Aerosolized Antibiotics: Current and Future

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Introduction

This paper is written for the practicing pulmonologist, critical care intensivist, and respiratory therapist active in the treatment of patients with respiratory infections. At present, aerosolized antibiotic therapy is an unproven therapy. For the average patient, the caregiver does not routinely think of the aerosol route in the treatment of bronchitis or pneumonia. Yet, for the clinical investigator interested in aerosol therapy, aerosolized antibiotics have always been thought of as having important potential for the treatment of respiratory infections. All of the classic advantages of aerosol therapy apply to antibiotics. They treat the target organ directly and spare the body systemic toxicity. However, in spite of the attractiveness of the aerosol route for the treatment of respiratory infection, aerosolized antibiotics have not been recognized as effective, except for a few conditions, such as cystic fibrosis. This paper reviews the history of aerosolized antibiotic therapy and attempts to define modern concepts of clinical aerosol delivery that may allow more definitive studies to define the true potential of this mode of therapy. Because of the differences in day-to-day care, instrumentation of the airway, and risks of infection, we address ambulatory patients and intubated patients separately.

Ambulatory Patients–Cystic Fibrosis

Topical treatment of the respiratory tract via aerosolization or instillation of antibiotics has been practiced anecdotally for years in patients with cystic fibrosis.[1–4] The lack of effective oral therapy for the treatment of Gram-negative infections forced clinicians to develop methods for the off-label use of systemic antibiotics as aerosols. In addition, in patients with tracheostomies, similar preparations were used for direct instillation. Most of the older literature consisted of case reports in which aerosolized antibiotics were used to stabilize a patient's respiratory function. A few large-scale trials were undertaken, primarily in Europe, which indicated that some clinical benefit could be realized.[3] These effects were defined as small but statistically significant increases in respiratory function, as well as reduced frequency of exacerbations requiring hospitalization. These observations were further supported by a single placebo-controlled study that defined the role of aerosolized tobramycin in the United States.[5] As a group, these studies indicate that patients with the typical flora found in cystic fibrosis (Gram-negative organisms) respond to aerosolized therapy with an increase in function, estimated by spirometric improvements of 5–10%. In addition, their decline in pulmonary function appears to be blunted, with an increased interval between hospitalizations requiring parenteral antibiotic therapy.

In one study, instilled tobramycin was used as adjunctive therapy in hospitalized patients in conjunction with parenteral antibiotics, in an attempt to improve clinical response. Clinical outcome was not affected.[6]

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Thus, in cystic fibrosis (thought to be a paradigm for bronchiectasis in general) and possibly bronchitis, aerosolized antibiotic therapy is probably a useful therapy, but it has not displaced systemic therapy as the most important modality for the treatment of respiratory infection. It is not clear why this is so. Systemic agents, especially aminoglycosides, have been criticized as primary agents of lung infection because of limited penetration into respiratory secretions. This is the rationale for aerosolized and other forms of topical therapy to the respiratory tract. In studies where sputum levels have been measured following aerosolized antibiotics, increases in drug concentration are often reported to be an order of magnitude higher than levels expected from parenteral regimens. Despite these differences, clinical experience indicates that systemic therapy is more effective than aerosolized therapy in these patients. If levels of antibiotics, as measured in secretions, was the dominant factor responsible for the success of therapy, aerosolized antibiotics should displace systemic therapy as the primary mode of treatment, especially in hospitalized patients. These observations would suggest that the issue of antibiotic penetration into the inflamed, infected airway and secretions is not completely understood and that the sputum level, especially for aminoglycosides, may not adequately describe the pharmacokinetics of these drugs to the point where we can predict their effectiveness from levels alone.

From a practical point of view, the day-to-day use of aerosolized antibiotic therapy has been confined to off-label use in cystic fibrosis and, now, with approved tobramycin, routine therapy in patients with well established disease. Patients who do not have cystic fibrosis but do have advanced bronchiectasis often behave similarly to cystic fibrosis patients in that their respiratory tracts become colonized with Gram-negative organisms such as Pseudomonas. In the past, it would not have been unusual for pulmonologists to treat these patients in a similar manner to patients with cystic fibrosis—that is, with aerosolized off-label use of aminoglycosides. In more recent years, however, the advent of useful oral agents for the suppression of Gram-negative infection has become the first line of therapy. Thus, in all forms of severe bronchiectasis, aerosolized therapy remains adjunctive at best.

Antibiotics serve as a useful paradigm for modern aerosolized drugs. Most aerosolized agents, especially those delivered via nebulizer, are bronchodilators used to treat asthma patients. Aerosolized bronchodilators can be titrated directly to the patient's symptoms. Response to therapy can be assessed in real time using spirometry and other indices of respiratory distress as end points. Bronchodilators, which are safe enough to deliver to the patient continuously, allow individual titration of dose to the measured response at the bedside. This approach is not possible with aerosolized antibiotics. The dose-response relationship can only be estimated, and our understanding of the mechanisms of therapy appears to be incomplete. An approach to defining the important variables in these patients is described below.

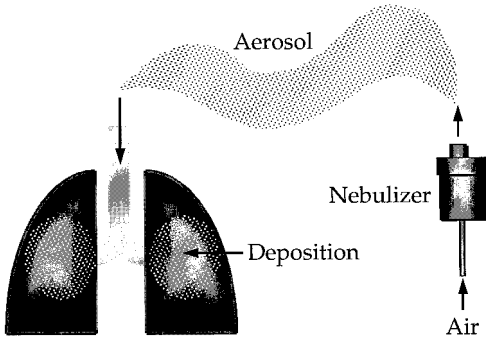

Fig. 1. Components of an aerosol delivery system: the aerosol, the aerosol generator (nebulizer shown), and the patient's respiratory tract.

Principles of Aerosol Therapy in the Ambulatory Patient

There are three components to an aerosol delivery system (Figure 1): (1) the aerosol, which is characterized by the mass median aerodynamic diameter (MMAD), (2) the aerosol generator, in this case a nebulizer, and (3) the pathophysiologic condition of the patient's lung. All three factors must be considered in the delivery of an aerosolized drug. Several reviews have addressed these principles in detail.[7–9] Briefly, the deposition of an aerosolized drug can be quantitated by measuring the variables defined in Equation 1 (the mass balance):

$$\text{deposition} = \text{inhaled mass} - \text{exhaled mass}$$

The *inhaled mass* is an important term, which is defined by the aerosol delivery system as well as by the patient's breathing pattern.[10] Many aerosolized antibiotics are delivered via nebulization. It has been generally observed that the efficiency of a nebulizer depends on the nebulizer itself, the physical properties of the solution, and the pattern of breathing. All of these factors are summed in the *inhaled mass*, and this quantity can be studied in vitro in bench experiments (Fig. 2). As shown in Figure 2, in vitro testing can also facilitate measurement of the aerodynamic characteristics of the aerosol (MMAD), often by using cascade impaction. Prior to clinical studies, bench testing is useful to confirm the preservation of the chemical structure of the drug after nebulization, the aerodynamic behavior of the particles, adequate efficiency of the nebulizer, and, for gamma camera studies, to define the relationship between radiolabel and drug activity. For a given patient, the individual quantities describing deposi-

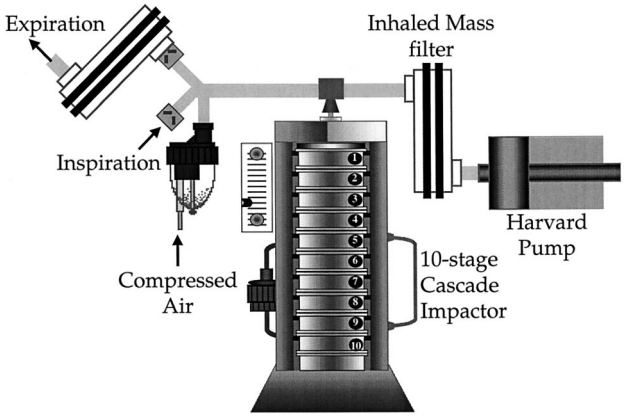

Fig. 2. Components of a standard bench setup for characterizing aerosol delivery systems. The piston pump simulates a given breathing pattern. The aerosol generator (nebulizer) is configured with tubing and connectors appropriate for the clinical situation. Filters are interposed to capture particles that would be inhaled by the patient (inhaled mass filter). Particles not presented to the patient are captured by the filter on the exhalation line. A cascade impactor is used to measure mass median aerodynamic diameter.

tion as defined by Equation 1 can be directly measured during aerosol delivery, using absolute filters or gamma camera techniques, as illustrated in Figure 3. Equation 1 determines the total dose of drug to the patient. Regional studies employing radioisotopes and the gamma camera define the quantity of deposited aerosol that actually resides in the lung and its distribution within the airways.

The first study measuring these variables in patients with cystic fibrosis was performed by Ilowite et al in 1987.[11] They used the mass balance filter technique to measure deposition in a group of ambulatory patients with cystic fibrosis who were inhaling aerosolized gentamicin nebulized during spontaneous breathing. The initial quantity of drug placed in the nebulizer was 160 mg and the device produced an aerosol with an MMAD of 1.1 μm. Figure 4 illustrates the importance of breathing pattern. With the patients breathing tidally in a steady state but without further guidance from the investigators (non-controlled pattern), the quantity of drug deposited in the lungs varied by an order of magnitude. This variation was significantly reduced in some of those patients by repeating the deposition measurement with a standardized controlled breathing pattern. Following a single treatment, the deposition of drug in the lungs was related to levels in expectorated sputum (Figure 5). Gentamicin levels ranged from 50 μg/mL to 800 μg/mL of expectorated sputum. The level of antibiotic decreased rapidly, as measured by serial samples of expectorated sputum.

While the levels of antibiotic in the sputum seemed to vary in a random manner, these authors found that sputum levels could be predicted using a combination of data from the mass balance measurement and regional analysis from the gamma camera. As illustrated in Figure 6, peak sputum level was not clearly related to lung deposition. However, the pattern of deposited aerosol within the lung could be

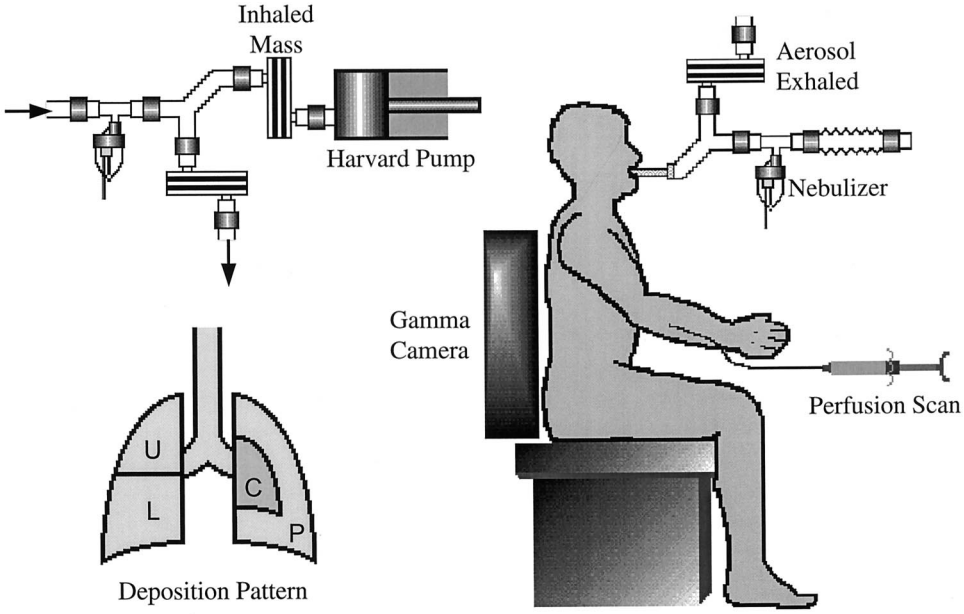

Fig. 3. Right: Diagram of gamma camera study designed to measure factors important in aerosol deposition: patient sitting in front of camera inhaling aerosol in a manner duplicating a typical clinical situation. Upper left: *Inhaled mass* is measured by filters and bench studies. Gamma camera can be calibrated via injection of macro-aggregates (perfusion scan). Lower left: Computerized regions of interest can be used to determine sites of deposition in the lung.

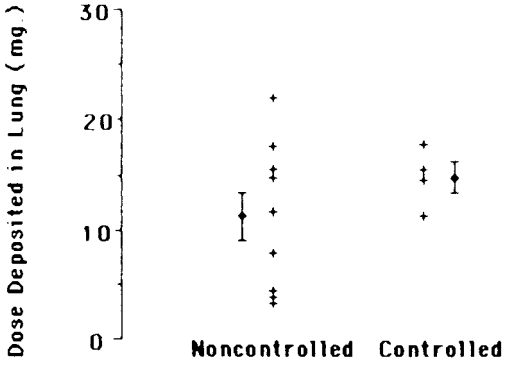

Fig. 4. Deposition of aerosol in controlled and noncontrolled breathing. Values are means ± SEM. The coefficient of variation was markedly reduced in the group with controlled breathing (18.6% versus 60.2%). (From Reference 11, with permission.)

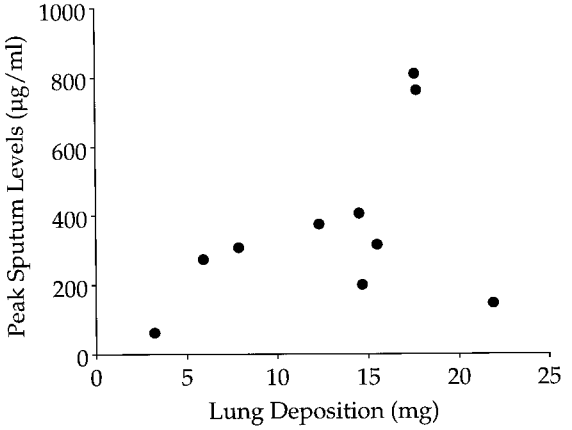

Fig. 6. Gentamicin levels in sputum versus lung deposition, from aerosolized gentamicin. (From Reference 11, with permission.)

estimated and quantified using the gamma camera by analysis of computer-generated regions of interest (Fig. 7). These regions defined the distribution of radioactivity in central and peripheral regions, the ratio of which (C/P) estimates the preference for particles to be deposited in central airways.[7,12] When normalized for regional lung volume, the C/P ratio indicates the tendency for deposition in large airways within the central lung region illustrated in Figure 7. Figure 8 shows the influence of this variable in analysis of secretions. In Figure 8, the sputum levels depicted in Figure 5 (peak levels) are divided by the milligram of gentamicin deposited in the patient (vertical axis). This value is plotted against the regional distribution of the deposited aerosol in the lung (C/P ratio). The good correlation observed demonstrates that peak sputum level is reasonably described by both the quantity of drug deposited and its initial distribution in the airways. Finally, the tendency of inhaled particles to deposit in the central airways was related to the degree of airway obstruction (Fig. 9). Patients with more airway obstruction had increased deposition in central airways.

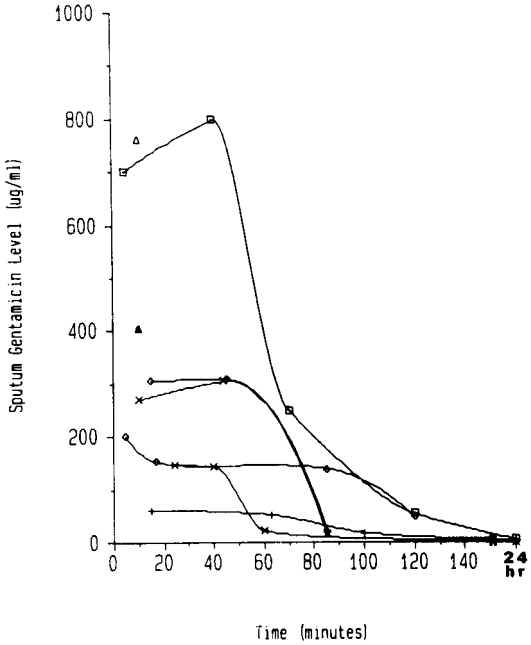

Fig. 5. Gentamicin levels in sputum versus time. Peak sputum levels averaged 307.5 ± 264 (SD) µg/mL and decreased rapidly over the next two hours. Two patients produced a single sample only. (From Reference 11, with permission.)

Subsequent clinical trials using tobramycin have found high levels of drug in expectorated sputum. Placebo-controlled trials have found improved spirometry and reduced frequency of hospitalization.[5] However, there have been no comparisons between aerosol therapy and systemic oral therapy in outpatients. In addition, the results of adjuvant therapy with aerosols have not been analyzed with respect to total and regional deposition. It is uncertain whether the results of previous trials are related to inadequacy of therapy, failure to penetrate peripheral airways, or the fact that sputum level per se does not predict efficacy.

In summary, in the ambulatory patient, our understanding of mechanisms of protection using aerosolized therapy remains incomplete. The availability of suitable oral antibiotics for the treatment of acute exacerbations of chronic bronchitis and bronchiectasis involving Gram-negative organisms has reduced the anecdotal use of aerosolized agents. In cystic fibrosis patients chronically colonized with these organisms, the use of aerosolized antibiotics, particularly tobramycin, has been beneficial. Further studies are necessary to define the role of these agents in patients with acute exacerbations requiring hospitalization.

The Intubated Patient

The intubated patient presents a different problem. In contrast to the patient with chronic bronchiectasis, most

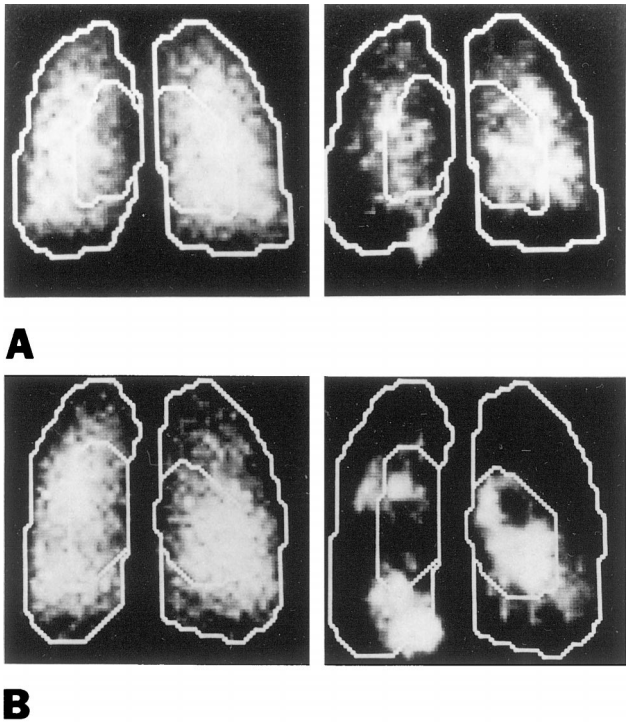

Fig. 7. Gamma camera images from two subjects with cystic fibrosis. Left: ^{133}Xenon equilibrium images, which define the outer lung regions as well as regional lung volume. Right: Deposition images following inhalation of radiolabeled gentamicin aerosol. Central regions of interest were drawn to encompass 30% of the total lung region. The distribution of radioactivity can be expressed as the ratio of activity in the central region to that in the peripheral region (C/P ratio). The aerosol pattern was normalized for volume by dividing the aerosol C/P by the xenon C/P. The ratio for subject A was 1.2. The ratio for subject B, with a more "central" distribution C/P, was 2.5. (From Reference 11, with permission.)

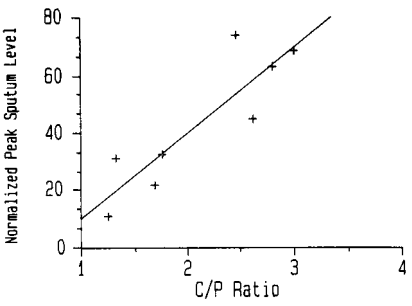

Fig. 8. Effect of site of deposition on sputum gentamicin level (in μg/mL). Sputum level, normalized for the amount deposited (μg/mL sputum divided by mL gentamicin deposited), is plotted against the ratio of activity in the central region to that in the peripheral region (C/P ratio). A significant correlation was obtained ($r = 0.888$, $p < 0.05$). (From Reference 11, with permission.)

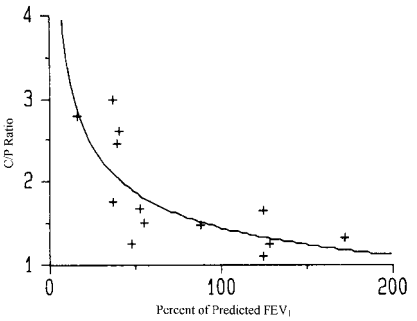

Fig. 9. Effect of pulmonary function on central deposition versus peripheral deposition. Forced expiratory volume in the first second (FEV_1) (as percent of predicted) is plotted against the ratio of activity in the central region to that in the peripheral region (C/P ratio). An exponential relationship was seen ($r = 0.76$, $p < 0.05$) (ie, the more obstructed the patient, as assessed by the forced expiratory volume in the first second, the more central the aerosol distribution. (From Reference 11, with permission.)

intubated patients (intubated without primary respiratory infection) initially have a relatively benign upper respiratory flora and limited evidence of lower respiratory tract infection. Once intubated, however, the flora of the upper respiratory tract changes. After several days, the airways become colonized with organisms considered more pathogenic. Many of these patients develop infection of the deep lung, with substantial mortality. While the process leading to the development of ventilator-associated pneumonia (VAP) is incompletely understood, it appears that enteric organisms from the gastrointestinal tract often colonize the oropharynx.[13] The presence of the endotracheal tube or tracheostomy may result in local inflammation, promoting infection in the intrapulmonary airways, which may lead to pneumonia. Additional factors, such as bacterial adherence, the use of systemic antibiotics, the local flora of a particular intensive care unit (ICU), and nutrition factors may be involved.[14] Once established, treatment of VAP with systemic antibiotics is usually effective. However, there are important associated toxicities. These toxicities may be related to the pneumonia itself, adverse effects of drugs, or to more prolonged residence in the ICU. They include *Clostridium difficile* toxicity in the lower gastrointestinal tract, renal failure, line sepsis, fungal overgrowth with systemic infection, and the development of bacterial resistance.

Mechanically ventilated patients are at greatest risk for pneumonia among hospitalized patients. Their risk is 6–21-fold greater than nonintubated patients.[15] The incidence of VAP ranges from 5% to 70% of all intubated patients, depending on the series. It is generally accepted that 7 days is the mean length of time for intubated patients to develop deep lung infection. The overall incidence is estimated to be 350,000 cases per year, with a mortality risk of 20–70%.[16–18]

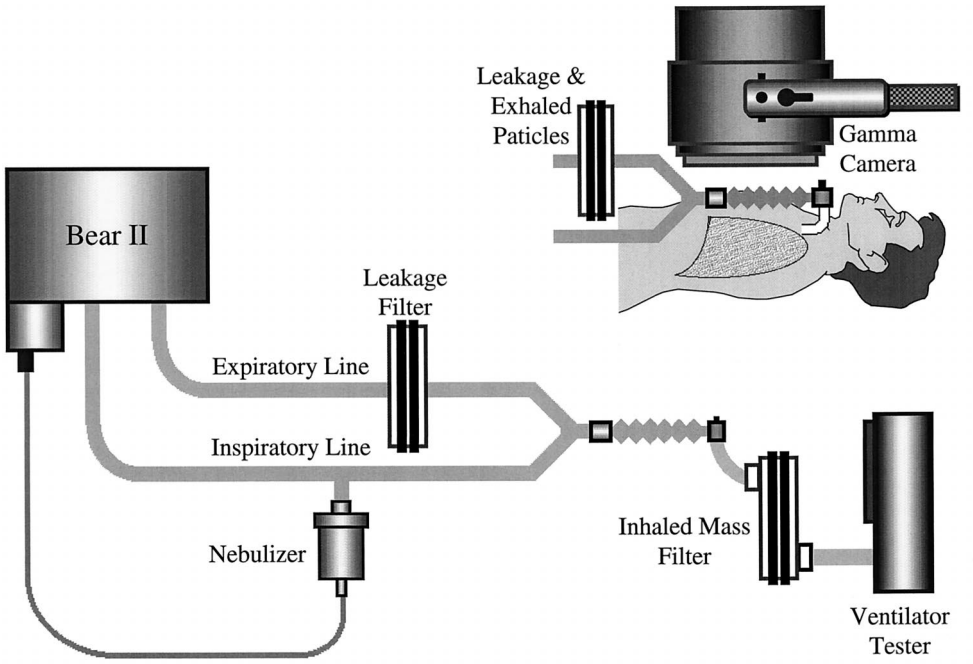

Fig. 10. Bench testing setup for aerosol delivery in patients maintained on mechanical ventilation. The principles are similar to those described in Figure 2. The setup duplicates the clinical delivery of aerosols with the *inhaled mass* determined by the inspiratory filter at the distal end of a tracheostomy tube or endotracheal tube. Using filters in the expiratory line, total aerosol deposition in patients can be determined. If the particles are radiolabeled, gamma camera images can be obtained as shown. (From Reference 30, with permission.)

The proposed path described above, of oral colonization leading to tracheobronchitis and pneumonia, has influenced several strategies to prevent deep lung infection. For example, selective decontamination of the digestive tract involves the attempt to eradicate organisms from the oropharynx and stomach using high-dose poorly-absorbed oral antibiotics. This approach has been controversial. Initial trials appeared to show some benefit in that the incidence of deep lung infection was reduced, with a possible reduction in mortality.[19–21] However, subsequent studies have not confirmed this observation in all patients.[22,23] In addition, the practice of using broad-spectrum antibiotics in all patients in the ICU can contribute to the development of resistance. Selective decontamination of the digestive tract is being investigated, and may be effective in post-trauma patients.[24] However, it is not universally practiced and is still considered experimental therapy.

The earliest studies on prevention of VAP used targeted topical therapy to the oropharynx. Using atomizers and poorly-absorbed Polymyxin antibiotics, intubated patients were treated prophylactically. This approach reduced Gram-negative infection in the deep lung secondary to susceptible organisms.[25] However, large clinical trials identified the emergence of resistant organisms and, ultimately, found no improvement in mortality.[26] The availability of systemic agents effective against Gram-negative organisms resulted in the discontinuance of this approach.

The failure of oropharyngeal atomization and the mixed results of its more extensive gastrointestinal counterpart, selective decontamination of the digestive tract, has led to the opinion that topical therapy in the prevention of VAP remains ineffective, and prophylaxis is not routinely recommended.[27] While disappointing, previous studies have, in general, involved the prophylactic treatment of all patients, and they have not used therapy directed primarily to the intrapulmonary airways and deep lung. Thus the potential utility of aerosolized antibiotics remains to be tested. The design of an appropriate study, however, has been limited by several basic difficulties. The first is the lack of a clinical indicator defining those patients who need prophylaxis to prevent VAP. The second is the reported difficulty in delivering aerosolized agents to the lungs of intubated mechanically ventilated patients.[28,29]

Measuring Aerosol Delivery in the Intubated Patient

Early studies measuring particle deposition in the lungs of intubated patients indicated that the efficiency of aerosol delivery was quite low (2–7%).[28] This was attributed to inherent inefficiencies of the nebulizer delivery system

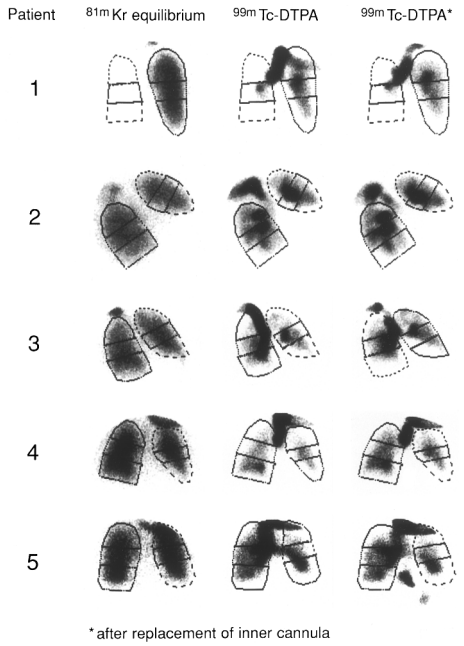

Fig. 11. Krypton equilibrium and technetium deposition images in 5 ventilator-dependent patients. Actual patient orientation is shown. The lung outline was determined by an ^{81m}Krypton equilibrium image (left column) and subsequently superimposed over the ^{99m}technetium-DTPA deposition images. Middle column: Deposition images obtained at ~100,000 counts/min after ~3–5 minutes of nebulization. Right column: Deposition images obtained immediately after the tracheotomy tube inner canula was replaced. The right lung outline for each patient was estimated from the chest radiograph. (From Reference 33, with permission.)

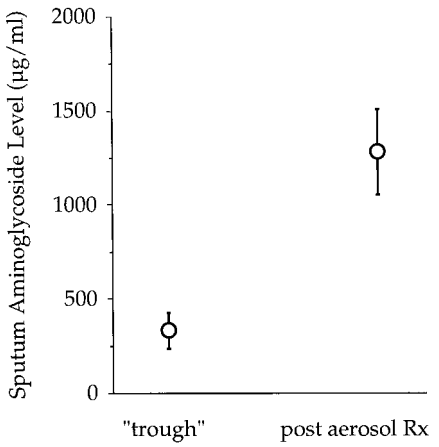

Fig. 12. Gentamicin sputum levels (means ± SD) obtained immediately prior to (left) and immediately following (right) aerosolized gentamicin nebulization in intubated patients receiving aerosol therapy every 8 hours. (From Reference 34, with permission.)

and the difficulty for particles to negotiate the endotracheal or tracheostomy tube.[29] However, by taking the same approach to nebulization via the ventilator as shown above for spontaneous breathing, the factors important to aerosol delivery using mechanical ventilation have been defined. As shown in Figure 10, the ventilator and its tubing (including the endotracheal tube) can be viewed as an extension of the nebulizer. Filters placed distal to the endotracheal (or tracheostomy) tube determine the *inhaled mass*, just as in Figure 2. Cascade impactors interposed in the circuit measure the MMAD of aerosols presented to the patient. Gamma camera imaging can be performed on intubated patients and, using filters, the dose to the patient and regional deposition to the lung can be determined using the same principles developed for spontaneously-breathing individuals. Over the last decade, serial in vitro and in vivo studies have determined the factors important in aerosol delivery during mechanical ventilation. Those factors include the nebulizer, the ventilator, the conditions of ventilation (eg, breathing pattern, humidification), and the position of devices in the circuitry.[30–32] These principles are now well described and, as will be shown below, it is now possible to develop efficiencies of aerosol delivery that exceed those previously reported in spontaneously-breathing patients.

It is possible to measure deposition in the intubated patient and to define regional distribution of drug in the lung. Figure 11 shows images from 5 tracheostomized patients maintained on long-term mechanical ventilation.[33] The left vertical column depicts ^{81m}krypton equilibrium images, which define regional ventilation. The other columns show aerosol images following inhalation of ^{99m}technetium-labeled aerosol. The images were obtained with the original tracheostomy tube in place (middle column) and with the tube changed (right column). This picture reveals qualitative information that demonstrates that if the lung is ventilated, particles do deposit within airways. Further, while the tubing captures particles, the amount of aerosol deposited in the tube is small, compared to lung deposition.[34] Studies of aerosolized antibiotics have revealed that significant amounts of aerosolized aminoglycoside can be deposited in the parenchyma of these patients and that levels of deposition during therapy can exceed those reported for spontaneously-breathing patients. Figure 12 shows the gentamicin levels of sputum suctioned from the airways of patients receiving aerosolized gentamicin (80 mg in the nebulizer every 8 h). In a "steady state" the trough level just prior to a treatment averaged about 300 μg/mL of sputum. Following therapy, levels approached 1,500 μg/mL. These levels are higher than those reported in Figure 5 and reflect the increased efficiency of aerosolized delivery in patients with an optimized ventilator/nebulizer system. Deposition averaged 22% of the original amount of drug placed in the nebulizer. This level of efficiency is more than double that reported for spontaneously-breathing cystic fibrosis patients (7.5%).[11,34]

Targeted Aerosol Prophylaxis in the Intubated Patient

A Human Model for Respiratory Infection: the Respiratory Care Unit. We have established a human model of Gram-negative infection in mechanically ventilated patients. This model is designed to study the process of colonization in the upper airway, using serial samples of secretions from patients who are clinically stable but instrumented and ventilated, living in the hospital. In this environment, serial assessment of these patients has allowed development of techniques for quantitating airway secretions,[35] maximizing aerosol delivery,[36] and defining potential indices for response, such as reduction in the volume of secretions, reduction in bacterial growth, and changes in inflammatory cytokines.[34] These variables may serve as potential surrogates for important clinical end points, such as reduction of VAP, mortality, and the incidence of resistant organisms. Early studies using this model found that aerosolized aminoglycosides delivered via ventilator can significantly reduce the volume of sputum quantitatively suctioned from the proximal airways of these patients. In addition, in the same patients, the growth of pathogenic bacteria is effectively suppressed. Consistent with the hypothesis that the instrumented patient develops associated inflammation in the proximal airways, we have found markedly elevated levels of inflammatory cytokines in the secretions. These include TNF-α, interleukin 1-β, soluble ICAM-1, and neutrophil elastase. These levels approach those seen systemically in patients with shock and acute respiratory distress syndrome. While their meaning in terms of clinical outcome remains obscure, we have shown that these levels correlate with the volume of secretions and that cytokine levels are reduced in concert with reduction in sputum volume following therapy with aerosolized antibiotics.[34]

The respiratory care unit patient or a step-down unit patient is clinically stable. Presently, it has been shown that antibiotics can be delivered to the intubated patient with measured effects. What is unclear is the clinical importance of any of these observations. To approach VAP and other ICU conditions, we have begun to study secretions in a similar manner in ICU patients. Early studies indicate that sputum volume can be quantitatively measured in the medical ICU. After 7 days in the unit, in patients without pneumonia as their initial diagnosis, a significant increase in secretions can be detected.[37] Follow-up studies will be designed to determine whether this increase in secretions serves as a useful predictor of clinical infection. If so, sputum volume may help define a targeted patient population to receive prophylactic aerosolized antibiotics.

Summary

Aerosolized antibiotic therapy appears to have potential for targeted therapy to the airways and deep lung to prevent VAP in patients at high risk for this disease. The definition of that high-risk population is important if this model is to be successful. We are attempting to define susceptible patients by measuring the volume of airway secretions, which mirrors the inflammation milieu of the central airways. Elevated sputum volume is marked by heavy growth of pathogenic organisms and high levels of inflammatory cytokines. Large-scale clinical trials are necessary to define the usefulness of these surrogates in defining a targeted population and for assessing the potential of aerosolized antibiotic prophylactic therapy for preventing pneumonia and mortality. If successful, the aerosol approach may avoid systemic therapy and its associated complications.

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