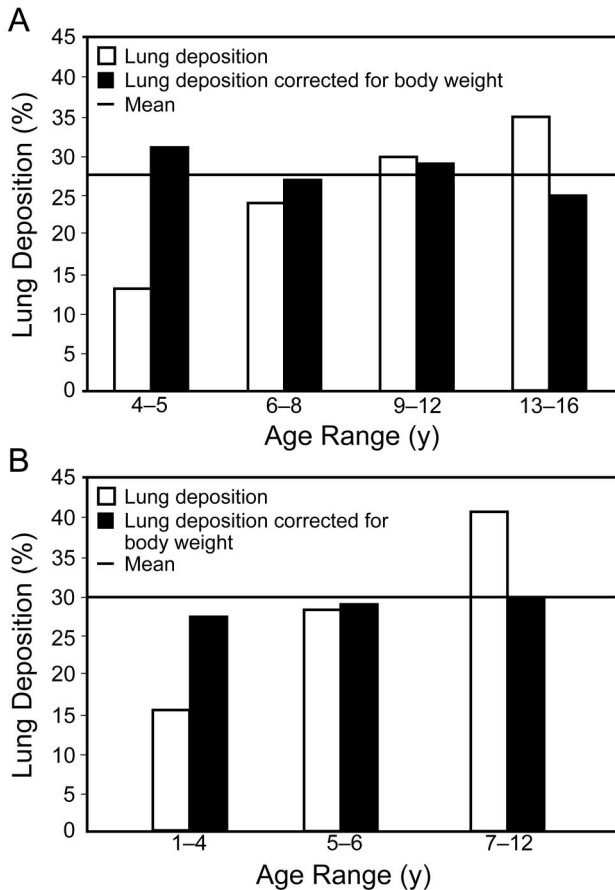


Fig. 3. Lung deposition corrected for body weight. Note that although deposition increases with the age of the child, the deposition per ideal body weight, a good surrogate for relative airway deposition, remains constant. Therefore no dose adjustment is needed for age or weight. (Part A is based on data in Reference 68. Part B is based on data in Reference 69.)

by the youngest of children. Large studies and meta-analyses confirm that medication can be delivered as effectively by pMDI or DPI as it can by jet nebulization, even for young children, the elderly, and those with severe disease.¹⁸ Despite this, medication appears to work sub-optimally in many patients.⁷⁰ In some cases, patients are unable to use the medication effectively because they have not been taught how to use the aerosol device. All devices require some education, and just handing a device to the patient will not ensure appropriate use.¹⁵ One of the key roles of the RT is educating patients in the appropriate use of devices and checking their use with each visit.

There are also patients who just will not take their medication (Fig. 4).⁷¹ The most common cause of asthma medications not working is that the patient is not adherent to prescribed therapy.⁷² Others may have poor response to therapy because they do not have the disease for which the therapy is being used. For example, although bronchodilators and inhaled corticosteroids are very effective for the

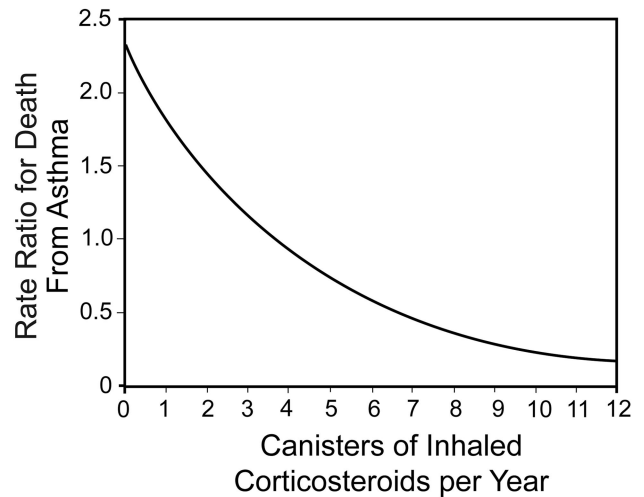


Fig. 4. Inhaled corticosteroid use lowers the risk of death from asthma. Data from the Saskatchewan Health database strongly suggests that the relative risk of death from asthma is in inverse proportion to the frequency with which patients prescribed inhaled corticosteroids fill their prescriptions. (From Reference 71, with permission.)

treatment of asthma, they are relatively ineffective for treating CF and are absolutely ineffective for the wheezing of an inhaled foreign body.

Our challenges are to be sure that the patients are using their medications properly and effectively and that they understand that this is important. While pharmacologists strive to make better medications and engineers are constantly improving delivery devices, it is the therapist who has the most difficult task—to make a “better patient” by teaching them to understand and use their medications effectively.

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