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A randomized trial of the amikacin fosfomycin inhalation system for the adjunctive therapy of Gram-negative ventilator-associated pneumonia: IASIS Trial

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Running Title: Amikacin fosfomycin aerosol for bacterial pneumonia

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ABSTRACT

Background: Clinical failures in ventilator-associated pneumonia (VAP) caused by Gram-negative bacteria are common and associated with substantial morbidity, mortality, and resource utilization.

Methods: We assessed the safety and efficacy of the amikacin fosfomycin inhalation system (AFIS) for the treatment of Gram-negative bacterial VAP in a randomized double-blind, placebo-controlled, parallel group, phase 2 study between May 2013 and March 2016. We compared standard of care in each arm plus 300 mg amikacin/120 mg fosfomycin or placebo (saline), delivered by aerosol twice daily for 10 days (or to extubation if <10 days) via the investigational eFlow Inline System (PARI GmbH, Germany). The primary efficacy endpoint was change from baseline in the Clinical Pulmonary Infection Score (CPIS) during the randomized course of AFIS/placebo, using the subset of patients with microbiologically proven baseline infections with Gram-negative bacteria.

Results: 143 patients were randomized, 71 to AFIS, 72 to placebo. Comparison of CPIS change from baseline between treatment groups was not different (P=0.70). The secondary hierarchical endpoint of no mortality and clinical cure at Day 14 or earlier was also not significant (P=0.68) nor the hierarchical endpoint of no mortality and ventilator free days (P=0.06). Mortality was 17 (24%) in AFIS, 12 (17%) in placebo P=0.32. The AFIS group had significantly fewer positive tracheal cultures on Days 3 and 7 compared to placebo.

Conclusions: In this trial of adjunctive aerosol therapy compared to standard of care intravenous antibiotics in patients with Gram-negative VAP, AFIS was ineffective in improving clinical outcomes despite reducing bacterial burden.

ClinicalTrials.gov Identifier: NCT01969799

INTRODUCTION

Ventilator-associated pneumonia (VAP) caused by Gram-negative bacteria is associated with substantial morbidity, mortality, and resource utilization.[1-3] Clinical failures may be attributable both to the increasing prevalence of multidrug-resistant (MDR) pathogens[4] and to poor lung penetration of intravenously administered antibiotics.[5] Aerosolized antibiotic therapy to directly treat lung infections has been reported, but generalization of these studies to clinical practice has been limited by inadequately described delivery methods, formulations not optimized for airway tolerability, results from only a small number of patients or a single center, and/or lack of concurrent matched controls.[6-10] Recently, an experimental drug-device combination, AFIS (amikacin fosfomycin inhalation system), was reported to deliver high concentrations of amikacin plus fosfomycin to the lung exceeding the minimal inhibitory concentrations (MICs) for a large panel of amikacin-resistant Gram-negative bacteria.[11-14] We report herein the results of a Phase 2, placebo-controlled, multicenter, double-blind trial of the AFIS for the treatment of Gram-negative bacterial VAP in patients receiving standard of care intravenous (IV) antibiotics.

MATERIALS AND METHODS

Study Design

The study was conducted in intensive care units (ICUs) in France, Hungary, Greece, Spain, Turkey, and the United States (US), between May 2013 and March 2016. Informed consent was obtained for all participants. The trial was conducted according to the Declaration of Helsinki, the Notes for Guidance on Good Clinical Practice (GCP; 2000; CPMP/ICH/135/95), the International Council on Harmonisation (ICH) GCP, any local applicable regulations and was approved by the US FDA and all regulatory bodies of participating countries.

After screening, a centralized randomization procedure assigned patients to receive AFIS or placebo (1:1) with stratification according to region (Europe, the US); APACHE II score (≤15, >15); and age (≤60, >60 years). All patients received IV meropenem or imipenem (dose based on local regulatory guidelines) for Gram-negative coverage for 7 days, and longer if clinically indicated. Randomization and the first AFIS/placebo treatment had to occur within 72 hours of initiating IV antibiotics for the episode of pneumonia. Study treatment consisted of AFIS or placebo administered twice daily for up to 10 days. AFIS included 300 mg amikacin base and 120 mg fosfomycin, with pH and osmolality adjusted by HCl, in 6 mL of sterile, preservative-free water. Placebo included 6 mL of 0.9% saline. AFIS/placebo were administered with an investigational inline vibrating plate electronic nebulizer (PARI GMBH, Starnburg, Germany) placed proximal to the ventilator Y-connector and run continuously over approximately 12 minutes. Humidity was maintained during treatment. Any ventilator model was allowed as long as the bias flow was <4 L/min. Ventilator settings were not changed and the nebulizer was left in place during the AFIS/placebo treatment period. The Investigator could change or add additional IV antibiotics based on MIC report, clinical failure, allergy, or adverse event attributed to the IV drug. MRSA antibiotics were permitted if clinically indicated. If local antibiograms indicated likely resistance to carbapenems, IV colistin methanosulfate (or Polymyxin B) or an aminoglycoside other than amikacin could be added. If a patient's condition improved

sufficiently to allow extubation, administration of AFIS/placebo ceased but data collection on outcomes continued. Switching to oral antibiotics was not allowed before Day 7. The follow-up period included assessments on Days 14 and 28.

Study procedures included bronchoalveolar lavage (BAL) (either via bronchoscope or blind mini-BAL) prior to first dose of AFIS/placebo. Daily assessment through Day 14 included components of the Clinical Pulmonary Infection Score (CPIS).[15] Baseline CPIS was calculated using results for the first 5 variables and CPIS on subsequent days used all 7 variables (e-Tables 1-3 in the e-Appendix 1). CPIS was determined by a blinded central reviewer. Safety was assessed by monitoring adverse events, use of concomitant medications, results of urinalysis (through Day 10) and clinical chemistry, vital signs, and changes in airway peak and plateau pressures before and after study drug administration and oximetry during administration. Hematology, clinical chemistry, tracheal aspirate samples (if patient was still intubated), and chest x-rays were performed on Days 3, 7, 10 and 14 (and as needed according to standard of care). Isolates from positive tracheal aspirate samples were shipped to a central laboratory for confirmation of identity and measurement of MICs against a panel of antibiotics. Samples for pharmacokinetic measurements were obtained on Days 3 and 10. An independent Data Safety Monitoring Board reviewed safety data at 50 and 100 patients and recommended continuing the study.

Patient Population

Eligible patients were males and non-pregnant, non-lactating females, ≥18 and ≤80 years of age; intubated and mechanically-ventilated with a diagnosis of pneumonia, defined as the presence of new or progressive infiltrate(s) with signs of infection (fever >38^{o}C, leukopenia [<4,000 WBC/mm^{3}], or leukocytosis [≥12,000 WBC/mm^{3}]), and with PaO_2/FiO_2 ≤350 mmHg, APACHE II score >10 within the previous 24 hours, and presence, or high suspicion, of Gram-

negative organism(s) by either Gram stain or culture of respiratory secretions from a sample obtained within the previous 7 days. Exclusion criteria are in e-Appendix 1.

Efficacy Endpoints

The primary endpoint was change from baseline in CPIS during the planned 10-day treatment period. Secondary endpoints included a hierarchical composite endpoint of mortality and time to clinical cure (defined as both absence of Gram-negative bacteria [negative culture or no sputum available to culture in an extubated patient at Day 14 or earlier] and CPIS of <6 at Day 14 or earlier), a hierarchical composite endpoint of mortality and ventilator-free days, number of ventilator-free days, number of ICU days, microbiological response rates at Day 14 in patients whose baseline BAL or purulent tracheal aspirate was positive for MDR Gram-negative bacteria, mortality, and clinical relapse rates after Day 10 (defined as a new episode of pneumonia requiring reinstitution of IV antibiotics). MDR was defined as resistance to all antibiotics in 2 of the following 3 antibiotic classes: β-lactams, including carbapenems; aminoglycosides and fluoroquinolones.

Statistical Analyses

A sample size of 140 patients provided 80% power to detect an effect size (difference in means/standard deviation [SD]) of 0.53 at any given timepoint (2-sided 0.05-level t test); this corresponded approximately to a difference in means of 1.5 with SD=2.8.

Efficacy analyses were performed for the microbiologically evaluable intent-to-treat population (MITT), defined as patients who received AFIS/placebo and whose baseline BAL/mini-BAL, or purulent tracheal aspirate was positive for Gram-negative bacteria, either by culture or by PCR. Safety analyses included all treated patients. Methods for handling missing CPIS data are in e-Appendix 1. Change from baseline in CPIS was assessed using a repeated measurement mixed model analysis, including treatment effect, visit, and randomization

stratification factors as fixed effects and patient as a random effect. Baseline CPIS was a covariate in the model. Comparisons at specific time points used a linear contrast statement.

Secondary efficacy endpoints were tested sequentially in the order described above (to preserve the overall type I error rate of 0.05) using a gatekeeper approach. The 2 hierarchical composite secondary endpoints were analyzed using the win-ratio method[16] using pairs of patients matched for presence and absence of MDR Gram-negative bacteria and APACHE II score. Numbers of ventilator-free days and ICU days were compared for Days 1-28 using a Wilcoxon rank sum test, with stratification based on randomization factors. Microbiological response rate (Day 14) and clinical relapse rate (Days 11-28) were compared using a Cochran-Mantel-Haenszel test, with stratification based on randomization factors. Mortality through Day 28 was compared using the log-rank test, and summarized using the Kaplan-Meier method.

RESULTS

Disposition

Of 164 screened patients, 143 met eligibility criteria and were randomized to AFIS (n=71) or placebo (n=72) (Figure 1). Gram-negative bacteria were present in 142 patients at baseline, 137 had positive cultures, five positive PCRs. In these five patients we conducted the PCR analysis of both DNA and RNA, all had RNA signals indicating live bacteria. 143 patients received ≥1 dose of AFIS/placebo, with 65 patients receiving all 10 days of planned treatment (AFIS: n=36; placebo: n=29; e-Table 4). Of the 78 patients who discontinued treatment early, only three in the AFIS group discontinued due to adverse events. Twenty-seven were extubated prior to finishing the 10-day treatment course.

Patient Characteristics

Patient characteristics were comparable between arms (Table 1). 32 different Gram-negative organisms were recovered from baseline samples (Table 2). Twenty nine (20%) patients had polymicrobial Gram negative infections. Methicillin-resistant *Staphylococcus aureus* (MRSA) was recovered in 10 (7%) patients.

Efficacy

CPIS improvement from baseline did not differ between groups (P = 0.70) (Figure 2). Mean (± SD) CPIS at Day 10 were 5.0±3.1 for the AFIS group compared with 4.8±3.4 in the placebo group (P = 0.81). In a pre hoc analysis, we found no differences in CPIS outcomes in subgroups of age, baseline Apache score, and gender. Similarly, in a pre hoc analysis for patients without MDR or PDR bacteria, the AFIS group (n=48) at Day 10 had a -0.59 change in the CPIS while the placebo group (n=55) had a -0.88 change, p=0.38. In the patients with MDR or PDR bacteria, the AFIS group (n=23) at Day 10 had a 0.09 change in the CPIS while the placebo group (n=16) had a change 0.20, p=0.89.

Results for the secondary efficacy endpoints are listed in Table 3. The hierarchical composite endpoints of mortality and time to clinical cure, and of mortality and ventilator-free days were not different between groups (P=0.68, P=0.06, respectively). From Day 1 to 28, the mean number of days in the ICU was not different (P=0.09). Duration of IV antibiotics was comparable in both groups. Mortality through Day 28 was 24% in the AFIS group (n=17) and 17% in the placebo group (n=12) (Figure 3). There was clinical relapse between Days 11 through 28 in 10 (14%) in the AFIS group, and 14 (20%) in the placebo group. The AFIS group had significantly fewer positive tracheal cultures on Days 3 and 7 compared to placebo.

Effect in pan-resistant (PDR) bacteria

A post hoc exploratory tabulation was conducted in patients (AFIS n=9, Placebo n=4) with pan-resistant bacteria. All were infected with *Acinetobacter*. All these organisms had an amikacin MIC > 1024 mg/L. However, with the combination of amikacin and fosfomycin the MIC_{50} and the MIC_{90} were 128 mg/L and 256 mg/L respectively. Of the 9 AFIS patients, there were three deaths, one each from intracerebral hemorrhage, septic shock, and end stage renal disease. Of the four placebo patients, there were two deaths, one each from cardiac arrest and septic shock. In the survivors the ventilator free days were AFIS 19.3, Placebo 8.5. Clinical cure at day 14 in AFIS was 66.7% versus 25.0% for placebo (P = 0.16).

Safety Analysis

Amongst patients without microbiologic eradication, one patient in the AFIS group compared to 8 in the placebo group (P=0.02) showed a ≥4-fold increase in MICs exceeding the parenteral breakpoint for an intravenous antibiotic with Gram-negative activity. There were two severe adverse events (one in each group with bronchospasm) leading to discontinuation of therapy. Both patients recovered without sequelae. The overall incidence of treatment emergent adverse events was comparable in both groups (Table 4).

Pharmacokinetics

Median amikacin and fosfomycin concentrations in tracheal aspirates obtained 15 minutes after completion of AFIS treatment on Day 3 were 7720 μg/mL and 2430 μg/mL and at Day 10 were 7780 μg/mL and 2685 μg/mL. Low median plasma concentrations of amikacin and fosfomycin were observed 10 minutes prior to AFIS administration on Days 3 (463 ng/mL and 246 ng/mL) and 10 (512 ng/mL and 296 ng/mL).

DISCUSSION

This study demonstrated that adjuvant therapy with AFIS in VAP with varying degrees of bacterial resistance has no effect on the clinical course by multiple measures including serial CPIS, clinical cure rates, ventilator free and ICU days, and mortality. Two hypotheses could explain the discordance of the clinical outcomes and Days 3 and 7 tracheal culture results. Although the protocol limited intravenous antibiotics to a maximum of 72 hours prior to first dose for the treatment of pneumonia, the overall median in the AFIS group was 6 days due to treatment of other infections versus 4 days in the placebo group. This difference could have a noticeable impact on outcome since two days of intravenous meropenem in a pig pseudomonas VAP model has been shown to reduce the lung bacterial burden by over ten fold.[14] Further support that these patients had already been partially treated for VAP is the US cohort (n=32), that had median of only 3 days of prior IV antibiotics. In this cohort, the CPIS score difference was 1.88 (P=0.02). However the US cohort did not show any trends in clinical cure or mortality suggesting that even if AFIS was give earlier, clinical outcomes were not likely to be changed.

The second hypothesis is that the antibiotic combination and delivery system chosen was not adequate. Factors affecting the efficacy of an aerosol antibiotic include choice of antibiotic(s), formulation, delivery device efficiency, continuous versus breath activated delivery, particle size, presence or absence of humidity, ventilator settings, and pretreatment with sedative agents and/or bronchodilators.[6,9,17] In AFIS, the choice of a combination of amikacin plus fosfomycin was intended to provide effective antimicrobial activity against bacteria that were highly resistant to amikacin alone. Support for not choosing aminoglycoside monotherapy was provided by observing higher levels of amikacin resistance develop in strains associated with VAP after exposure to amikacin than after exposure to amikacin plus fosfomycin.[12] Likewise, use of colistin methanosulfate as monotherapy was not chosen; as a prodrug, the rate of conversion to active drug is not known, and it has high mucin binding that might limit its effectiveness.[18] Furthermore, colistin aerosols, as well as ceftazidime aerosols, have been

reported to commonly cause discoordination of breathing during inhalation, requiring sedation.[8,9] In AFIS, we used a formulation optimized for airway exposure instead of an IV formulation, which typically does not have permeant anions such as chloride added to prevent cough.[19] In vitro modeling suggested that approximately 15% of the dose of an antibiotic is deposited in the lung using the PARI inline nebulizer.[20] Similar in vitro modeling of jet nebulizers reported approximately 4-fold less deposition.[21] The high tracheal concentrations of antibiotics confirm high delivery, suggesting the failure of efficacy was not due to inadequate delivery of drug. The AFIS formulation did not cause discoordination of breathing and no patient required sedation during aerosol administration.

We investigated whether the use of the last observed value carried forward (LOCF) for calculation of CPIS values affected our results. At baseline, there was only one patient with missing data, at day 10 all fields had 5% or less missing data with the exception of chest radiographs (11%) and tracheal secretions (15%), the latter not surprising given the number of patients extubated by day 10. However, a preplanned sensitivity analysis using only available data to calculate CPIS values had results similar to the LOCF method.

A failed trial led us to investigate if we could identify a subset of responders which would be hypothesis generating for a future trial. The PDR patients were the first subgroup identified. We examined the EU population as the US population had a positive CPIS signal. We conducted a post hoc analysis in the EU patients that were enrolled who received 2 days or less of IV antibiotics prior to randomization. In this analysis, the EU AFIS group (n= 21) at Day 10 had a -0.58 change in the CPIS while the placebo group (n=18) had a -1.73 change, p=ns. There were not enough patients in the one day IV antibiotics category to conduct a meaningful analysis. We observed that the EU patients on average had been in the ICU for a week longer than the US patients prior to randomization. We then examined the subset of EU patients that were in the ICU for less than five days and received 2 or fewer days of IV antibiotics prior to randomization. In this group, there was increased CPIS signal in both groups, the AFIS group

(n= 8) at Day 10 had a -3.00 change in the CPIS, the placebo group (n=9) had a -2.50 change, p=ns. Thus, if one were to conduct another study, one should consider limiting both the number of days of prior antibiotics and length of stay in the ICU in order to maximize a signal from adjunctive aerosolized antibiotics.

The requirement of standard of care antibiotics in this study including a carbapenem and other coverage if resistance was suspected or proven likely contributed to the lack of efficacy seen with AFIS. However, our results confirm the finding that the adjuvant use of aerosolized antibiotics compared to intravenous therapy in patients with VAP or tracheobronchitis decreases the emergence of bacterial resistance.[7] Further studies, such as in the minority of patients that still have positive tracheal cultures at Day 14, are needed to evaluate aerosolized antibiotics as a stewardship tool. The microbiology results in this multi-national trial illustrate the daunting task of developing novel antibiotics for Gram-negative bacterial infections. Interestingly, *Enterobacteriaceae* were the leading VAP pathogens in our study, confirming recent epidemiological findings.[22] In addition, over 30 different bacterial species were collected in baseline BAL samples, with multiple different mechanisms of resistance. Any novel antibiotic that only addresses a narrow number of bacteria, or is limited to one specific mechanism of resistance, will not address the general problem of antibiotic-resistant infections. Further studies of aerosolized antibiotics should likely target pan-resistant pathogens where the likelihood of successful therapy with IV antibiotics is less reliable.

CONCLUSIONS

In conclusion, adjunctive use of AFIS in patients receiving standard of care antibiotic therapy did not affect the clinical course of VAP due to Gram-negative bacteria. This study used a delivery system, drug combination and formulation optimized for aerosol delivery, and failed to show any clinical efficacy despite a reduction in bacterial burden. These results cannot be generalized to all aerosolized antibiotics or to patients infected with bacteria that are pan-resistant, but any recommendations for general use need to be based on controlled clinical data from future trials.

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e-Appendix 1.

Exclusion Criteria: Criteria for exclusion included hypersensitivity to aminoglycosides, fosfomycin, imipenem, meropenem, or colistin; systemic antibiotic therapy for pneumonia for >72 hours before time of randomization; PaO_2/FiO_2 ≤100 mmHg plus diffuse chest radiograph infiltrates; refractory septic shock (persistent shock in spite of adequate fluid resuscitation and vasopressors); flail chest, large pleural effusions, lung cancer, lung abscess, bronchial obstruction, suspected atypical pneumonia, chemical pneumonitis, cystic fibrosis, immunocompromised (neutropenia not due to current infection, leukemia, lymphoma, HIV with CD4 counts <200 cell/mm^3, splenectomy, recent organ transplantation, or receiving cytotoxic chemotherapy or high-dose steroids); serum creatinine >4 mg/dL (unless on renal replacement therapy); history of ototoxicity; hepatotoxicity (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >3X the upper limit of normal); mechanical ventilation for >28 days; Glasgow Coma Scale score of 3; or recent participation in other drug or device trial.

e-Table 1. The Clinical Pulmonary Infection Score (CPIS)

The CPIS was calculated on the basis of points (sub-scores) assigned for various signs and symptoms of pneumonia. At baseline, the CPIS consisted of 5 sub-scores:

1. temperature [°C]
2. blood leukocytes [/mm^3]
3. tracheal secretion
4. oxygenation
5. pulmonary radiography

Seven sub-scores were needed for post-baseline CPIS derivation:

1. temperature [°C]
2. blood leukocytes [/mm^3]
3. tracheal secretion
4. oxygenation
5. pulmonary radiography
6. progression of pulmonary infiltrate
7. culture of tracheal aspirate

Assignment of points to the sub-scores is described in e-Table 2. The CPIS was the sum of sub-score points.

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e-Table 2. CPIS Scoring system.

Sub-scores	Points
Temperature (°C)	
>36 and ≤38.4	0 points
≥38.5 and ≤38.9	1 point
≥39 or ≤36	2 points
Blood leukocytes, /mm^3	
≥4,000 and ≤11,000	0 point
<4,000 or >11,000	1 point
Band forms ≥50%	1 point
Tracheal secretions	
Absence of tracheal secretions	0 points
Presence of nonpurulent tracheal secretions	1 point
Presence of purulent tracheal secretions	2 points
Oxygenation	
PaO_2/FIO_2, mm Hg > 240 or ARDS (ARDS defined as PaO_2/FIO_2 ≤ 200, pulmonary artery wedge pressure ≤ 18 mm Hg and acute bilateral infiltrates)	0 points
PaO_2/FIO_2, mm Hg ≤ 240 and no ARDS	2 points
Pulmonary radiography	
No infiltrate	0 points
Diffuse (or patchy) infiltrate	1 point
Localized infiltrate	2 points
Progression of pulmonary infiltrate	
No radiographic progression	0 points
Radiographic progression (no CHF or ARDS)	2 points
Culture of tracheal aspirate	
Pathogenic bacteria cultured in rare or light quantity or no growth	0 points
Pathogenic bacteria cultured in moderate or heavy quantity	1 point
Same pathogenic bacteria seen on Gram stain, add 1 point	+ 1 point

CPIS = Clinical Pulmonary Infection Score; ARDS = acute respiratory distress syndrome; CHF = congestive heart failure.

Word Count: 1322

Point: Should inhaled antibiotic therapy be routinely used for the treatment of bacterial lower respiratory tract infections in the ICU setting? Yes

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Conflict of interest statement: Dr. Wunderink has personally received consultation fees from Bayer

Routine use of aerosolized antibiotics is the most rational approach to the current treatment dilemmas for severe hospital-acquired pneumonia (HAP) requiring endotracheal intubation or ventilator-associated pneumonia (VAP). The two main issues for HAP/VAP are inappropriate initial therapy and ineffective therapy for multidrug resistant (MDR) pathogens, particularly gram negative bacilli such as *Pseudomonas aeruginosa* and *Acinetobacter* species. The emergence of extended spectrum beta-lactamases (ESBL) and carbapenem resistance in Enterobacteriaceae (CRE) have made even common pathogens such as *Escherichia coli* difficult to treat.

The most common justification for combination antibiotic therapy for MDR GN pathogens has been avoidance of inappropriate initial therapy.[1] Inappropriate initial therapy has consistently been associated with worse outcomes. Increasing resistance to the β-lactam core antibiotic treatment makes any single β-lactam unreliable as monotherapy. Resistance rates as high as 40% for each of the three main β-lactam classes – penicillins, cephalosporins, and carbapenems – make combination empirical therapy mandatory in most ICUs of large teaching institutions. The most reliable second agent in institutions with high rates of MDR pathogens is an aminoglycoside. Fluoroquinolone overusage has resulted in significant resistance rates and unclear benefit for its use as combination therapy.

What that means in practical terms is that a large proportion of patients with serious HAP/VAP are being treated with the equivalent of intravenous aminoglycoside monotherapy. The failure rate of intravenous aminoglycoside monotherapy is so high that all HAP/VAP guidelines recommend against this.[1] Unfortunately, this equivalent of aminoglycoside monotherapy is also being given during the first three days of therapy while awaiting culture results. This time period may be critical for control of infection. Salvage therapy started after three days for completely inappropriate initial therapy is often ineffective.[2] Whether this failure to rescue is true for aminoglycoside monotherapy in MDR pathogen HAP/VAP is unknown.

The bigger concern addressed by routine aerosolized antibiotics is ineffective intravenous antibiotic therapy for MDR pathogens. Many clinicians are unaware of the high failure and recurrence rates of standard intravenous therapy for HAP/VAP. A registration trial of prolonged infusion doripenem compared with imipenem/cilastatin was stopped early for excess mortality and higher clinical failure rates in the doripenem group.[3] While the differences between treatments were significant, the more important point is the high failure rate in both groups. As seen in the Figure, clinical success rates for most of the pertinent gram negative pathogens were distressingly low. These results are likely best case scenario since this and similar trials exclude patients with neutropenia, solid organ and bone marrow transplants, active treatment for malignancy and significant immunocompromise.

Various manipulations have been tried to improve the outcome of intravenous antibiotic treatment of HAP/VAP patients. By far the most common has been combination therapy with either an aminoglycoside or a fluoroquinolone in addition to a β-lactam. Repeatedly and consistently, meta-analyses of combination therapy compared to monotherapy for HAP/VAP do not find a benefit to combination therapy: both are associated with low clinical success rates.[4]

Longer duration of therapy has also been suggested as a strategy to improve outcome of antibiotic treatment of HAP/VAP.[3] A large multicenter RCT clearly demonstrated no survival benefit to continuing therapy for 14-15 days compared to 7-8 days.[5] A higher recurrence rate within 28 days of starting therapy for patients infected with *P. aeruginosa* and other nonfermenters in the 8-day group led some to call for longer treatment despite no difference in overall mortality (and in fact, lower mortality specifically in the nonfermenter group with 8 days of therapy). However, the need for greater than 8 days of therapy essentially represents failure of the original therapy and, rather than continuing a failing therapy, switch to alternative treatment regimens is needed. Continuing therapy to 15 days significantly increases the risk of superinfection with antibiotic-resistant pathogens.

Pharmacokinetic and pharmacodynamic (PK/PD) optimization is the third strategy to address the high failure rate of current antibiotic therapy for HAP/VAP. The RCT of doripenem versus imipenem attempts to prove this strategy.[3] Doripenem has lower minimal inhibitory concentrations (MICs) than imipenem for most pathogens and was given as a prolonged 3-hour infusion, both of which would result in much greater time above the MIC, the key PK/PD predictor of successful treatment with β-lactams, compared to imipenem. As seen in the Figure, despite this apparently unfair PK/PD advantage for doripenem, excess mortality and clinical failure with doripenem forced early stoppage of the trial. Another large RCT[6] and recent meta-analysis[7] confirm that prolonged infusion does not clearly lead to better outcomes despite better PK/PD parameters.

Advantages of routine use of aerosolized antibiotics address each of the problems with current intravenous treatment of HAP/VAP. The greatest advantage is that levels achieved in the lung are logs greater than can be achieved by intravenous dosing: levels in the 5,000 µg/ml range have been achieved in bronchoalveolar lavage fluid.[8] Very few pathogens have MICs to aminoglycosides that cannot be easily achieved locally by aerosolization. Only absolute resistance, such as *Stenotrophomonas maltophilia* or *Proteus* sp. for polymixin B, would make aerosolized antibiotics ineffective.

Based on these considerations, adding aerosolized antibiotics as initial empirical therapy for HAP/VAP patients is likely to lead to substantial bacterial killing even if β-lactam resistance is present. The risk of nephrotoxicity with combinations of other nephrotoxins will also be minimized compared with intravenous aminoglycosides or polymixins. Therefore, initial empirical aerosol combination therapy is likely to achieve all the benefits demonstrated for empirical intravenous combination therapy.[9]

Use of aerosolized antibiotics also addresses the ineffectiveness of typical intravenous antibiotic therapy. The most likely explanation for the failure of doripenem (and imipenem) monotherapy[3] is the presence of a highly carbapenem-resistant clone in the original pneumonia. Given that $10^8 – 10^{10}$ bacteria/ml. may be present in the alveolar spaces in some HAP/VAPs, the presence of a mutant with β-lactam resistance is highly likely. Alternatively, presence of an inducible β-lactamase may lead to a false laboratory determination of susceptibility if the sample is taken prior to exposure to a β-lactam. These two reasons may explain the development of carbapenem resistance while still on therapy in up to 50% of Pseudomonas pneumonias.[10] In many circumstances, normal host defenses can control this subpopulation once the majority of bacteria are killed with antibiotics. Unfortunately, both overt immunocompromise and the immunoparalysis seen in many ICU patients,[11] specifically those who develop nosocomial infections, may make this unreliable. Concomitant use of a different antibiotic with non-overlapping resistance will usually address this subgroup. However, the benefit of intravenous combination therapy discussed above limit their contribution to control of these resistant subpopulations.[3,9] The same limitations are not true for aerosol therapy.

The greatest hesitancy for routine use of aerosolized antibiotics is limited clinical experience. However, available data suggests that the theoretical benefits of aerosolized antibiotics can be achieved. The first RCT was limited by unclear criteria for VAP and for endpoints and a study population limited to trauma patients likely to have good host immunity.[12] However, despite no difference in their criteria for clinical cure, bacteria eradication occurred in a much higher proportion of patients receiving aerosolized

aminoglycosides (68% versus 31%). A more current and pertinent study demonstrated that aerosolized ceftazidime and tobramycin were equivalent to intravenous therapy with the same agents, with trends toward more successful treatment and decreased antibiotic resistance developing on therapy.[13] Two additional pilot studies demonstrated greater sterilization of airway secretions and, importantly, less total antibiotics and fewer new antibiotic prescriptions, suggesting more effective therapy and fewer recurrences.[8,14] In addition, use of aerosolized antibiotics for CRE and MDR HAP/VAP appears to have better outcomes than combination intravenous therapy.[15,16]

Given the consistent high failure rates with even optimized intravenous antibiotic therapy and the increasing incidence of MDR pathogens, aerosolized antibiotics should routinely be used in patients at risk for MDR pathogens. Significant further work is needed on optimization of delivery and appropriate formulations for aerosol delivery. However, given that the proportion of suspected HAP/VAP patients without risk factors for MDR pathogens in some ICUs is only 10%,[9] the need for treatment better than current intravenous therapy is desperately needed.

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Counterpoint: Should inhaled antibiotic therapy be routinely used for the treatment of bacterial lower respiratory tract infections in the ICU setting? No

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The utilization of antimicrobial agents is a relatively new phenomena arising at the start of the twentieth century. In critically ill patients with microbiologically confirmed infections the timely administration of appropriate antibiotic therapy (i.e., an antibiotic regimen with activity against the causative bacterial pathogen based on in vitro testing) is associated with a lower risk of mortality (1). Unfortunately, antibiotics are frequently prescribed to patients devoid of bacterial infection. The emergence of antibiotic resistance shortly followed the introduction of these agents and the steady escalation of resistance up to the present has been directly associated with increasing antibiotic consumption (2). The impact of antibiotic resistance on healthcare and global economics is highlighted by a recent Wellcome Trust report estimating that by 2050 more than ten million deaths will be attributed to antimicrobial resistance, greater than the number of deaths attributed to cancer (3). Given the rise in antibiotic resistance and its link to consumption, we must carefully consider whether any new indication for antibiotics is justifiable.

Bacterial lower respiratory tract infections (BLRTIs) are relatively common in patients requiring mechanical ventilation. Antibiotics have been employed prophylactically and therapeutically for BLRTIs including ventilator-associated pneumonia (VAP) and ventilator-associated tracheobronchitis (VAT) (4,5). The lung concentration of antibiotics is an important factor influencing clinical outcomes and the emergence of resistance. Meta-analyses of trials evaluating tigecycline have shown increased mortality relative to comparator antibiotics including studies of hospital-associated pneumonia (6). The use of off-label high dose tigecycline (100mg every 12hrs) has been shown to achieve greater clinical cure rates compared to approved dosing and to the comparator imipenem-cilastin suggesting that under dosing of tigecycline contributed to the observed poor outcomes in prior studies (7). Similarly, ceftobiprole was compared to linezolid and ceftazidime in patients with hospital-acquired pneumonia (HAP)/VAP and found to be inferior, in large part thought to be due to under dosing in critically ill patients (8). Moreover, in vitro studies suggest that antibiotic concentrations below a specific threshold termed the mutation prevention concentration (MPC) can be associated with

greater emergence of antibiotic resistance which is particularly important in the lung given the variable penetration of antibiotics into the epithelial lining fluid (Figure 1) (9,10). Taken together, these data support the premise that antibiotic delivery to the lung is a key determinant of clinical cure and resistance emergence.

The rise in BLRTIs attributed to multidrug-resistant (MDR) bacteria and the inadequacy of pulmonary penetration of systemically administered antibiotics have served as the main rationale for the development of aerosolized antibiotics (11). Most nebulizers are designed to deliver drugs to the proximal airways and not the lung parenchyma. Deposition location in the lung is a function of particle size, usually expressed as mass median aerodynamic diameter (MMAD) (Figure 2). Typical jet nebulizers have a variable particle size of about 5µm MMAD. To reach distal lung units optimal size is about 1 - 3µm MMAD, but no available jet nebulizer can consistently produce such a small particle size. Additionally, delivery to distal lung units is impeded by humidity in the ventilator circuit, which can cause hydroscopic growth and a rainout effect in the endotracheal tube (11). Moreover, inherent differences in delivered aerosol between commercial nebulizer systems are significant with differences between devices exceeding10-fold (12). Vibrating mesh-aperture plate nebulizers use a fixed aperture size to produce consistent particle sizes of 2- 3 µm MMAD and an aerosol output 2-3 times greater than a jet nebulizer (13). Moreover, vibrating mesh nebulizers can be used without changing ventilator settings. Given that increasing numbers of MDR bacteria have minimum inhibitory concentrations (MICs) to carbapenems and β-lactams ≥ 256 mg/L, achievable antibiotic concentrations of at least 6400 mg/L in the lung are required to overcome the influence of sputum antagonism (11). Large comparative studies of various aerosol antibiotic delivery devices are currently lacking and needed with appropriate outcome assessments.

The evidence in support of the routine use of aerosolized antibiotics for the treatment of VAP and VAT is lacking. A recent meta-analysis concluded that there is insufficient evidence for inhaled antibiotic therapy as primary or adjuvant treatment of VAP or VAT (14). However, only

six studies with a total of 305 patients were identified that met full criteria for inclusion in the analysis. The authors concluded that additional, better-powered randomized-controlled trials are needed to assess the efficacy of inhaled antibiotic therapy for VAP and VAT. However, another meta-analysis reviewed 16 studies for the treatment of VAP with aerosolized colistin (15). Despite the evidence quality being graded as “very low” to “low”, this meta-analysis found that clinical cure and microbiologic eradication were greater with aerosolized colistin while overall mortality was unaffected. Despite lacking evidence the use of aerosolized antibiotics for BLRTIs has increased over the past decade in many parts of the world, especially in countries like China and India that have experienced dramatic increases in BLRTIs attributed to MDR bacteria (16). Unfortunately, the expanding use of colistin in these countries for the treatment and eradication of MDR bacteria has been associated with the emergence of plasmid mediated colistin resistance (17). The development of colistin resistance in carbapenem-resistant *Enterobacteriaceae*, including New Delhi metallo-β-lactamase-1 (NDM-1) strains, brings a renewed sense of urgency to minimize any further resistance emergence and to prevent spread of these extremely drug-resistant (XDR) bacteria (18).

It can be argued that any new indication for antibiotics needs careful scrutiny, especially in environments where MDR and XDR pathogens are already endemic. This has been the argument for restricting the routine use of selective digestive decontamination to prevent BLRTIs due to concerns of further resistance emergence (19). In order for a new pharmaceutical to be licensed by the FDA, sufficient data has to be presented on preclinical safety, appropriate dose and formulation, and a defined clinical indication showing efficacy. These standards are both to protect the safety of patients and to prevent use of agents that are not proven. Not one currently or previously tested aerosolized antibiotic for adjunctive use in VAP or VAT has yet to meet all these criteria. Aerosol toxicology studies have been conducted only on tobramycin solution and aztreonam lysine, both approved for use in cystic fibrosis. Aerosolized colistin has been associated with respiratory failure and can cause direct damage

to lung tissue when not administered correctly, leading to potentially serious and life-threatening side effects (20). Potential indications for the approval of adjunctive aerosol antibiotics in the treatment of BLRTIs could potentially include: decreased time to recovery in patients with BLRTIs sensitive to the parenteral administered antibiotics; the treatment of patients with MDR and XDR pathogens; or to decrease the emergence of resistant bacteria. The latter may be difficult to obtain FDA approval for as it may not have any direct benefit to the treated patient, but might be an effective antibiotic stewardship tool.

Table 1 outlines the important questions that need to be addressed prior to accepting the routine utilization of aerosolized antibiotics for the treatment of BLRTIs. It is imperative to determine whether aerosolized antibiotics are effective in treating VAP and VAT, and what outcomes can be employed to determine their clinical utility. We also need to understand which classes of antibiotics are most effective when administered as aerosols and whether combination aerosol therapy offers advantages over single agents. The duration of treatment is also important, especially if adjunctive aerosolized antibiotics can reduce the overall duration of treatment and the emergence of resistant bacteria. Two pharmaceutical companies are currently conducting programs that are attempting to meet the FDA standards for approval (NCT01969799, NCT01799993). In Scotland, there are three possible verdicts in a criminal trial, guilty, not guilty, and not proven. I ask readers acting as the jury on the use of aerosolized adjunctive antibiotics for BLRTIs to return a verdict of “not proven”. Hopefully the ongoing clinical trials will allow a more definitive answer soon.

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FIGURE LEGEND

Figure 1. Serum or tissue antibiotic concentration assessed over time after delivery. Drug concentrations below the minimum inhibitory concentration (MIC) suggest that the pathogen is neither susceptible nor will first-step resistant mutants be inhibited. Drug concentrations between the MIC and the mutation prevention concentration (MPC) suggest that the pathogen is susceptible but that first-step resistant mutants will not be inhibited. Antibiotic concentrations above the MPC will achieve susceptibility for the pathogen as well as inhibit first-step mutant strains. The table provides estimates of the epithelial lining fluid (ELF) antibiotic concentrations after parenteral administration (see reference 9).

Figure 2. Aerosol deposition in the oro-pulmonary space according to generated particle size.

TABLE 1. OUTSTANDING QUESTIONS REGARDING AEROSOLIZED ANTIBIOTICS FOR THE TREATMENT OF BACTERIAL LOWER RESPIRATORY TRACT INFECTIONS (BLRTIs)

1. Which type of BLRTI to treat with aerosolized antibiotics?

    - Ventilator-associated pneumonia (VAP)
    - Ventilator-associated tracheobronchitis (VAT)
    - Prophylactic administration to prevent VAP, VAT and the emergence of antimicrobial resistance

2. Which antibiotic to aerosolize and at what dose?

    - Amikacin – 400 mg every 12 hours
    - Aztreonam – 75 mg every 8 hours
    - Ceftazidime – 15 mg/kg every 3 hours
    - Colisitin – 1 to 2 million units (80 to 160 mg) every 12 hours
    - Tobramycin – 300 mg every 12 hours

3. Should combination aerosolized antibiotic treatment be employed?

    - Amikacin 300 mg and Fosfomycin 120 mg every 12 hours

4. What is the optimal delivery device for aerosolized antibiotics in ventilated patients?

    - Ultrasonic nebulizer
    - Jet nebulizer
    - Breath-enhanced jet nebulizer
    - Vibrating mesh nebulizer

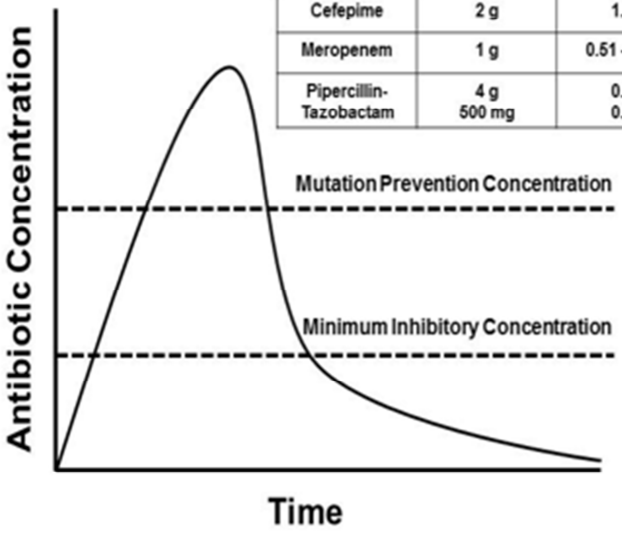
5. What is the optimal duration of treatment with aerosolized antibiotics in ventilated patients?

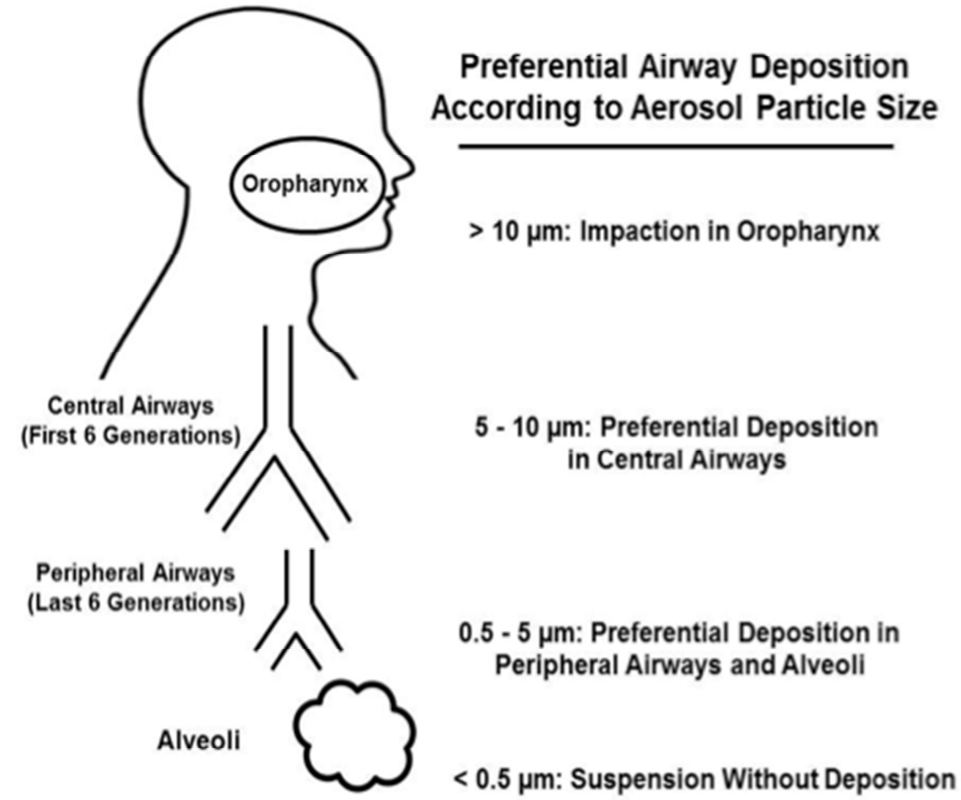
    - 3 days
    - 5 days
    - 7 days
    - 10 days

6. What outcomes should be employed to determine the clinical effectiveness of aerosolized antibiotics in ventilated patients?

    - Thirty day all-cause mortality
    - Clinical cure
    - Microbiologic eradication
    - Ventilator-free days
    - Prevention of acquired antibiotic resistance
    - Reduction in the Clinical Pulmonary Infection Score

Drug	Dose	ELF/Plasma Ratio	Measurement Time
Gentamicin	240 mg	0.30	1 hour
Tobramycin	7-10 mg/kg	0.12	1 hour
Vancomycin	15 mg/kg	0.18	18 hours
Cefepime	2 g	1.00	8 hours
Meropenem	1 g	0.51 – 1.04	1 – 4 hours
Pipercillin-Tazobactam	4 g 500 mg	0.60 0.90	Steady State





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Doctor Kollef and I completely agree on the pragmatic Scottish verdict of "not proven" regarding the issue of aerosolized antibiotics.[1] No clinical trials have met the rigorous FDA criteria for an indication in HAP/VAP and all published studies represent off label use. However, while the theoretical benefits of antibiotic aerosolization are not yet proven in clinical trials, the verdict on the current state of antibiotic treatment for HAP/VAP is clearly “guilty as charged”.

High clinical failure rates have been documented in clinical trials even prior to the emergence of significant antibiotic resistance.[2] Current antibiotics under development offer little potential for superior treatment but are mainly designed to fight a rearguard action against the emergence of antibiotic resistance.[3] The current crisis in antibiotics is not due to a new phenomenon but rather reflects the inability and reluctance of the pharmaceutical industry to continue to invest in new antibiotics to treat resistant infections.

Unfortunately, patients and their loved ones have the mistaken idea that pneumonia is a preventable and treatable complication of mechanical ventilation or hospitalization. Multiple studies have demonstrated that this is only partially true, in particular treatment of VAP. Only the recent appearance of articles about extremely drug-resistant (XDR) and pan-drug-resistant (PDR) bacteria in the lay press and the presidential executive orders regarding the crisis in antibiotic resistance[4] have raised awareness that pneumonia has not necessarily been a treatable infection. However, the idea that pneumonia should be treatable drives a reluctance to shift to more comfort care measures in patients with prolonged mechanical ventilation.[5]

To expect new antibiotics, optimized pharmacokinetics/pharmacodynamic protocols, and antibiotic stewardship to lead to improved outcome for patients with HAP/VAP meets Einstein's definition of insanity, paraphrased as “doing the same thing over and over again and expecting different results”. While each of these may have an important role in slowing the development of resistance, they are unlikely to decrease morbidity or mortality.

Aerosolized antibiotics are not the only possibility to take HAP/VAP treatment to a different level. Adjunctive passive immunization with monoclonal or polyclonal antibodies, extremely narrow spectrum antibiotics effective against a single pathogen while leaving the remainder of the normal respiratory microbiome intact, and availability of rapid accurate diagnostic platforms with improved determination of antibiotic susceptibility offer other exciting potentials. What is clear is that we need to keep searching for better therapies for patients with HAP/VAP until the verdict for one of these "not (yet) proven" therapies is reversed.

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I was a PI in the Cardeas study.

Antibiotic resistance in multidrug-resistant (MDR) bacteria has emerged as one of the most important determinants of outcome in patients with serious infections, including ventilator-associated pneumonia (VAP). In the US more than 700,000 healthcare-associated infections, many of which are caused by antibiotic-resistant Gram-negative bacteria (GNB), occur annually with almost half of these in critically ill patients (1). In Europe there is increasing prevalence of carbapenemase-producing *Enterobacteriaceae*, in particular with the rapid spread of carbapenem-hydrolysing oxacillinase-48 (OXA-48) and New Delhi metallo-beta-lactamase-producing *Enterobacteriaceae* (2). Escalating rates of antibiotic resistance add substantially to the morbidity, mortality, and costs related to infection in hospitalized patients (3). Given these worrisome trends it is appealing to consider the use of aerosolized antibiotics for the treatment of VAP especially when dealing with highly resistant pathogens, inadequate delivery of systemic antibiotics to the lung, or toxicities related to the use of parenteral agents such as aminoglycosides and polymyxins. However, it is also important to consider the potential downside of increasing use of aerosolized antibiotics for VAP.

A recent consensus statement from the Antimicrobial Stewardship and Resistance Working Groups of the International Society of Chemotherapy recommended as a key point for antibiotic utilization that clinicians "Prescribe drugs at their optimal dose, mode of administration and for the appropriate length of time, adapted to each clinical situation and patient characteristics" (4). Unfortunately, many patients are treated with antibiotics for suspected VAP or tracheal colonization when pneumonia is not present. Additionally, inadequate delivery of antibiotic concentrations to the lung, due to insufficient parenteral dosing or augmented renal clearance, can result in greater likelihood of treatment failures when VAP is present as noted by Dr. Wunderink (5). The indiscriminate use of aerosolized antibiotics in environments where parenteral antibiotics are not optimally administered, especially without

clear data indicating ideal aerosolized antibiotic selection, dosing, delivery mechanism, and duration of therapy, is likely to simply drive further resistance.

It is also important to consider the availability of new parenteral antibiotics for the treatment of VAP. Two new antibiotics targeting MDR GNB (ceftolozane-tazobactam, ceftazidime-avibactam) have recently been approved by the FDA, and over the next 3 to 5 years several other new antibiotics directed against MDR GNB are likely to become available including carbavance, plazomicin, eravacycline, relebactam, brilacidin, BAL30072, aztreonam-avibactam, carbapenems combined with ME 1071, and S-649266 a novel siderophore cephalosporin. These agents will potentially provide enhanced activity against β-lactamase producers, carbapenem-resistant bacteria, and in some cases even metallo-β-lactamase producing bacteria. Therefore, the use of aerosolized antibiotics needs to be considered against the backdrop of these novel agents. In addition to new antibiotics there has been progress in the development of vaccines and immunotherapies directed against MDR GNB. A vaccine candidate targeting *Pseudomonas aeruginosa* is in clinical development and the results from a phase 2/3 clinical trial in ICU patients requiring mechanical ventilation should be available soon (6). Similarly, the development of monoclonal antibodies targeting virulence factors in MDR GNB such as the type 3 secretion mechanism in *Pseudomonas aeruginosa* hold promise for future non-antibiotic therapy of VAP (7).

In summary, aerosolized antibiotics for the treatment of VAP are likely to be a valuable addition to our therapeutic armamentarium, especially for the treatment of infections attributed to MDR GNB. However, the use and delivery of aerosolized antibiotics should be guided by indications supported by appropriately designed clinical trials and should only be used to treat salvageable patients with true infections given the variability of documented practices (8). Only in this way can we be sure to optimize the use of these new agents without further promotion of global antibiotic resistance (Figure).

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FIGURE LEGEND

Figure 1. Circular nature of increasing antibiotic administration leading to greater resistance and higher rates of inappropriate antibiotic therapy, morbidity and mortality attributed to bacterial infections.