

# Aerosolized Antibiotics in Mechanically Ventilated Patients

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## Introduction

### Topical Delivery of Antibiotics to the Lung

### Tracheobronchitis

### Aerosolized Antibiotic Delivery in the Medical Intensive Care Unit

### Summary

**Aerosolized antibiotics are potentially useful in intensive care. At State University of New York at Stony Brook we developed a human model of tracheobronchitis in intubated patients. The model provides daily specimens of airway secretions, allowing serial studies of airway inflammation and testing of therapy modes. The presence of local infection is defined by a unique method of quantified sputum collection. Bench models have been developed that illustrate the factors that limit aerosol delivery to intubated patients. With those models clinical trials have defined possible indications for targeted aerosol therapy to patients at risk for deep lung infection. An efficient aerosolized-antibiotics method that delivers the aerosol past the endotracheal tube has been established, and with that method the drug levels in pulmonary secretions exceed by several orders of magnitude the levels expected with intravenous therapy. Potential end points of therapy are being evaluated, including the rate of bacterial resistance and the incidence and definition of deep lung infection. Key words: aerosol, antibiotics, tracheobronchitis. [Respir Care 2004;49(6):635–639. © 2004 Daedalus Enterprises]**

## Introduction

In the hospital, mechanically ventilated patients are at greatest risk for ventilator-associated pneumonia, with reported risk in intubated patients 6–21-fold greater than nonintubated patients.<sup>1</sup> The incidence of ventilator-associated pneumonia ranges from 5 to 70% of all intubated patients, depending on the series. It is generally accepted that 7 days is the mean amount of time for intubated patients to develop deep lung

infection. The overall incidence is estimated to be 350,000 cases per year, and the mortality risk is 20–70%.<sup>2–4</sup> The widespread use of systemic antibiotics in the intensive care unit may be responsible for increased incidence of superinfection, systemic toxicity, emerging bacterial resistance, and increasing costs. In intubated patients respiratory infections may originate in the proximal airways, at sites of inflammation in the region of the endotracheal tube. Topical aerosol therapy targeted to patients with emerging tracheobronchitis may prevent deep lung infection. Though theoretically desirable, aerosolized antibiotics are not commonly used, for many reasons, including the lack of clear indications for the initiation of therapy, the fear of fostering bacterial resistance, the difficulty of delivering aerosols to intubated patients, the lack of appropriate drugs, and the problems in choosing end points of therapy for critically ill patients. The present report summarizes the airway infection model developed at the State University of New York at Stony Brook, describes methods for efficient aerosolized-antibiotics delivery during mechanical ventilation, and presents preliminary data that this therapy is effective.

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### Topical Delivery of Antibiotics to the Lung

To minimize systemic toxicity, topical aerosol therapy should attain therapeutic levels in the airways but limit drug exposure to the rest of the body. Essentially, this becomes a problem in dose-versus-response superimposed on the complex pharmacokinetics of aerosol delivery. To begin to study this problem in intubated patients Palmer et al<sup>5</sup> applied to these subjects the same principles that were described in an earlier review that defined aerosol delivery techniques for spontaneously breathing cystic fibrosis patients.<sup>6</sup> Figure 1 illustrates the “mass balance” technique for measuring lung deposition in an intubated patient. Aerosol particles are captured from the ventilator circuit on an inspiratory filter before they enter the patient. The quantity of drug captured by the inspiratory filter is the “inhaled mass” (ie, the amount that enters the patient’s airway).

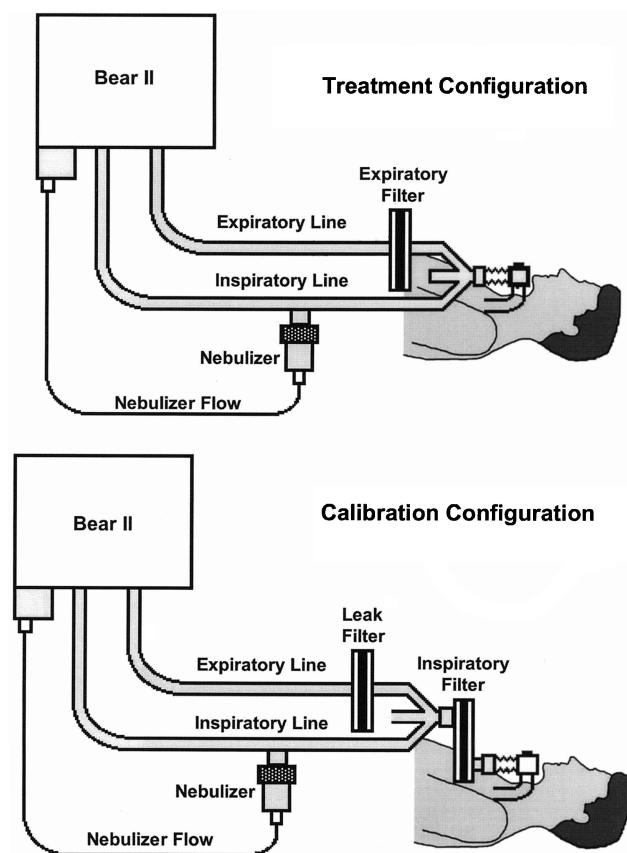


Fig. 1. Mass balance method used to measure lung deposition. In the treatment configuration exhaled particles and particles that bypass the patient are captured by the expiratory filter. In the calibration configuration particles that reach the patient at the inspiratory point of the tracheostomy tube are captured by the inspiratory filter, and particles that bypass the patient are captured by the leak filter. Tracheostomy tube (inner cannula) and Y-piece deposition are measured with a well counter (radioactivity meter). (From Reference 5, with permission).

Inhaled mass can be measured in vivo by interposing a filter in the circuit just before the endotracheal or tracheostomy tube (calibration run). Then, in a separate experiment, another dose of antibiotic is nebulized and the patient inhales the aerosol; some particles deposit in the airways (deposition) and the rest are exhaled. The quantity captured on the expiratory filter is the “exhaled mass.” Deposition in the patient is determined by subtracting the exhaled mass from the inhaled mass (see Fig. 1).<sup>5</sup>

How effective is nebulizer delivery in raising sputum levels of antibiotic? In the study by Palmer et al, after 5 days of therapy every 8 hours, with 80 mg of gentamicin placed in the nebulizer, the mean sputum concentrations before (trough) and after (peak) aerosol treatment were  $289 \pm 41.4 \mu\text{g/mL}$  and  $1,179 \pm 394.5 \mu\text{g/mL}$ , respectively. Serum concentrations were undetectable in most determinations, except for a single patient who was in renal failure, which suggests that that method avoided systemic exposure to drug.<sup>5</sup>

### Tracheobronchitis

The State University of New York at Stony Brook model of early airway infection described the process of upper-airway colonization by taking serial samples of secretions from intubated patients. The first group of studies reported on clinically stable ventilator-dependent patients who were instrumented, ventilated, and living in a respiratory care unit. Those serial patient assessments allowed development of techniques for quantitating airway secretions,<sup>7</sup> maximizing aerosol delivery,<sup>8</sup> and defining potential indices of response, such as reduction in the volume of secretions, reduction in bacterial growth, and changes in inflammatory cytokines.<sup>5</sup> Patients in the respiratory care unit were often found to have inflamed airways with substantial volumes of purulent sputum produced over 4 hours.

Can aerosolized antibiotics affect those secretions? Figure 2 shows the results from our first studies. Secretion volume differed markedly among patients, but after 2 weeks of aerosol antibiotics the secretion volume decreased in every patient. In addition, sputum cultures revealed significant reduction in bacterial growth, often with sterilization of the sputum (Fig. 3). Over time, bacteria return, but a patient can be treated repeatedly with this regimen without the emergence of antibiotic resistance.<sup>5</sup> Our experience in the respiratory care unit indicates that we can deliver aerosolized antibiotics, create high levels of drug in the sputum, and decrease sputum volume, bacterial growth, and cytokines, which suggests reduced airway inflammation. Though those studies have established a form of “dose-versus-response,” using tracheobronchitis as the indication, the meaning of the response remains to be further defined. Establishing clinical end points remains a major challenge in studies designed to prevent or treat

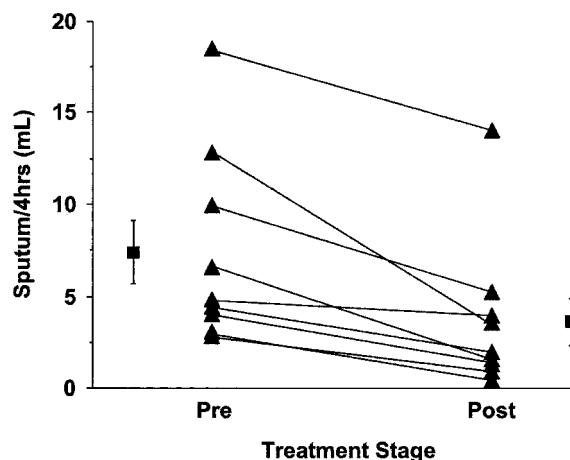


Fig. 2. The 4-hour collection volume of airway secretions before (Pre) and after (Post) administration of aerosolized antibiotics. Data were collected from 9 trials, with 5 samples obtained over 1 week. The sputum volume decreased significantly ( $p = 0.002$ ). Each triangle represents the mean of 5 days of volume measurement. The squares with error bars represent the mean  $\pm$  SEM of the 9 patients' data. (From Reference 5, with permission).

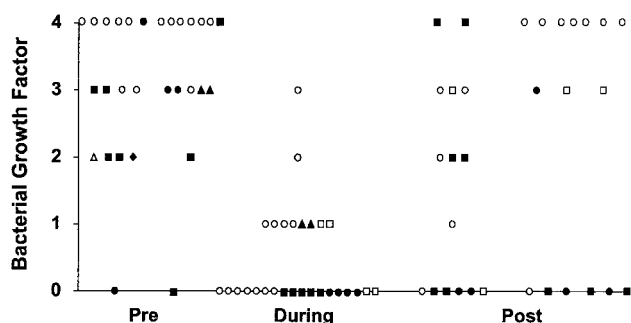


Fig. 3. Bacterial growth from tracheal aspirate cultures obtained during 9 trials of aerosolized antibiotics. Cultures were obtained weekly 2–3 weeks before, during, and 2–3 weeks after aerosolized antibiotics. Open circles: *Pseudomonas aeruginosa*. Solid circles: *Proteus mirabilis*. Solid squares: *Serratia marcescens*. Solid triangles: *Acinetobacter calcoaceticus*. Open squares: *Providencia stuarti*. Open triangles: *Enterobacter aerogenes*. Solid diamonds: *Klebsiella pneumoniae*. The quantity of growth is assessed on a graded scale of 0 to 4. (From Reference 5, with permission).

ventilator-associated infections. In the Palmer et al study<sup>5</sup> we used new methods to determine the effects of aerosolized antibiotics on secretions and found significant effects on sputum volume and bacterial growth. The 4-hour sputum collection method is a potentially important means for evaluating airway pathophysiology and response to drug therapy. Other emerging indices include the clinical pulmonary infection score,<sup>9</sup> which includes airway secretions and other variables (eg, temperature, white-cell count, chest radiograph) in defining the presence and severity of airway infection. To eliminate the inaccuracies of subjective impressions of sputum volume, which are dependent on

frequency and method of suctioning, we have used quantitative volumetric assessment with 4-hour time periods.<sup>7</sup> The clinical importance of small sputum-volume changes over 4 hours is unknown, but this same methodology can be used to monitor secretion increases in critically ill patients. The clinical impact could be considerable if these changes are shown to predict pneumonia.

It is now clear that in a controlled environment such as the respiratory care unit, we can deliver aerosolized antibiotic to intubated patients. With regard to critically ill patients the questions remaining include “to whom,” “when,” “for how long,” and “to what end?”

### Aerosolized Antibiotic Delivery in the Medical Intensive Care Unit

More recently our group has begun to study critically ill patients in the medical intensive care unit. The transition from the respiratory care unit experience involves many uncertainties, including changes in aerosol delivery systems, confirming indications for therapy, and defining clinically relevant end points. Though the studies cited above have demonstrated success in aerosol delivery to patients in a respiratory care unit, our ability to predict delivery in general is hampered by the fact that modern ventilators are not designed with aerosol delivery in mind. Modern ventilator design does not include regulatory standards that relate to aerosol delivery. Previous studies have measured patient- and ventilator-related factors that affect aerosol generation and inhalation for nebulizers on the bench,<sup>8,10,11</sup> but models to predict nebulized drug delivery during mechanical ventilation have not been validated in vivo. Besides the variables already studied to some degree in vitro (eg, humidity, nebulizer type), newer ventilator designs may further complicate prediction of drug delivery. The use of constant flow in the ventilator tubing (eg, bias flow) may increase aerosol losses as adult ventilator systems are becoming similar in design to neonatal ventilators, which are known to be inefficient in aerosol delivery.<sup>12</sup> Another variable, breath-actuated nebulization, is an important factor in spontaneously breathing patients<sup>13</sup> but is not a feature of all modern ventilators.

As a first step in assessing this problem we recently performed a detailed in vitro assessment of modern ventilators, repeating some of the earlier studies and looking at additional variables such as bias flow.<sup>14</sup> In addition, that study had an in vivo component, in which we predicted how the dominant variables defined on the bench would affect clinically important variables (eg, sputum level of aerosolized antibiotic) in the antibiotic treatment scheme described above. Figure 4 shows the bench setup. To assess variables not found on each ventilator we controlled common variables and varied the settings (Fig. 5). On the bench the major factors that affected aerosol delivery were

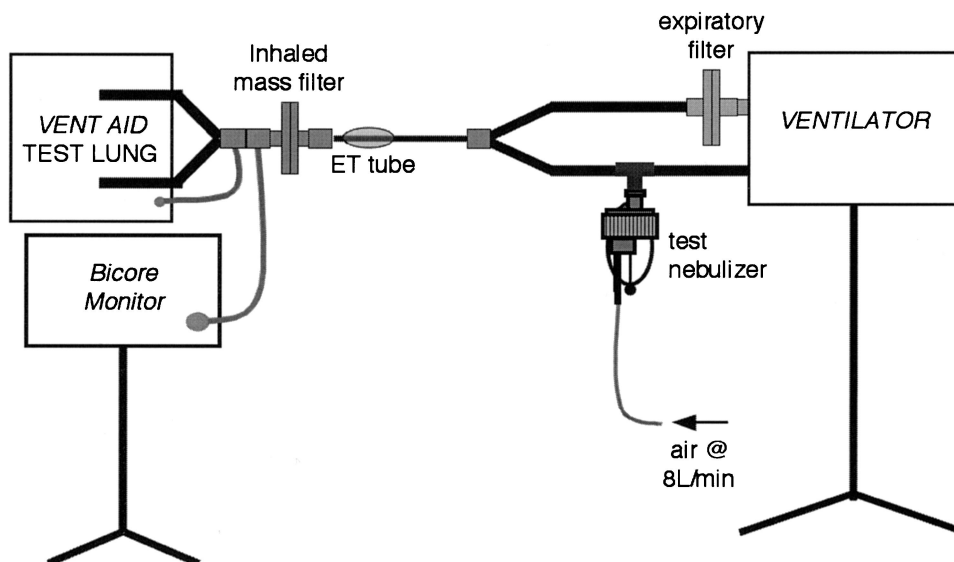


Fig. 4. Experimental apparatus for testing delivery of aerosolized antibiotic. The nebulizer was placed in the inspiratory line about 15 cm before the Y-piece and triggered either by breath actuation or powered continuously by a separate pressure source. Aerosol was captured by the inhaled mass filter just distal to the endotracheal (ET) tube. For particle sizing experiments a cascade impactor was placed between the endotracheal tube and the inhaled mass filter. The Bicore monitor confirmed the breathing pattern during nebulization. (From Reference 14, with permission).

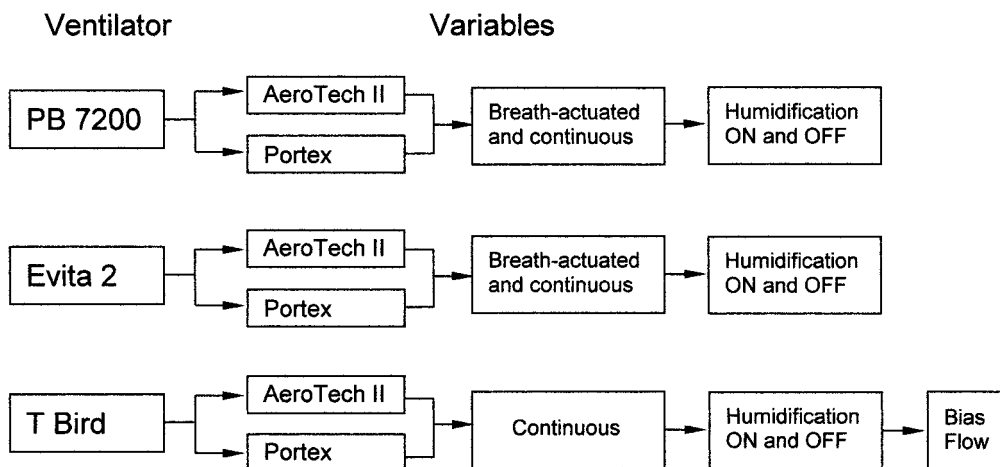


Fig. 5. Bench test protocol. PB = Puritan-Bennett (Adapted from Reference 14).

humidity and breath-actuation of the nebulizer. Table 1 shows the results of that *in vivo* study (levels of antibiotic in suctioned sputum following treatment with either breath-actuated or continuous nebulization in humidified or dry gas). Data were normalized for different antibiotics by dividing each measured level by the amount of drug placed in the nebulizer. The data were paired as each condition was tested in the same patient. Sputum levels varied over a wide range but most of the variation was accounted for by the 2 major variables, breath-actuation and humidity. The *in vitro* bench studies predicted the *in vivo* ratio between dry and humidified gas.

### Summary

In summary, our data suggest that controlled *in vitro* studies of devices can provide useful information on aerosol delivery and lead to better design of devices for control of aerosolized antibiotic therapy. With control of drug delivery it is now possible to test other parts of the hypothesis that developing airway infection can be detected and defined by objective criteria such as sputum volume or clinical pulmonary infection score and treated with topical therapy.

## AEROSOLIZED ANTIBIOTICS IN MECHANICALLY VENTILATED PATIENTS

Table 1. Sputum Levels of Antibiotics

Nebulizer Activation Method	Number of Pairs	Nonhumidified (mean $\pm$ SD $\mu\text{g/mL/mg}$ )	Humidified (mean $\pm$ SD $\mu\text{g/mL/mg}$ )	NH/H	p
Breath actuation	14	$12.57 \pm 6.70$	$3.23 \pm 2.03$	3.89	$<0.001$
Continuous	10	$1.83 \pm 0.91$	$0.83 \pm 0.33$	2.2	0.0005
All ventilators	24	$8.10 \pm 7.41$	$2.23 \pm 1.96$	3.63	0.0002

NH/H = ratio of nonhumidified to humidified  
(Adapted from Reference 14).

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