

# The Role of Aerosolized Antimicrobials in the Treatment of Ventilator-Associated Pneumonia

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The ability to deliver high concentrations of antimicrobial agents directly to the site of pneumonia is attractive, especially with the availability of high-efficiency nebulizers. A major focus of inhaled antimicrobial therapy has been to prevent and treat ventilator-associated pneumonia (VAP). VAP occurs commonly in mechanically ventilated patients and is associated with significant morbidity and high mortality. Moreover, the emergence of VAP due to multiple-drug-resistant Gram-negative organisms that are resistant to any form of systemic antimicrobial therapy has provided an impetus to explore inhaled antimicrobial treatment as an adjunct to systemic therapy. Tobramycin solution for inhalation and colistimethate sodium have been formulated for delivery via inhalation. Although these agents are being increasingly employed in intensive care units, the intricacies involved in their use are not appreciated by many clinicians. This review discusses the role of these agents in the prevention and treatment of VAP, with an emphasis on some of the problems associated with their use. Further research is needed to support the use of inhaled antimicrobial therapy in patients with VAP. *Key words: antimicrobial, antibiotics, pneumonia, aerosol, ventilator-associated pneumonia, VAP, mechanical ventilation, tobramycin, colistimethate sodium.* [Respir Care 2007;52(7):866–884. © 2007 Daedalus Enterprises]

## Introduction

The traditional approach to the treatment of pneumonias in critically ill patients is to administer antibiotics via the systemic circulation. Because the airways provide a direct pathway to the lung cells and tissues, aerosolized delivery offers an alternative route, with antibiotic delivery directly to the air/liquid interface in the lung. New and improved delivery devices have made it possible to administer precise doses of inhaled drugs, with pulmonary delivery of 50–70% of the nominal dose.<sup>1,2</sup> Compared to systemic routes of administration (both enteral and parenteral), inhalation achieves higher pulmonary concentrations of antibiotics,<sup>3,4</sup> with the potential to reduce systemic toxicity. In fact, sputum and lung tissue antibiotic levels achieved after inhalation are many-fold higher than those obtained after intravenous administration,<sup>3,4,5–9</sup> and they well exceed the minimum inhibitory concentration required for treatment of infection with most common organisms that cause tracheobronchitis or pneumonia.<sup>3,8,9</sup> The emergence of multiple-drug-resistant Gram-negative infections due to *Pseudomonas aeruginosa* or *Acinetobacter baumannii*<sup>10</sup> has provided further impetus to the use of inhaled antimicrobial therapy as an adjunct to systemic treatment. The publication of several comprehensive reviews within the past few years<sup>11–17</sup> reflects the renewed interest in inhaled antimicrobial therapy for treatment of pneumonia in critically ill patients.

Achieving adequate antimicrobial concentrations for sufficient duration is a prerequisite for successful treatment of pneumonia. Although effective antibiotic levels are achieved in the lung parenchyma after systemic administration, antibiotic penetration into the airway lumen and intraluminal secretions is limited.<sup>3,6,18,19</sup> Moreover, inhibitory factors could prevent eradication of organisms within intraluminal secretions.<sup>3,6</sup> A lingering infection/coloniza-

tion propagates an inflammatory response within the airways<sup>8,20</sup> that could damage the airway wall and lead to airway obstruction. Bacteria within the airway lumen also serve as a source for subsequent development of pneumonia and bacteremia. Thus, patients with cystic fibrosis (CF) (or bronchiectasis) have persistent colonization of the airways with Gram-negative organisms such as *P. aeruginosa*.<sup>21</sup> Long-term treatment of patients with CF with aerosolized tobramycin (TOBI, Novartis Pharmaceuticals, East Hanover, New Jersey) improves lung function, decreases density of *P. aeruginosa* in sputum, and reduces hospitalizations.<sup>22,23</sup> Despite an increase in the rate of resistant organisms with TOBI inhalation, compared to a placebo treated group, no significant clinical problems were observed in patients with CF.<sup>22,23</sup> Inhaled antimicrobial therapy was also employed for treatment in patients with non-CF bronchiectasis,<sup>24–27</sup> but the outcomes in this group were not as favorable as those in CF patients.

Microorganisms that cause pneumonia in mechanically ventilated patients are often similar to those encountered in patients with CF or bronchiectasis (eg, *Pseudomonas* species, *Acinetobacter* species, and methicillin-resistant *Staphylococcus aureus*),<sup>28,29</sup> and these may not be effectively treated with systemic antibiotic therapy alone.<sup>30–32</sup> Several investigators have studied the efficacy of inhaled antimicrobial therapy for prevention of ventilator-associated pneumonia (VAP),<sup>33–39</sup> and as an adjunct to systemic antibiotics for treatment of established VAP.<sup>40–44</sup> Although inhaled antibiotic therapy appears to be theoretically attractive and relatively straightforward, clinicians may not appreciate the many complexities of this form of therapy. For example, some earlier investigators simply instilled the antibiotics through the endotracheal tube (ETT)<sup>35,36</sup> or used intravenous formulations for inhalation.<sup>8,26,38,41</sup> Thus, several misconceptions about inhaled antimicrobial therapy arose from inadequate techniques employed in the past. This review discusses some of the complex factors that influence treatment of VAP with inhaled tobramycin and colistin. Specifically, the use of inhaled amphotericin B for prophylaxis of fungal pneumonia in neutropenic patients,<sup>45–47</sup> and inhaled pentamidine for the prophylaxis of pneumonia due to *Pneumocystis jirovecii*<sup>48,49</sup> are discussed elsewhere.

## Devices for Delivery of Inhaled Antimicrobial Agents

In mechanically ventilated patients, nebulizers have been the devices of choice for inhaled antimicrobial therapy. The poor efficiency of nebulizers to deliver aerosol to the lung periphery was a major limitation to their widespread use.<sup>50,51</sup> Considering the inefficiency of nebulizers in this setting, it was unclear if adequate drug deposition could be consistently achieved in the lung. Moreover, depending on the techniques employed for nebulization in their ventila-

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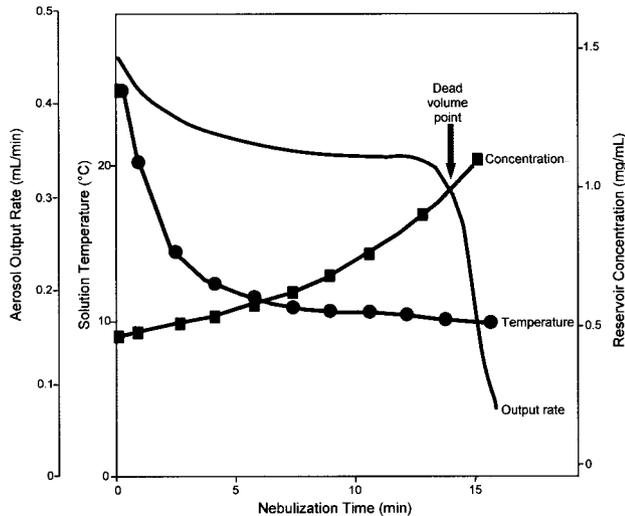


Fig. 1. Predicted nebulizer aerosol output, solution temperature, and drug concentration in the reservoir during jet nebulization. The data points are not derived from actual experiments with any particular jet nebulizer. (Adapted from Reference 65, with permission.)

tor-supported patients, Miller and colleagues<sup>52</sup> found a 20-fold variation in the antibiotic concentrations achieved in tracheal aspirates. Four major factors that influence nebulizer operation in intubated and mechanically ventilated patients are well known.<sup>2,53,54</sup> These factors include the mass output of the nebulizer, the aerosol particle size, the composition of the inhaled gas and breathing pattern, and the presence of lung disease. These factors are briefly discussed below.

### Jet Nebulizers

**Nebulizer Output.** Jet nebulizer output is affected by the fill volume,<sup>55–58</sup> airflow and pressure operating the nebulizer,<sup>58,59</sup> continuous or intermittent nebulization,<sup>52,57</sup> placement of the nebulizer in the ventilator circuit,<sup>60</sup> solution properties,<sup>59,61</sup> duration of treatment,<sup>55,58,62</sup> and use of a spacer.<sup>63</sup> A certain volume of solution (the dead or residual volume) fails to be nebulized in a jet nebulizer. The residual volume, which ranges from 1 mL to 3 mL, can be reduced by using a nebulizer that has a conical shape, by improving the wetness of the plastic surfaces, and by reducing the internal surface area of the nebulizer.<sup>64,65</sup> During operation of a jet nebulizer, the solution concentration increases and its temperature decreases secondary to evaporative losses (Fig. 1). The increased solution concentration and cooling both influence nebulizer output and particle size.<sup>64,65</sup>

**Aerosol Particle Size.** The optimal particle size for penetration of aerosols into the deeper parts of the lung is between 1  $\mu\text{m}$  and 5  $\mu\text{m}$ . Nebulizer design, solution char-

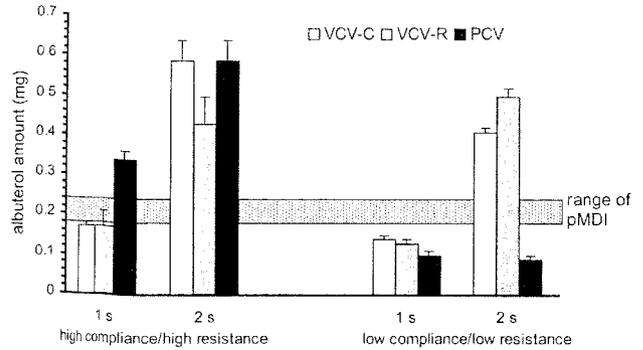


Fig. 2. Aerosol delivery from a metered-dose inhaler (MDI) versus from a jet nebulizer, in bench models of pressure-controlled and volume-controlled ventilation. The lung mechanics were varied by selecting 2 settings of resistance and compliance, which represent high and low time constants. For each condition the amount of aerosol delivered during inspiratory times of 1 s or 2 s were measured. The nebulizer efficiency was influenced by inspiratory time, pattern of inspiratory flow, and lung mechanics. In contrast, the efficiency with the MDI (stippled area) remained fairly constant under the various conditions simulated in the bench model. VCV-C = volume-controlled ventilation with a constant inspiratory flow. VCV-R = volume-controlled ventilation with a descending-ramp flow pattern. PCV = pressure-controlled ventilation. (From Reference 72, with permission.)

acteristics (density, viscosity, surface tension) and volume, gas pressure and flow, baffle design, and the ratio of liquid to gas flow influence aerosol particle size.<sup>66–68</sup> Droplet size decreases when gas flow increases, whereas droplet size increases with increase in the ratio of liquid to gas flow.

**Composition of Inhaled Gas and Ventilatory Parameters.** The presence of humidity in the circuit increases aerosol losses in the ventilator circuit and reduces drug delivery by 40% or more.<sup>52,55,69</sup> The density of the inhaled gas,<sup>70,71</sup> and ventilatory parameters<sup>72</sup> (Fig. 2) also influence drug delivery to the lung. The size of the ETT is not a significant barrier to aerosol delivery in adults, provided that the factors mentioned above are carefully considered and controlled during inhalation therapy.<sup>73</sup>

**Presence of Lung Disease.** The presence of lung disease significantly alters the deposition of aerosols in the lung.<sup>74,75</sup> The amount of drug deposition in the lung influences the clinical response. Iacono and colleagues<sup>76</sup> found that 6 months of aerosolized cyclosporine improved forced expiratory volume in the first second (FEV<sub>1</sub>) in patients with persistent acute rejection after lung transplantation, but patients who received < 20 mg of drug per allograft did not respond as well as those who received higher doses.<sup>76</sup>

The variability in performance of various nebulizers emphasizes the need for carefully controlling aerosol delivery

techniques, especially when drugs with a narrow safety margin are employed.<sup>77,78</sup> Important disadvantages of jet nebulizers are the requirement for a power source, inconveniently long treatment time, need for equipment setup and cleaning, and significant variations in the performance of various nebulizers, both within the same brand and across different brands.<sup>9,58,79–81</sup>

### Ultrasonic Nebulizers

**Nebulizer Output.** With ultrasonic nebulizers the source and flow of the gas used to carry the aerosol to the patient can influence droplet size and drug concentration. A low flow rate produces smaller particles and a higher concentration of aerosol, whereas a high flow rate yields larger droplets and a lower aerosol concentration. In some ultrasonic nebulizers, the solution to be nebulized is placed directly over the transducer, whereas in others there is a water couplant chamber between the transducer and the medication chamber.<sup>82</sup> Similar to jet nebulizers, the drug solution becomes more concentrated during operation; in contrast to jet nebulizers, however, the solution temperature increases by 10–15°C after 10 min of ultrasonic nebulization.<sup>66,83</sup> Most ultrasonic nebulizers have a higher rate of nebulization and a shorter operation time than jet nebulizers.

**Aerosol Particle Size.** In ultrasonic nebulizers, the aerosol particle size is inversely proportional to the piezoelectric crystal vibration frequency, and drug output is directly proportional to the amplitude of crystal vibration.<sup>65,82</sup> Generally, the aerosol particle size is larger with ultrasonic nebulizers than with jet nebulizers.

**Composition of Inhaled Gas and Ventilatory Parameters.** Kemming and co-workers<sup>84</sup> confirmed different rates of aerosol production with various ultrasonic nebulizers in a bench study of adult mechanical ventilation, and noted higher efficiency of ultrasonic nebulizers with volume-controlled ventilation than with pressure-controlled ventilation. Moreover, the settings of positive end-expiratory pressure and inspiratory flow did not influence drug delivery from an ultrasonic nebulizer, but prolonging the inspiratory time was noted to increase nebulizer output.<sup>85</sup>

**Presence of Lung Disease.** The influence of lung disease on drug deposition with ultrasonic nebulizers is similar to that with jet nebulizers.<sup>74,75</sup>

In an *in vitro* model of mechanical ventilation, commercially available ultrasonic nebulizers demonstrated poor efficiency (range 3.1 ± 0.3% to 10.1 ± 2.0%) in delivering <sup>99m</sup>technetium-labeled human serum albumin.<sup>86</sup> The efficiency of the nebulizers could also be improved by increasing the volume of the solution.<sup>86</sup> The cost and bulk

of ultrasonic nebulizers and their relative inefficiency in nebulizing drug suspensions are major limitations to their use, although ultrasonic nebulizers have been employed during mechanical ventilation.<sup>87,88</sup>

### Vibrating Mesh/Aperture Plate Nebulizers

Newer-generation nebulizers that employ a vibrating mesh or plate with multiple apertures to produce an aerosol<sup>89</sup> have a high rate of nebulization, with drug output 2–3 times higher than jet nebulizers.<sup>89–91</sup> Unlike in ultrasonic nebulizers, the temperature of the solution does not change during operation of a vibrating mesh nebulizer, and proteins and peptides can be nebulized with minimal risk of denaturation. The vibrating mesh nebulizers have several advantages over jet nebulizers, and they are likely to find increasing use for delivery of specific (nonbronchodilator) aerosols in ventilator-dependent patients.

### Efficiency of Drug Delivery

Bench studies with models that simulate clinical use,<sup>52,55,57,69,84–86</sup> gamma scintigraphy with radiolabeled drugs,<sup>92</sup> and pharmacokinetic studies<sup>93,94</sup> have been employed to characterize the efficiency of aerosol delivery devices in ventilator circuits. A “mass balance” technique uses matching ventilator circuits and ventilatory parameters to correlate the results of *in vitro* tests with those in patients receiving mechanical ventilation.<sup>52,57</sup> With continuously operating nebulizers, < 10% of the nominal dose is delivered to the lower respiratory tract. With specialty jet nebulizers that produce an aerosol with a high fine-particle fraction, and by optimizing ventilator settings, the efficiency of drug delivery to the lower respiratory tract could be twice as high (approximately 20% of the nominal dose or higher).<sup>8</sup> Comparable efficiency of drug delivery was achieved with an ultrasonic nebulizer (Siemens SUN) and a newer-generation vibrating aperture plate nebulizer (AeroNeb Pro).<sup>88</sup> Modern nebulizers have vastly improved the ability to deliver antibiotic therapy. Nebulizer delivery as high as 50–70% of the nominal dose of an antibiotic solution is achieved with the Pulmonary Drug Delivery System Clinical, a breath-synchronized version of the AeroNeb Pro.<sup>95</sup>

Palmer and colleagues<sup>8</sup> found that after administration of 800 mg of gentamicin every 8 hours with a nebulizer to intubated patients, the levels of gentamicin in sputum increased from a trough level of approximately 300 µg/mL to approximately 1,200 µg/mL post-therapy. The concentrations achieved are, however, dependent on the efficiency of the nebulizer employed.<sup>96</sup> Recently, Mercier and co-workers<sup>97</sup> compared the delivery of sulfite-free amikacin sulfate with AirLife Misty-Neb, AeroNeb Pro, and the Pulmonary Drug Delivery System. The Pulmonary Drug

Delivery System delivered a higher percentage of the nominal dose ( $51 \pm 11\%$ ) than did AeroNeb Pro ( $31 \pm 4\%$ ) or Misty-Neb ( $7 \pm 0.5\%$ ) to a filter placed distal to an ETT. Clearly, adequate amounts of antibiotics can be delivered to the lungs of mechanically ventilated patients with newer-generation nebulizers, and this should no longer be a limiting factor for inhalation therapy with antimicrobial agents.

A powder inhaler that employs PulmoSphere tobramycin (Nektar, Mountain View, California) is also being developed and shows higher pulmonary deposition than standard jet nebulizer.<sup>98</sup> However, powder inhalers have not been adapted for clinical use in mechanically ventilated patients.<sup>99</sup> Likewise, it would be impractical to use metered-dose inhalers to deliver the doses of antimicrobial agents employed in clinical practice.

### Methods to Enhance Aerosol Delivery

**Nonhumidified Circuits.** Heating and humidifying the gas in the ventilator circuit prevents drying of the airway mucosa. With jet nebulizers, humidification leads to an increased loss of aerosol in the ventilator circuit<sup>1,52,55,57</sup> and reduces drug delivery to the lower respiratory tract by 40% or more. The treatment interval may be 45 min up to an hour with some nebulizers, and inhaling dry gas for extended periods could lead to drying of the tracheal mucosa and inspissation of intraluminal secretions. Moreover, with careful attention to the technique of administration, the impact of humidity on drug delivery can be overcome by delivering a somewhat higher drug dose.<sup>1</sup> In addition, the impact of humidity may not be as significant with newer-generation nebulizers, such as the Pulmonary Drug Delivery System Clinical, compared to conventional jet nebulizers.

**Use of Helium-Oxygen Mixture.** Use of helium-oxygen mixture (heliox) instead of nitrogen-oxygen mixture reduces drug output from nebulizers.<sup>70,71</sup> To optimize drug delivery, a jet nebulizer should be operated with a nitrogen-oxygen mixture and the aerosol particles entrained in a circuit that contains helium-oxygen.<sup>71</sup> The use of heliox by this technique enhances drug delivery to the lung in mechanically ventilated patients.<sup>71,100</sup> Likewise, mechanically ventilated piglets with healthy lungs had lung tissue concentrations of ceftazidime that were 5–30-fold higher than intravenous administration, and were further increased by employing 65%/35% heliox as the operating gas.<sup>101</sup> However, in animals with experimental *P. aeruginosa* bronchopneumonia, lung tissue concentrations achieved after ventilation with helium-oxygen were no different than those achieved after ventilation with nitrogen-oxygen mixture.<sup>101</sup> Further studies are needed to examine the role of heliox in the delivery of inhaled antimicrobials in patients with VAP.

**Use of a Spacer.** The addition of a spacer in the inspiratory limb of the ventilator circuit improves the efficiency of aerosol delivery from both jet<sup>56,63</sup> and ultrasonic nebulizers.<sup>86</sup>

### Pulmonary Deposition and Systemic Bioavailability

#### Instillation

A few investigators avoided the use of nebulizers by directly instilling antimicrobials into the lungs via the endotracheal or tracheostomy tube.<sup>34–36,102,103</sup> The distribution of instilled antimicrobials in the lung is not known, but systemic drug concentrations were higher after instillation than after aerosolization.<sup>7,104</sup> In mechanically ventilated patients, Badia and colleagues<sup>105</sup> found that instillation of imipenem/cilastatin achieved higher concentrations in respiratory secretions than did nebulization. In contrast, tobramycin concentrations in respiratory secretions after instillation were similar to those after nebulization. These investigators noted that instillation of tobramycin could result in significant accumulation in patients with renal failure.<sup>105</sup> Another novel approach is to suspend the drug in a perfluorocarbon emulsion, and this technique could improve delivery of antimicrobials into poorly ventilated areas of pneumonia.<sup>106</sup> However, instillation of tobramycin as an adjunct to parenteral antibiotics did not produce any improvement in clinical outcomes among hospitalized patients.<sup>41</sup>

#### Inhalation

Delivery of drugs to the distal airways occurs more homogeneously with aerosolization<sup>107,108</sup> than after direct endotracheal instillation, even among patients with pneumonia.<sup>57,92</sup> In mechanically ventilated patients with nosocomial pneumonia, both nebulization and endotracheal administration achieved high bronchial concentrations of ceftazidime.<sup>7</sup> The bronchial concentrations of ceftazidime exceeded the minimum inhibitory concentration for 90% of the most important pathogens responsible for nosocomial infections for up to 12 hours after intravenous infusion and for up to 24 hours after endotracheal and aerosol administration.<sup>7</sup> However, sputum components may inhibit aminoglycoside activity (Figure 3). Tobramycin activity is inhibited by CF sputum, *P. aeruginosa* growth begins to be inhibited at 10 times the minimum inhibitory concentration, and colony-forming units start decreasing at 25 times the minimum inhibitory concentration.<sup>3</sup> Thus, relatively high concentrations of aminoglycosides are needed to reduce the density of *P. aeruginosa* in sputum and a higher mean peak concentration of the drug in sputum may provide greater efficacy.

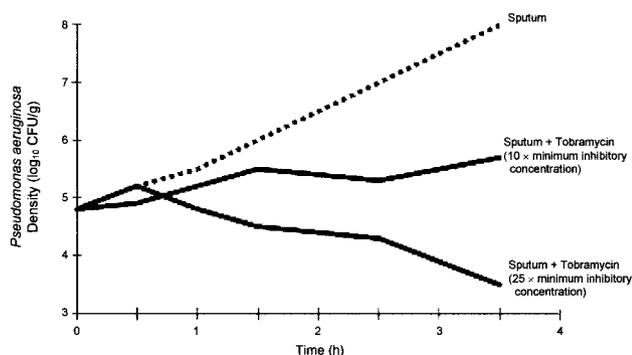


Fig. 3. Inhibition of in vitro tobramycin activity by sputum from cystic fibrosis patients. Tobramycin concentrations 25-fold higher than the minimum inhibitory concentration were required to produce a reliable bactericidal effect in the presence of sputum. CFU = colony-forming unit. (From Reference 3, with permission.)

Although high sputum levels of antibiotics are achieved after inhalation, these may not predict the actual lung deposition, especially in areas involved with pneumonia. Ilowite and colleagues<sup>109</sup> found a fair correlation of gentamicin sputum levels with lung deposition determined by scintigraphy; however, it is unclear if sputum levels predict the efficacy of inhaled antimicrobial treatment. In patients undergoing thoracic surgery, Le Conte and co-workers<sup>107</sup> found that nebulization of 300 mg of tobramycin prior to surgery produced lung tissue levels ( $5.5 \mu\text{g/g}$  after 4 h, and  $3.61 \mu\text{g/g}$  after 12 h) that were much higher than the serum levels. Further investigations along these lines are needed to develop uniform dosing strategies for nebulized antibiotics in patients with VAP.

Deposition in central airways is common in mechanically ventilated patients.<sup>50,57</sup> Moreover, significant deposition occurs in the ETT. Deposition on the internal surface of the ETT could be beneficial, as it prevents microbial biofilm formation on the internal surface of the tube.<sup>110</sup> In mechanically ventilated patients, antimicrobial deposition on the tube could remove one source of microorganisms that have the potential to cause pneumonia when they are displaced into the depths of the lung.<sup>110,111</sup> The presence of other lung diseases (eg, obstructive airway diseases) could also alter drug deposition, because drug deposition preferentially occurs in areas of airway obstruction.

In the past, variability in dosing was a problem with conventional nebulizers. In patients with CF, tobramycin via inhalation (300 mg twice a day for 28 d) with a single nebulizer/compressor combination produced a 3-log difference in sputum drug concentration.<sup>9</sup> In ventilator-dependent patients, variability of sputum levels could be reduced by controlling the breathing pattern.<sup>109</sup> Furthermore, a slow and deep breathing pattern could be used to enhance pulmonary deposition of the inhaled antimicrobial agent.

Significant systemic absorption of antibiotics occurs after inhalation. In mechanically ventilated patients, the systemic blood levels are due to antibiotic absorption from the lung, because the presence of an artificial airway precludes gastrointestinal absorption.<sup>93</sup> The systemic absorption of antibiotic may be increased in patients with VAP, because lung infection and inflammation increase the permeability of the alveolar capillary barrier.<sup>112</sup> Thus, in an experimental model of severe lung infection there was no difference in the plasma amikacin levels after intravenous or nebulizer administration of a 3-fold higher dose.<sup>113</sup> However, systemic antibiotic levels after inhalation are inadequate to treat systemic infection, which occurs frequently in patients with VAP.<sup>9,114,115</sup> Therefore, inhaled antimicrobials cannot be employed as sole agents to treat VAP, and their role is considered as an adjunct to treatment with systemic antibiotics. However, when highly efficient nebulizers are employed, high pulmonary deposition and significant absorption of antimicrobial agents from the lung have the potential to produce systemic toxicity in some patients.<sup>8</sup>

## Formulations

In the past, inhaled antibiotic solutions were made from intravenous formulations that contained preservatives such as phenol and bisulfites. These solutions were often hypertonic, their pH was not adjusted, and the preservatives mentioned above contributed to airway irritation, coughing, and bronchoconstriction. Although several antibiotics (tobramycin, colistin, gentamicin, amikacin, ceftazidime, neomycin, carbenicillin, amphotericin B, and pentamidine) have been administered via inhalation, this review will focus on inhaled tobramycin and colistin, because these 2 antibiotics have been specifically formulated in solutions for aerosolized delivery.

Aminoglycosides are recommended for aerosolized therapy because of their proven safety record,<sup>22,23</sup> concentration-dependent bactericidal effects, acceptable taste, and minimal systemic absorption after inhalation.<sup>9</sup> TOBI is tobramycin solution for inhalation. It is a sterile, preservative-free, nonpyrogenic solution with pH (6.0) and salinity adjusted for use with a nebulizer. Each 5-mL ampule contains 300 mg tobramycin. Following inhalation, tobramycin remains concentrated mainly in the airways. The drug achieves high concentrations in sputum but does not accumulate with long-term use.

Tobramycin has in vitro activity against a wide range of Gram-negative organisms, including *P. aeruginosa*, and it achieves a bactericidal effect in concentrations equal to or slightly greater than inhibitory concentrations. It is specially formulated for use with the Pari LC Plus reusable nebulizer (Pari, Midlothian, Virginia) and PulmoAide compressor (DeVilbiss, Jackson, Tennessee). The usual rec-

ommended dose is 300 mg twice a day, for both adults and children older than 6 years. TOBI should be given in alternating periods of 28 days, with a 28-day on/28-day off cycle.<sup>22</sup>

Inhaled tobramycin is generally well tolerated.<sup>22,23,116</sup> Patients receiving TOBI may experience hearing loss and even vestibular toxicity; however, voice changes and tinnitus are the common complaints. In the trial by Ramsey and colleagues,<sup>22</sup> patients who received TOBI experienced voice alteration (12.8% vs 6.5%, respectively) and tinnitus (3.1% vs 0%, respectively) more often than those who received placebo. The incidence of voice alteration declined over the period of the study.<sup>23</sup>

Colistin is available as colistin sodium or as the prodrug pentasodium colistinmethanesulfonate (also called colistimethate sodium or colistimethanesulfonate), which must be converted to its active form by hydrolysis in vitro and in vivo.<sup>117</sup> Colistin sulfate is usually used topically, and colistimethate sodium (150 mg colistin base activity per vial) is used for parenteral and aerosol therapy.<sup>118</sup> Colistimethate sodium is a polypeptide cationic antibiotic, and its surface active properties allow it to penetrate and disrupt the bacterial cell membrane. It has bactericidal activity against most strains of *Enterobacter aerogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, *P. aeruginosa*, and *A. baumannii*. *Stenotrophomonas maltophilia* strains are usually susceptible, whereas *Proteus* species, *Serratia* species, *Burkholderia* species, *Providencia* species, and *Edwardsiella* species are usually resistant to colistin.<sup>119</sup> Colistin may also neutralize lipopolysaccharide molecules of Gram-negative bacteria, and this property may confer some anti-endotoxin activity.<sup>120,121</sup> The bactericidal effect of colistin is concentration-dependent, and at high concentrations considerable post-antibiotic effects are observed.

The recommended dose of *intravenous* colistin base is 2.5–5 mg/kg/d, divided into 2 or 4 equal doses. However, there is a difference in the potency of the formulations in the United States and United Kingdom, and to avoid confusion in dosing, a system based on International Units (IU) is recommended.<sup>17</sup> Pure colistin base has a potency of 30,000 IU/mg. Promixin (Profile Therapeutics, United Kingdom), an *inhaled* formulation of colistin, is approved for treatment of CF in several European countries. The recommended dose for aerosolized colistimethate sodium in the United Kingdom is 40 mg (or 500,000 IU, 1 mg of this formulation is equivalent to 12,500 IU) every 12 hours for patients with body weight ≤ 40 kg.<sup>122</sup> The dose is doubled (80 mg or 1 million IU every 12 h) for patients with body weight > 40 kg, and could be increased to 160 mg (2 million IU) every 8 hours for patients with recurrent infections.<sup>122</sup>

Transient neurological disturbances (circumoral paresthesia, tingling, pruritis, vertigo, dizziness, and slurred speech) occur after colistin administration.<sup>123–125</sup> Nephro-

toxicity may occur and is probably dose-dependent.<sup>126,127</sup> Overdose may result in apnea and neuromuscular blockade.<sup>128</sup> For the reasons mentioned above, colistin should be used with caution in patients with impaired renal function, and in combination with aminoglycosides and polymyxin. Colistin is also known to produce bronchospasm.<sup>129</sup> Nebulization of colistimethate sodium is better tolerated and causes less bronchoconstriction than colistin sulfate.<sup>130</sup> Moreover, substantial foaming occurs during nebulization of colistin, which makes it difficult to aerosolize and to determine the exact dose of drug administered.<sup>131</sup> Thus, colistimethate sodium is preferred over colistin sulfate for inhalation therapy.

### Experimental Data

Clinical trials in patients with VAP are complicated by the difficulties involved in controlling a host of factors that could influence the outcomes of treatment. Data from experimental studies, in which the diagnosis of pneumonia is well established, the type of microorganism is known, and the timing and dose of antibiotic administration can be better controlled, could provide valuable insights for clinicians. Goldstein and colleagues found that lung deposition of nebulized amikacin was significantly greater in animals with healthy lungs than in animals with severe *E. coli* bronchopneumonia.<sup>113,132</sup> Moreover, amikacin was more homogeneously distributed in the lungs of healthy animals, compared to heterogeneous distribution in infected animals, and lung amikacin concentrations were lowest in the most severely affected dependent lung regions.<sup>113,132</sup> Loss of lung aeration had a differential effect on pulmonary amikacin concentrations after intravenous and aerosolized administration.

In mechanically ventilated piglets with experimentally-induced severe *E. coli* bronchopneumonia, amikacin tissue concentrations in the nebulized group were reduced, but they tended to increase in the intravenous group.<sup>133</sup> Increased tissue concentrations after intravenous administration are probably due to increased permeability of the alveolar-capillary barrier from severe lung infection, whereas bronchiolitis and mucus plugging could reduce nebulized lung delivery to the site of infection. Despite this discrepancy, lung amikacin concentrations were 3–30 times higher after nebulization than after intravenous therapy (Fig. 4). Moreover, lung tissue concentrations of amikacin were significantly higher in areas with early stages of bronchopneumonia than in segments with confluent bronchopneumonia and lung abscess.<sup>133</sup> No such differences occurred when amikacin was given intravenously. These data suggest that nebulized antibiotics may be most effective in the early stages of VAP.

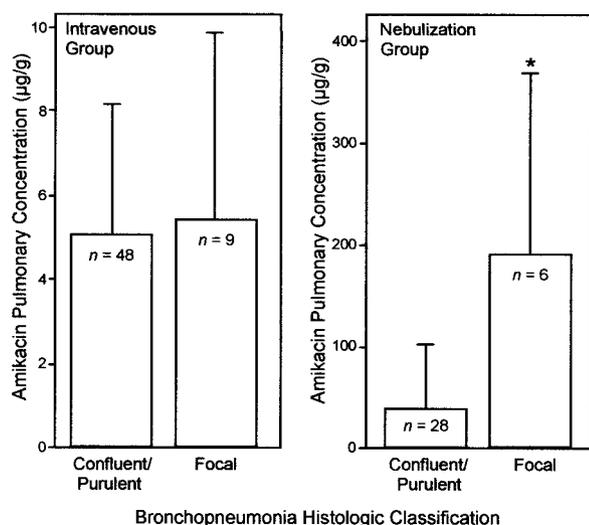


Fig. 4. Pulmonary amikacin concentration in lung areas with different severity of bronchopneumonia in mechanically ventilated piglets. Left: Amikacin lung concentration after 2 intravenous doses of 15 mg/kg, given 24 hours apart. Right: Amikacin lung concentration after 2 nebulized doses of 40 mg/kg, 24 hours apart. The nebulized doses were given via ultrasonic nebulizer. The error bars represent one standard deviation. The *n* values are the number of lung segments analyzed. The differences are not significant, except for the nebulization/focal group (\*  $p < 0.001$ ). Note the difference in the amikacin concentration in the 2 panels. (Adapted from data in Reference 133.)

## Clinical Studies

### Ventilator-Associated Pneumonia

Ventilator-associated pneumonia is undoubtedly one of the most important infections encountered in mechanically ventilated patients. Patients who develop pneumonia more than 48 hours after intubation are included under the broad umbrella of VAP.<sup>134</sup> Recognition of pneumonia could, however, pose problems in mechanically ventilated patients.<sup>134,135</sup> Most often the diagnosis is based on radiologic (a new infiltrate) and clinical features (fever, purulent tracheal secretions, and an elevated white-blood-cell count). Positive cultures of blood or pleural fluid that are identical to respiratory secretions, or histopathologic evidence of pneumonia help to confirm the diagnosis, but these are positive in the minority of patients.

VAP is common among mechanically ventilated patients.<sup>134</sup> VAP develops in approximately 20% of intubated and ventilated patients, and the prevalence increases with the duration of mechanical ventilation.<sup>136,137</sup> In the United States, approximately 300,000 patients develop VAP annually.<sup>138</sup> Not only is VAP a common infection, it also increases the risk of all-cause mortality by 2–2.5 times, compared to patients without VAP.<sup>139–142</sup> The crude mortality from VAP has been reported to be 20–70%, and the

mortality attributable to VAP could be as high as 50% of all patients who die with the infection.<sup>143</sup> The development of VAP is associated with longer duration of mechanical ventilation, intensive care unit (ICU) stay, and hospital stay, and higher cost.<sup>139–142</sup> In the setting of mechanical ventilation, inhaled antimicrobials have been employed to prevent the occurrence of VAP, to treat established VAP (as an adjunct to systemic antimicrobial therapy), to treat VAP due to multiple-drug-resistant organisms, and to treat tracheobronchitis in patients receiving long-term ventilation.

### Prevention of VAP

Prevention of VAP is of utmost importance, and there are several guidelines on methods to prevent its occurrence.<sup>144–146</sup> One of the 5 goals of the “Saving 100,000 Lives” campaign, launched by the Institute for Health Care Improvement (<http://www.ihc.org>), is to prevent VAP and deaths from VAP by implementing a set of interventions known as the “ventilator bundle.”<sup>147</sup> This bundle includes 4 components: elevation of the head end of the bed to 30–45°, daily interruption of sedation, daily assessment of readiness to extubate, and prophylaxis for deep venous thrombosis and peptic ulcer disease. The first 2 components of the bundle are specifically targeted at preventing VAP, and the latter 2 components are aimed at preventing other complications associated with mechanical ventilation. Moreover, the importance of hand hygiene in the prevention of infections in the ICU cannot be overemphasized.<sup>148</sup>

Oropharyngeal colonization with Gram-negative organisms is thought to be the precursor of pneumonia in ventilator-supported patients. Once established in the oropharynx, organisms gain entry to the lower respiratory tract by several mechanisms, including micro-aspiration around the low-pressure cuff of the ETT, along the artificial airway, or by gross aspiration of oropharyngeal secretions.<sup>134,149</sup> Other pathways for development of VAP include hematogenous spread of infection from elsewhere in the body, inhalation of biofilm lining the inner surface of the artificial airway, or spread of infection from the pleural space.<sup>134,144,149</sup> Attempts to reduce or prevent Gram-negative colonization have been ongoing for almost 50 years. The use of inhaled antimicrobials fell into disfavor after the publication of a study by Feeley and co-workers.<sup>36</sup> These investigators sprayed polymyxin B into the posterior pharynx every 4 hours in each and every patient, including nonintubated patients, admitted to their unit over a period of 7 months.<sup>36</sup> Although the incidence of pseudomonas pneumonia decreased, there was an increase in pneumonia with polymyxin-resistant organisms, which carried a high mortality.<sup>36</sup> Preventive use of inhaled antimicrobial

## AEROSOLIZED ANTIMICROBIALS IN VENTILATOR-ASSOCIATED PNEUMONIA

Table 1. Treatment of Pulmonary Infections With Inhaled Antimicrobials in Hospital Patients

First Author Year	No. of Patients	Study Design	Treatment	Route	Treatment Duration (d)	Clinical Outcomes
Klustersky <sup>151</sup> 1972	15	Randomized controlled	Gentamicin 40 mg every 3 h vs intramuscular gentamicin	Endotracheal	ND	Endotracheal cure rate superior to systemic (100% vs 25%, $p < 0.01$ )
Klustersky <sup>157</sup> 1979	38	Randomized placebo-controlled double-blind	Sisomicin 25 mg every 8 h vs placebo + systemic therapy	Endotracheal	7	Endotracheal cure rate superior to placebo (77% vs 45%, $p < 0.05$ )
Sorensen <sup>158</sup> 1986	5	Observational	Tobramycin 40 mg or amikacin 200 mg every 4 h + systemic therapy	Endotracheal	7	100% cure rate Patients had not responded to systemic therapy
Stoutenbeek <sup>40</sup> 1986	25	Observational	Cefotaxime or ceftazidime 50–100 mg/kg 4 times a day + systemic therapy and gut decontamination	Aerosolized	ND	97% cure rate
Brown <sup>41</sup> 1990	41	Randomized placebo-controlled double-blind	Tobramycin 40 mg every 8 h vs placebo + tobramycin intravenous + cefazolin/piperacillin	Catheter through endotracheal tube	$\geq 4$	No differences in clinical outcomes Pathogens eliminated in 56% with tobramycin vs 25% with placebo
Palmer <sup>8</sup> 1998	6	Observational	Gentamicin 80 mg or amikacin 400 mg every 8 h	Aerosolized	14–21	Decrease in volume of purulent secretions
LeConte <sup>107</sup> 1993	38	Randomized placebo-controlled	Tobramycin (6 mg/kg/d) once daily or placebo + systemic therapy	Aerosolized	5	Extubation on day 10 38% with tobramycin vs 18% with placebo 2 deaths with tobramycin vs 4 with placebo

ND = no data

therapy was thought to be harmful and was largely abandoned from clinical practice.

Of note, an earlier report by the same group of investigators in the same unit employed a randomized controlled design with a similar technique of polymyxin administration in over 700 patients.<sup>35</sup> The major difference between the 2 studies was that Klick and co-workers administered the polymyxin intermittently in 8-week cycles, alternating with 8 weeks of saline placebo.<sup>35</sup> These investigators observed a significant decrease in the incidence of pseudomonas pneumonia, without an increase in the incidence of pneumonia due to resistant organisms.<sup>35</sup>

Careful analysis of the 2 studies described above<sup>35,36</sup> reveals that the aerosol was sprayed into the posterior pharynx, and in intubated patients half the dose was instilled into the ETT. The drug concentrations achieved in the lung and the distribution of the antibiotic in the lung were not determined. Continuous use of the antibiotic,<sup>36</sup> but not intermittent administration,<sup>35</sup> was associated with emergence of drug resistance. Although intermittent use of antimicrobials did reduce the incidence of pseudomonas pneumonia, the lack of a change in overall mortality led to a rapid decline in interest in this approach to prevent VAP.

More recently, investigators found that inhaled tobramycin, ceftazidime, or colistin could reduce the occurrence of VAP without significant emergence of drug-resistant bacteria.<sup>33–38</sup> In a placebo-controlled study, inhaled ceftazidime (250 mg every 12 h for up to 7 d) reduced the number of cases of pneumonia on ICU day 14 and throughout the ICU stay.<sup>38</sup> Moreover, levels of inflammatory cytokines (tumor necrosis factor alpha [TNF- $\alpha$ ], interleukin-1 $\beta$  [IL-1 $\beta$ ], and IL-8) were significantly reduced by ceftazidime. A meta-analysis of 5 randomized controlled trials favored the use of inhaled antimicrobials as a means of preventing VAP, but the overall mortality was not reduced with this approach.<sup>39</sup> Therefore, most experts do not currently recommend the use of inhaled antimicrobials to prevent VAP.<sup>14,15,150</sup>

### Treatment of Established VAP

In non-CF patients with established VAP, the use of inhaled antibiotics has shown limited benefit.<sup>44,151</sup> The current approach to treatment of VAP recommends collection of microbiological specimens when VAP is suspected and the use of broad-spectrum antibiotic therapy to cover all

Table 2. Treatment With Inhaled Colistinmethanesulfonate for Infections Due to Multiresistant Gram-Negative Infections

First Author Year	Setting	Number of Patients	Mean Age (y)	Mean APACHE II Score	Dosage and/or Duration of Colistin	Sites of Infection	Pathogen	Mortality Rate (%)	Clinical Cure (%)
Michalopoulos <sup>44</sup> 2005	ICU	8	59.6	14.6	Range 1.5–6 MIU/d Mean duration 10.5 d	Pneumonia	7 <i>Acinetobacter baumannii</i> 1 <i>Pseudomonas aeruginosa</i>	12.5	87.5
Kwa <sup>68</sup> 2005	ICU, medical wards	21	60.6	23.1	2–4 MIU/d Median duration 14 d	Pneumonia	17 <i>Acinetobacter baumannii</i> 4 <i>Pseudomonas aeruginosa</i>	46.7	85.7
Berlana <sup>169</sup> 2005	ICU (84%) Medical (11%) Surgical (5%)	80 (85 courses: 71 aerosol, 12 I.V. or IM, 2 intrathecal)	57	ND	Mean aerosol 12 ± 8 d Mean I.V. or IM 11 ± 6 d Intrathecal: 8 d and 10 d	Pneumonia: 60 courses UTI: 2 courses Bacteremia: 2 courses Central nervous system infection: 2 courses	69 <i>Acinetobacter baumannii</i> 11 <i>Pseudomonas aeruginosa</i>	18	92 (microbiological cure)
Hamer <sup>167</sup> 2000	Medical wards	3	57	ND	2–5 MIU/d Mean duration 12.6 d	Pneumonia 2/3 patients Tracheobronchitis 1/3 patients	<i>Pseudomonas aeruginosa</i>	0	100

APACHE = Acute Physiology and Chronic Health Evaluation  
 ICU = intensive care unit  
 MIU = million international units  
 ND = no data  
 I.V. = intravenous  
 IM = intramuscular  
 UTI = urinary tract infection

likely pathogens.<sup>29</sup> Early administration of appropriate antibiotics improves the prognosis in patients with VAP,<sup>152–154</sup> but significant mortality occurs even in patients who receive early appropriate systemic antibiotic therapy and adequate supportive therapy.<sup>152,153,155,156</sup> Therefore, alternative methods of treatment, including inhaled antimicrobials, are being actively explored in an attempt to reduce VAP-associated mortality. Inhaled antimicrobials should not be employed as monotherapy for such serious infections, because bacteremia and systemic illness often accompany the pneumonia. Even as an adjunct to systemic antibiotic therapy, the role of inhaled antimicrobials is questionable at this time.<sup>13–15</sup>

During the past 35 years, a few investigators have reported on the efficacy of aminoglycosides administered via the ETT or as an aerosol to patients with severe Gram-negative bronchopneumonia (Table 1). The therapy was given alone or as a combination.<sup>40,151,157,158</sup> Stoutenbeek and colleagues<sup>40</sup> employed systemic and aerosolized antibiotics in combination with selective topical gastrointestinal decontamination in patients with pneumonia due to *Pseudomonas* species or *Enterobacteriaceae* species. They reported a clinical cure rate of 96%, without emergence of resistant organisms, which is an impressive result, considering the low treatment success rate in pneumonia caused by the organisms mentioned above.<sup>31,159</sup> The lack of a control group was a major drawback of this study.<sup>40</sup> Isolated case reports also reported successful treatment with endotracheally administered or aerosolized aminoglycosides in mechanically ventilated patients with pneumonia that did not respond to systemic therapy.<sup>158,160,161</sup> Another retrospective analysis, reported only in abstract form, described 12 ventilated patients with suspected *P. aeruginosa* pneumonia.<sup>162</sup> TOBI (300 mg twice a day) was administered for up to 14 days, in addition to intravenous ceftazidime, imipenem, or trovafloxacin. After TOBI, *P. aeruginosa* was either eradicated (10 patients) or its density markedly reduced (1 patient). Clinical improvement occurred in 8 patients, and no adverse local reactions were noted. These patients had a high mortality rate (8 of 12 patients), but none of the deaths were attributed to VAP.<sup>162</sup>

### Treatment of VAP Due to Multiple-Drug-Resistant Organisms

After the 1950s and 1960s, the clinical use of polymyxins was largely abandoned because of reports of excessive toxicity.<sup>123,124</sup> The recent resurgence of interest in colistin coincided with the emergence of multiple-drug-resistant strains of *P. aeruginosa* and *A. baumannii*. The increased prevalence of these organisms in the ICU poses a global threat because of the very high mortality rate associated

with these infections.<sup>159,163</sup> Parenteral or inhaled colistin has been employed as the last line of defense against these organisms. Several retrospective case series have reported on the use of *parenteral colistin* in the treatment of pneumonia and other serious infections in patients who did not have CF.<sup>125,128,164–166</sup> Despite the high severity of illness in the patients treated, these studies have shown a consistent clinical efficacy (> 50% efficacy in most studies), an acceptable toxicity profile, and the lack of emergence of colistin-resistant *P. aeruginosa* and *A. baumannii* strains.

The experience with *inhaled colistin* as an adjunct to parenteral antibiotics for treatment of VAP caused by multiple-drug-resistant Gram-negative microorganisms is even more limited than that with parenteral colistin (Table 2). In a retrospective analysis of 8 patients with pneumonia due to *A. baumannii* or *P. aeruginosa* (1 patient), administration of inhaled colistin (1.5 to 6 million IU/d in 3 or 4 divided doses) in addition to systemic antibiotic therapy (including parenteral colistin) for a mean of 10.5 days resulted in a higher cure rate (7 of 8 patients) than that achieved with parenteral colistin alone (30 of 45 patients, 67%).<sup>44</sup> However, the small number of patients was an important limitation, and the results were not statistically significant.<sup>44</sup> Hamer reported 2 patients with nosocomial pneumonia and 1 patient with tracheobronchitis due to multiple-drug-resistant *P. aeruginosa* who improved after supplemental therapy with inhaled colistin.<sup>167</sup>

Kwa and co-workers<sup>168</sup> reported successful outcome in 85.7% of patients after administration of 2–4 million IU of nebulized colistin in 21 patients with pneumonia due to *A. baumannii* and *P. aeruginosa* that was susceptible only to polymyxin. Likewise, Berlana and colleagues<sup>169</sup> studied 80 patients, most of whom were admitted in the ICU and had infections with *A. baumannii* (86%) or *P. aeruginosa* (14%). These investigators<sup>169</sup> administered colistin via aerosol (71 courses), parenterally (12 courses), or intratracheally (2 courses), but pneumonia was the most predominant infection (60 of 85 treatment courses). Microbiological cure was achieved in 92%, and 82% of the patients survived.<sup>169</sup>

Importantly, colistin-resistant isolates were not reported in these studies, even among patients with persistently positive cultures for *P. aeruginosa* or *A. baumannii*. Moreover, nephrotoxicity and neurotoxicity, which were major limiting factors to the use of colistin in the past, were not common, particularly among patients with normal renal function at baseline.<sup>170</sup> Thus, inhaled colistin could be employed in critically ill patients with multiple-drug-resistant Gram-negative pneumonia, provided that recommended dosages are used, renal function is closely monitored, and other potential nephrotoxic agents are avoided.

Table 3. Optimal Technique for Drug Delivery Via Jet Nebulizer in Ventilated Patients

1. Review order, identify patient, and assess need for bronchodilator.
2. Suction endotracheal and airway secretions.
3. Place drug in nebulizer to fill volume of 4–6 mL.
4. Place nebulizer in the inspiratory line 46 cm from the patient Y connector.
5. Turn off flow-by or continuous flow during nebulizer operation.
6. Remove HME from circuit (do not disconnect humidifier).
7. Set gas flow to nebulizer at 6–8 L/min.
  - a. Use a ventilator if it meets the nebulizer flow requirements and cycles on inspiration, or
  - b. Use continuous flow from external source.
8. Adjust ventilator volume or pressure limit to compensate for added flow.
9. Tap nebulizer periodically, until nebulizer begins to sputter.
10. Remove nebulizer from circuit, rinse with sterile water and dry, store in safe place.
11. Reconnect humidifier or HME, return ventilator settings and alarms to previous values.
12. Monitor patient for adverse response.
13. Assess outcome and document findings.

HME = heat-and-moisture exchanger (Adapted from Reference 171.)

### Treatment of Tracheobronchitis

Patients receiving long-term ventilation via tracheostomy often develop chronic tracheobronchitis, with production of excessive purulent secretions and Gram-negative organisms colonizing their airways, but they do not have pneumonia. Excessive secretions may prevent such patients from weaning. In such patients, Palmer and co-workers<sup>8</sup> found that administering aminoglycoside antibiotics via a specialty nebulizer (Aerotech II) produced high antibiotic levels in the sputum. Repeated administration of aminoglycoside antibiotics, with each course given for 5 days, significantly reduced Gram-negative organisms without increasing resistant organisms. Moreover, the levels of inflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , soluble intercellular adhesion molecule-1, and neutrophil elastase) decreased in parallel with reduction in sputum volume after administration of inhaled antimicrobials.<sup>8</sup> Another patient with *P. aeruginosa* tracheobronchitis was successfully treated with an 11-day course of inhaled colistin in combination with parenteral ceftazidime.<sup>167</sup> In patients with persistently increased respiratory secretions and antimicrobial colonization, inhaled antimicrobials could be employed to facilitate weaning from the ventilator.

### Technique of Administration

An optimal technique of administration is of utmost importance to ensure the success of inhaled antimicrobial

therapy. Adequate lung tissue concentrations can be achieved only by employing nebulizers with high output efficiency that produce an aerosol with an appropriate particle size, and by careful attention to other factors that influence drug deposition in the lung.<sup>1,2</sup> For conventional jet nebulizers, the optimal technique of administration is shown in Table 3.<sup>171</sup> For ultrasonic nebulizers and other newer-generation nebulizers, the technique of administration recommended by the manufacturer must be followed.

## Systemic Versus Inhaled Antimicrobials

### Systemic Antimicrobial Therapy

Parenteral administration of antimicrobials is a well established and clinically tested method of treating VAP. If adequate therapy is provided early in the infection, most patients are able to survive the infection. However, systemic therapy with antimicrobial agents has important drawbacks for treatment of VAP, as described below.

1. Considerable morbidity and mortality continue to occur as a result of VAP, despite widespread use of systemic antibiotics.<sup>139–142</sup> This may be due to lack of appropriate antibiotics, or inadequate dose or frequency of administration.<sup>152–154,172</sup>

2. Organisms develop resistance, and use of antibiotics with broad spectrum of susceptibility selects for multiple-drug-resistant organisms that are resistant to any drug that could be administered via the systemic route.<sup>173</sup>

3. The dose of systemic antibiotics is often limited by systemic toxicity.<sup>174</sup>

4. Penetration of antibiotics into the airway lumen and lung parenchyma is limited. Moreover, inhibitory factors in sputum could further limit the ability of antibiotics to kill microorganisms in sputum. After intravenous administration, the concentrations of antibiotics achieved in purulent sputum are much lower than the target level of 40–100 mg/L.<sup>3,6,18,19</sup>

5. The choice of antibiotics, the dosage employed, and other problems of administration may interfere with the ability of antibiotics to effectively treat pneumonia.<sup>29,172</sup>

### Inhaled Antimicrobials

The use of inhaled antimicrobials may appear relatively uncomplicated; however, several problems associated with their use are discussed below.

1. Penetration. The penetration of inhaled antimicrobials into infected tissues from the airway lumen is a concern. In normal lungs, inhaled antibiotics have shown good penetration. However, airflow may be preferentially directed away from areas of consolidated lung, and this may favor distribution of the antibiotic into areas of less involved lung parenchyma.<sup>113,133</sup> Although systemic absorp-

tion of the antibiotic occurs, the levels achieved are not adequate to treat infection in other parts of the body.<sup>4,107,114</sup> Thus, inhaled antimicrobials cannot be employed as sole agents to treat VAP, but only as an adjunct to systemic antibiotic therapy.

2. Inactivation by Inhibitors in Sputum. Sputum contains inhibitors that reduce antibiotic activity, with an increase in minimum inhibitory concentration for aminoglycosides to 10–25-fold higher than that observed *in vitro*.<sup>3,6</sup> Although high antibiotic concentrations are achieved in sputum after inhalation, organisms may remain protected from the antibiotic effects because they are bound in mucus where antibiotics may not have access.

3. Changes During Aerosolization. Solutions undergo changes during nebulization. Solutions in jet nebulizers undergo cooling and become more concentrated during nebulization.<sup>65</sup> Drugs, especially proteins, liposomes, and genes, could also be affected by shear stress during jet nebulization.<sup>175</sup> In contrast, solutions are heated during ultrasonic nebulizer operation.<sup>66,68,83</sup> The heat produced is proportional to the frequency of vibration, and, because high frequencies produce smaller particles, heat generation could be a problem with ultrasonic nebulizers designed to produce small particles.<sup>176</sup> This problem is much less pronounced with the newer generation of vibrating mesh or aperture plate nebulizers, which produce minimal heat during operation.<sup>89</sup>

4. Expense. Most aerosol delivery systems are expensive. High-efficiency systems are in clinical trials. Their ability to control dosage may be important. The amount of drug deposition in the lower respiratory tract has shown marked variation with devices employed in the past.<sup>9,96</sup> To avoid this variability, inhaled TOBI is marketed for use with the Pari LC Plus nebulizer and PulmoAide compressor. Other inhaled antimicrobials for clinical use may have to be similarly employed with specified delivery systems.

5. Emergence of Resistant Strains. VAP is usually due to a polymicrobial infection, and infecting organisms are phenotypically diverse. The multiple strains of organisms present in the airways may have different levels of antibiotic susceptibility, and emergence of resistant organisms is always of concern, especially with routine, long-term therapy.<sup>36</sup> Haphazard and unrestricted use of inhaled antimicrobials could be harmful by selecting for more resistant organisms that carry a high mortality.<sup>36</sup>

6. Local Toxicity. Adverse effects due to inhaled antimicrobials are mostly due to local effects on the airways and lung parenchyma, and they are of mild to moderate severity. Cough and bad taste are the commonly reported adverse effects.<sup>177,178</sup> Antibiotics for inhalation need to be specially formulated to prevent irritant effects. Thus, the osmolality, content of chloride ions, and pH have to be adjusted to prevent local irritant effects.<sup>179–181</sup>

7. Airway Narrowing. Preservatives in drug solutions, such as disodium ethylenediaminetetraacetic acid (EDTA) or benzalkonium chloride, may cause bronchoconstriction or airway hyperresponsiveness that may not be completely prevented by albuterol pretreatment.<sup>182–185</sup> The occurrence of bronchospasm is reduced, but not totally avoided, by using the preservative-free inhaled TOBI rather than the intravenous formulation.<sup>186,187</sup> Bronchospasm occurs after inhaled antimicrobials, especially after colistin administration,<sup>129,188</sup> and requires pretreatment with a short-acting bronchodilator, such as albuterol.<sup>189,190</sup> Bronchospasm in some patients with asthma may be refractory to albuterol.<sup>190</sup> In patients who are refractory or intolerant of albuterol, ipratropium inhalation is recommended.<sup>189,190</sup>

8. Systemic Effects. Nephrotoxicity<sup>191–193</sup> or neurotoxicity<sup>194</sup> are rare. Patients with renal failure who receive inhaled aminoglycosides require monitoring of serum aminoglycoside levels.<sup>8</sup>

9. Ventilator Adjustment. Adjustments in ventilator settings may be needed.<sup>195</sup> The humidifier should not be turned off.

10. Appropriate Cleaning and Storage. Careful attention needs to be given to maintaining sterility. Contamination of the nebulizer solution could lead to nosocomial pneumonia.<sup>196,197</sup>

11. Environmental Problems. Inhalation of aerosolized antimicrobials, particularly pentamidine and colistin, can cause adverse effects on health care workers.<sup>198</sup> Moreover, antibiotic aerosols in the environment have the potential to change the microbial flora, with selection of more antibiotic resistant pathogens.<sup>187</sup>

12. Unapproved Use. While inhaled antimicrobials add to the cost of treatment, the benefits of such treatment have not been clearly established. Moreover, the United States Food and Drug Administration has not yet approved the application of inhaled TOBI and colistin for treatment of VAP. Thus, the cost-efficacy of these drugs for treatment is not known and there are insufficient data to support their “off-label” use.

### Unresolved Questions

Several issues about the use of inhaled antimicrobials have not been satisfactorily addressed:

1. Which patients with VAP should receive inhaled antimicrobials? Should such treatment be applied as an adjunct to systemic treatment for all patients with VAP, those who develop VAP after more than 5 days of intubation, when the incidence of resistant organisms increases, or only those patients who develop pneumonia due to infection with multiple-drug-resistant organisms?

2. What is the optimal site of antibiotic delivery? In patients with CF, bronchial deposition of antimicrobials may suffice to reduce the density of *P. aeruginosa* in the

airway lumen. In contrast, patients with VAP may need more distal deposition of aerosol, and obstruction of the small airways by inflammation and cellular debris may hinder drug deposition in the distal lung parenchyma.

3. Which antimicrobial is best in terms of efficacy, safety, and lack of emergence of resistance? Several different antimicrobials have been employed, although formulations for inhalation are available only for tobramycin and colistin. In contrast to Gram-negative organisms, antimicrobial agents that kill Gram-positive organisms have not been commonly delivered via inhalation.

4. What is the optimal dose, frequency of use, and duration of treatment? It is unclear by what margin the local concentration of antibiotics needs to exceed the minimum inhibitory concentration of the pathogens, and whether the parenteral resistance breakpoint is relevant in the setting of inhaled antimicrobial therapy. Hence, precision of dosing is critical with inhaled antibiotic therapy.

5. Should therapy be guided by clinical or microbiological data (ie, culture negativity)? With nebulized antibiotics, samples obtained from the airways could show culture negativity while bacteria are still present in lung parenchyma.

To resolve these issues, large scale randomized placebo-controlled studies with well designed protocols, and clearly stated, clinically relevant outcomes are needed.

### Conclusion

In theory, the use of inhaled antimicrobial therapy could have several advantages for treatment of VAP; however, the use of such therapy in intubated and mechanically ventilated patients is beset with many problems. Despite the enhanced efficiency of newer-generation nebulizers to deliver aerosols to the lower respiratory tract in such patients, other problems, such as inadequacy of data on deposition and distribution, the risk of bacterial resistance, effects on the environment, and the lack of well-defined indications and end points for successful therapy are barriers to routine use of such treatment. Moreover, formulations for inhalation therapy are limited, and minimal data support the high cost of such therapies. Much more data on efficacy and safety of inhaled antimicrobial therapy in specified populations of patients with VAP are needed before such therapy could be recommended for routine clinical use.

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