Use of Adjunctive Aerosolized Antimicrobial Therapy in the Treatment of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* Ventilator-Associated Pneumonia

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BACKGROUND: Adjunctive aerosolized antibiotics (AAA) have been recommended in the setting of Gram-negative ventilator-associated pneumonia (VAP), but little is known about their influence on clinical outcomes. OBJECTIVE: To assess outcomes associated with AAA for the treatment of *Pseudomonas aeruginosa* (PA) and *Acinetobacter baumannii* (AB) VAP. METHODS: A retrospective, single-center cohort study at Barnes-Jewish Hospital in St Louis, Missouri. Consecutive subjects treated for bronchoalveolar lavage-confirmed PA or AB VAP between January 1, 2004 and December 31, 2009 were enrolled. Records of subjects treated with AAA were compared to those who did not receive AAAs (NAAA). RESULTS: Ninety-three patients were evaluated (NAAA $n = 74$, AAA $n = 19$, inhaled colistin $n = 9$, inhaled tobramycin $n = 10$). Patients receiving AAA were significantly more likely to be infected with multidrug-resistant bacteria (52.6% vs 14.9%, $P < .001$) and had greater Acute Physiology and Chronic Health Evaluation II scores (21.4 ± 5.7 vs 17.5 ± 5.3, $P = .004$) compared to patients receiving NAAA. NAAA subjects experienced a shorter time from VAP onset to appropriate intravenous antibiotic initiation (0.5 ± 0.9 d vs 2.6 ± 5.4 d, $P = .038$), but length of intravenous therapy was similar between groups (12.8 ± 8.5 d vs 17.8 ± 13.3 d, $P = .16$). The NAAA group demonstrated significantly shorter mechanical ventilation duration (18.9 ± 15.9 d vs 38.4 ± 32.4 days, $P < .001$), intensive care unit stay (37.5 ± 42.5 d vs 56.3 ± 31.3 d, $P = .001$), and hospital stay (39.0 ± 42.5 d vs 58.3 ± 33.4 d, $P = .001$). However, Kaplan-Meier curves for the probability of 30-day survival from VAP onset demonstrated that patients receiving AAA had statistically greater survival ($P = .030$ by the log rank test). CONCLUSIONS: Patients with PA and AB VAP may experience favorable survival when treated with AAA, despite greater severity of illness and a greater incidence of multidrug-resistant infection. Large randomized trials are needed to further explore this therapy. *Key words: ventilator-associated pneumonia; aerosolized antibiotics; Pseudomonas aeruginosa; Acinetobacter baumannii.* [Respir Care 2012;57(8):1226–1233. © 2012 Daedalus Enterprises]

Introduction

Ventilator-associated pneumonia (VAP) remains one of the most common ICU acquired infections and is associated with greater ICU length of stay, mortality, and healthcare costs.[1,2] Cases of late-onset VAP (occurring ≥ 5 d after initiation of mechanical ventilation) are more apt to be caused by multiple-drug-resistant (MDR) isolates and correlate with higher incidences of morbidity and mortality.[3]

In 2004 the Infectious Diseases Society of America released a report entitled "Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates, a Public Health Crisis Brews."[4] Despite this report calling widespread attention to the lack of new antimicrobials in the drug development pipeline, a limited number of new agents have been approved in the years following the report's release. This prompted the

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publication of a follow-up initiative calling for the creation of 10 new antibiotics by the year 2020.[5] While these proposals are of the utmost importance, clinicians have been left in the interim to identify alternative strategies to treat infection, hence the focus on adjunctive aerosolized antimicrobials (AAA) for patients with VAP.

SEE THE RELATED EDITORIAL ON PAGE 1348

Systemic therapies utilized in the treatment of MDR VAP are often unsatisfactory due to toxicity and suboptimal pulmonary concentrations, making AAA more appealing. A limited number of studies have been published, demonstrating conflicting results with regard to the efficacy of adjunctive inhaled antibiotics. Furthermore, the existing literature has been criticized due to small sample sizes and lack of control groups.[6-8]

Given that the utilization of AAA is poorly described, we undertook an analysis of our experience with AAA. The purpose of this study was to compare clinical outcomes in patients treated with AAA versus those who did not receive inhaled therapy for VAP attributed to *Pseudomonas aeruginosa* or *Acinetobacter baumannii.*

QUICK LOOK

Current knowledge

Ventilator-associated pneumonia (VAP) remains one of the most common ICU-acquired infections, and is associated with longer ICU stay and higher mortality and costs. Adjunctive aerosolized antibiotics have been recommended for Gram-negative VAP, but little is known about their influence on clinical outcomes.

What this paper contributes to our knowledge

Patients with *Pseudomonas aeruginosa* and *Acinetobacter baumannii* VAP may have better survival with adjunctive aerosolized antibiotics, despite greater severity of illness and a greater incidence of multi-drug-resistant infection. Large randomized trials are required to define the role of adjunctive aerosolized antibiotics in Gram-negative VAP.

Methods

Study Design and Patients

This retrospective single center cohort study was conducted at Barnes-Jewish Hospital, a 1,250 bed urban academic medical center in St Louis, Missouri. Patients admitted between January 1, 2004, and December 31, 2009, diagnosed with bronchoalveolar lavage (BAL) confirmed *Pseudomonas* or *Acinetobacter* VAP were eligible for the study. Patients were excluded if they had a diagnosis of cystic fibrosis, had never received appropriate intravenous antibiotics, were mechanically ventilated for < 48 hours, received $< =72$ hours of antibiotic therapy, or were transitioned to comfort care measures. All subjects were enrolled only once. Records of subjects treated with AAA were compared to those who did not receive AAA (NAAA).

Characteristics evaluated included patient age, comorbid conditions, and Acute Physiology and Chronic Health Evaluation (APACHE) II at time of BAL. Treatment related factors and clinical outcomes data, including duration of hospital stay and mechanical ventilation as well as time to death, were also assessed. Data were collected from electronic medical records, pharmacy and microbiology databases, and an informatics query. Due to the retrospective nature of the investigation, consent was waived. The study was approved by the Washington University School of Medicine Human Studies Committee prior to any data collection or analysis. No external funding was required to complete this evaluation.

Definitions

VAP was defined as the presence of a new or progressive pulmonary infiltrate and 2 of the following: temperature > 38.3°C or < 36.0°C, leukocyte count $> 12{,}000$/mL or $< 4{,}000$/mL, or purulent tracheal secretions.[9] The diagnosis of VAP was microbiologically confirmed by BAL culture demonstrating substantial growth for *Pseudomonas aeruginosa* or *Acinetobacter baumannii*, defined as $> 10^4$ colony-forming units per mL. The presence or absence of a new or progressive radiographic infiltrate was based on the interpretation of the chest radiograph by board-certified radiologists who were blinded to the study. All classifications, including the radiographs and laboratory data used in their determinations, were reviewed by one of the investigators (HMA) and confirmed by a second investigator (MHK). The onset of VAP was taken as the time when confirmatory BAL was performed. The modi-

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fied Clinical Pulmonary Infection Score was also assessed on the day VAP was diagnosed and 72 hours after the diagnosis of VAP.[10]

Antimicrobial treatment was classified as appropriate if the initially prescribed antibiotic regimen was active against the identified isolates of *Pseudomonas aeruginosa* or *Acinetobacter baumannii*, based on in vitro susceptibility testing. Multiple-drug-resistance referred to isolates demonstrating resistance to 3 or more antibiotic classes. AAAs included either colistin 150 mg inhaled twice daily or tobramycin 300 mg inhaled twice daily, both standard doses and frequencies across the institution, as determined by the Pharmacy Department of Barnes-Jewish Hospital. These dosages were selected based on the available medical literature and local experience with the use of AAA.[7] The selection of either colistin or tobramycin was based on the susceptibility patterns for *Pseudomonas aeruginosa* or *Acinetobacter baumannii* identified in the BAL cultures. The microbiology laboratory performed antimicrobial susceptibility of the isolates using the disk diffusion method, according to guidelines and break points established by the Clinical Laboratory and Standards Institute. When *Pseudomonas aeruginosa* or *Acinetobacter baumannii* isolates were susceptible to both tobramycin and colistin, selection of the AAA agent was left to the team treating the patient in the specific ICU, which included a clinical doctor of pharmacy.

Dosing of AAA and Delivery Equipment

Patients received colistin 150 mg twice daily, dissolved in 5 mL of 0.9% sodium chloride, or 300 mg of tobramycin, in 5 mL 0.9% sodium chloride, twice daily. Nebulizers that generated optimal droplet sizes (1–5 μm) (Airlife, CareFusion, San Diego, California) were employed for the delivery of the AAA over a 15–20 min time period. The nebulizer was positioned in the inspiratory limb of the ventilator circuit, about 30 cm from the endotracheal tube. The 840 ventilator system (Puritan Bennett, Boulder, Colorado) was the primary ventilator system used at Barnes-Jewish Hospital during the course of this study. Humidification was discontinued during delivery of the aerosol, and suctioning through the endotracheal tube was avoided following administration of AAA, unless clinically indicated.

Statistics

Categorical data were analyzed using a chi-square or Fisher exact test, as appropriate. Differences in normally distributed continuous data were assessed by the Student *t* test and non-normally distributed data by the Mann-Whitney U test. Kaplan-Meier curves were used to evaluate differences between patients receiving AAA and NAAA for time to expiration from BAL; the log-rank test was utilized to determine statistical significance when comparing curves. P values $< .05$ were considered statistically significant. Statistical analysis was performed using statistics software (SPSS 18.0, SPSS, Chicago, Illinois).

Results

Baseline demographics and characteristics are shown in Table 1; an explanation of subject exclusion may be found in Figure 1. Ninety-three consecutive patients were enrolled (NAAA $n = 74$, AAA $n = 19$). AAA patients had statistically greater APACHE II scores, compared to patients receiving NAAA. Twenty-eight (30.1%) patients were excluded who were transitioned to palliative care: 9 (9.7%) receiving AAA, and 19 (20.4%) receiving NAAA. Treatment related factors are shown in Table 2. NAAA subjects experienced a shorter time from VAP onset to appropriate intravenous antibiotic initiation (0.5 ± 0.9 d vs 2.6 ± 5.4 d, $P = .038$), but length of intravenous therapy was similar between groups (12.8 ± 8.5 d vs 17.8 ± 13.3 d, $P = .16$). The use of parenteral colistin and aminoglycosides was significantly greater among patients receiving AAA (see Table 1).

The NAAA group demonstrated significantly shorter mechanical ventilation duration (18.9 ± 15.9 d vs 38.4 ± 32.4 d, $P < .001$), ICU stay (37.5 ± 42.5 d vs 56.3 ± 31.3 d, $P = .001$), and hospital stay (39.0 ± 42.5 d vs 58.3 ± 33.4 d, $P = .001$). Similar differences were found when nonsurvivors were excluded from the analysis for mechanical ventilation duration (20.0 ± 17.0 d vs 32.4 ± 15.1 d, $P = .001$), ICU stay (40.6 ± 46.1 d vs 49.6 ± 20.0 d, $P = .01$), and hospital stay (41.9 ± 46.3 d vs 51.2 ± 20.8 d, $P = .01$).

Thirty day mortality was less for patients receiving AAA, compared to those receiving NAAA (0.0% vs 17.6%, $P = .063$). However, when the patients transitioned to palliative care were included in the mortality analysis, there was no difference in hospital mortality between groups (32.1% vs 33.3%, $P = .91$). Kaplan-Meier curves depicting the probability of 30-day survival from VAP onset demonstrated that patients receiving AAA had a statistically greater survival ($P = .030$ by the log rank test) (Fig. 2). This survival advantage for patients receiving AAA was confirmed for the subgroup of patients having APACHE II scores > 16 ($P = .004$) (Fig. 3). Thirty-day mortality and duration of mechanical ventilation, intensive care, and hospital stay were similar for patients treated with aerosolized colistin and those treated with aerosolized tobramycin. The number of patients with microbiologically confirmed recurrent VAP was similar between patients receiving AAA and NAAA (10.5% vs 14.9%, $P = .48$). No patients had AAA treatment, or the duration

Table 1. Baseline Demographics

	NAAA (n = 74)	AAA (n = 19)	P
Age, y	54.5 ± 16.7	54.0 ± 15.8	.58
Male, no. (%)	49 (66.2)	14 (73.7)	.60
White, no. (%)	52 (70.3)	9 (47.4)	.13
Body mass index, kg/m^2	29.5 ± 10.4	28.4 ± 6.9	.95
Location at time of BAL, no. (%)			.59
Surgical ICU	49 (66.2)	11 (57.9)	
Medical ICU	25 (33.8)	8 (42.1)	
APACHE II at BAL	17.5 ± 5.3	21.4 ± 5.7	.004
CPIS at VAP diagnosis	7.6 + 0.8	7.4 ± 1.1	.38
CPIS 72 h after VAP diagnosis	6.4 ± 0.8	6.2 ± 1.0	.28
ΔCPIS	1.1 ± 0.7	1.2 ± 0.5	.84
Comorbidities, no. (%)			
Pulmonary	22 (29.7)	6 (31.6)	> .99
Cardiovascular	39 (52.7)	13 (68.4)	.30
Diabetes	22 (29.7)	5 (26.3)	> .99
Hemodialysis	3 (4.1)	3 (15.8)	.10
Liver failure	7 (9.5)	1 (5.3)	> .99
Immunosuppressed	11 (14.9)	3 (15.8)	> .99
Malignancy	18 (24.3)	5 (26.3)	> .99
Co-administration of Intravenous Antibiotics, no. (%)			
Vancomycin	9 (12.2)	5 (26.3)	.15
Colistin	2 (2.7)	4 (21.1)	.02
Aminoglycoside	20 (27.0)	13 (68.4)	.001
Anti-pseudomonal*	71 (95.9)	16 (84.2)	.10

± values are mean ± SD.
* Includes cefepime, piperacillin-tazobactam, imipenem, or meropenem.
AAA = received adjunctive aerosolized antibiotics
NAAA = did not receive AAA
BAL = bronchoalveolar lavage
APACHE = Acute Physiology and Chronic Health Evaluation
CPIS = Clinical Pulmonary Infection Score
VAP = ventilator-associated pneumonia

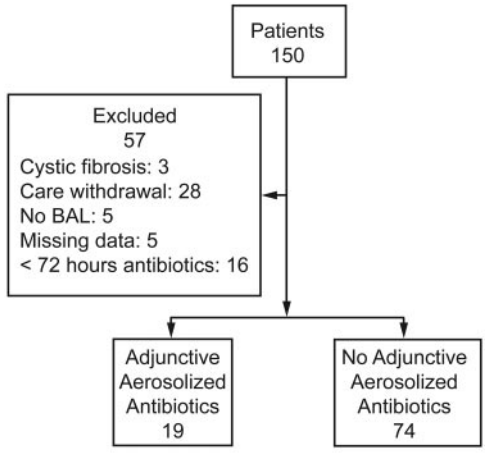

Fig. 1. Patient enrollment. BAL= bronchoalveolar lavage

of AAA, discontinued prematurely due to intolerance of the administered aerosols.

Discussion

We demonstrated that, despite a greater severity of illness and infection with MDR pathogens, patients with VAP attributed to *Pseudomonas aeruginosa* or *Acinetobacter baumannii* receiving AAA had significantly greater 30-day survival, compared to patients who did not receive AAA. This observation was confirmed among the patients with the greatest severity of illness as assessed by APACHE II score > 16. No difference was observed in outcomes between inhaled colistin and inhaled tobramycin for patients receiving AAA.

Our findings support the results of other recent publications. Czosnowski et al evaluated patients with VAP, microbiologically confirmed by BAL cultures.[7] *Pseudomonas aeruginosa, Acinetobacter baumannii*, or both were isolated in 45, 14, and 1 episode(s), respectively. Aerosolized tobramycin, amikacin, and colistimethate were used in 44, 9, and 9 episodes, respectively. Systemic antibiotics

Table 2. Treatment Related Factors

	NAAA (n = 74)	AAA (n = 19)	P
Time from admission to BAL, d	13.6 ± 12.1	18.7 ± 16.0	.11
Time from BAL to intravenous antibiotics*, d	0.5 ± 0.9	2.6 ± 5.4	.04
Time from BAL to inhaled antibiotics, d		3.0 ± 3.1	
Total duration intravenous antibiotics*, d	12.8 ± 8.5	17.8 ± 13.3	.16
Pseudomonas aeruginosa, no. (%)†	60 (81.1)	14 (73.7)	.53
Acinetobacter baumannii, no. (%)†	16 (21.6)	5 (26.3)	.76
Multidrug-resistant pathogen, no. (%)	11 (14.9)	10 (52.6)	< .001
Polymicrobial infection, no. (%)	22 (29.7)	6 (31.6)	> .99
Stenotrophomonas	7 (9.5)	1 (5.3)	
Staphylococcus aureus	4 (5.4)	0 (0)	
Proteus	3 (4.1)	2 (10.5)	
Klebsiella	2 (2.7)	2 (10.5)	
Enterobacter	2 (2.8)	1 (5.3)	
Serratia	2 (2.8)	0 (0)	
Haemophilus	0 (0)	1 (5.3)	
Escherichia coli	1 (1.4)	0 (0)	
Moraxella	1 (1.4)	0 (0)	
Parinfluenza	0 (0)	1 (5.3)	
Herpes simplex virus	1 (1.4)	1 (5.3)	
Cytomegalovirus	1 (1.4)	1 (5.3)	
Mold	1 (1.4)	0 (0)	
Concurrent bacteremia, no. (%)	7 (9.5)	1 (5.3)	> .99
Inhaled Antimicrobials, no. (%)			
Colistin 150 mg BID		9 (47.4)	
Tobramycin 300 mg BID		10 (52.6)	
Duration of Inhaled Antimicrobials, d			
Colistin 150 mg BID		8.9 ± 6.7	
Tobramycin 300 mg BID		11.0 ± 3.9	

± values are mean ± SD.
* Refers to the administration of appropriate antibiotic therapy. The onset of ventilator-associated pneumonia was taken as the time when confirmatory bronchoalveolar lavage (BAL) was performed.
† Two patients in the NAAA group grew both *Pseudomonas* and *Acinetobacter* on BAL culture.
AAA = received adjunctive aerosolized antibiotics
NAAA = did not receive AAA
BAL = bronchoalveolar lavage
BID = bis in die (twice a day)

were used in 59 (98%) of the 60 episodes. Clinical success was achieved in 36 (73%) of the 49 first episodes of VAP, 8 (73%) of 11 subsequent episodes, 17 (85%) of 20 episodes that were failing intravenous monotherapy, and 30 (79%) of 38 episodes with MDR *Pseudomonas aeruginosa* or *Acinetobacter baumannii*. Microbiologic success was achieved in 29 (71%) of 41 evaluable episodes. Six (10.0%) patients died from VAP. Michalopoulos et al also evaluated 60 critically ill patients treated with aerosolized colistin for VAP due to MDR pathogens: *Acinetobacter baumannii* 37/60 cases, *Pseudomonas aeruginosa* 12/60 cases, and *Klebsiella pneumoniae* strains 11/60 cases.[11] Half of the isolated pathogens were susceptible only to colistin. Fifty-seven patients received concomitant intravenous treatment with colistin or other antimicrobial agents. Bacteriological and clinical response of VAP was observed in 50/60 (83.3%) patients. No adverse effects related to inhaled colistin were recorded. All cause hospital mortality was 25%, while mortality attributable to VAP was 16.7%.

Given the increasing resistance of Gram-negative bacteria associated with VAP, and the limited lung concentrations of parenterally administered antibiotics, increasing interest in the optimal administration of aerosolized antibiotics has emerged. Luyt et al evaluated amikacin penetration into the alveolar epithelial lining fluid of mechanically ventilated patients with Gram-negative nosocomial pneumonia receiving amikacin via a novel lung delivery system.[12] The median (and range) epithelial lining fluid amikacin and maximum serum amikacin concentrations were 976.1 μg/mL (135.7–16,127.6 μg/mL) and 0.9 μg/mL (0.62–1.73 μg/mL), respectively. The median (and range)

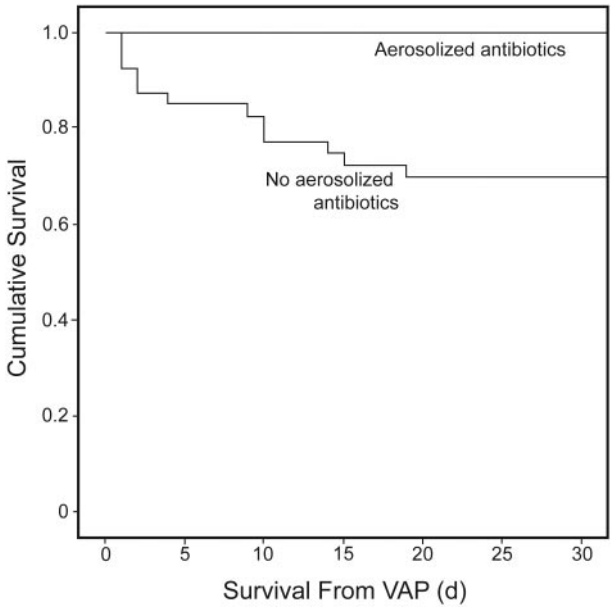

Fig. 2. Kaplan-Meier curves depicting the probability of survival from ventilator-associated pneumonia (VAP) in patients receiving adjunctive aerosolized antibiotics and patients who did not receive adjunctive aerosolized antibiotics ($P = .030$ by log rank test).

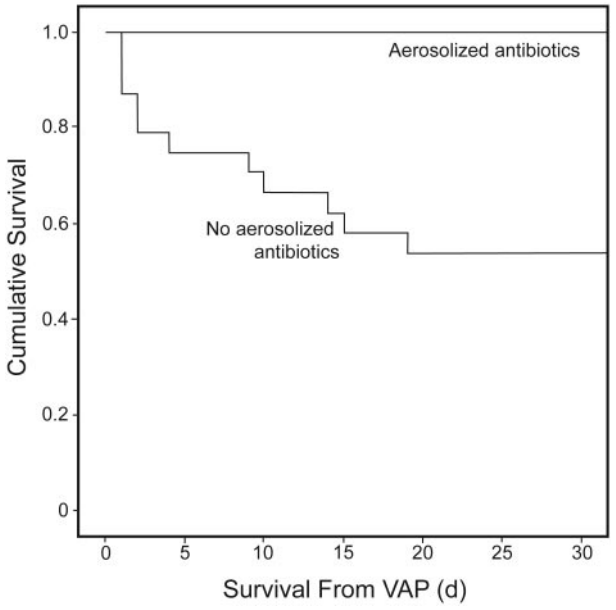

Fig. 3. Kaplan-Meier curves depicting the probability of survival from ventilator-associated pneumonia (VAP) in patients receiving adjunctive aerosolized antibiotics and patients who did not receive adjunctive aerosolized antibiotics ($P = .004$ by log rank test) for the subgroup of patients having Acute Physiology and Chronic Health Evaluation II scores > 16.

total amount of amikacin excreted in urine during the first and second 12-hour collection on day 3 were 19 μg (12.21–28 μg) and 21.2 μg (14.1–29.98 μg), respectively. During the study period, daily serum amikacin measurements were below the level of nephrotoxicity. Sixty-four unexpected adverse events were reported, among which 2 were deemed possibly due to nebulized amikacin: one episode of worsening renal failure, and one episode of bronchospasm. Palmer et al also examined patients with VAP and ventilator-associated tracheobronchitis to determine the benefit of 14 days of aerosolized antibiotics, either vancomycin or gentamicin or both, for infections attributed to Gram-negative and Gram-positive bacteria.[13] Patients receiving aerosolized antibiotics had reduced signs of respiratory infection, reduction in Clinical Pulmonary Infection Score, lower white-blood-cell count at day 14, reduced bacterial resistance, reduced use of systemic antibiotics, and increased weaning from mechanical ventilation (all $P \leq .05$).

Most recently, Lu et al evaluated 40 patients with VAP caused by *Pseudomonas aeruginosa* in a randomized comparative phase II trial of aerosolized antibiotics versus parenteral antibiotics.[14] Twenty patients received nebulized ceftazidime (15 mg/kg every 3 h) and amikacin (25 mg/kg/d), while 17 patients infected by susceptible strains received intravenous ceftazidime (90 mg/kg/d, continuous administration) and amikacin (15 mg/kg/d). In 3 patients infected by intermediate strains, amikacin was replaced by ciprofloxacin (400 mg every 12 h). After 8 days of antibiotic administration, the aerosol and intravenous groups were similar in terms of successful treatment (70% vs 55%), treatment failure (15% vs 30%), and superinfection by other microorganisms (15% vs 15%). Acquisition of antibiotic resistance was observed exclusively in the intravenous group. Aerosolized colistin along with intravenous doxycycline has also recently been shown to be successfully utilized for the treatment of recurrent *Stenotrophomonas maltophilia* failing re-treatment with intravenous trimethoprim/sulfamethoxazole.[15] This case illustrates the problem of antibiotic re-utilization, which is often associated with antibiotic resistance to the re-utilized antibiotic, as well as other antibiotic classes, and greater morbidity and mortality.[16] Empiric aerosolized antibiotic therapy for VAP using broader-spectrum agents (aminoglycosides, colistin) may be useful in patients relapsing or failing parenteral antibiotic therapy until susceptibility patterns can be identified.

The overall poor development of AAA to date is partly due to the fact that, during mechanical ventilation, high amounts of the particles dispersed by conventional nebulizers remain in the ventilatory circuit and the tracheobronchial tree, therefore not reaching the distal lung and, hence, less drug is available in the alveolar compartment.[17] With the development of new generations of nebulizers that use a vibrating mesh or plate with multiple apertures to produce an aerosol, antibiotic aerosolization in patients with VAP has renewed potential. This is supported by the study conducted by Luyt et al, demonstrating that delivery of

aerosolized amikacin using a vibrating mesh nebulizer can achieve very high aminoglycoside concentrations in the epithelial lining fluid of mechanically ventilated patients with nosocomial pneumonia, while maintaining safe serum amikacin concentrations.[12] However, the clinical impact of amikacin delivery with this system remains to be determined and will be examined in a large randomized controlled trial.[12] Similarly, arbekacin, an aminoglycoside with activity against both antibiotic-resistant Gram-negative bacteria and methicillin-resistant *Staphylococcus aureus*, is currently undergoing study as an AAA.

There are several important limitations of our study that should be noted. First, the study was performed at a single center and the results may not be generalizable to other institutions. However, the findings from other investigators corroborate the potential role of aerosolized antibiotics for the treatment of VAP attributed to Gram-negative bacteria.[6-8,11-15] Second, the retrospective and observational nature of this study limits our ability to establish causality between the use of aerosolized antibiotic therapy and 30-day survival. However, the potential negative impact to the individual patient with VAP from delayed appropriate antibiotic treatment may warrant consideration of aerosolized antibiotic therapy, especially when MDR bacterial infection is suspected.[18] Similarly, treatment biases may have occurred due to the retrospective nature of this study, including the potential to omit patients at high risk of death from the AAA group. Third, the lack of 30-day mortality in the group receiving AAA suggests that the sample size was too small to identify this outcome or that there was a selection bias in the administration of AAA. Another important limitation of our study was that it did not allow for a comparison between colistin or tobramycin to determine which might be the more optimal AAA. Similarly, we did not perform a cost effectiveness analysis and cannot make specific recommendations between colistin and tobramycin for use in AAA regimens. We also excluded patients who were transitioned to palliative care from our analysis. This was done since none of these patients completed their course of AAA, due to the severity of their underlying disease that was independent of the episode of VAP.

Another important limitation of our study was that it was focused on VAP attributed to *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Therefore, our data cannot be applied to patients having VAP attributed to other pathogens. We also observed that significantly more patients receiving AAA had co-administration of intravenous colistin or an aminoglycoside. This raises the possibility that at least a portion of the survival advantage among patients treated with AAA may be attributed to the use of these agents (colistin or an aminoglycoside), rather than to their specific routes of administration.

Conclusions

In summary, our data suggest that patients with VAP attributed to *Pseudomonas aeruginosa* or *Acinetobacter baumannii* may experience favorable survival when treated with AAA, despite infection with MDR bacteria. Large randomized trials are needed to further explore this therapy, especially in light of reports demonstrating increasing resistance to both of these antimicrobial agents.[19]

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