Ventilator-associated infection: the role for inhaled antibiotics

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Purpose of review
Despite multiple protocols for the prevention of ventilator-associated pneumonia (VAP), respiratory infections have not been eliminated in the ICU. The profound disruption in both airway integrity and mucociliary clearance caused by the endotracheal tube makes it unlikely there will ever be a zero rate of respiratory infection in critically ill ventilated patients or a 100% cure rate when infection is present. In fact, options for treatment are diminishing as bacteria resistant to most, or in some hospitals all, systemic antibiotics increase in prevalence from our liberal use of systemic antibiotics. Inhaled therapy with proper delivery will result in the high concentrations of antibiotics needed in the treatment of increasingly resistant organisms.

Recent findings
Data from many recent investigations have focused on inhaled antibiotics as: adjunctive therapy to systemic antibiotic for VAP, monotherapy for VAP, and as monotherapy for ventilator-associated tracheobronchitis. The clinical outcomes of these studies will be reviewed as well as their effect on multidrug-resistant organisms.

Summary
The present review will focus on the rationale for inhaled therapy, the current studies examining the delivery and clinical efficacy of inhaled antibiotics, and the potential role for this mode of delivery actually decreasing antibiotic resistance in the respiratory tract.

Keywords
aerosolized antibiotics, bacterial resistance, inhaled antibiotics, ventilator-associated pneumonia, ventilator-associated tracheobronchitis

INTRODUCTION

Ventilator-associated pneumonia (VAP) remains the ICU infection associated with the highest morbidity and mortality [1–3]. The actual incidence of ventilator-associated tracheobronchitis (VAT) and VAP remains controversial, because of the poor sensitivity and specificity of the current diagnostic techniques and the overlap between proximal airway infection and deep lung infection [4▪,5–7]. There is, however, no doubt that ventilator-associated infections remain a significant problem despite a multitude of protocols designed to prevent them [8,9▪▪,10▪▪]. They are responsible for up to 50% of the antibiotics used in the ICU. Furthermore, in many ICUs, *Acinetobacter baumanii*, *Pseudomonas aeruginosa*, and carbapenemase *Enterbacteriaciae* spp. are increasing in prevalence, and in some hospitals, these pathogens are now resistant to all antibiotics including colistin [11–17,18▪▪].

ICU physicians in many regions of the world with endemic multidrug resistant (MDR) or extensively drug-resistant (XDR) Gram-negatives are responding to the lack of effective systemic antibiotics by adding inhaled antibiotics empirically to their treatment regimens [19–29]. Empiric therapy remains the only choice as 45 years after the initial instillation of antibiotics into an endotracheal tube or a tracheostomy tube, we have no commercially available US Food and Drug Administration (FDA)-approved inhaled drugs in the market for ventilated patients (listed below).

Aerosolized antibiotics used in mechanically ventilated patients for respiratory infection (off-label use and US FDA-approved):

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KEY POINTS

- Ventilator-associated respiratory infections caused by increasingly resistant Gram-negative organisms are a challenge for intensivists to treat.
- Inhaled antibiotics when delivered properly may become an important part of treating these infections.
- Early data suggest that unlike systemic antibiotics, they may actually reduce the emergence of new resistance.

(1) Amikacin
(2) Amikacin proprietary preparation (phase 3 enrolling patients; Bayer Healthcare delivered with proprietary pulmonary drug delivery system)
(3) Amikacin/fosfomycin proprietary preparation (phase 1 completed; delivered with Pari investigational eFlow inline nebulizer)
(4) Colistin
(5) Colistin methanesulfonate [prodrug of colistin (polymyxin E)]
(6) Ceftazidime
(7) Gentamicin
(8) Tobramycin
(9) Tobramycin proprietary preparation (US FDA approved for spontaneous breathing cystic fibrosis patients known to be colonized with *P. aeruginosa*)
(10) Sisomycin
(11) Vancomycin

Because of costs, urgency of treatment, and lack of alternatives, many physicians are using the nebulizers their hospitals have on the shelf which vary considerably from country to country, and their function when placed in a ventilator circuit is not well defined. In fact, the majority of the published research on inhaled therapy in the ICU neither describes the method of aerosolization nor the known deposition site or the concentration achieved in the lung or secretions, which implies these investigations have not met the criteria for acceptable antimicrobial therapy. The dose is described, but is empiric. To outwit the current pathogens, we have to pay far more attention to the details. Dhand [30] has written a detailed review of the types of devices and factors that influence delivery and efficacy. This review will focus on the current clinical trials.

PATHOPHYSIOLOGY OF RESPIRATORY INFECTIONS AND THE RATIONALE FOR INHALED THERAPY

Difficulty in treatment is understandable when one examines the pathway of microbial transfer from the oropharynx to the tracheobronchial tree, and to the more distal alveolar tissue. Figure 1 shows the airway of an intubated critically ill patient and all the contributing factors that may lead to respiratory infection with resistant organisms that are difficult to treat. Pathogenic bacteria that are frequently MDR organisms (MDROs) colonize the oropharynx of critically ill patients before or soon after intubation. Within 24 h of the placement of the endotracheal tube, there is localized injury to the mucosa near the cuff, and mucociliary clearance is dramatically impaired. The pathogens that colonize the oropharynx enter the proximal airway directly from micro-aspiration. Oral secretions then pool near the cuff and migrate under the cuff to the more distal airway. Alternatively, organisms may have a direct entry into the lung via the lumen of the endotracheal tube from bacteria residing in the ventilator circuit. This process may progress from colonization to infection in the tracheobronchial tree and is called VAT [31].

Increasing attention is being paid to the process outlined above. VAT has been viewed in two distinct paradigms (Table 1). The differences are important as they could effect treatment decisions. The first paradigm emphasizes evidence of local infection, the lack of deep lung infection, and signs of systemic toxicity such as fever and increased white count [32,33].

The second paradigm views VAT as an anatomic area of suppurative infection which may or may not have systemic signs of infection associated with it, and the presence of radiographic changes does not preclude it [34]. The hypothesis is that it represents an area of infection that may not respond well to systemic antibiotics. Major factors for lack of response may include: the concentrations in the airway may be lower than in the bloodstream, the bacteria in this environment may require 10–25 times the minimum inhibitory concentration for bactericidal activity [35], and the presence of biofilm may decrease the efficacy of systemic antibiotics due to lack of penetration [36]. When VAP is present and treated with systemic antibiotics, this more proximal area of infection may persist and act as a reservoir of infected secretions that continue to promote recurrent infections. Alternatively, if ventilator-associated tracheobronchitis-anatomic (VAT-A) is present its early treatment may prevent progression to VAP.

CLINICAL TRIALS FOR TREATING VENTILATOR-ASSOCIATED TRACHEOBRONCHITIS AND/OR VENTILATOR-ASSOCIATED PNEUMONIA

A description of the earliest evidence supporting the use of inhaled antimicrobials was performed by

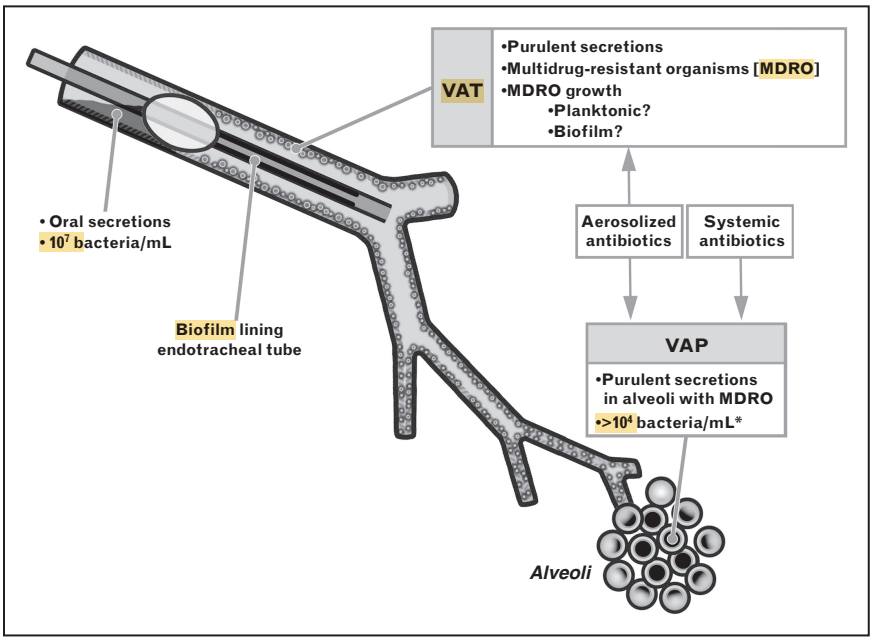

FIGURE 1. The multifactorial process that leads to VAT and VAP. Subglottic secretions, disturbed mucociliary clearance, damaged mucosa, and bacterial biofilm may all play a role in the pathogenesis of proximal and distal infections. Within a few days of ICU admission, the bacteria frequently become MDROs. *The cut-off of 10^4 colony-forming units per milliliter for the microbiological diagnosis of VAP may not pertain to patients with prolonged mechanical ventilation. Reproduced from Palmer *et al.* [51].

Ioannidou *et al.* [37] in a meta-analysis of small randomized controlled trials (RCTs) done from 1950 to 2007. The clinical efficacy of topical administration (aerosolization or instillation) with or without concurrent usage of systemic antibiotics for treatment of VAP was examined. There were only five RCTs [38–42] with a combined total of 176 patients suitable for analysis. Antibiotics used included tobramycin, sisomycin, and gentamicin. In four of the five trials, the aerosolized antibiotic was adjunctive to intravenous (i.v.) therapy [39–42]. This meta-analysis demonstrated that patients receiving aerosolized or instilled antibiotics had higher rates of resolution of signs and symptoms of VAP (clinical diagnosis), intention-to-treat fixed-effect model: [odds ratio (OR) 2.39, 95% confidence interval (CI) 1.29–4.44]; random-effect model (OR 2.75, 95% CI 1.06–7.17), and when analyzed for clinically evaluable patients had an OR of 3.14 (95% CI 1.48–6.70). There were no statistically significant differences between the therapeutic regimens for mortality or toxicity.

More recent studies are shown in Table 2. This table describes the method of delivery of aerosol, and the clinical and microbial effects of therapy.

Table 1. Two paradigms for ventilator-associated pneumonia (ventilator-associated tracheobronchitis)

Criteria	VAT	VAT-A[a]
Clinical signs and symptoms	Temperature (>38°C) or leukocyte count above 12000/ml, or leukopenia below 4000/ml (at least one of these) + new onset of purulent endotracheal secretions or change in sputum	Purulent secretions
Volume of secretions	–	≥2 ml/4 h
Radiology CXR or CT	No new infiltrate	Radiographic findings do not preclude VAT
Gram stain	ETA: PMNLs with bacteria on Gram stain	PMNLs with organisms on Gram stain[b]
Endotracheal culture	ETA (moderate to heavy growth) or quantitative ETA ≥10^{5-6} cfu/ml	Moderate to heavy growth on semiquantitative cultures
BAL cultures	Not required but if BAL done CFU must be <10^4 cfu/ml	Not used

BAL, bronchoalveolar lavage; CFU, colony-forming units; CT, computed tomography; CXR, chest X-ray; ETA, endotracheal aspirates; PMNLs, polymorphonuclear leukocytes; VAT, ventilator-associated tracheobronchitis.
[a]VAT-A, anatomic definition of infected site not related to systemic signs or symptoms of infection.
[b]Criteria that determine antibiotic chosen.

Table 2. Delivery device and microbiological and clinical response to aerosolized antibiotics in the ICU (2005–2014) [49]

Authors	Year	Setting	Design	Indication	Drug and method of aerosolization; no. of patients on AA or i.v. or placebo	Organisms in patients	Number of patients with eradication of causative organism	Number of patients with newly resistant organisms	Clinical response	Adverse events
Berlana *et al* [43]	2005	ICU, Spain	Retrospective chart review, 1 arm; examined microbiologic outcomes	VAP 49/71 [69%] were VAP, clinical diagnosis + quantitative cultures; VAT or colonized 22/71 [31%]	Colistin $n=71$; aerosolized with various compressors; 68/71 [96%] also on i.v.	*Acinetobacter baumanii* 60; *Pseudomonas* 11; all susceptible to colistin	*Acinetobacter baumanii* 33/33 [100%]; *Pseudomonas aeruginosa* 4/7 [57%]	No new resistance seen	Not described; only studies microbiologic response	No renal impairment observed
Palmer *et al.* [34]	2008	ICU, United States	Randomized double blind placebo controlled	VAT $\geq$2 ml sputum/4 h and organism on Gram stain	Vancomycin and/or gentamicin jet nebulizer; placebo 24; 19/24 [79%] also on i.v.; AA 19; 17/19 [89%] also received i.v.	Multiple species of Gram-negative and Gram-positive organisms	AA 6/8 [75%] at day 14; placebo; 3/14 [21%]	Placebo 8/24 [33%], AA 0/19 [0%]	AA vs. placebo; resolution of VAP [adjusted odds ratio 0.29, 95% CI 0.13–0.66, $P=0.006$]. Reduced use of systemic antibiotic ($P=0.042$); increased weaning ($P=0.046$)	No bronchial constriction
Kofteridis *et al* [28]	2010	ICU, Greece	Retrospective review, matched case control	VAP; clinical diagnosis + endotracheal secretions or BAL	Colistin; aerosolization not described; i.v. and aerosolized colistin 43; i.v. colistin 43	*Acinetobacter* 66; *Klebsiella* 12; *Pseudomonas* 8; all susceptible to colistin	i.v. = 17/34 [50%]; i.v. + AA, 19/42 [45%] $P=0.679$	No resistance in AA group; resistance in i.v. group not described	AA + i.v. vs. i.v.; clinical cure ($P=0.679$); mortality ($P=0.289$)	Renal impairment no different in either group; no neurotoxicity in either group
Korbila *et al.* [27]	2010	ICU, Greece	Retrospective review, matched case control	VAP; clinical diagnosis and quantitative cultures of respiratory specimens	Colistin; aerosolized via Siemens Servo ventilator, aerosolized colistin + i.v. 78; i.v. colistin 43	MDR Gram-negative organisms; *Acinetobacter baumanii, Pseudomonas aeruginosa, Klebsiella* spp.; all colistin-susceptible	Not described	Not described	Cure; i.v. + AA 62/78 [79%] vs. i.v. = 26/43 [60%], $P=0.025$; ICU mortality 28/78 [36%] vs. 17/43 [40%] $P=0.92$	No bronchial constriction
Rattanaumpawan *et al.* [29]	2010	ICU, Thailand	Open-label RCT	VAP; clinical diagnosis + Gram-negative in secretions	Colistin; aerosolization not described; AA + i.v. 51; placebo + i.v. 49	Colistin-susceptible *Pseudomonas aeruginosa* and *Acinetobacter baumanii*	AA + i.v. 31/51 [61%]; placebo + i.v. 19/49 [39%], $P=0.03$	Not described	AA + i.v. 26/51 [51%]; placebo + i.v. 25/49 [51%], $P=0.84$; AA group, shorter days of i.v. antibiotic	No difference in renal impairment or bronchial constriction
Lu *et al.* [44]	2011	ICU France	Randomized trial comparing AA to i.v. antibiotics	VAP; clinical diagnosis + BAL or mini-BAL	Vibrating plate nebulizer; nebulized amikacin and ceftazidime ($N=20$); amikacin and ceftazidime i.v. ($N=20$)	*Pseudomonas aeruginosa* susceptible to drugs	AA 16/16 [100%] on day 5; i.v. 7/15 [47%] on day 5	AA day 9, 0/12 [0%]; i.v. day 9, 5/11 [45%]	AA 14/20 [70%]; i.v. 11/20 [55%]; P=NS	AA-hypoxemia 3/20 [15%]; expiratory filter occluded 3/20 [15%]; 1/20 [5%] cardiac arrest

Arnold *et al.* [45]	2012	MICU; SICU; United States	Retrospective chart review with cohort study	VAP; clinical diagnosis + BAL	Colistin; vibrating plate; inhaled antibiotics; colistin ($N=9$), tobramycin ($N=10$). All patients also on i.v.; i.v. only ($n=74$)	*Pseudomonas aeruginosa* and *Acinetobacter baumanii* susceptible to drug administered	Not described	Not described	Increased survival by Kaplan–Meier for AA + i.v. ($P=0.030$)	AA + i.v.; 1 episode of bronchial constriction; 1 episode of renal impairment
Lu *et al.* [46]	2012	ICU, France	Prospective, observational comparator	VAP; clinical dx + BAL or blind mini-BAL	Colistimethate; vibrating plate nebulizer; 3 arms; [1] cohort group with organisms susceptible to β-lactams Tx = i.v. only ($N=122$) [2]; group with organisms resistant to β-lactams Tx = i.v. + AA ($N=15$) [3]; group with organisms resistant to β-lactams Tx = AA alone ($N=28$)	*Pseudomonas aeruginosa* and *Acinetobacter* spp.; β-lactam susceptible; *Pseudomonas aeruginosa* and *Acinetobacter baumanii*-susceptible to colistin resistant to β-lactams	Not reported	Reported for patients with recurrent infection; AA 4/16 [25%] converted from β-lactam resistant to susceptible after inhaled therapy; i.v. 24/32 = 75% of isolates developed new resistance; 6/32 became resistant to all β-lactams	Clinical cure; β-lactam susceptible; 81/122 [66%]; β-lactam resistant 29/43 [67%] $P=$NS; mortality; β-lactams susceptible on i.v.; 28/122 [7%]; β-lactam resistant on AA 7/43 [16%]; $P=0.357$	No renal toxicity observed; creatinine similar in both groups
Niederman *et al.* [47]	2012	Multisite phase 2 trial in United States; Spain and France	VAP clinical diagnosis; proprietary amikacin BAY41–6551 vibrating mesh nebulizer; 67 patients divided into three groups	VAP; clinical diagnosis + BAL or tracheal aspirates	All received i.v. antibiotics according to ATS Guidelines 2005; inhaled amikacin† at 400 mg Q 12H and 400 mg Q 24H; placebo normal saline Q 12H	Gram-negative organisms; predominant species *Pseudomonas*	Inhaled amikacin† 22/33 [68.8%]; placebo 10/16 [62.5%]	Not described	Inhaled amikacin† Q 12, 93.8% [15/16], inhaled amikacin† Q 24H 75.0% [12/16], and placebo 87.5% [14/16] [$P=0.467$]; mean number of antibiotics per patient per day; inhaled amikacin† Q12 0.9/day in the q12h, inhaled amikacin† q24h 1.3/day in the q24h, and placebo 1.9/day in the placebo groups ($P=0.02$ between groups)	
Doshi *et al.* [48]	2013	Medical; surgical; ICUs United States	Retrospective multicenter cohort study	VAP diagnosed; by BAL or endotracheal secretions	Colistin; aerosolized with jet nebulizers or vibrating mesh nebulizer; i.v. only = 51 patients; i.v. + AA colistin = 44	i.v. patients; *Acinetobacter* 25/51 [49%]; *Pseudomonas* 35/51 [69%]; ESBL 9/51 [18%]; i.v. + AA; *Acinetobacter* 36/44 [82%]; *Pseudomonas* 18/44 [41%]; ESBL 2/44 [5%]; all organisms susceptible to colistin	i.v. 27/51 [53%]; i.v. + AA 18/44 [41%]; $P=0.805$	Not described	In patients diagnosed with BAL; i.v. 9/32 [31.3%]; i.v. + AA 19/35 [57%] $P=0.033$	Not reported

(*Continued*)

Table 2 (*Continued*)

Authors	Year	Setting	Design	Indication	Drug and method of aerosolization; no. of patients on AA or i.v. or placebo	Organisms in patients	Number of patients with eradication of causative organism	Number of patients with newly resistant organisms	Clinical response	Adverse events
Tumbarello *et al.* [49]	2013	ICU, Italy	Retrospective cohort study	VAP diagnosed by BAL with organisms with COS	Colistin; jet or ultrasonic nebulizers; i.v. = 104; i.v. + AA 104	i.v.; *Acinetobacter* 72/104 [69%]; *Pseudomonas* 24/104 [23%]; *Klebsiella* 8/104 [8%]; i.v. + AA; *Acinetobacter* 56/104 [54%]; *Pseudomonas* 28/104 [27%]; *Klebsiella* 20/104 [19%]; all organisms were COS	i.v. 52/84 [62%]; i.v. + AA 42/82 [51%]; $P = 0.08$	Not reported	i.v. 57/104 [55%]; i.v. + AA; 72/104 [69%]; $P = 0.03$	Not reported
Palmer *et al.* [50▪▪]	2014	MICU; SICU; United States	Randomized, double-blind, placebo-controlled	VAT $\geq$ 2 ml sputum/4 h and organism on Gram stain	Jet nebulizer; placebo + i.v. $N = 18$; inhaled antibiotic + i.v. $N = 24$; inhaled antibiotics included vancomycin and/or aminoglycoside determined by Gram stain; i.v. antibiotics were all chosen by the responsible physician	Predominantly MDROs including MRSA and Gram-negative MDROs	AA + i.v. 26/27 [96%] isolates; placebo + i.v. 2/23 [9%] isolates	AA + i.v. 0/16 [0%] of new resistance to aerosolized drug, 2/16 [13%] new MDROs; placebo + i.v. 6/11 [56%] new resistance	Aerosol + i.v. vs. placebo + i.v.; CPIS deceased significantly only in AA, $P = 0.0008$	Creatinine similar in both groups at end of trial, no renal toxicity

AA, aerosolized antibiotic; COS, colistin only susceptible; CPIS, clinical pulmonary infection score; HAP, hospital-acquired pneumonia; i.v., intravenous; MDR, multidrug-resistant; MDROs, multidrug-resistant organisms; MICU, medical intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*; RCT, randomized controlled trial; SICU, surgical intensive care unit; VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis.
[a]A proprietary amikacin BAY41–6551 (NCT01004445).

CLINICAL TRIALS USING INHALED THERAPY TO TREAT VENTILATOR-ASSOCIATED TRACHEOBRONCHITIS

There are only two RCTs examining the effect of aerosolized antibiotics targeted on VAT, and both are by the same authors [34,50▪▪]. Patients were not excluded if they had co-existing VAP as the VAT-A definition was used. Prior work by this group had shown that with the optimization of delivery, peak antibiotic concentrations in respiratory secretions were 200-fold greater than the levels achieved in the blood of patients receiving systemic therapy [51]. The investigators hypothesized that treating the proximal airway infection (VAT-A) with very high concentrations of antibiotics would reduce or prevent signs and symptoms of respiratory tract infection and might also decrease bacterial resistance by eliminating bacterial populations [34]. Patients were randomized to aerosolized antibiotic or placebo targeted at the organisms on Gram stain in their tracheal aspirates. Systemic antibiotics were given by the responsible physicians, as indicated by clinical signs and symptoms of pneumonia. Both groups were on similar amounts of appropriate systemic antibiotics for the organism(s) in the tracheal aspirate. Patients receiving aerosolized antibiotics had significantly decreased signs of respiratory infection, were extubated more often, had decreased need for additional antibiotics, and had decreased bacterial resistance at the end of the treatment. In the seven patients with only VAT-A, none progressed to VAP. These findings suggest an important role for aerosolized therapy in the ICU for the treatment of patients with VAT and VAP.

Most recently, in another randomized, double-blind, placebo-controlled study, critically ill intubated patients with prolonged mechanical ventilation were randomized if they exhibited signs of respiratory infection (purulent secretions and Clinical Pulmonary Infection Score ≥ 6) and VAT-A [50▪▪]. Using a well characterized jet nebulizer aerosol delivery system with humidification turn off, inhaled antibiotic or saline placebo was given for 14 days or until extubation. The responsible clinician determined administration of systemic antibiotics for VAP and any other infection. Compared with placebo, inhaled antibiotics significantly reduced Clinical Pulmonary Infection Score (mean $\pm$ SEM, PRE 9.3 ± 2.7 to POST 5.3 ± 2.6 vs. PRE 8.0 ± 23 to POST 8.6 ± 2.10; $P = 0.0008$), and the volume of secretions (mean $\pm$ SEM, PRE 6.9 ± 4.7 ml/4 h decreased to POST 1.1 ± 1.3 ml/4 h vs. PRE 8.80.69 ml/4 h to POST 6.3 ± 4.3 ml/4 h; $P < 0.001$). The effects on bacterial growth are shown in Fig. 2.

Aerosolized colistin for ventilator-associated infection

Highly resistant *P. aeruginosa* and *A. baumanii* have led to the reintroduction of colistin (polymyxin E) in an aerosolized form, as well as its prodrug, colistimethate sodium (CMS). Colistin's bactericidal

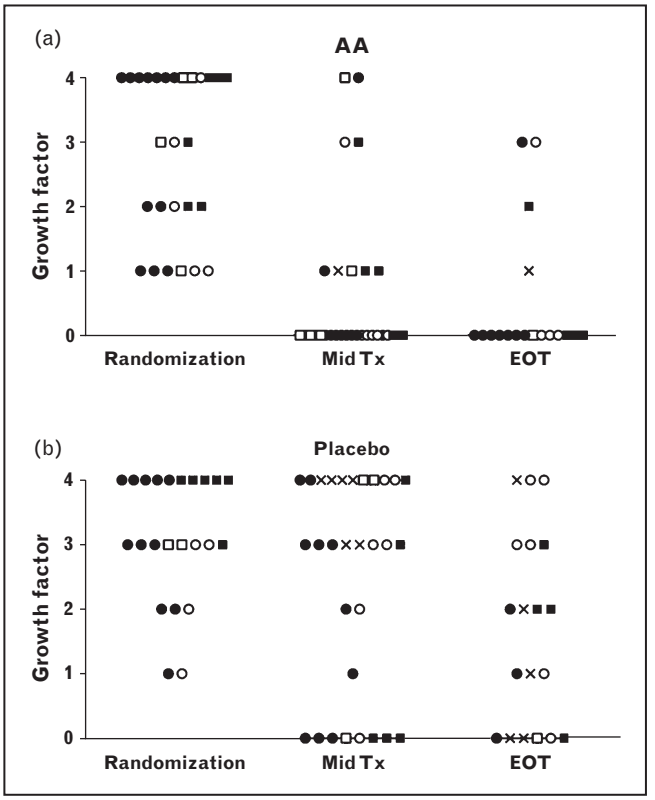

FIGURE 2. Bacterial growth from tracheal aspirates obtained at time of randomization, mid-treatment (Mid-Tx), and at end of treatment (EOT) for (a) aerosolized antibiotics (AA) and (b) placebo. Growth is quantified using a graded scale 0–4 from semiquantitative cultures: multidrug-resistant Gram-negative organisms (filled circles), nonresistant Gram-negative organisms (open circles), resistant Gram-positive organisms (filled squares), nonresistant Gram-positive organisms (open squares), and newly resistant organisms on treatment (X). Some patients had multiple isolates. At Mid-Tx, all the isolates with zero growth represent organisms detected at randomization that did not grow in isolates sampled at Mid-Tx. At EOT, the isolates with zero growth represent organisms detected at randomization and Mid-Tx that did not grow in samples obtained at EOT. There was a clear difference in pattern of bacterial growth between AA and placebo. Two AA isolates demonstrated persistent growth at EOT: one methicillin-resistant *Staphylococcus aureus* (filled square) that was not eradicated by AA, but had no Gram-positive cocci on Gram stain, and one persistent *Acinetobacter* (filled circle) with organisms present on Gram stain. More newly resistant organisms were seen in the placebo group. Reproduced from Palmer *et al.* [50▪▪].

activity works via destabilization of the lipopolysaccharide (LPS) of the outer membrane, and in addition, it neutralizes the LPS, thereby decreasing antiendotoxin activity [52]. Its i.v. use was discontinued for about 40 years because of its neurological and renal toxicity when used parenterally and the advent of less toxic antibiotics. There have been multiple small nonrandomized clinical trials, one RCT, one review, and one meta-analysis focused on aerosolized and i.v. colistin treatment for MDR Gram-negative species, in particular, *Acinetobacter* spp. and *Pseudomonas* spp. [20,22–25,27,28,43,45,46,48,49,53–56]. Both these bacteria produce extended-spectrum β-lactamases, as well as metallo-β-lactamases. *Acinetobacter* is often sensitive only to polymyxin B or colistin (polymyxin E), and there are now reports of colistin resistance as well.

Studies of adjunctive therapy from 2007 through 2011 have been reviewed previously and will not be covered in detail here [31,57]. Recent colistin studies are included in Table 2.

In a retrospective cohort study, Arnold *et al.* [45] assessed the treatment of VAP caused by *P. aeruginosa* and *A. baumannii* VAP. Patients with only i.v. therapy ($n=74$) were compared to those who received adjunctive inhaled colistin ($n=19$) and adjunctive inhaled tobramycin ($n=10$). This was a retrospective study and the cohort group had a much lower Acute Physiology and Chronic Health Evaluation II (APACHE II) than the group that received inhaled therapy. Drugs were aerosolized via a nebulizer that generated particles that were 1–5 μm for the delivery of the aerosolized antibiotic over a 15–20-min time period.

Those treated with inhaled antibiotics had more MDROs (52.6 vs. 14.9%; $P=0.001$) and higher APACHE II scores (21.4 ± 5.7 vs. 17.5 ± 5.3; $P=0.004$). Despite these marked differences in patient acuity and bacterial susceptibility, the Kaplan–Meier curves for the probability of 30-day survival from VAP onset demonstrated that patients receiving an aerosolized antibiotic had statistically greater survival ($P=0.030$ by the log-rank test).

The effects of high-dose nebulized colistin (5 million international units every 8 h) were investigated by Lu *et al.* [46] in a prospective observational comparative study testing the efficacy of nebulized colistin for treating VAP caused by MDR Gram-negative vs. susceptible organisms treated with i.v. antibiotics [46]. One hundred and sixty-five patients with VAP caused by *P. aeruginosa* and *A. baumannii* were enrolled. There were 122 patients having VAP caused by *P. aeruginosa* and *A. baumanii* susceptible to β-lactams, aminoglycosides, or quinolones and treated with i.v. antibiotics for 14 days. The second group included 43 patients having VAP caused by MDR *P. aeruginosa* and *A. baumannii* and treated with nebulized colistin (5 million international units every 8 h) either in monotherapy ($n=28$) or combined to a 3-day i.v. aminoglycoside treatment for 7–19 days. The primary endpoint was clinical cure rate. Aerosol was delivered using vibrating plate nebulizer with no humidification. The clinical cure rate was 66% in the sensitive strain group and 67% in the MDR strain group (difference −1%, lower limit of 95% CI for difference −12.6%). There was no difference in the inhaled monotherapy group vs. the inhaled therapy + 3 days of i.v. aminoglycoside therapy. Mortality was not different between groups. This investigation demonstrated a therapeutic effect that was noninferior to i.v. β-lactams associated with aminoglycosides or quinolones for treating VAP caused by susceptible *P. aeruginosa* and *A. baumannii*. This study raises the question: If the patient had received both i.v. and inhaled therapy throughout the treatment, would the outcome have been more robust?

The question was addressed by Tumbarello *et al.* [49] in a retrospective 1 : 1 matched case-control study, to evaluate the efficacy and safety of aerosolized + i.v. colistin vs. i.v. colistin alone in 208 patients in the ICU, with VAP caused by colistin only susceptible (COS) *A. baumannii*, *P. aeruginosa*, or *Klebsiella pneumoniae*. The medication was delivered with jet or ultrasonic nebulizers. The aerosolized antibiotic-intravenous (AA-i.v). colistin cohort had a higher clinical cure rate (69.2 vs. 54.8%; $P=0.03$) and required fewer days of mechanical ventilation after VAP onset (8 vs. 12 days; $P=0.001$). One hundred and sixty-six patients had post-treatment cultures. Eradication of the causative organism was more common in the AA-i.v. colistin group (63.4 vs. 50%; $P=0.08$), although the difference was not significant. No differences in ICU mortality, length of ICU stay after VAP onset, or rates of acute kidney injury (AKI) during colistin therapy were seen between the i.v. or the AA-i.v. arms.

In a similar study, organisms were MDR, but not exclusively COS. Doshi *et al.* [48] conducted a retrospective multicenter cohort study comparing i.v. colistin alone vs. colistin given in aerosolized and i.v. forms. Baseline characteristics were similar between the two groups. Twenty patients (39.2%) receiving i.v. and 24 (54.5%) receiving i.v. + aerosolized colistin achieved clinical cure ($P=0.135$). There was no difference in microbiologic cure rates between the i.v. and the i.v. + aerosolized colistin groups (40.7 vs. 44.4%; $P=0.805$). The i.v. group demonstrated a trend towards higher mortality (70.4 vs. 40%; $P=0.055$) attributable to pneumonia.

In the subgroup analysis of patients with high-quality respiratory cultures (bronchoalveolar lavage), there was a significantly higher clinical cure rate for those in the i.v. + aerosolized group compared to the i.v. group (57.1 vs. 31.3%; $P = 0.033$).

HOW DO AEROSOLIZED ANTIBIOTICS AFFECT EMERGENCE OF BACTERIAL RESISTANCE COMPARED WITH SYSTEMIC ANTIBIOTICS?

Increased bacterial resistance in the ICU has been shown to have a direct relationship to the amount of systemic antibiotics used. The relationship between inhaled therapy and emergence of MDRO is limited. The meta-analysis of Ioannidou *et al.* [37] mentioned previously described a 6.5% (6/46) incidence of new resistance at the end of treatment in the five RCTs included. Table 3 shows recent data on the eradication of pathogens and the emergence of resistance for studies published between 2005 and 2014 mentioned previously. Six trials report data on the emergence of resistance [28,34,43,46,50▪▪]. In these trials, no new resistance to drug administered was detected. Included are four RCTs with resistance data. Kofteridis *et al.* [28] described no new resistance in the group that received aerosol, but there were no data provided for the patients that reviewed only systemic antibiotics. Palmer *et al.* demonstrated that 8 of the 24 placebo participants acquired resistant organisms during treatment compared with 0 of the 19 aerosolized antibiotic patients ($P = 0.0056$) [34]. In the placebo group receiving only systemic antibiotics, four participants with sensitive bacteria (three *P. aeruginosa* and one *K. pneumoniae*) developed resistance on treatment. Two participants acquired a resistant *Acinetobacter* and two acquired methicillin-resistant *Staphylococcus aureus*. One of the 19 aerosolized antibiotic participants transiently acquired a resistant organism, a resistant *Acinetobacter* that resolved during therapy. All patients who acquired resistant organisms received systemic antibiotics. Lu *et al.*'s [44] randomized trial of i.v. vs. inhaled antibiotics (as exclusive treatment) again showed the emergence of resistance only in the comparator group that received systemic antibiotics.

In another investigation with more chronically ventilated patients, inhaled antibiotics eradicated 26 of the 27 organisms present at randomization compared with 2 of the 23 organisms in the placebo group ($P = 0.0001$), despite both groups being on similar amounts of appropriate systemic antibiotics. Inhaled antibiotics eradicated the original resistant organism on culture and Gram stain at the end of the treatment in 14 out of the 16 patients compared with 1 of the 11 for placebo ($P = 0.001$) [50▪▪]. Resistance to systemic antibiotics significantly increased in the placebo patients receiving only systemic antibiotics ($P = 0.03$). In chronically intubated critically ill patients, inhaled therapy successfully eradicated existing MDROs and reduced the pressure from systemic agents for new respiratory resistance.

In Lu *et al.*'s [46] study mentioned previously, which compared systemic therapy given for VAP with β-lactam-susceptible organisms to high-dose nebulized colistin administered to patients with *Pseudomonas* resistant to β-lactams, the emergence of resistance was described. In patients who had susceptible organism and received i.v. therapy, 75% of the patients who had either not responded or had recurrent VAP acquired resistance to β-lactams. Interestingly, in the patients on nebulized colistin with β-lactam-resistant organisms, 25% of those with recurrent VAP now had organisms susceptible to β-lactams.

These studies all suggest that inhaled therapy may have a beneficial effect decreasing the emergence of resistance supporting our initial hypothesis that very high antibiotic concentrations may eradicate the highly resistant organisms.

Table 3. Clinical response in aerosolized antibiotic group vs. placebo group[a]

	Randomization			EOT		
	AA ($n = 24$)	Placebo ($n = 18$)	*P* value	AA ($n = 24$)	Placebo ($n = 18$)	*P* value
CPIS*	9.3 ± 2.7	8.0 ± 2.1	0.5000[b]	5.3 ± 2.6	8.6 ± 2.6	0.0008[b]
Volume/4 h**	6.9 ± 4.7	8.9 ± 0.69	0.12	1.1 ± 1.3	6.3 ± 4.3	<0.001
Systemic WBC***	17.1 ± 1.9	12.6 ± 1.2	0.18	13.3 ± 1.3	13.9 ± 1.5	0.726

AA, aerosolized antibiotics; CPIS, Clinical Pulmonary Infection Score; EOT; end of treatment. Wilcoxon analyses: AA randomization vs. AA EOT. Placebo randomization vs. placebo EOT. Not significant for any parameters in the table. Modification of [40] ([50▪▪]).

[a]Both groups were on equivalent amounts of systemic antibiotics.

[b]Mann–Whitney test.

*$P < 0.0001$.

**$P < 0.0500$.

***$P < 0.0280$.

CONCLUSION

Ventilator-associated infections caused by Gram-negative MDROs are increasingly challenging to treat. As can be seen from this review, large multisite trials are needed to answer the following questions:

(1) What are the concentrations of antibiotics needed to eradicate MDROs in the proximal airway in areas of thick purulent secretion (VAT-A)?
(2) What are the best delivery devices to achieve the concentrations necessary to treat VAT and VAP?
(3) Can inhaled antibiotics reduce or eliminate systemic antibiotic use?
(4) Can inhaled therapy consistently decrease the emergence of newly resistant organisms?

The answer to these questions will determine if inhaled therapy may become one of our most effective tools for the treatment of ventilator-associated infections caused by MDROs.

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Conflicts of interest

The Research Foundation of the State University of New York has licensed patents to Nektar Therapeutics for the use of inhaled antibiotics.

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