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

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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

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KEY POINTS

- Carefully engineered, proven delivery systems are needed to ensure appropriate, well tolerated administration of aerosolized antibiotics; intravenous formulations are not recommended for aerosolized use.
- Compared with intravenous administration, aerosolization has the advantage of high local concentrations and fast clearance, which in turn may yield improved efficacy and decreased risk of microbial resistance.
- Combination aerosolized therapy is probably needed to provide broad-spectrum coverage against both Gram-negative and Gram-positive pathogens.

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 SO_2^-, 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 well 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 ceftazidine [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 ceftazidine 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 10 000-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 ceftazidine 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 12 390 μg/ml (range, 6910–17 000 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.

CLINICAL TRIALS OF AEROSOLIZED ANTIBIOTICS FOR VAP

Two meta-analyses of clinical trials of aerosolized antibiotics in VAP patients have been published recently [17▪▪,19,26,30,31,32▪▪,33▪▪] (Table 2). Many trials were single-center with inadequate enrollment to detect statistically significant between-group differences, had methodological flaws (e.g., no control group), and failed to report or standardize delivery method and particle size. Both superiority and noninferiority trials have been conducted. The null hypothesis is that there is no difference between groups for a superiority design and that the experimental treatment is inferior to the standard treatment for a noninferiority trial. When a difference is demonstrable, results are more robust for superiority trials, especially when sample size is not large, because noninferiority trials often yield wide confidence intervals, thereby subjecting the equivalency conclusion to criticism. Nevertheless, the authors concluded that aerosolized antibiotics are suitable as adjuncts to systemic antibiotic therapy, especially in patients with MDR pathogens or nonresponding VAP [30,31]. This section focuses on key trials selected because of recent publication and outcomes with implications for future studies (Table 1).

The author (M.H.K.) and colleagues reported that adjunctive aerosolized antibiotics were associated with improved survival in a retrospective, single-center, cohort trial of patients with VAP due to *Pseudomonas aeruginosa* or *Acinetobacter baumannii*

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* MIC_{90}; fosfomycin: ≥68-fold higher than MRSA MIC_{90}

IV, intravenous; MIC_{90}, 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 q24 h) 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 MIC_{90} 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 MIC_{90} 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].

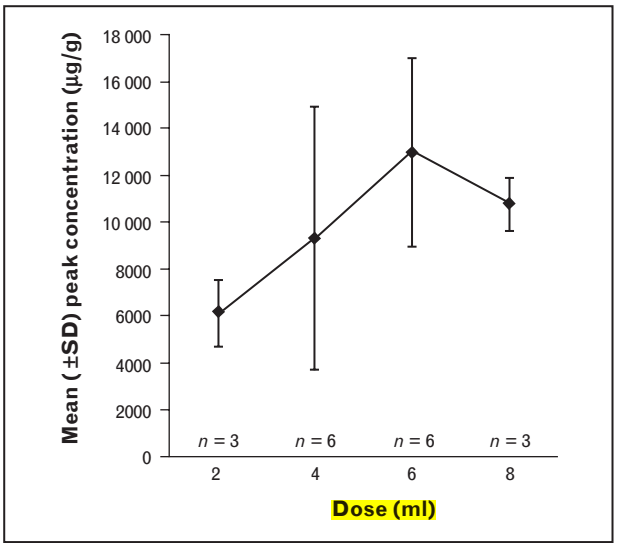

FIGURE 1. Peak amikacin concentrations in tracheal aspirates after aerosolized amikacin 50 mg/ml (with fosfomycin 20 mg/ml) by PARI Investigational eFlow Inline Nebulizer System in a phase 1, dose-escalation trial of seven patients with ventilator-associated pneumonia [26]. The breakpoint for Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Acinetobacter* spp. is 16 µg/ml. SD, standard deviation.

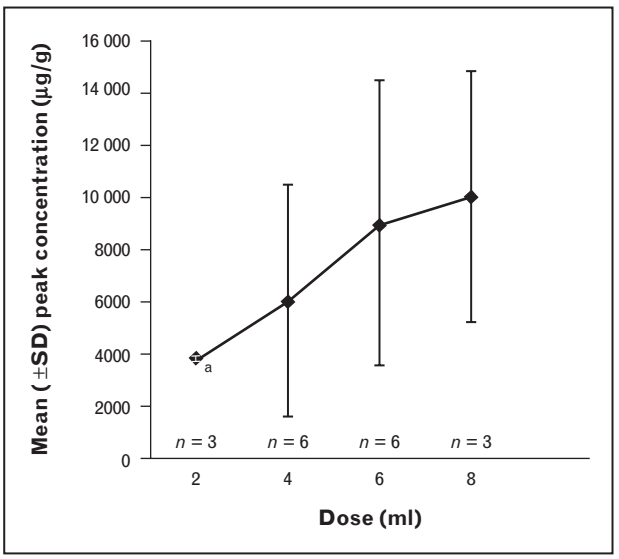

FIGURE 2. Mean peak fosfomycin concentrations in tracheal aspirates after aerosolized fosfomycin 20 mg/ml (with amikacin 50 mg/ml) by PARI Investigational eFlow Inline Nebulizer System in a phase 1, dose-escalation trial of seven patients with ventilator-associated pneumonia [26]. The minimal inhibitory concentration for 90% (MIC_{90}) for methicillin-resistant *Staphylococcus aureus* (MRSA) is 32 µg/ml. SD, standard deviation. a, The SD bar for the 2-ml dose is very small and is shown in white inside the data point.

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

M.H.K. has received grants from NIAID and the Barnes-Jewish Hospital Foundation and is on the speaker's bureau for Cubist. C.W.H. has received funding for preparing or editing manuscripts from Cardeas Pharma Corp., CareFusion, Infectious Diseases Society of America, and Johnson & Johnson. A.B.M. is CEO of Cardeas Pharma Corp, which is developing the combination of amikacin and fosfomycin.

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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.

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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.

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