Aerosolized antibiotics: do they add to the treatment of pneumonia?

Marin H. Kollef*, Cindy W. Hamiltonbc, and A. Bruce Montgomeryd

Purpose of review
The increasing rate of ventilator-associated pneumonia (VAP) caused by multidrug-resistant pathogens warrants the development of new treatment strategies. Carefully engineered delivery systems are undergoing evaluation to test the hypothesis that aerosolized administration of antibiotics will provide high local concentrations and fast clearance, which in turn may improve efficacy and decrease the risk of microbial resistance.

Recent findings
Recent studies indicate that aerosolized delivery systems for specially formulated antibiotics yield high local concentrations with rapid clearance and low systemic exposure. Preliminary clinical studies reveal that aerosolized delivery of antibiotics is well tolerated and active, when combined with intravenous antibiotics. No single aerosolized antibiotic is likely to provide broad-spectrum activity against both Gram-negative and Gram-positive bacteria.

Summary
Large multicenter trials are needed to determine whether preliminary findings will translate to improved clinical activity and decreased microbial resistance in VAP patients, and to optimize the use of aerosolized antibiotics.

Keywords
aerosolized antibiotics, pharmacokinetics, ventilator-associated pneumonia

INTRODUCTION
Ventilator-associated pneumonia (VAP) continues to be associated with substantial morbidity and mortality, which are even greater when appropriate therapy is delayed [1]. A portion of this mortality was recently shown to be directly attributable to VAP in a causal analysis [2]. VAP is also associated with a statistically significant resource utilization burden [3*]. This burden occurs despite the use of pharmacologic and pharmacodynamic principles to optimize administration of antibiotic therapy. For example, prolonged and intermittent infusion of β-lactam antibiotics failed to improve mortality and clinical cure rates in a meta-analysis of randomized studies [4], although benefit was seen in a more recent meta-analysis of mainly nonrandomized studies that focused on carbapenems and piperacillin/tazobactam [5*]. Clinical failure may be attributable to the high prevalence of multidrug-resistant (MDR) pathogens [6*] and poor perfusion of intravenously administered antibiotics to the consolidated areas of the lung [7]. VAP is one of the major sites for emergence of MDR pathogens [6*] because subtherapeutic antibiotic concentrations in the lung necessitate longer duration of therapy, thereby favoring selection of resistant bacteria. Aerosolized therapy, including antibiotics, is frequently administered during mechanical ventilation, but strategies are not standardized and therefore probably not ideal [8*]. Collectively, these findings form the basis for reconsidering aerosolized delivery of antibiotics to determine how to optimize delivery of antibiotics to the infection site.

This review begins with an overview of technologic considerations learned from the use of...
aerosolized antibiotic therapy in cystic fibrosis patients and preliminary studies of VAP patients. Next, this review summarizes recent clinical trials of VAP patients treated with aerosolized antibiotics. In addition, technical terms that might not be understood by readers unfamiliar with this topic are defined (Table 1). VAP is also included in Table 1 because existing definitions have been criticized as being inaccurate and unreliable [9]. Diagnostic criteria generally include clinical signs and symptoms, serial radiographs, and microbiology; however, the first two criteria are subject to interobserver variability. The optimal sampling method and need for invasive techniques are subjects of ongoing debate [9]. To resolve these issues, the Centers for Disease Control (CDC) recently proposed a surveillance definition based on objective, recordable data [10], but more evaluations are needed to confirm its usefulness [9].

**TECHNOLOGIC CONSIDERATIONS FOR AEROSOLIZED ANTIBIOTICS**

The role of aerosolized antibiotics that deliver high local concentrations with low systemic exposure is well established in the treatment of chronic endobronchial *Pseudomonas* infections in cystic fibrosis patients [11,12]. This role, however, has not been proven in a multicenter trial of mechanically ventilated patients despite 30 years of effort. Definitive trials are lacking for many reasons, including choice of antibiotics, formulations not optimized for aerosolized administration, and lack of effective delivery system with appropriate particle sizes. Clinical trial inadequacies are described in the next section.

**Choice of antibiotics**

Colistin, aminoglycosides, β-lactams, monobactams, carbapenems, and fosfomycin have been studied or proposed as aerosolized agents, and each has problems.

Colistin, a polymyxin, is likely the most complicated antibiotic for aerosolized use. Colistimethate (colistin methanosulfate) is a chemically derived inactive prodrug of the antibiotic colistin. Activation of the prodrug by hydrolysis is slow and releases formaldehyde-bisulfite adducts. Colistin is a collection of closely related cyclic cationic peptides (also known as polymyxin E) that act as detergents on cell membranes of Gram-negative bacteria. These peptides can also act on mammalian cells and, at high concentrations, can cause airway and alveolar damage. The major active component, polymyxin E1, was abandoned as a potential drug because a well tolerated dose was not found in preclinical studies [13,14]. In an unfortunate accident in a patient with cystic fibrosis, colistin methanosulfate was reconstituted and allowed to mostly convert to active colistin before administration, which led to fatal acute respiratory distress syndrome [14]. Furthermore, the dose differs by country. In the United States, the dose represents the active moiety, not the prodrug. Therefore, 150 mg in the United States is equivalent to 390 mg in the European Union [15]. Pharmacokinetic evaluation is problematic because

| Table 1. Definitions of ventilator-associated pneumonia and technical terms |
|-------------------------------------------------|
| Technical terms | Definitions |
|------------------|-------------|
| Hydroscopic growth | Increase in particle size of aerosol droplets because of the absorption of water from the humidified environment |
| Permeant anion | An anion that can freely cross cell membranes, such as Cl⁻ (larger anions, such as SO₄²⁻, are too large to be permeable) |
| Sputum antagonism | Active binding of mucin that prevents an antibiotic from being biologically active (sputum antagonism is common with aminoglycosides) |
| Ventilator-associated pneumonia | Pneumonia in a patient who has been mechanically ventilated for at least 48 h (the definition is evolving to become more reliable and objective) |
| Ventilator bias flow | Airflow in the ventilator circuit that is continuous, and is used to flush the tubing and to prevent rebreathing of exhaled gases as continuous to minimize condensation in the tubing |
samples can continue to convert to the active form after recovery, thereby preventing elucidation of active drug levels in vivo. In fact, published articles do not specify the time between reconstitution and administration, another variable that affects the amount of active drug. These issues make it challenging to develop a Food and Drug Administration (FDA)-approved colistimethate formulation as an aerosolized drug and also confound interpretation of published clinical trials.

Aerosolized aminoglycosides have been used in cystic fibrosis patients to treat chronic endobronchial infections due to Pseudomonas and other Gram-negative infections. Their concentration-dependent bactericidal action is better suited for aerosolized use than cell wall active antibiotics (e.g., cephalosporins) because aerosolized delivery typically yields high endobronchial peak levels but short half-lives. The main drawback to aminoglycoside use is sputum antagonism, which requires a dose up to 25 times the minimal inhibitory concentration (MIC) to achieve bactericidal concentrations [16,17]. Additionally, recent emergence of highly resistant Gram-negative bacteria requires delivery at concentrations not yet achieved by aerosolized aminoglycosides as monotherapy [18].

Aerosolized cephalosporins have been evaluated for VAP patients, such as a single-center trial of ceftazidime [19], and the monobactam aztreonam has been studied in cystic fibrosis patients [12,20,21]; both antibiotics were studied in patients with Gram-negative infections. Efficacy, however, requires frequent administration because the bactericidal activity of β-lactams depends on time above MIC and because of rapid airway clearance. The most successful VAP trial required ceftazidime administration every 3 h [19], which is impractical for widespread use.

Carbapenems, like penicillins, can cause allergies; aerosolized doripenem was terminated in phase 1 for the same reason [22,23].

Fosfomycin, a phosphonic acid, represents a unique class of antibiotic that interferes with cell wall assembly and has both Gram-negative and Gram-positive activity. Fosfomycin monotherapy is not recommended because mutation or resistance develops rapidly; this can be decreased by 100-fold to 1000-fold by adding an aminoglycoside [24]. Fosfomycin has been successfully combined with tobramycin to treat chronic endobronchial infections due to Pseudomonas and methicillin-resistant Staphylococcus aureus (MRSA) in cystic fibrosis patients [25]. A formulation with amikacin was recently evaluated in a phase 1 trial of VAP patients [26].

**Optimization for aerosolized administration**

A well tolerated aerosolized formulation should be preservative free and not hyperosmolar, and have near-neutral pH and at least 30 mEq of permeant anion [27]. Two FDA-approved formulations of aztreonam lysine and tobramycin solution for inhalation meet these criteria, but intravenous antibiotic formulations do not. The preferred permeant anion is chloride; aerosols without it induce coughing [27]. Studies of formulations without a permeant anion, such as ceftazidime dissolved in water, have required sedation of the patient with propofol [19].

**Effective delivery system with appropriate particle sizes**

Most nebulizers are designed to deliver drugs to the airway, not the lung parenchyma. Deposition location is a function of particle size, usually expressed as mass median aerodynamic diameter (MMAD). To optimize airway delivery, typical jet nebulizers have a particle size of about 5 μm MMAD. To reach the lungs, optimal size is about 3 μm MMAD, but no available jet nebulizer can produce such a small particle. Additionally, delivery to the lung parenchyma is impeded by humidity in the ventilator circuit, which can cause hydroscopic growth and a rainout effect in the endotracheal tube [28].

Experience with a jet nebulizer placed in the proximal arm of a ventilator delivering a 300-mg nominal dose of tobramycin solution for inhalation illustrates the challenge of larger particle size with subsequent hydroscopic growth. Mean tracheal concentrations were 900 μg/g [29]. This concentration is unlikely to eliminate infection caused by Gram-negative bacteria with MIC >32 μg/ml because of the need for 25-fold higher concentrations to overcome sputum antagonism. Thus, it is not surprising that adapting nebulizers used in spontaneously breathing patients for mechanically ventilated patients has not been very effective in treating VAP because of MDR pathogens. Jet nebulizers also introduce additional air into the ventilator circuit that may lead to ventilator alarms.

The need for improved delivery has led to the development of two devices. The Nektar Bayer Pulmonary Drug Delivery System (hereafter, PDDS) is a single-use nebulizer inserted distal to the ventilator wye. A ceramic vibrating plate nebulizer delivers drug during inspiration. The nebulizer is triggered by a separate airway pressure-sensing device. The reported particle size is 4.7 μm MMAD, and the humidity is turned off. In a pharmacokinetic trial [17], the initial mean sputum concentration was 11 900 μg/ml after 400 mg of amikacin
sulfate twice daily; however, the median was less than 6400 μg/ml, indicating wide variation in concentration delivered. Delivery time averaged 50 min [17**]. Not surprisingly, bronchospasm was an adverse effect because the formulation did not have a permeant anion.

The PARI Investigational eFlow Inline Nebulizer System (hereafter, PARI) is a multiple-use, single-patient device that is placed on the inspiratory limb of the ventilator circuit. A stainless steel vibrating plate nebulizer is placed in a coaxial position to the ventilator air flow and is run continuously. Ventilator bias flow is minimized and the inspiratory limb acts as a spacer device, with the aerosolized cloud building up during exhalation. Against conventional wisdom, the humidity is left on, but the initial particle size is about 2.8 μm, growing to 3.2 μm with humidity, so particles are small enough to avoid the rainout effect. The initial mean peak tracheal concentration was 12390 μg/ml (range, 6910–17000 μg/ml) after amikacin HCl 300 mg with fosfomycin 120 mg in a phase 1 trial in VAP patients [26]. Total delivery time averaged 12 min. No drug-related respiratory adverse effects were reported [26]. Therefore, both systems can deliver high antibiotic concentrations in VAP patients. PARI has the slight advantage of suitability for multiple use in a single patient, obviating the need to open the ventilator circuit before and after treatment, which in turn reduces the risk of superinfection.

**Table 2. Recent clinical trials of aerosolized antibiotics in patients with ventilator-associated pneumonia**

| Reference          | Design                                      | Number of patients | Treatment                                      | Outcomes (aerosol vs. control)                                      |
|--------------------|---------------------------------------------|--------------------|-----------------------------------------------|------------------------------------------------------------------|
| Arnold et al. [32**]| Retrospective, single-center, cohort        | 93                 | Adjunct aerosolized colistin or tobramycin vs. intravenous antibiotics | 30-day mortality: 0 vs. 18%                                      |
| Lu et al. [19]     | Prospective, randomized                     | 40                 | Aerosolized ceftazidime and amikacin vs. intravenous ceftazidime and amikacin | Success: 70 vs. 55%; superinfection: 15 vs. 15%; day-28 mortality: 10 vs. 5% |
| Lu et al. [33**]    | Prospective, observational, comparative (not randomized) | 165                | Aerosolized colistin ± IV aminoglycosides vs. IV β-lactams plus aminoglycosides or quinolones | Clinical cure: 67 vs. 66%; superinfection: 6 vs. 13%; mortality: 16 vs. 23% |
| Niederman et al. [17**]| Double blind, randomized                    | 69                 | Aerosolized amikacin (q12 h, q24 h) or placebo, each with IV antibiotics | Target concentration: 50 vs. 17%; clinical cure: 94 vs. 75 vs. 88% |
| Montgomery et al. [26]| Double-blind, randomized, phase 1            | 4                  | Escalating doses of aerosolized amikacin and fosfomycin | Amikacin: ≥98-fold higher than P. aeruginosa MIC₉₀; fosfomycin: ≥68-fold higher than MRSA MIC₉₀ |

IV, intravenous; MIC₉₀, minimal inhibitory concentration for 90% of isolates; MRSA, methicillin-resistant *Staphylococcus aureus*; q, every.
[32**]. Colistin 150 mg or tobramycin 300 mg was administered twice daily over 15–20 min by nebulizers generating droplets of 1–5 μm (Airlife, CareFusion, San Diego, California, USA). The nebulizer was positioned in the inspiratory limb of the ventilator circuit, about 30 cm from the endotracheal tube. Humidification was discontinued during aerosol delivery. Patients who received aerosolized colistin (n = 9) or tobramycin (n = 10) had worse severity of illness scores (P = 0.004) and more MDR infections (P < 0.001) than those who received intravenous antibiotics alone (n = 74). Despite these risk factors, 30-day survival was higher in patients who received adjunctive aerosolized antibiotics (P = 0.03 for Kaplan–Meier curve by log rank test) [32**].

Lu et al. [19] reported that aerosolized ceftazidime and amikacin yielded similar outcomes compared with the same antibiotics administered intravenously in a randomized trial of patients with VAP due to *P. aeruginosa*. The nebulizer was Aeroneb Pro, AeroGen Corporation, Galway, Ireland (hereafter, AeroGen). Dosages were ceftazidime 15 mg/kg every 3 h for 8 days and amikacin 25 mg/kg daily for 3 days, each administered over 30 min. These findings are remarkable because the experimental group received aerosolized antibiotics alone without intravenous therapy. Interestingly, acquisition of resistant *P. aeruginosa* was limited to the group receiving intravenous therapy. On the other hand, aerosolized antibiotics were associated with obstruction of the expiratory filter in three of 20 patients, including one who experienced respiratory arrest and was successfully resuscitated [19]. The high aerosol doses and frequent administration likely contributed to filter obstruction.

Lu et al. [33**] reported that aerosolized colistin was noninferior to intravenous β-lactams plus aminoglycosides or quinolones in patients with VAP because of *P. aeruginosa* or *A. baumannii* in a prospective, observational, comparative trial that was not randomized. The experimental group received aerosolized high-dose colistin alone (n = 28) or with intravenous aminoglycosides (n = 15) and had VAP because of MDR pathogens, whereas the control group had VAP because of susceptible strains (n = 122). Colistimethate 400 mg (European dose) was administered by AeroGen nebulizer over 60 min every 8 h for 7–19 days. As expected, the experimental group had more risk factors (e.g., prolonged length of stay before enrollment, previous VAP). Nevertheless, both groups had similar rates of clinical cure, radiographic clearance of consolidation, and improved lung volumes/aeration. Interestingly, acquisition of resistance was infrequent in the experimental group, and 25% of patients with previously MDR pathogens and persistent or relapsed VAP actually recovered susceptibility to β-lactam antibiotics. Renal function impairment was observed in 12% of patients who received aerosolized colistin, but changes in serum creatinine over time were nearly identical between groups [33**].

Niederman et al. [17**] described the results with an investigational drug–device combination (BAY41-6551) of amikacin formulated for inhalation and the PDDS nebulizer in a double-blind trial. Patients with Gram-negative pneumonia at risk for MDR pathogens were randomly assigned to receive aerosolized amikacin 400 mg every 12 or 24 h (q12 h or q24h) or placebo, each administered with standard intravenous antibiotics. The primary endpoint represented 25 times the MIC of 256 μg/ml, and was defined as a tracheal aspirate amikacin maximal concentration greater than or equal to 6400 μg/ml and a ratio of area under the aspirate concentration–time curve to MIC greater than or equal to 100 on day 1. Response rates for this endpoint were 50% for amikacin q12 h and 17% for amikacin q24 h. Although clinical cure rates were not different across groups (P = 0.47), the mean number of antibiotics per patient per day was lower in the experimental group at end of therapy (0.9 vs. 1.3 vs. 1.9 days; P = 0.02). Aerosolized amikacin was well tolerated; the only treatment-related adverse events were two episodes of mild bronchospasm in one patient [17**].

The author (A.B.M.) and colleagues [26] observed high sputum (and low systemic) concentrations after amikacin and fosfomycin by PARI nebulizer in patients with VAP or ventilator-associated tracheobronchitis in a double-blind, randomized, phase 1 trial. Each patient received three escalating doses of amikacin 50 mg/ml and fosfomycin 20 mg/ml at 24-h intervals. On day 3, patients were randomly assigned to two doses of amikacin and fosfomycin or placebo at 2-h intervals. Initial results in the first seven patients at 15 min after dosing revealed that amikacin concentrations in tracheal aspirates were more than or equal to 178-fold higher than the MIC90 of 16 μg/ml for Enterobacteriaceae, *P. aeruginosa*, and *Acinetobacter* spp. in a recent trial [34]; mean levels after the 6-ml dose were greater than or equal to 800-fold higher (Fig. 1). Fosfomycin concentrations were greater than or equal to 54-fold higher than the MIC90 of 32 μg/ml for MRSA isolates [35]; mean levels after the 6-ml dose were greater than or equal to 281-fold higher (Fig. 2). Plasma concentrations were more than 2000-fold lower; the highest were 1.4 μg/ml for amikacin and 0.8 μg/ml for fosfomycin [26].
CONCLUSION

The increasing rate of VAP attributed to MDR pathogens warrants the development of simple and efficient aerosolized delivery of antibiotics into the lower respiratory tract. Not only is improved clinical efficacy a potential result of such advances, but the emergence of microbial resistance may be reduced if higher antibiotic concentrations are delivered to the infection site and duration of antibiotic exposure is shortened. After 30 years of work, the field is progressing with development of carefully engineered delivery technology and ongoing large multicenter trials. The use of aerosolized antibiotics in VAP is promising but not yet proven.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Iregui M, Ward S, Sherman G, et al. Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. Chest 2002; 122:262–268.

2. Belkaert M, Timot JF, Vansteelandt S, et al. Attributable mortality of ventilator-associated pneumonia: A reappraisal using causal analysis. Am J Respir Crit Care Med 2011; 184:1133–1139.

3. Kollef MH, Hamilton CW, Ernst FR. Economic impact of ventilator-associated pneumonia in a large matched cohort. Infect Control Hosp Epidemiol 2012; 33:250–256.

VAP continues to place a statistically significant burden on resource utilization, even when VAP is defined by the new specific International Classification of Disease-9 code.

4. Tamma PD, Putcha N, Suh YD, et al. Does prolonged beta-lactam infusions improve clinical outcomes compared to intermittent infusions? A meta-analysis and systematic review of randomized, controlled trials. BMC Infect Dis 2011; 11:181.

5. Falagas ME, Tansari GS, Ikawa K, Vardakas KZ. Clinical outcomes with extended or continuous versus short-term intravenous infusion of carbapenems and piperacillin/tazobactam: A systematic review and meta-analysis. Clin Infect Dis 2013; 56:272–282.

The use of extended or continuous infusions of broad-spectrum beta-lactam antibiotics was associated with lower mortality than short-term infusions; however, this meta-analysis included mostly nonrandomized trials.

6. Sievert DM, Ricks P, Edwards JR, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009–2010. Infect Control Hosp Epidemiol 2013; 34:1–14.

The proportion of resistant isolates did not increase compared with the previous reporting period; however, nearly 20% of pathogens from healthcare-associated infections were MDR phenotypes.

7. Kiem S, Schentag JJ. Interpretation of antibiotic concentration ratios measured in epithelial lining fluid. Antimicrob Agents Chemother 2008; 52:24–36.
Antimicrobial agents

8. Ehmann S, Roche-Campo F, Sferrazza Papa GF, et al. Aerosol therapy during mechanical ventilation: an international survey. Intensive Care Med 2013; 39:1048–1056.

Intensivists routinely use aerosolized therapy during mechanical ventilation but fail to apply scientific knowledge likely to facilitate optimal use.

9. Metto G, Pinciroli R, Patel N, Berra L. Ventilator associated pneumonia: evolving definitions and preventive strategies. Respir Care 2013; 58:990–1007.

The definition of VAP is evolving because popular criteria are inaccurate and unreliable.

10. Centers for Disease Control and Prevention. Ventilator-associated event (VAE) surveillance definition for ventilator-associated events is based on objective criteria intended to identify a broad range of conditions and complications that occur in mechanically ventilated adults.

11. Ramsey BW, Pepe MS, Quan JM, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic fibrosis inhaled tobramycin study group. N Engl J Med 1999; 340:23–30.

12. McCoy KS, Quittner AL, Oermann CM, et al. Inhaled aztreonam lysine for chronic airway Pseudomonas aeruginosa in cystic fibrosis. Am J Respir Crit Care Med 2008; 178:921–928.

13. VanDevanter DR, Rose LM, Spriegel KH. 28-day inhalation toxicityology of polymyxin E1, the major active component of colistin, in rats and dogs (poster P236). Presented at European Cystic Fibrosis Congress June 6–9, 2001, Vienna, Austria.

14. McCoy KS. Compound colistimethate as possible cause of fatal acute respiratory distress syndrome. N Engl J Med 2002; 347:2310–2311.

15. Coulthard K. Maximizing the efficacy and safety of colistimethate therapy. Pediatr Pulmonol 2004; 38:193–195.

16. Mendelman PM, Smith AL, Levy J, et al. Aminoglycoside penetration, inactivation, and efficacy in cystic fibrosis sputum. Am Rev Respir Dis 1985; 132:761–765.

17. Niederman MS, Chastre J, Corkery K, et al. Bay41-6551 achieves bactericidal tracheal aspirate amikacin concentrations in mechanically ventilated patients with Gram-negative pneumonia. Intensive Care Med 2012; 38:263–271.

The ability of aerosolized amikacin to produce target tracheal aspirate concentrations (and low serum levels) in this first phase 2 trial provides proof of concept for new-generation vibrating mesh plate nebulizers as a carefully engineered delivery system. More trials are needed to determine the role of aerosolized antibiotics and whether they will improve clinical outcomes in patients with VAP including mortality, length of stay, and emergence of resistance.

18. Montgomery AB, Rhomberg P, Abuan T, Jones R. Synergistic effects for a combination of amikacin and fosfomycin against selected resistant Gram-negative pathogens (abstract 43023 and poster). Am J Respir Crit Care Med 2013; 187:A3236.

19. Lu Q, Yang J, Liu Z, et al. Nebulized ceftazidime and amikacin in ventilator-associated pneumonia caused by Pseudomonas aeruginosa. Am J Respir Crit Care Med 2011; 184:106–115.

20. Retsch-Bogart GZ, Quittner AL, Gibson RL, et al. Efficacy and safety of inhaled aztreonam lysine for airway Pseudomonas aeruginosa in cystic fibrosis. Chest 2009; 135:1129–1132.

21. Oermann CM, Retsch-Bogart GZ, Quittner AL, et al. An 18-month study of the safety and efficacy of repeated courses of inhaled aztreonam lysine in cystic fibrosis. Pediatr Pulmonol 2010; 45:1121–1134.

22. Hilas O, Ezzo DC, Jodlowski TZ, Doripenem (doribax), a new carbapenem antibacterial agent. Pharm Ther 2008; 53:134–180.

23. Sorbello A. Doripenem safety review. 2013. Available at www.fda.gov/ohrms/dockets/ac/08/slides/2008-4364s1-05-FDA-Sorbello.pdf.

24. MacLeod DL, Barker LM, Sutherland JL, et al. Antibacterial activities of a fosfomycin/tobramycin combination: a novel inhaled antibiotic for bronchiectasis. J Antimicrob Chemother 2009; 64:829–836.

25. Trapnell BC, McColley SA, Kissner DG, et al. Fosfomycin/tobramycin for inhalation in patients with cystic fibrosis with pseudomonas airway infection. Am J Respir Crit Care Med 2012; 185:171–178.

The ability to suppress P. aeruginosa infection and maintain pulmonary function in cystic fibrosis patients with alternating aerosolized antibiotic therapy may have therapeutic implications for VAP patients.

26. Montgomery AB, Vallence S, Abuan T, et al. A randomized double-blind placebo-controlled dose-escalation phase 1 study of aerosolized amikacin and fosfomycin delivered via the PARI investigational eFlow Inline nebulizer system in mechanically ventilated patients (abstract 42767 and poster 42767). Am J Respir Crit Care Med 2013; 187:A3236.

27. Eschenbacher WL, Boushey HA, Sheppard D. Alteration in osmolarity of inhaled aerosols cause bronchoconstriction and cough, but absence of a permeant anion causes cough alone. Am Rev Respir Dis 1984; 129:211–215.

28. Miller DD, Amin MM, Palmer LB, et al. Aerosol delivery and modern mechanical ventilation: in vitro/in vivo evaluation. Am J Respir Crit Care Med 2003; 168:1055–1209.

29. Clark R, Hoslet L, Abtsonen K, Donehower B. Evaluation of the disposition and safety of tobramycin solution for inhalation in ventilator associated pneumonia or tracheobronchitis patients (poster). Presented at American Thoracic Society International Conference 2003, Seattle, WA.

30. Abu-Salah T, Dhand R. Inhaled antibiotic therapy for ventilator-associated tracheobronchitis and ventilator-associated pneumonia: an update. Adv Ther 2011; 28:728–747.

31. Wood GC. Aerosolized antibiotics for treating hospital-acquired and ventilator-associated pneumonia. Expert Rev Anti Infect Ther 2011; 9:993–1000.

32. Arnold HM, Sawyer AM, Kollef MH. Use of adjunctive aerosolized antimicrobial therapy in the treatment of Pseudomonas aeruginosa and Acinetobacter baumannii ventilator-associated pneumonia. Respir Care 2012; 57:1226–1233.

The ability to demonstrate an association between adjunctive aerosolized therapy and improved survival in patients with VAP provides proof of concept in a single-center cohort trial. Well designed trials are needed to confirm the benefit of adjunctive aerosolized therapy, especially in patients with MDR infection.

33. Lu Q, Luo R, Bodin L, et al. Efficacy of high-dose nebulized colistin in ventilator-associated pneumonia caused by multdrug-resistant Pseudomonas aeruginosa and Acinetobacter baumannii. Anesthesiology 2012; 117:1335–1347.

The ability to demonstrate noninferiority between aerosolized high-dose colistin for MDR pathogens and intravenous therapy for susceptible pathogens supports the rationale for concentrating antibiotics in the lung as a therapeutic strategy for MDR infection. Well designed trials are needed to confirm the benefit of adjunctive aerosolized therapy, especially in patients with MDR infection and as a strategy to prevent further emergence of antibiotic resistance.

34. Zhanel GG, Adam HJ, Low DE, et al. Antimicrobial susceptibility of 15,644 Staphylococcus aureus and Pseudomonas aeruginosa isolates from Canadian hospitals: results of the CANWARD 2007–2009 study. Diagn Microbiol Infect Dis 2011; 69:291–306.

35. Alvarez S, Jones M, Berk SL. In vitro activity of fosfomycin, alone and in combination, against methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother 1985; 28:689–690.