Formulation of Aerosolized Therapeutics*

Robert J. Kuhn, PharmD

Pseudomonas aeruginosa (PA), which colonizes the airways of approximately 90% of patients with cystic fibrosis (CF) at some point during their lives, is an important contributor to the vicious cycle of infection and inflammation leading to bronchiectasis and eventual respiratory failure. Oral antibiotic therapy is often ineffective in treating PA infections. Instead, in-hospital IV aminoglycoside therapy administered in combination with other IV antibiotics, such as β-lactams or quinolones, is the mainstay of treatment. The specific chemical and physical properties of CF sputum require high serum antibiotic levels for effective antimicrobial treatment; however, IV aminoglycoside therapy is associated with an increased risk of ototoxicity and nephrotoxicity. In an attempt to avoid systemic toxicity and effectively treat PA infections, clinicians have combined IV antibiotics with sterile solutions of saline or water to aerosolize the mixture for inhalation. Experience with such “home brews” has clearly demonstrated that IV preparations are neither intended nor medically indicated for inhalation. Patients may experience coughing, mucosal irritation, or bronchospasm in response to the preservatives, stabilizing agents, and other additives commonly found in IV preparations. While the rationale for aerosolized drug delivery remains compelling, concerns about uniform dose delivery, ineffective nebulization, and therapeutic adherence arise. Since the 1940s, when these efforts began, ongoing research and clinical trials have identified several additional factors affecting inhaled drug delivery and deposition in the airways. This article chronicles some of the challenges faced by researchers and elucidates factors critical to the reformulation of a safe and effective antibiotic solution for aerosolized delivery.

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Key words: aerosolized; bronchiectasis; cystic fibrosis; Pseudomonas aeruginosa

Abbreviations: CF = cystic fibrosis; MIC = minimal inhibitory concentration; MMAD = mass median aerodynamic diameter; PA = Pseudomonas aeruginosa

The inhalation of aerosolized therapeutic agents for local deposition in the airways confers numerous theoretical advantages over parenteral systemic delivery. The investigation of inhaled antibiotics for a variety of pathologic airway diseases, such as cystic fibrosis (CF), bronchiectasis, and asthma is ongoing. Along a separate yet parallel path, researchers have been conducting inhalation trials for several years with the protein hormone insulin, whereby systemic uptake and circulation is desirable. Recently, our increased understanding of the ideal properties for an inhaled therapeutic agent, coupled with the rapid expansion of aerosol device technology, has stimulated research and clinical trials in the aerosol delivery of several therapeutic agents. Among those agents on a lengthy list, some of the more promising include the following: leuprolide acetate for the treatment of infertility, postmenopausal breast cancer, and prostate cancer; morphine and fentanyl for the prevention of allograft rejection; α1-antitrypsin proteinase inhibitor for the treatment of congenital emphysema; and growth hormone-releasing factor for the treatment of pituitary causes of short stature.

Rationale for Aerosolized Drug Delivery: Two Models

Aerosolized therapeutic agents may be delivered to the airway via the nasal cavity or the oropharynx. The nasal route is less efficient due to the smaller surface area available for drug absorption and the fact that some of the drug may be swallowed. In addition, the relatively rapid onset of mucociliary clearance in the nose may result in some of the drug being eliminated prior to reaching systemic circulation. Drugs delivered to the tracheobronchial or pulmonary compartments tend to have greater systemic absorption.

Insulin-Dependent Diabetes

The most efficient delivery route for therapeutic agents that are intended to act systemically has been the parenteral route. Despite early failures and frustrations with the aerosolized delivery of insulin to diabetic patients, the disadvantages of parenteral administration, including injection site reactions and pain, patient tolerance and adherence issues, and cost, have motivated clinicians and manufacturers to persist. Researchers have made significant progress in the development of an inhaled insulin delivery system designed to provide effective therapy while avoiding injections. This and other advances in diabetes research offer hope for improved therapeutic adherence, simplified management, and optimized long-term outcomes (see the article by Laube in this issue for more information about aerosolized insulin delivery).

CF

Airway diseases are logical candidates for treatment with aerosolized drugs. Aerosolized formulations of corticosteroids have been used in the treatment of CF, bronchiectasis, asthma, and obstructive lung disease for some time. The use of bronchodilators, mucolytics, and anti-inflammatory drugs to decrease airway inflammation, as adjunctive therapy to standard airway clearance techniques and chest percussion, and to improve mucociliary clearance are important in patients with CF. Antibiotic therapy is essential to reduce and manage PA infection.1,2

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History and Evolution of Aerosolized Therapeutics
to decrease bacterial density in sputum, to improve lung function, and to enhance patient quality of life (Table 1).

The administration of oral antibiotic therapy to combat common pathogens of CF infection, particularly *Pseudomonas aeruginosa* (PA), is usually ineffective. Typically, infections have been managed with in-hospital IV administration of aminoglycosides in combination with a β-lactam or quinolone antibiotic; however, the effectiveness of this treatment approach is suboptimal because of the relatively low penetration of aminoglycosides into the sputum of CF patients. Often, large IV doses are required to achieve therapeutic concentrations of the drug in the airways, thereby increasing the risk of systemic toxicity (i.e., ototoxicity and nephrotoxicity). The parenteral antibiotics that are capable of airways penetration tend to be ineffective against Gram-negative organisms such as PA. In addition, therapeutic effectiveness, issues relating to the cost of hospitalization during IV therapy, the increased risk of acquiring nosocomial infections, and the diminution of the patient’s quality of life are also important considerations.

**Aerosolized Antibiotics in CF: An Historical Perspective**

As an interim attempt at delivering drugs by direct contact with the airways, inhaled antibiotic preparations were prepared from IV medications that were not originally intended for delivery to the airways. Several of these preparations contained preservatives, such as phenol and bisulfites, that may contribute to airway irritation, coughing, and bronchoconstriction.

Initial attempts at aerosolization with neomycin and other polymyxins were made about 50 years ago. Then, in the 1950s, penicillin G was aerosolized to treat patients with pneumococcal pneumonia. Unfortunately, this acidic solution was associated with unpleasant side effects, such as stinging and bronchospasm, probably due to its pH and to ingredients in the solution that were not intended for inhalation. Soon after its introduction, the antibiotic gentamicin was used in nebulizers to treat patients with CF. Patients received treatment by sleeping inside humidified tents into which the antibiotic was directed.

Over the next 20 years, other antimicrobial agents that were not formulated or intended for aerosolization, including ticarcillin disodium, ceftazidime, and carbencillin, also were used with variable results. These agents were administered in doses ranging from 500 to 2,000 mg as in hypertonic solutions, which proved to be quite irritating to bronchial smooth muscle and produced cough and bronchoconspasm in patients.

<table>
<thead>
<tr>
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<td>Less systemic toxicity</td>
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Aerosolized amphotericin B, a colloidal suspension, also has been used by a number of clinicians in managing CF. However, colloidal suspensions, by definition, do not nebulize well. When diluted with normal saline solution, they will often precipitate. Sterile water for injection (USP) should be used when the aerosolized delivery of amphotericin B is attempted.

Gentamicin for parenteral administration contains phenol as a preservative. In addition to an unpleasant taste, phenol is a neurotoxin and is listed by the National Institute for Occupational Safety and Health as being hazardous for occupational exposure. In addition, phenol may increase the time required for nebulization of a solution. Further, some IV formulations of gentamicin contain methylparaben and propylparaben, which are detergents that can alter particle size and dispersal characteristics, as well as sodium bisulfite and ethylenediaminetetraacetic acid, which are both known to cause bronchoconstriction.

Colistin sulphomethate is used extensively in Europe for inhalation therapy in the treatment of patients with CF. However, in the United States, only the prodrug sterile colistimethate sodium (USP) is available, and it must be converted to its active form. An additional drawback to the aerosolization of this agent is the significant foaming that occurs with nebulization. This makes ascertaining the exact dose of the drug to be delivered to the patient difficult and cumbersome. Bronchospasm also has been associated with this agent.

**Challenges in Aerosolized Antimicrobial Administration in CF**

CF is a multisystem disorder resulting from a mutation in the gene encoding a chloride channel protein, the CF transmembrane conductance regulator. This mutation results in abnormal ion transport across epithelial membranes and a consequent reduction in the water content of exocrine secretions, including thick purulent mucus.

Several other challenges must be taken into account when treating infectious respiratory exacerbations in patients with CF via the direct delivery of antimicrobial agents to the lumen of the airways. One of the most important considerations is drug distribution. Particle size and mode of administration have been shown to play an important role in pulmonary drug distribution, and the use of different delivery devices can result in variations in particle sizes for the same drug. Moreover, the adequate treatment of respiratory infections in situ depends on a sufficient concentration of drug particles reaching the site of infection in the airways. This is a particular challenge in CF patients. Factors such as the physical and chemical composition of mucus and the degree of parenchymal destruction and bronchiectasis in CF patients can significantly alter drug distribution and bioavailability.

Two classes of antagonistic sputum components have been identified. They include small molecules, which physically decrease antibiotic penetration into bacteria, and large glycoprotein molecules, which bind and sequester aminoglycosides. Soluble sputum components such as monovalent and divalent cations antagonize aminoglyco-

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**Table 1—Aerosol Delivery**

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side bioactivity. For effective bacteriocidal activity, sufficient quantities of an antibiotic must penetrate the thick, purulent endobronchial secretions to reach the lumen of the airways in CF patients.

**Particle Size and Drug Deposition**

As the major factor influencing drug deposition, particle size represents a critical challenge for effective inhaled antibiotic therapy. In CF patients, drug particles need to reach the bronchioles, where the disease process usually begins, and then extend toward the bronchi.

Therapeutic aerosols are typically heterodisperse. They are composed of particles of different sizes, and drug deposition is directly influenced by the mass median aerodynamic diameter (MMAD) of the particles. Half the aerosol mass is contained in particles smaller than the MMAD, and half is contained in particles larger than the MMAD. Particle sizes ranging from 1 to 5 μm appear to be optimal for reproducible drug delivery to the airways.\(^5,7\) Particles < 1 μm are typically exhaled, have short transit times in the lungs, and may be deposited in the alveoli. Particles > 5 μm tend to be deposited in the central airways and the oropharynx where they may be cleared by swallowing, or they may remain in the inhalation device.

The deposition pattern of inhaled particles also is dependent on the rate of nebulized flow, as well as on the size and branching of the target airways.\(^3,5\) Deposition site and pattern influence both the therapeutic effect and the occurrence of adverse events.

**Delivery Device Characteristics**

In addition to patient factors such as therapeutic adherence, breathing or breath-holding patterns, degree of airway disease, and pulmonary function that can affect the efficiency of drug delivery, another important consideration relates to the device or delivery system characteristics. Not all devices are compatible with all drugs. Antibiotics are commonly aerosolized by nebulizing a solution of the drug. There are several types of these devices, including jet nebulizers and those that employ ultrasonic waves. However, not all nebulizers are practical for delivering the mass of aminoglycoside needed for optimal treatment outcomes. MMAD and the range of particle size, output, and drug deposition all may vary according to the device.\(^3,8\)

For example, with jet nebulizers particle size is inversely related to gas flow rate.\(^5\) In contrast, with ultrasonic nebulizers < 2 MHz, particle size is a function of the length of the capillary waves produced on the surface of the liquid.\(^9\) Further, aerosolization of a parenteral antibiotic agent can produce changes in the chemical composition, aerodynamics, and physical properties of the drug. For example, when an IV solution is nebulized, it may absorb water within the respiratory tract, whereby the particle size increases and delivery to the site of infection is reduced.\(^5\)

**CF Sputum and Aminoglycoside Penetration**

Although the efficacy of aminoglycoside antibiotics against the dominant CF airway pathogens has been demonstrated clearly, several other issues need to be addressed for effective aerosolization to occur and for determination of the optimal dose of the drug to the airways of CF patients. It has been shown that the maximal sputum concentration of aminoglycosides while patients are receiving IV therapy is often below the minimal inhibitory concentration (MIC) in vitro.\(^10\) A pharmacokinetic evaluation of aerosolized tobramycin solution for inhalation showed that the mean peak concentrations of the drug in sputum were > 15-fold higher following aerosol administration compared with parenteral administration.\(^11\) This suggests that aerosol administration of this antibacterial agent was capable of maintaining a high concentration in the sputum and a low serum level. Drug delivery targeted to the site of infection also may permit a lower total drug dosage. Figure 1 shows in vitro inhibition of tobramycin activity by CF in the sputum. At 10 times the MIC, PA growth is inhibited, while at 25 times the MIC, the colony-forming units begin to show a decrease.\(^10\)

**CF Sputum and Aminoglycoside Penetration and Bioactivity**

Aminoglycosides have variable penetration into sputum of CF patients,\(^15\) probably because of small molecules that physically decrease drug penetration into bacteria.\(^5\) Physiologic deposition of the drug in the lung of a CF patient is more variable than in the lung of a healthy person. This is in part due to the binding of polyacations, such as aminoglycosides, by sputum glycoproteins (mucins and DNA) in CF patients. Glycoproteins bind approximately 90% of the drug. Glycoprotein concentrations vary among CF patients, depending on the degree of purulence. Although the average sputum glycoprotein content is 60 mg/g, it can be as high as 135 mg/g. Accordingly, the drug dosage required to maximize deposition and absorption may vary significantly. Soluble sputum components, such as monovalent and divalent cations, vary little among patients.\(^13\) Divalent ions bind approximately 5% of a given dose of aminoglycosides, and DNA binds approximately

![Image](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21967/ on 06/25/2017)
another 2%. The use of recombinant human DNase from the sputum of CF patients appears not to affect this binding.14

A study by Mendelman et al10 showed a progressive increase in sputum tobramycin concentration with increasing duration of drug administration. While this study used IV tobramycin, it will be important to assess whether the same effect can be achieved using aerosolized tobramycin solution for inhalation.

In addition to interpatient variations in sputum purulence, other variations for aminoglycoside absorption include the degree of disease severity, pulmonary function, and the level of coughing and expectoration.

**IDEAL PROPERTIES OF AEROSOLIZED THERAPEUTIC AGENTS IN CF PATIENTS**

Aerosolized therapeutics (ie, proteins, peptides, antibiotics, and antivirals) all require certain properties for successful delivery (Table 2).

The ideal aerosol should be isotonic. In healthy adults, the osmolality of bronchial secretions is equal to that of the intracellular fluids.5 If large amounts of hypotonic or hypertonic solutions or solutions with an altered pH are introduced into the airways, mucosal irritation may result.5,7 However, studies in the setting of CF show that the airway mucus of CF patients is hypotonic.15 The addition of hypertonic solutions, or even normally isotonic solutions, can result in mucosal irritation.7,15

The ideal aerosolized therapeutic clearly should be sterile and nonpyrogenic. It should be available in a standard unit of use for ease of dosing. Further, inherent drug properties influence taste, and a solution that is pleasant tasting or tasteless can enhance patient acceptance. Patient factors, including minute ventilation, breathing and breath-holding patterns, the presence and degree of airway obstruction, cooperation, and body position, may result in delivery variations as great as 10-fold.16,17 Thus, the ideal aerosolized drug also should have a wide margin of dosage safety.

Therapeutic agents intended for aerosol delivery should be free of preservatives and toxic materials. Such ingredients have proven to be a clear drawback in the aerosolization of IV drugs. Parenteral agents are typically formulated to include buffers and pH adjusters. These substances are undesirable in aerosolized formulations because these additives can alter particle size and drug deposition, in addition to causing unpleasant side effects such as coughing and bronchoconstriction (Table 3).

The ideal aerosolized antibiotic solution should be easily nebulized and should not foam or yield a precipitate.

<table>
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<th><strong>Table 2—Aerosol Properties</strong></th>
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<tr>
<td>Isotonic</td>
</tr>
<tr>
<td>Sterile or pyrogen-free</td>
</tr>
<tr>
<td>Unit of use</td>
</tr>
<tr>
<td>Tasteless or pleasant tasting</td>
</tr>
<tr>
<td>No preservatives or toxic materials</td>
</tr>
<tr>
<td>Solutions that can be easily nebulized</td>
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<tr>
<td>Good chemical stability</td>
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Variations in surface tension can affect proper suspension and nebulization. Lastly, the ideal aerosol should be chemically stable.

**SUMMARY**

There has been renewed interest in the aerosolization of various classes of therapeutic agents, including antibiotics, antivirals, proteins, and peptides. Inhalation offers several potential benefits, which include improved targeting to the intended site of action, reduced systemic toxicity, reduced cost of administration, improved patient acceptance and therapeutic adherence, and less disruption in the patient’s lifestyle. The ideal characteristics for an aerosolized therapeutic require a sterile, chemically stable preparation with no additives or preservatives to cause untoward side effects such as bronchospasm, and the agent should be deliverable via a reproducible delivery system. In the specific setting of antipseudomonal therapy in CF patients, drug choice is important since certain classes of antibiotics have reduced bioactivity because of sputum antagonism in CF patients.

The disadvantages of aerosol delivery are few when compared with the advantages. Increasing research into delivery systems and the pharmacokinetics and pharmacodynamics of a variety of therapeutic agents suggests that a growing number of treatments will be delivered by this method in the future.

**REFERENCES**


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<tr>
<td>Phenol containing IV tobramycin is above NIOSH limits for exposure, considered to be a neurotoxin, produces unpleasant taste, and may increase nebulization time</td>
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<tr>
<td>Sodium metabisulfites may cause bronchoconstriction</td>
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<tr>
<td>Methylparabens and propylparabens cause alteration of particle size and dispersal characteristics</td>
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<tr>
<td>Hypotonic and hypertonic solutions cause cough and mucosal irritation</td>
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<td>Chronic exposure may lead to bronchospasm</td>
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*NIOSH = National Institute for Occupational Safety and Health.*


Cystic Fibrosis Foundation. Consensus conference: use of aerosolized antibiotics in CF patients (vol VIII). Bethesda, MD: Cystic Fibrosis Foundation, 1997; section I


International Association of Cystic Fibrosis Adults. The 1997 North American Cystic Fibrosis Conference. IACFA 1997; 51:12–16

Smaldone GC. Deposition of nebulized drugs: is the pattern important? J Aerosol Med 1994; 7:525–533