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.

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.[1,2] Compared to systemic routes of administration (both enteral and parenteral), inhalation achieves higher pulmonary concentrations of antibiotics,[3,4] 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,[3,4,5–9] and they well exceed the minimum inhibitory concentration required for treatment of infection with most common organisms that cause tracheobronchitis or pneumonia.[3,8,9] The emergence of multiple-drug-resistant Gram-negative infections due to *Pseudomonas aeruginosa* or *Acinetobacter baumannii*[10] 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[11–17] 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.[3,6,18,19] Moreover, inhibitory factors could prevent eradication of organisms within intraluminal secretions.[3,6] A lingering infection/colonization propagates an inflammatory response within the airways[8,20] 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*.[21] 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.[22,23] 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.[22,23] Inhaled antimicrobial therapy was also employed for treatment in patients with non-CF bronchiectasis,[24–27] 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*),[28,29] and these may not be effectively treated with systemic antibiotic therapy alone.[30–32] Several investigators have studied the efficacy of inhaled antimicrobial therapy for prevention of ventilator-associated pneumonia (VAP),[33–39] and as an adjunct to systemic antibiotics for treatment of established VAP.[40–44] 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)[35,36] or used intravenous formulations for inhalation.[8,26,38,41] 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,[45–47] and inhaled pentamidine for the prophylaxis of pneumonia due to *Pneumocystis jiroveci*[48,49] 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.[50,51] 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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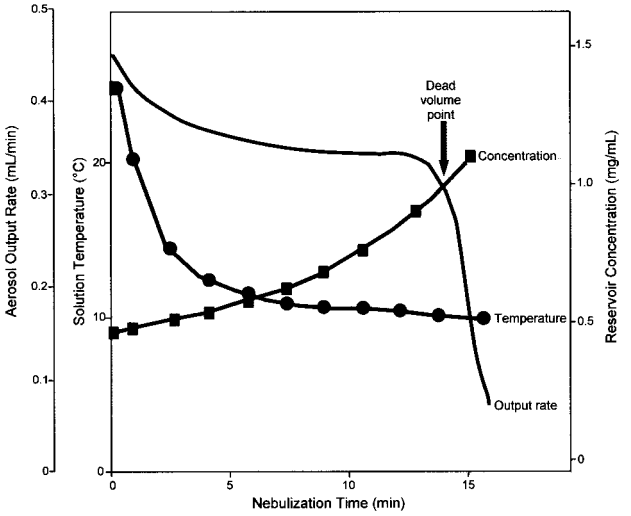

Fig. 1. Predicted nebulizer aerosol output, solution temperature, and drug concentration in the reservoir during jet nebulization. The data points are not derived from actual experiments with any particular jet nebulizer. (Adapted from Reference 65, with permission.)

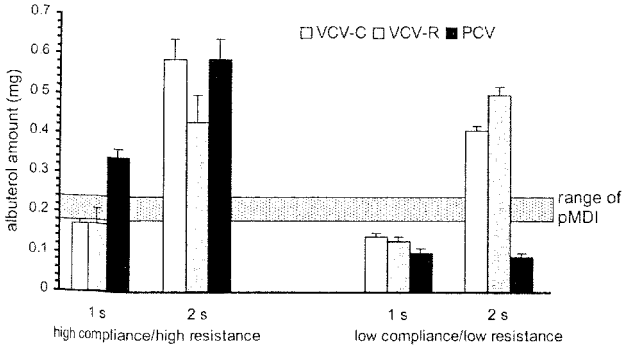

Fig. 2. Aerosol delivery from a metered-dose inhaler (MDI) versus from a jet nebulizer, in bench models of pressure-controlled and volume-controlled ventilation. The lung mechanics were varied by selecting 2 settings of resistance and compliance, which represent high and low time constants. For each 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.)

tor-supported patients, Miller and colleagues[52] 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.[2,53,54] 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,[55–58] airflow and pressure operating the nebulizer,[58,59] continuous or intermittent nebulization,[52,57] placement of the nebulizer in the ventilator circuit,[60] solution properties,[59,61] duration of treatment,[55,58,62] and use of a spacer.[63] 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.[64,65] 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.[64,65]

Aerosol Particle Size. The optimal particle size for penetration of aerosols into the deeper parts of the lung is between 1 μm and 5 μm. Nebulizer design, solution characteristics (density, viscosity, surface tension) and volume, gas pressure and flow, baffle design, and the ratio of liquid to gas flow influence aerosol particle size.[66–68] 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.[52,55,69] The density of the inhaled gas,[70,71] and ventilatory parameters[72] (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.[73]

Presence of Lung Disease. The presence of lung disease significantly alters the deposition of aerosols in the lung.[74,75] The amount of drug deposition in the lung influences the clinical response. Iacono and colleagues[76] found that 6 months of aerosolized cyclosporine improved forced expiratory volume in the first second (FEV_1) 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.[76]

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.[77,78] 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.[9,58,79–81]

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.[82] 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.[66,83] 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.[65,82] 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[84] 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.[85]

Presence of Lung Disease. The influence of lung disease on drug deposition with ultrasonic nebulizers is similar to that with jet nebulizers.[74,75]

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 ^{99m}technetium-labeled human serum albumin.[86] The efficiency of the nebulizers could also be improved by increasing the volume of the solution.[86] 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.[87,88]

Vibrating Mesh/Aperture Plate Nebulizers

Newer-generation nebulizers that employ a vibrating mesh or plate with multiple apertures to produce an aerosol[89] have a high rate of nebulization, with drug output 2–3 times higher than jet nebulizers.[89–91] 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,[52,55,57,69,84–86] gamma scintigraphy with radiolabeled drugs,[92] and pharmacokinetic studies[93,94] 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.[52,57] 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).[8] Comparable efficiency of drug delivery was achieved with an ultrasonic nebulizer (Siemens SUN) and a newer-generation vibrating aperture plate nebulizer (AeroNeb Pro).[88] 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.[95]

Palmer and colleagues[8] 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.[96] Recently, Mercier and co-workers[97] 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 ± 11%) than did AeroNeb Pro (31 ± 4%) or Misty-Neb (7 ± 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.[98] However, powder inhalers have not been adapted for clinical use in mechanically ventilated patients.[99] 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[1,52,55,57] 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.[1] 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.[70,71] 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.[71] The use of heliox by this technique enhances drug delivery to the lung in mechanically ventilated patients.[71,100] 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.[101] 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.[101] 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[56,63] and ultrasonic nebulizers.[86]

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.[34–36,102,103] The distribution of instilled antimicrobials in the lung is not known, but systemic drug concentrations were higher after instillation than after aerosolization.[7,104] In mechanically ventilated patients, Badia and colleagues[105] 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.[105] 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.[106] However, instillation of tobramycin as an adjunct to parenteral antibiotics did not produce any improvement in clinical outcomes among hospitalized patients.[41]

Inhalation

Delivery of drugs to the distal airways occurs more homogenously with aerosolization[107,108] than after direct endotracheal instillation, even among patients with pneumonia.[57,92] In mechanically ventilated patients with nosocomial pneumonia, both nebulization and endotracheal administration achieved high bronchial concentrations of ceftazidime.[7] 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.[7] 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.[3] 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.

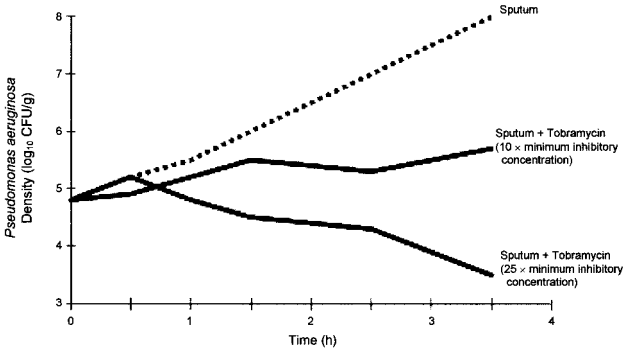

Fig. 3. Inhibition of in vitro tobramycin activity by sputum from cystic fibrosis patients. Tobramycin concentrations 25-fold higher than the minimum inhibitory concentration were required to produce a reliable bactericidal effect in the presence of sputum. CFU = colony-forming unit. (From Reference 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[109] 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[107] found that nebulization of 300 mg of tobramycin prior to surgery produced lung tissue levels (5.5 μg/g after 4 h, and 3.61 μg/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.[50,57] 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.[110] 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.[110,111] 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.[9] In ventilator-dependent patients, variability of sputum levels could be reduced by controlling the breathing pattern.[109] 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.[93] 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.[112] 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.[113] However, systemic antibiotic levels after inhalation are inadequate to treat systemic infection, which occurs frequently in patients with VAP.[9,114,115] 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.[8]

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,[22,23] concentration-dependent bactericidal effects, acceptable taste, and minimal systemic absorption after inhalation.[9] 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.[22]

Inhaled tobramycin is generally well tolerated.[22,23,116] 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,[22] 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.[23]

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.[117] Colistin sulfate is usually used topically, and colistimethate sodium (150 mg colistin base activity per vial) is used for parenteral and aerosol therapy.[118] 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.[119] Colistin may also neutralize lipopolysaccharide molecules of Gram-negative bacteria, and this property may confer some anti-endotoxin activity.[120,121] 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.[17] 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 $\leq$ 40 kg.[122] 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.[122]

Transient neurological disturbances (circumoral paresthesia, tingling, pruritis, vertigo, dizziness, and slurred speech) occur after colistin administration.[123–125] Nephrotoxicity may occur and is probably dose-dependent.[126,127] Overdose may result in apnea and neuromuscular blockade.[128] 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.[129] Nebulization of colistimethate sodium is better tolerated and causes less bronchoconstriction than colistin sulfate.[130] Moreover, substantial foaming occurs during nebulization of colistin, which makes it difficult to aerosolize and to determine the exact dose of drug administered.[131] 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.[113,132] Moreover, amikacin was more homogenously 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.[113,132] 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.[133] 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.[133] 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.

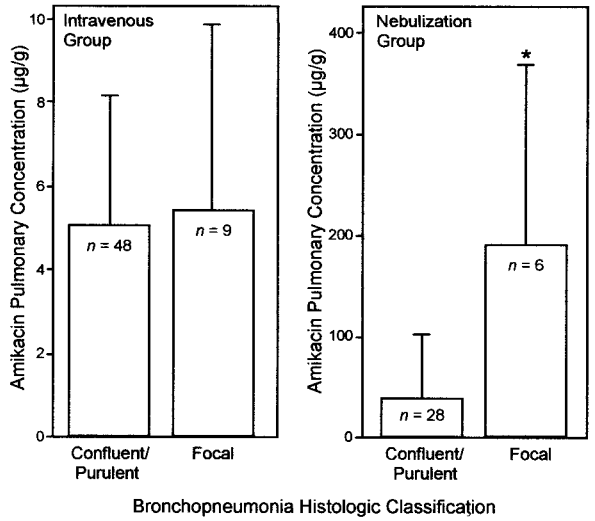

Fig. 4. Pulmonary amikacin concentration in lung areas with different severity of bronchopneumonia in mechanically ventilated piglets. Left: Amikacin lung concentration after 2 intravenous doses of 15 mg/kg, given 24 hours apart. Right: Amikacin lung concentration after 2 nebulized doses of 40 mg/kg, 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.[134] Recognition of pneumonia could, however, pose problems in mechanically ventilated patients.[134,135] 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.[134] VAP develops in approximately 20% of intubated and ventilated patients, and the prevalence increases with the duration of mechanical ventilation.[136,137] In the United States, approximately 300,000 patients develop VAP annually.[138] 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.[139–142] 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.[143] The development of VAP is associated with longer duration of mechanical ventilation, intensive care unit (ICU) stay, and hospital stay, and higher cost.[139–142] 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.[144–146] One of the 5 goals of the "Saving 100,000 Lives" campaign, launched by the Institute for Health Care Improvement (http://www.ihi.org), is to prevent VAP and deaths from VAP by implementing a set of interventions known as the "ventilator bundle."[147] 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.[148]

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.[134,149] 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.[134,144,149] 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.[36] 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.[36] Although the incidence of pseudomonas pneumonia decreased, there was an increase in pneumonia with polymyxin-resistant organisms, which carried a high mortality.[36] Preventive use of inhaled antimicrobial

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
Klastersky[151] 1972	15	Randomized controlled	Gentamicin 40 mg every 3 h vs intramuscular gentamicin	Endotracheal	ND	Endotracheal cure rate superior to systemic (100% vs 25%, $p < 0.01$)
Klastersky[157] 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[158] 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[40] 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[41] 1990	41	Randomized placebo-controlled double-blind	Tobramycin 40 mg every 8 h vs placebo + tobramycin intravenous + cefazolin/piperacillin	Catheter through endotracheal tube	≥ 4	No differences in clinical outcomes Pathogens eliminated in 56% with tobramycin vs 25% with placebo
Palmer[8] 1998	6	Observational	Gentamicin 80 mg or amikacin 400 mg every 8 h	Aerosolized	14–21	Decrease in volume of purulent secretions
LeConte[107] 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.[35] 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.[35] These investigators observed a significant decrease in the incidence of pseudomonas pneumonia, without an increase in the incidence of pneumonia due to resistant organisms.[35]

Careful analysis of the 2 studies described above[35,36] 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,[36] but not intermittent administration,[35] 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.[33–38] 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.[38] Moreover, levels of inflammatory cytokines (tumor necrosis factor alpha [TNF-α], interleukin-1β [IL-1β], 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.[39] Therefore, most experts do not currently recommend the use of inhaled antimicrobials to prevent VAP.[14,15,150]

Treatment of Established VAP

In non-CF patients with established VAP, the use of inhaled antibiotics has shown limited benefit.[44,151] 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[44] 2005	ICU	8	59.6	14.6	Range 1.5–6 MIU/d Mean duration 10.5 d	Pneumonia	7 *Acinetobacter baumanii* 1 *Pseudomonas aeruginosa*	12.5	87.5
Kwa[168] 2005	ICU, medical wards	21	60.6	23.1	2–4 MIU/d Median duration 14 d	Pneumonia	17 *Acinetobacter baumanii* 4 *Pseudomonas aeruginosa*	46.7	85.7
Berlana[169] 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 *Acinetobacter baumanii* 11 *Pseudomonas aeruginosa*	18	92 (microbiological cure)
Hamer[167] 2000	Medical wards	3	57	ND	2–5 MIU/d Mean duration 12.6 d	Pneumonia 2/3 patients Tracheobronchitis 1/3 patients	*Pseudomonas aeruginosa*	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.[29] Early administration of appropriate antibiotics improves the prognosis in patients with VAP,[152–154] but significant mortality occurs even in patients who receive early appropriate systemic antibiotic therapy and adequate supportive therapy.[152,153,155,156] 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.[13–15]

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.[40,151,157,158] Stoutenbeek and colleagues[40] 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.[31,159] The lack of a control group was a major drawback of this study.[40] 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.[158,160,161] Another retrospective analysis, reported only in abstract form, described 12 ventilated patients with suspected *P. aeruginosa* pneumonia.[162] 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.[162]

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.[123,124] 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.[159,163] 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.[125,128,164–166] 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%).[44] However, the small number of patients was an important limitation, and the results were not statistically significant.[44] 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.[167]

Kwa and co-workers[168] 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[169] studied 80 patients, most of whom were admitted in the ICU and had infections with *A. baumannii* (86%) or *P. aeruginosa* (14%). These investigators[169] administered colistin via aerosol (71 courses), parenterally (12 courses), or intrathecally (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.[169]

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.[170] 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 coworkers[8] 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-α, IL-1β, soluble intercellular adhesion molecule-1, and neutrophil elastase) decreased in parallel with reduction in sputum volume after administration of inhaled antimicrobials.[8] Another patient with *P. aeruginosa* tracheobronchitis was successfully treated with an 11-day course of inhaled colistin in combination with parenteral ceftazidime.[167] 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.[1,2] For conventional jet nebulizers, the optimal technique of administration is shown in Table 3.[171] 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.[139–142] This may be due to lack of appropriate antibiotics, or inadequate dose or frequency of administration.[152–154,172]

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.[173]

3. The dose of systemic antibiotics is often limited by systemic toxicity.[174]

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.[3,6,18,19]

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

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.[113,133] Although systemic absorp-

tion of the antibiotic occurs, the levels achieved are not adequate to treat infection in other parts of the body.[4,107,114] 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.[3,6] 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.[65] Drugs, especially proteins, liposomes, and genes, could also be affected by shear stress during jet nebulization.[175] In contrast, solutions are heated during ultrasonic nebulizer operation.[66,68,83] 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.[176] This problem is much less pronounced with the newer generation of vibrating mesh or aperture plate nebulizers, which produce minimal heat during operation.[89]

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.[9,96] 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.[36] Haphazard and unrestricted use of inhaled antimicrobials could be harmful by selecting for more resistant organisms that carry a high mortality.[36]

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.[177,178] 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.[179–181]

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.[182–185] The occurrence of bronchospasm is reduced, but not totally avoided, by using the preservative-free inhaled TOBI rather than the intravenous formulation.[186,187] Bronchospasm occurs after inhaled antimicrobials, especially after colistin administration,[129,188] and requires pretreatment with a short-acting bronchodilator, such as albuterol.[189,190] Bronchospasm in some patients with asthma may be refractory to albuterol.[190] In patients who are refractory or intolerant of albuterol, ipratropium inhalation is recommended.[189,190]

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

9. Ventilator Adjustment. Adjustments in ventilator settings may be needed.[195] 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.[196,197]

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

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.

REFERENCES

1. Dhand R. Bronchodilator therapy, 2nd ed. In: Tobin M. Principles and practice of mechanical ventilation. New York: McGraw Hill; 2006:1277–1310.
2. Dhand R, Mercier E. Effective inhaled drug administration to mechanically ventilated patients. Expert Opin Drug Deliv 2007;4(1): 47–61.
3. Mendelman PM, Smith AL, Levy J, Weber A, Ramsey B, Davis RL. Aminoglycoside penetration, inactivation, and efficacy in cystic fibrosis sputum. Am Rev Respir Dis 1985;132(4):761–765.
4. Eisenberg J, Pepe M, Williams-Warren J, Vasiliev M, Montgomery AB, Smith AL, Ramsey BW. A comparison of peak sputum tobramycin concentration in patients with cystic fibrosis using jet and ultrasonic nebulizer systems. Aerosolized Tobramycin Study Group. Chest 1997;111(4):955–962.
5. Odio W, Van Laer E, Klastersky J. Concentrations of gentamicin in bronchial secretions after intramuscular and endotracheal administration. J Clin Pharmacol 1975;15(7):518–524.
6. Levy J, Smith AL, Kenny MA, Ramsey B, Schoenknecht FD. Bioactivity of gentamicin in purulent sputum from patients with cystic fibrosis or bronchiectasis: comparison with activity in serum. J Infect Dis 1983;148(6):1069–1076.
7. Bressolle F, de la Coussaye JE, Ayoub R, Fabre D, Gomeni R, Saissi G, et al. Endotracheal and aerosol administration of ceftazidime in patients with nosocomial pneumonia: pharmacokinetics and absolute bioavailability. Antimicrob Agents Chemother 1992; 36(7):1404–1411
8. Palmer LB, Smaldone GC, Simon SR, O'Riordan TG, Cuccia A. Aerosolized antibiotics in mechanically ventilated patients: delivery and response. Crit Care Med 1998;26(1):31–39.
9. Geller DE, Pitlick WH, Nardella PA, Tracewell WG, Ramsey BW. Pharmacokinetics and bioavailability of aerosolized tobramycin in cystic fibrosis. Chest 2002;122(1):219–226.
10. Jones RN. Resistance patterns among nosocomial pathogens: trends over the past few years. Chest 2001;119(2 Suppl):397S-404S.
11. Wood CG, Boucher BA. Aerosolized antimicrobial therapy in acutely ill patients. Pharmacotherapy 2000;20(2):166–181.
12. Cole PJ. The role of nebulized antibiotics in treating serious respiratory infections. J Chemother 2001;13(4):354–362.
13. Klepser ME. Role of nebulized antibiotics for the treatment of respiratory infections. Curr Opin Infect Dis 2004;17(2):109–112.
14. Lesho E. Role of inhaled antibacterials in hospital-acquired and ventilator-associated pneumonia. Expert Rev Anti Infect Ther 2005; 3(3):445–451.
15. Hagerman JK, Hancock KE, Klepser ME. Aerosolised antibiotics: a critical appraisal of their use. Expert Opin Drug Deliv 2006;3(1): 71–86.
16. Linden PK, Paterson DL. Parenteral and inhaled colistin for treatment of ventilator-associated pneumonia. Clin Infect Dis 2006;43 Suppl 2:S89-S94.
17. Falagas ME, Kasiakou SK, Tsiodras S, Michalapoulos A. The use of intravenous and aerosolized polymyxins for the treatment of infections in critically ill patients: a review of the recent literature. Clin Med Res 2006;4(2):138–146.
18. Pennington JE. Penetration of antibiotics into respiratory secretions. Rev Infect Dis 1981;3(1):67–73.
19. Valcke Y, Pauwels R, Van der Straeten M. Pharmacokinetics of antibiotics in the lungs. Eur Respir J 1990;3(6):715–722.
20. Palmer LB, Smaldone GC, Simon S, O'Riordan T, Morra L. Tracheal aspirates in long-term mechanically ventilated patients: a human model of gram-negative infection and airway inflammation. Chest 1995;108(5):1326–1332.
21. Robinson P. Cystic fibrosis. Thorax 2001;56(3):237–241.
22. Ramsey BW, Pepe MS, Quan JM, Otto KL, Montgomery AB, Williams-Warren J, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. N Engl J Med 1999;340(1):23–30.
23. Moss RB. Administration of aerosolized antibiotics in cystic fibrosis patients. Chest 2001;120(3 Suppl):107S–113S.
24. Orriols R, Roig J, Ferrer J, Sampol G, Rosell A, Ferrer A, Vallano A. Inhaled antibiotic therapy in non-cystic fibrosis patients with

bronchiectasis and chronic bronchial infection by *Pseudomonas aeruginosa*. Respir Med 1999;93(7):476–480.
25. Barker AF, Couch L, Fiel SB, Gotfried MH, Ilowite J, Meyer KC, et al. Tobramycin solution for inhalation reduces sputum *Pseudomonas aeruginosa* density in bronchiectasis. Am J Respir Crit Care Med 2000;162(2 Pt 1):481–485.
26. Drobnic ME, Sune P, Montoro JB, Ferrer A, Orriols R. Inhaled tobramycin in non-cystic fibrosis patients with bronchiectasis and chronic bronchial infection with *Pseudomonas aeruginosa*. Ann Pharmacother 2005;39(1):39–44.
27. Scheinberg P, Shore E. A pilot study of the safety and efficacy of tobramycin solution for inhalation in patients with severe bronchiectasis. Chest 2005;127(4):1420–1426.
28. Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in medical intensive care units in the United States. National Nosocomial Infections Surveillance System. Infect Control Hosp Epidemiol 2000;21(8):510–515.
29. American Thoracic Society: Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171(4):388–416.
30. Jimenez P, Torres A, Rodriguez-Roisin R, de la Bellacasa JP, Aznar R, Gatell JM, Agusti-Vidal A. Incidence and etiology of pneumonia acquired during mechanical ventilation. Crit Care Med 1989; 17(9):882–885.
31. Crouch Brewer S, Wunderink RG, Jones CB, Leeper KV Jr. Ventilator-associated pneumonia due to *Pseudomonas aeruginosa*. Chest 1996;109(4):1019–1029.
32. Rello J, Ausina V, Ricart M, Castella J, Prats G. Impact of previous antimicrobial therapy on the etiology and outcome of ventilator-associated pneumonia. Chest 1993;104(4):1230–1235
33. Greenfield S, Teres D, Bushnell LS, Hedley-Whyte J, Feingold DS. Prevention of gram-negative bacillary pneumonia using aerosol polymyxin as prophylaxis. I. Effect on the colonization pattern of the upper respiratory tract of seriously ill patients. J Clin Invest 1973; 52(11):2935–2940.
34. Klastersky J, Huysmans E, Weerts D, Hensgens C, Daneau D. Endotracheally administered gentamicin for the prevention of infections of the respiratory tract in patients with tracheostomy: a double-blind study. Chest 1974;65(6):650–654.
35. Klick JM, du Moulin GC, Hedley-Whyte J, Teres D, Bushnell LS, Feingold DS. Prevention of gram-negative bacillary pneumonia using polymyxin aerosol as prophylaxis. II. Effect on the incidence of pneumonia in seriously ill patients. J Clin Invest 1975;55(3):514–519.
36. Feeley TW, Du Moulin GC, Hedley-Whyte J, Bushnell LS, Gilbert JP, Feingold DS. Aerosol polymyxin and pneumonia in seriously ill patients. N Engl J Med 1975;293(10):471–475.
37. Lode H, Hoffken G, Kemmerich B, Schaberg T. Systemic and endotracheal antibiotic prophylaxis of nosocomial pneumonia in ICU. Intensive Care Med 1992;18 Suppl 1:S24–S27.
38. Wood GC, Boucher BA, Croce MA, Hanes SD, Herring VL, Fabian TC. Aerosolized ceftazidime for prevention of ventilator-associated pneumonia and drug effects on the proinflammatory response in critically ill trauma patients. Pharmacotherapy 2002;22(8):972–982.
39. Falagas ME, Siempos II, Bliziotis IA, Michalopoulos A. Administration of antibiotics via the respiratory tract for the prevention of ICU-acquired pneumonia: a meta-analysis of comparative trials. Crit Care 2006;10(4):R123.
40. Stoutenbeek CP, van Saene HK, Miranda DR, Zandstra DF, Langrehr D. Nosocomial gram-negative pneumonia in critically ill patients: a 3-year experience with a novel therapeutic regimen. Intensive Care Med 1986;12(6):419–423.
41. Brown RB, Kruse JA, Counts GW, Russell JA, Christou NV, Sands ML. Double blind study of endotracheal tobramycin in the treatment of gram-negative bacterial pneumonia. The Endotracheal Tobramycin Study Group. Antimicrob Agents Chemother 1990;34(2): 269–272.
42. Le Conte P, Potel G, Clementi E, Legras A, Villers D, Bironneau E, et al. [Administration of tobramycin aerosols in patients with nosocomial pneumonia: a preliminary study.] Presse Med 2000; 29(2):76–78. *(article in French)*
43. Sobieszczyk ME, Furuya EY, Hay CM, Pancholi P, Della-Latta P, Hammer SM, Kubin CJ. Combination therapy with polymyxin B for the treatment of multidrug-resistant Gram-negative respiratory tract infections. J Antimicrob Chemother 2004;54(2):566–569.
44. Michalopoulos A, Kasiakou SK, Mastora Z, Rellos K, Kapaskelis AM, Falagas ME. Aerosolized colistin for the treatment of nosocomial pneumonia due to multidrug-resistant Gram-negative bacteria in patients without cystic fibrosis. Crit Care 2005;9(1):R53–R59.
45. Reichenspurner H, Gamberg P, Nitschke M, Valantine H, Hunt S, Oyer PE, Reitz BA. Significant reduction in the number of fungal infections after lung-, heart-lung, and heart transplantation using aerosolized amphotericin B prophylaxis. Transplant Proc 1997; 29(1–2):627–628.
46. Schwartz S, Behre G, Heinemann V, Wandt H, Schilling E, Arning M, et al. Aerosolized amphotericin B inhalations as prophylaxis of invasive *aspergillus* infection during prolonged neutropenia: results of a prospective randomized multicenter trial. Blood 1999;93(11): 3654–3661.
47. Drew RH, Dodds Ashley E, Benjamin DK Jr, Duane Davis R, Palmer SM, Perfect JR. Comparative safety of amphotericin B lipid complex and amphotericin B deoxycholate as aerosolized antifungal prophylaxis in lung-transplant recipients. Transplantation 2004; 77(2):232–237.
48. Leoung GS, Feigal DW Jr, Montgomery AB, Corkery K, Wardlaw L, Adams M, et al. Aerosolized pentamidine for prophylaxis against *Pneumocystis carinii* pneumonia. The San Francisco community prophylaxis trial. N Engl J Med 1990;323(12):769–775.
49. US Public Health Service (USPHS); Infectious Diseases Society of America (IDSA); USPHS/IDSA Prevention of Opportunistic Infections Working Group. 2001 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons with human immunodeficiency virus. HIV Clin Trials 2001;2(6):493–554.
50. MacIntyre NR, Silver RM, Miller CW, Schuler F, Coleman RE. Aerosol delivery in intubated, mechanically ventilated patients. Crit Care Med 1985;13(2):81–84.
51. Fuller HD, Dolovich MB, Posmituck G, Pack WW, Newhouse MT. Pressurized aerosol versus jet aerosol delivery to mechanically ventilated patients: comparison of dose to the lungs. Am Rev Respir Dis 1990;141(2):440–444.
52. Miller DD, Amin MM, Palmer LB, Shah AR, Smaldone GC. Aerosol delivery and modern mechanical ventilation: in vitro/in vivo evaluation. Am J Respir Crit Care Med 2003;168(10):1205–1209.
53. Dhand R, Tobin MJ. Inhaled bronchodilator therapy in mechanically ventilated patients. Am J Respir Crit Care Med 1997;156(1): 3–10.
54. Dhand R. Basic techniques for aerosol delivery during mechanical ventilation. Respir Care 2004;49(6):611–622.
55. O'Riordan TG, Greco MJ, Perry RJ, Smaldone GC. Nebulizer function during mechanical ventilation. Am Rev Respir Dis 1992;145(5): 1117–1122.
56. O'Doherty MJ, Thomas SH, Page CJ, Treacher DF, Nunan TO. Delivery of a nebulized aerosol to a lung model during mechanical ventilation: effect of ventilator settings and nebulizer type, position, and volume of fill. Am Rev Respir Dis 1992;146(2):383–388.

57. O'Riordan TG, Palmer LB, Smaldone GC. Aerosol deposition in mechanically ventilated patients: optimizing nebulizer delivery. Am J Respir Crit Care Med 1994;149(1):214–219.
58. Hess D, Fisher D, Williams P, Pooler S, Kacmarek RM. Medication nebulizer performance: effects of diluent volume, nebulizer flow, and nebulizer brand. Chest 1996;110(2):498–505.
59. Coates AL, MacNeish CF, Meisner D, Kelemen S, Thibert R, MacDonald J, Vadas E. The choice of jet nebulizer, nebulizing flow, and addition of albuterol affects the output of tobramycin aerosols. Chest 1997;111(5):1206–1212.
60. Hughes JM, Saez J. Effects of nebulizer mode and position in a mechanical ventilator circuit on dose efficiency. Respir Care 1987; 32(12):1131–1135.
61. O'Riordan TG. Formulations and nebulizer performance. Respir Care 2002;47(11):1305–1312; discussion 1312–1313.
62. Newman SP, Pellow PGD, Clay MM, Clarke SW. Evaluation of jet nebulisers for use with gentamicin solution. Thorax 1985;40(9): 671–676.
63. Harvey CJ, O'Doherty MJ, Page CJ, Thomas SH, Nunan TO, Treacher DF. Effect of a spacer on pulmonary aerosol deposition from a jet nebuliser during mechanical ventilation. Thorax 1995; 50(1):50–53.
64. Dalby RN, Tiano SL, Hickey AJ. Medical devices for the delivery of therapeutic aerosols to the lungs. In: Hickey AJ, editor. Inhalation aerosols: physical and biological basis for therapy. New York: Marcel Dekker; 1996:441–473.
65. Rau JL. Design principles of liquid nebulization devices currently in use. Respir Care 2002;47(11):1257–1275; discussion 1275–1278.
66. Phipps PR, Gonda I. Droplets produced by medical nebulizers: some factors affecting their size and solute concentration. Chest 1990;97(6):1327–1332.
67. Stapleton KW, Finlay WH. Determining solute concentration within aerosol droplets output by jet nebulizers. J Aerosol Sci 1995;26: 137–145.
68. Niven RW. Atomization and nebulizers. In: Hickey AJ, editor. Inhalation aerosols: physical and biological basis for therapy. New York: Marcel Dekker; 1996:273–312.
69. Diot P, Morra L, Smaldone GC. Albuterol delivery in a model of mechanical ventilation: comparison of metered-dose inhaler and nebulizer efficiency. Am J Respir Crit Care Med 1995;152(4 pt 1):1391–1394.
70. Hess DR, Acosta FL, Ritz RH, Kacmarek RM, Camargo CA Jr. The effect of heliox on nebulizer function using a ß-agonist bronchodilator. Chest 1999;115(1):184–189.
71. Goode ML, Fink JB, Dhand R, Tobin MJ. Improvement in aerosol delivery with helium-oxygen mixtures during mechanical ventilation. Am J Respir Crit Care Med 2001;163(1):109–114.
72. Hess DR, Dillman C, Kacmarek RM. In vitro evaluation of aerosol bronchodilator delivery during mechanical ventilation: pressure-control vs. volume control ventilation. Intensive Care Med 2003; 29(7):1145–1150.
73. Dhand R. Special problems in aerosol delivery: artificial airways. Respir Care 2000;45(6):636–645.
74. Dolovich MB. Measuring total and regional lung deposition using inhaled radiotracers. J Aerosol Med 2001;14 Suppl 1:S35–S44.
75. Smaldone GC. Assessing new technologies: patient-device interactions and deposition. Respir Care 2005;50(9):1151–1158.
76. Iacono AT, Smaldone GC, Keenan RJ, Diot P, Dauber JH, Zeevi A, et al. Dose-related reversal of acute lung rejection by aerosolized cyclosporine. Am J Respir Crit Care Med 1997;155(5):1690–1698.
77. Iacono AT, Johnson BA, Grgurich WF, Youssef JG, Corcoran TE, Seiler DA, et al. A randomized trial of inhaled cyclosporine in lung-transplant recipients. N Engl J Med 2006;354(2):141–150.
78. Ceglia L, Lau J, Pittas AG. Meta-analysis: efficacy and safety of inhaled insulin therapy in adults with diabetes mellitus. Ann Intern Med 2006;145(9):665–675.
79. Alvine GF, Rodgers P, Fitzsimmons KM, Ahrens RC. Disposable jet nebulizers. How reliable are they? Chest 1992;101(2):316–319.
80. Loffert DT, Ikle D, Nelson HS. A comparison of commercial jet nebulizers. Chest 1994;106(6):1788–1792.
81. Waldrep JC, Keyhani K, Black M, Knight V. Operating characteristics of 18 different continuous-flow jet nebulizers with beclomethasone dipropionate liposome aerosol. Chest 1994;105(1):106–110.
82. Greenspan BJ. Ultrasonic and electrohydrodynamic methods for aerosol generation. In: Hickey AJ, editor. Inhalation aerosols: physical and biologic basis for therapy. New York: Marcel Dekker; 1996:313–335.
83. Steckel H, Eskandar F. Factors affecting aerosol performance during nebulization with jet and ultrasonic nebulizers. Eur J Pharm Sci 2003;19(5):443–455.
84. Kemming GI, Kreyling W, Habler O, Merkel M, Kleen M, Welte M, et al. Aerosol production and aerosol droplet size distribution during mechanical ventilation (IPPV) with a new ultrasonic nebulizer. Eur J Med Res 1996;1(7):321–327.
85. Williams L, Fletcher GC, Daniel M, Kinsella J. A simple in vitro method for the evaluation of an ultrasonic nebulizer for drug delivery to intubated, ventilated patients and the effect of nebulizer and ventilator settings on the uptake of fluid from the nebulizer chamber. Eur J Anaesthesiol 1999;16(7):479–484.
86. Thomas SH, O'Doherty MJ, Page CJ, Treacher DF, Nunan TO. Delivery of ultrasonic nebulized aerosols to a lung model during mechanical ventilation. Am Rev Respir Dis 1993;148(4 Pt 1):872–877.
87. Harvey CJ, O'Doherty MJ, Page CJ, Thomas SH, Nunan TO, Treacher DF. Comparison of jet and ultrasonic nebulizer pulmonary aerosol deposition during mechanical ventilation. Eur Respir J 1997; 10(4):905–909.
88. Pedersen KM, Handlos VN, Heslet L, Kristensen HG. Factors influencing the in vitro deposition of tobramycin aerosol: a comparison of an ultrasonic nebulizer and a high-frequency vibrating mesh nebulizer. J Aerosol Med 2006;19(2):175–183.
89. Dhand R. Nebulizers that use a vibrating mesh or plate with multiple apertures to generate aerosol. Respir Care 2002 47(12):1406–1416; discussion 1416–1418.
90. Geller DE, Rosenfeld M, Waltz DA, Wilmott RW; AeroDose TOBI Study Group. Efficiency of pulmonary administration of tobramycin solution for inhalation in cystic fibrosis using an improved drug delivery system. Chest 2003;123(1):28–36.
91. Dhand R. New frontiers in aerosol delivery during mechanical ventilation. Respir Care 2004;49(6):666–677.
92. Smaldone GC, Fuhrer J, Steigbigel RT, McPeck M. Factors determining pulmonary deposition of aerosolized pentamidine in patients with human immunodeficiency virus infection. Am Rev Respir Dis 1991;143(4 Pt 1):727–737.
93. Duarte AG, Dhand R, Reid R, Fink JB, Fahey PJ, Tobin MJ, Jenne JW. Serum albuterol levels in mechanically-ventilated patients and healthy subjects after metered-dose inhaler administration. Am J Respir Crit Care Med 1996;154(6 Pt 1):1658–1663.
94. Marik P, Hogan J, Krikorian J. Comparison of bronchodilator therapy delivered by nebulization and metered-dose inhaler in mechanically ventilated patients. Chest 1999;115(6):1653–1657.
95. Fink JB, MacLoughlin R. Impact of continuous and phasic aerosol generation on drug delivery during mechanical ventilation: an in vitro analysis. Poster presentation at the American College of Chest Physicians Annual Conference, November 2002. [Internet]. available at http://www.aerogen.com/publications/2002.htm. *(last accessed December 9, 2006)*

96. LiPuma JJ. Microbiological and immunologic considerations with aerosolized drug delivery. Chest 2001;120(3 Suppl):118S–123S.
97. Mercier E, Valat A, Fishman RS, Fink JB, Smith N, Gibbons K, et al. Aerosol delivery of amikacin by three nebulizers of varying efficiency in patients on mechanical ventilators (abstract). Am J Respir Crit Care Med 2004;169:A657.
98. Newhouse MT, Hirst PH, Duddu SP, Walter YH, Tarara TE, Clark AR, Weers JG. Inhalation of a dry powder tobramycin PulmoSphere formulation in healthy volunteers. Chest 2003;124(1):360–366.
99. Dhand R. Inhalation therapy with metered-dose inhalers and dry powder inhalers in mechanically ventilated patients. Respir Care. 2005;50(10):1331–1334; discussion 1344–1345.
100. Habib, DM, Garner SS, Brandeburg S. Effect of helium-oxygen on delivery of albuterol in a pediatric, volume-cycled, ventilated lung model. Pharmacotherapy 1999;19(2):143–149.
101. Tonnellier M, Ferrari F, Goldstein I, Sartorius A, Marquette CH, Rouby JJ. Intravenous versus nebulized ceftazidime in ventilated piglets with and without experimental bronchopneumonia: comparative effects of helium and nitrogen. Anesthesiology 2005;102(5):995–1000.
102. Klastersky J, Hensgens C, Noterman J, Mousawad E, Meunter-Carpentier F. Endotracheal antibiotics for the prevention of tracheobronchial infections in tracheotomized unconscious patients: a comparative study of gentamicin and aminosidin-polymyxin B combination. Chest 1975;68(3):302–306.
103. Rouby JJ, Poete P, Martin de Lassale E, Nicolas MH, Bodin L, Jarlier V, et al. Prevention of gram negative nosocomial bronchopneumonia by intratracheal colistin in critically ill patients: histologic and bacteriologic study. Intensive Care Med 1994;20(3):187–192.
104. Lake KB, Van Dyke JJ, Rumsfeld JA. Combined topical pulmonary and systemic gentamicin: the question of safety. Chest 1975;68(1):62–64.
105. Badia JR, Soy D, Adrover M, Ferrer M, Sarasa M, Alarcon A, et al. Disposition of instilled versus nebulized tobramycin and imipenem in ventilated intensive care unit (ICU) patients. J Antimicrob Chemother 2004;54(2):508–514.
106. Franz AR, Rohlke W, Franke RP, Ebsen M, Pohlandt F, Hummler HD. Pulmonary administration of perfluorodecaline-gentamicin and perfluorodecaline-vancomycin emulsions. Am J Respir Crit Care Med 2001;164(9):1595–1600.
107. Le Conte P, Potel G, Peltier P, Horeau D, Caillon J, Juvin ME, et al. Lung distribution and pharmacokinetics of aerosolized tobramycin. Am Rev Respir Dis 1993;147(5):1279–1282.
108. Mukhopadhyay S, Staddon GE, Eastman C, Palmer M, Davies ER, Carswell F. The quantitative distribution of nebulized antibiotic in the lung in cystic fibrosis. Respir Med 1994;88(3):203–211.
109. Ilowite JS, Gorvoy JD, Smaldone GC. Quantitative deposition of aerosolized gentamicin in cystic fibrosis. Am Rev Respir Dis 1987;136(6):1445–1449.
110. Adair CG, Gorman SP, Byers LM, Jones DS, Feron B, Crowe M, et al. Eradication of endotracheal tube biofilm by nebulised gentamicin. Intensive Care Med 2002;28(4):426–431.
111. Adair CG, Gorman SP, Feron BM, Byers LM, Jones DS, Goldsmith CE, et al. Implications of endotracheal tube biofilm for ventilator-associated pneumonia. Intensive Care Med 1999;25(10):1072–1076.
112. Mathay MA. Function of the alveolar epithelial barrier under pathologic conditions. Chest 1994;105(3 Suppl):67S–74S.
113. Goldstein I, Wallet F, Nicolas-Robin A, Ferrari F, Marquette CH, Rouby JJ. Lung deposition and efficiency of nebulized amikacin during *Escherichia coli* pneumonia in ventilated piglets. Am J Respir Crit Care Med 2002;166(10):1375–1381.
114. Touw DJ, Jacobs FA, Brimicombe RW, Heijerman HG, Bakker W, Briemer DD. Pharmacokinetics of aerosolized tobramycin in adult patients with cystic fibrosis. Antimicrob Agents Chemother 1997;41(1):184–187.
115. Cooney GF, Lum BL, Tomaselli M, Fiel SB. Absolute bioavailability and absorption characteristics of aerosolized tobramycin in adults with cystic fibrosis. J Clin Pharmacol 1994;34(3):255–259.
116. Burns JL, Van Dalfsen JM, Shawar RM, Otto KL, Garber RL, Quan JM, et al. Effect of chronic intermittent administration of inhaled tobramycin on respiratory microbial flora in patients with cystic fibrosis. J Infect Dis 1999;179(5):1190–1196.
117. Bergen PJ, Li J, Rayner CR, Nartion RL. Colistin methanesulfonate is an inactive prodrug of colistin against *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 2006;50(6):1953–1958.
118. Michalapoulos A, Kasiakou SK, Falagas ME. The significance of different formulations of aerosolized colistin (letter). Crit Care 2005;9(4):417–418.
119. Gales AC, Reis AO, Jones RN. Contemporary assessment of antimicrobial susceptibility testing methods for polymyxin B and colistin: review of available interpretative criteria and quality control guidelines. J Clin Microbiol 2001;39(1):183–190.
120. Gough M, Hancock RE, Kelly NM. Antiendotoxin activity of cationic peptide antimicrobial agents. Infect Immun 1996;64(12):4922–4927.
121. Evans ME, Feola DJ, Rapp RP. Polymyxin B sulfate and colistin: old antibiotics for emerging multiresistant gram-negative bacteria. Ann Pharmacother 1999;33(9):960–967.
122. Profile Pharma Limited. Promixin 1 MIU powder for nebuliser solution (package insert). West Sussex, UK; 2003.
123. Koch-Weser J, Sidel VW, Federman EB, Kanarek P, Finer DC, Eaton AE. Adverse effects of sodium colistimethate: manifestations and specific reaction rates during 317 courses of therapy. Ann Intern Med 1970;72(6):857–868.
124. Flanagan AD. Adverse effects of sodium colistimethate. Ann Intern Med 1971;74(1):143–144.
125. Linden PK, Kusne S, Coley K, Fontes P, Kramer DJ, Paterson D. Use of parenteral colistin for the treatment of serious infection due to antimicrobial-resistant *Pseudomonas aeruginosa*. Clin Infect Dis 2003;37(11):e154–e160.
126. Randall RE, Bridi GS, Setter JG, Bracket NC. Recovery from colistimethate nephrotoxicity. Ann Intern Med 1970:73(3):491–492.
127. Price DJ, Graham DI. Effects of large doses of colistin sulphomethate sodium on renal function. Br Med J 1970;4(5734):525–527.
128. Markou N, Apostolakos H, Koumoudiou C, Athanasiou M, Koutsoukou A, Alamanos I, Gregorakos L. Intravenous colistin in the treatment of sepsis from multiresistant Gram-negative bacilli in critically ill patients. Crit Care 2003;7(5):R78–R83.
129. Cunningham S, Prasad A, Collyer L, Carr S, Lynn IB, Wallis C. Bronchoconstriction following nebulised colistin in cystic fibrosis. Arch Dis Child 2001;84(5):432–433.
130. Westerman EM, Le Brun PPH, Touw DJ, Frijlink HW, Heijerman HGM. Effect of nebulized colistin sulphate and colistin sulphomethate on lung function in patients with cystic fibrosis: a pilot study. J Cystic Fibros 2004;3(1):23–28.
131. Beringer P. The clinical use of colistin in patients with cystic fibrosis. Curr Opin Pulm Med 2001;7(7):434–440.
132. Goldstein I, Wallet F, Robert J, Becquemin MH, Marquette CH, Rouby JJ. Lung tissue concentrations of nebulized amikacin during mechanical ventilation in piglets with healthy lungs. Am J Respir Crit Care Med 2002;165(2):171–175.
133. Elman M, Goldstein I, Marquette CH, Wallet F, Lenaour G, Rouby JJ; Experimental ICU Study Group. Influence of lung aeration on pulmonary concentrations of nebulized and intravenous amikacin in

ventilated piglets with severe bronchopneumonia. Anesthesiology 2002;971(1):199–206.
134. Chastre J, Fagon JY. Ventilator-associated pneumonia. Am J Respir Crit Care Med 2002;165(7):867–903.
135. Pingleton SK, Fagon JY, Leeper KV Jr. Patient selection for clinical investigation of ventilator-associated pneumonia: criteria for evaluating diagnostic techniques. Chest 1992;102(5 Suppl 1):553S–556S.
136. Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. JAMA 1995;274(8):639–644.
137. Safdar N, Dezfulian C, Collard HR, Saint S. Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. Crit Care Med 2005;33(10):2184–2193.
138. Kollef MH. What is ventilator-associated pneumonia and why is it important? Respir Care 2005;50(6):714–721.
139. Heyland DK, Cook DJ, Griffith L, Keenan S, Brun-Buisson C. The attributable morbidity and mortality of ventilator-associated pneumonia in the critically ill patient. The Canadian Critical Trials Group. Am J Respir Crit Care Med 1999;159(4 Pt 1):1249–1256.
140. Rello J, Ollendorf DA, Oster G, Vera-Llonch M, Bellm L, Redman R, Kollef MH; VAP Outcomes Scientific Advisory Group. Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. Chest 2002;122(6):2115–2121.
141. Girou E, Stephan F, Novara A, Safar M, Fagon JY. Risk factors and outcome of nosocomial infections: results of a matched case-control study of ICU patients. Am J Respir Crit Care Med 1998;157(4 Pt 1):1151–1158.
142. Bueno-Cavanillas A, Delgado-Rodriguez M, Lopez-Luque A, Schaffino-Cano S, Galvez-Vargas R. Influence of nosocomial infection on mortality rate in an intensive care unit. Crit Care Med 1994; 22(1):55–60.
143. George DL. Epidemiology of nosocomial pneumonia in intensive care unit patients. Clin Chest Med 1995;16(1):29–44.
144. Kollef MH. The prevention of ventilator-associated pneumonia. N Engl J Med 1999;340(8):627–634.
145. Dodek P, Keenan S, Cook D, Heyland D, Jacka M, Hand L, et al; Canadian Critical Care Trials Group; Canadian Critical Care Society. Evidence-based clinical practice guideline for the prevention of ventilator-associated pneumonia. Ann Intern Med 2004;141(4):305–313.
146. Guidelines for preventing health-care-associated pneumonia, 2003. Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. MMWR Recomm Rep 2004;53(RR-3):1–36.
147. Institute for Healthcare Improvement. Prevention of ventilator-associated pneumonia. [Internet]. Available at http://www.ihi.org/NR/rdonlyres/35B687FE-D4D0-44E5-A671E76D74BB8D9F/0/vap.pdf. *(last accessed May 14, 2007)*
148. Doebbeling BN, Stanley GL, Sheetz CT, Pfaller MA, Houston AK, Annis L, et al. Comparative efficacy of alternative hand-washing agents in reducing nosocomial infections in intensive care units. N Engl J Med 1992;327(2):88–93.
149. Craven DE, Steger KA. Epidemiology of nosocomial pneumonia: new perspectives on an old disease. Chest 1995;108 Suppl:1S–16S.
150. Liberati A, D'Amico R, Pifferi, Torri V, Brazzi L. Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. Cochrane Database Syst Rev 2004;(1): CD000022.
151. Klastersky J, Geuning C, Mouawad E, Daneau D. Endotracheal gentamicin in bronchial infections in patients with tracheostomy. Chest 1972;61(2):117–120.
152. Luna CM, Vujacich P, Niederman MS, Vay C, Gherardi C, Matera J, Jolly EC. Impact of BAL data on the therapy and outcome of ventilator-associated pneumonia. Chest 1997;111(3):676–685.
153. Kollef MH, Ward S. The influence of mini-BAL cultures on patient outcomes: implications for the antibiotic management of ventilator-associated pneumonia. Chest 1998;113(2):412–420.
154. Iregui M, Ward S, Sherman G, Fraser VJ, Kollef MH. Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. Chest 2002;122(1):262–268.
155. Alvarez-Lerma F. Modification of empiric antibiotic treatment in patients with pneumonia acquired in the intensive care unit. ICU-Acquired Pneumonia Study group. Intensive Care Med 1996;22(5): 387–394.
156. Rello J, Gallego M, Mariscal D, Sonora R, Valles J. The value of routine microbial investigation in ventilator-associated pneumonia. Am J Respir Crit Care Med 1997;156(1):196–200.
157. Klastersky J, Carpentier-Meunier F, Kahan-Coppens L, Thys JP. Endotracheally administered antibiotics for gram-negative bronchopneumonia. Chest 1979;75(5):586–591.
158. Sorensen VJ, Horst HM, Obeid FN, Bivins BA. Endotracheal aminoglycosides in gram negative pneumonia: a preliminary report. Am Surg 1986;52(7):391–394.
159. Fagon JY, Chastre J, Hance AJ, Montravers P, Novara A, Gibert C. Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. Am J Med 1993; 94(3):281–288.
160. Stillwell PC, Kearns GL, Jacobs RF. Endotracheal tobramycin in gram-negative pneumonitis. Drug Intell Clin Pharm 1988;22(7–8): 577–581.
161. McCall CY, Spruill WJ, Wade WE. The use of aerosolized tobramycin in the treatment of resistant pseudomonal pneumonitis. Ther Drug Monit 1989;11(6):692–695.
162. Clark RL, Morgan J, Donehower B, Cupp R. Adjunctive therapy of ventilator associated *Pseudomonas* pneumonia with aerosolized tobramycin solution for inhalation (abstract). Am J Respir Crit Care Med 2000;161:A652.
163. Fagon JY, Chastre J, Domart Y, Trouillet JL, Pierre J, Darne C, Gibert C. Nosocomial pneumonia in patients receiving continuous mechanical ventilation: prospective analysis of 52 episodes with use of a protected specimen brush and quantitative culture techniques. Am Rev Respir Dis 1989;139(4):877–884.
164. Levin AS, Barone AA, Penco J, Santos MV, Marinho IS, Arruda EA, et al. Intravenous colistin as therapy for nosocomial infections caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Clin Infect Dis 1999;28(5):1008–1011.
165. Garnacho-Montero J, Ortiz-Leyba C, Jimenez-Jimenez FJ, Barrero-Almodovar AE, Garcia-Garmendia JL, Bernabeu-WittelI M, et al. Treatment of multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia (VAP) with intravenous colistin: a comparison with imipenem-susceptible VAP. Clin Infect Dis 2003; 36(9):1111–1118.
166. Kasiakou SK, Michalopoulos A, Soteriades ES, Samonis G, Sermaides GJ, Falagas ME. Combination therapy with intravenous colistin for management of infections due to multidrug-resistant Gram-negative bacteria in patients without cystic fibrosis. Antimicrob Agents Chemother 2005;49(8):3136–3146.
167. Hamer DH. Treatment of nosocomial pneumonia and tracheobronchitis caused by multidrug-resistant *Pseudomonas aeruginosa* with aerosolized colistin. Am J Respir Crit Care Med 2000;162(1):328–330.
168. Kwa AL, Loh C, Low JG, Kurup A, Tam VH. Nebulized colistin in the treatment of pneumonia due to multidrug-resistant *Acinetobacter*

baumannii and *Pseudomonas aeruginosa*. Clin Infect Dis 2005; 41(5):754–757.
169. Berlana D, Llop JM, Fort E, Badia MB, Jodar R. Use of colistin in the treatment of multiple-drug-resistant gram-negative infections. Am J Health Syst Pharm 2005;62(1):39–47.
170. Falagas ME, Rizos M, Bliziotis JA, Rellos K, Kasiakou SK, Michalapoulos A. Toxicity after prolonged (more than four weeks) administration of intravenous colistin. BMC Infect Dis 2005;5(1):1.
171. Fink J. Aerosol drug therapy. In: Wilkins RL, Stoller JK, Scanlan CL, editors. Egan's fundamentals of respiratory care, 8th ed. St. Louis: Mosby; 2003:761–800.
172. Kollef MH. Inadequate antimicrobial treatment: an important determinant of outcome for hospitalized patients. Clin Infect Dis 2000; 31(Suppl 4):S131–S138.
173. Chastre J, Wolff M, Fagon JY, Chevret S, Thomas F, Wermert D, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA 2003;290(19):2588–2598.
174. Watling SM, Dasta JF. Aminoglycoside dosing considerations in intensive care unit patients. Ann Pharmacother 1993;27(3):351–357.
175. Nikander K. Some technical, physicochemical and physiological aspects of nebulization of drugs. Eur Respir Rev 1997;7(44):168–172.
176. Byron PR. Aerosol formulation, generation and delivery using non metered systems. In: Byron PR, editor. Respiratory drug delivery. Boca Raton, Florida: CRC Press; 1990:143–166.
177. Lifschitz MI, Denning CR. Safety of kanamycin aerosol. Clin Pharmacol Ther 1971;12(1):91–95.
178. Dickie KJ, De Groot WJ. Ventilatory effects of aerosolized kanamycin and polymyxin. Chest 1973;63(5):694–697.
179. Eschenbacher WL, Boushey HA, Sheppard D. Alteration in osmolarity of inhaled aerosols causes bronchoconstriction and cough, but absence of permeant anion causes cough alone. Am Rev Respir Dis 1984;129(2):211–215.
180. Godden DJ, Borland C, Lowry R, Higgenbottam TW. Chemical specificity of coughing in man. Clin Sci (Lond) 1986;70(3):301–306.
181. Lowry RH, Wood AM, Higgenbottam TW. Effects of pH and osmolarity on aerosol-induced cough in normal volunteers. Clin Sci (Lond) 1988;74(4):373–376.
182. Miszkiel KA, Beasley R, Rafferty P, Holgate ST. The contribution of histamine release to bronchoconstriction provoked by inhaled benzalkonium chloride in asthma. Br J Clin Pharmacol 1988;25(2): 157–163.
183. Miszkiel KA, Beasley R, Holgate ST. The influence of ipratropium bromide and sodium cromoglycate on benzalkonium chloride-induced bronchoconstriction in asthma. Br J Clin Pharamcol 1988; 26(3):295–301.
184. Downes H, Hirshman CA. Calcium chelators increase airway responsiveness. J Appl Physiol 1985;59(1):92–95.
185. Beasley R, Rafferty P, Holgate ST. Adverse reactions to the non-drug constituents of nebuliser solutions. Br J Clin Pharmacol 1988; 25(3):283–287.
186. Alothman GA, Alsaadi MM, Ho BL, Ho SL, Dupuis A, Corey M, Coates AL. Evaluation of bronchial constriction in children with cystic fibrosis after inhaling two different preparations of tobramycin. Chest 2002;122(3):930–934.
187. Prober CG, Walson PD, Jones J. Technical report: precautions regarding the use of aerosolized antibiotics. Committee on Infectious Diseases and Committee on Drugs. Pediatrics 2000;106(6):E89.
188. Dodd ME, Abbott J, Maddison J, Moorcroft AJ, Webb AK. Effect of tonicity of nebulized colistin on chest tightness and pulmonary function in adults with cystic fibrosis. Thorax 1997;52(7):656–658.
189. Quieffin J, Hunter J, Schechter MT, Lawson L, Ruedy J, Pare P, Montaner JS. Aerosol pentamidine-induced bronchoconstriction: predictive factors and preventive therapy. Chest 1991;100(3):624–627.
190. Dally MB, Kurrle S, Breslin ABX. Ventilatory effects of aerosol gentamicin. Thorax 1978;33(1):54–56.
191. Elwood CM, Lucas GD, Muehrcke RC. Acute renal failure associated with sodium colistimethate treatment. Arch Intern Med 1966; 118(4):326–334.
192. Hoffmann IM, Rubin BK, Iskandar SS, Schechter MS, Nagaraj SK, Bitzan MM. Acute renal failure in cystic fibrosis: association with inhaled tobramycin therapy. Pediatr Pulmonol 2002;34(5):375–377.
193. Laporta R, Ussetti P, Carreno M. Renal toxicity due to inhaled tobramycin in lung transplant recipients. J Heart Lung Transplantation 2006;25(5):608.
194. Lindesmith LA, Baines RD Jr, Bigelow DB, Petty TL. Reversible respiratory paralysis associated with polymyxin therapy. Ann Intern Med 1968;68(2):318–327.
195. Beaty CD, Ritz RH, Benson MS. Continuous in-line nebulizers complicate pressure support ventilation. Chest 1989;96(6):1360–1363.
196. Craven DE, Lichtenberg DA, Goularte TA, Make BJ, McCabe WR. Contaminated medication nebulizers in mechanical ventilator circuits: source of bacterial aerosols. Am J Med 1984;77(5):834–838.
197. Hamill RJ, Houston ED, Georghiou PR, Wright CE, Koza MA, Cadle RM, et al. An outbreak of *Burkholderia* (formerly *Pseudomonas*) *cepacia* respiratory tract colonization and infection associated with nebulized albuterol therapy. Ann Intern Med 1995;122(10): 762–766.
198. Balmes JR, Estacio PL, Quinlan P, Kelly T, Corkery K, Blanc P. Respiratory effects of occupational exposure to aerosolized pentamidine. J Occup Environ Med 1995;37(2):145–150. *Erratum in: J Occup Environ Med 1995;37(5):596.*