AEROSOLIZED ANTIBIOTIC THERAPY IN THE ICU

SUMMARY

Aerosolized antibiotics deliver treatment directly to the source of a ventilator-associated pneumonia (VAP). There are currently no large-scale randomized trials evaluating the efficacy of its use. A few small studies provide evidence to support the use of aerosolized antibiotics to treat pneumonia in patients infected with multi-drug resistant (MDR) organisms. This route of administration is especially useful when the minimum inhibitory concentrations for the MDR organism are too high to safely administer intravenous antimicrobial agents. Proper administration technique of the aerosolized antibiotic is needed to ensure optimal distribution and coating of the lungs.

RECOMMENDATIONS

- **Level 1**
  - **None**
- **Level 2**
  - **Nebulizers should create droplet sizes of 1–5 microns for optimal administration**
  - **Aerosolized antibiotics can be considered as adjunctive therapy to systemic (intravenous) antibiotics for the treatment of MDR VAP**
- **Level 3**
  - **All forms of current nebulizers provide adequate administration of antibiotics**
  - **Aerosolized antibiotics should not be administered with humidified air**
  - **Aerosolized antibiotics should be administered with breath actuated nebulizers**
  - **All patients receiving aerosolized antibiotics should be pretreated with aerosolized albuterol 2.5mg prior to each dose**
  - **Specific dosing:**
    - **Amikacin 400 mg aerosolized q 8-12 hrs**
    - **Colistin 150 mg aerosolized q 8-12 hrs**
    - **Gentamicin 80 mg aerosolized q 8 hrs**
    - **Tobramycin (TOBI®) 300 mg aerosolized q 12 hrs**
    - **Vancomycin 125 mg aerosolized q 8 hrs**
  - **Each dose should be diluted to a total volume of 4 mL.**

INTRODUCTION

Several attempts at aerosolizing antibiotic therapy were made as early as the 1950's. Antibiotics including penicillin G, ticarcillin, ceftazidime, and carbenicillin were all attempted, but were found to have severe side effects including bronchospasm (1). Other reports showed an increased association with the development of MDR bacteria, atypical bacteria, and increased pulmonary-related mortality (2). These poor outcomes ended research on aerosolized antibiotic therapy for several years, but likely occurred

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

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secondary to major methodological shortcomings such as indiscriminate use of antibiotics, the use of antibiotic solution instillation, and treatment of non-ventilated patients (2).

With the development of MDR gram-negative infections such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa,* the use of aerosolized antimicrobials in the ICU has been restudied. As aerosolized antibiotics are localized to the site of the infection, they provide high concentrations to the site of infection while reducing the risk of systemic side effects and decreasing the need for high serum levels. Currently, aerosolized antibiotics are well studied and utilized in the treatment of cystic fibrosis. However, there is an increasing amount of data in the literature suggesting use of aerosolized antibiotics may be beneficial in conjunction with systemic antibiotics for patients with MDR gram-negative VAP. The addition of adjunctive aerosolized antibiotics to systemic intravenous antimicrobials should be considered in patients who are non-responders to systemic antibiotics or have recurrent MDR VAP (3-5, 29-34).

LITERATURE REVIEW

Particle size

Aerosolized antibiotic therapy requires that the medication be nebulized into an airborne molecule. The ultimate determinate of drug deposition into critical portions of the lung requires that the particle be a particular size (6). Unfortunately, nebulizers are unable to produce identical size droplets. Therefore, the mean mass aerodynamic diameter (MMAD) best describes the distribution of the nebulized particle sizes (4,7). This means that 50% of the aerosol mass contains particles smaller than the MMAD while 50% of the aerosol mass is larger. Varying nebulizers will have different MMAD depending on the type and manufacturer.

Ideally, the particle will be one to five microns in size (4,6,7-9) This optimal size is based on the fact that particles that are too small (i.e. < one micron) will likely be quickly exhaled before reaching the lung tissue while large particles (i.e. >five microns) will be too heavy and become trapped on the surface of the endotracheal tube, trachea, and bronchus (6). The use of a slower respiratory rate with higher tidal volume and the use of an end-inspiratory breath hold will increase the likelihood that the particles will deposit on the bronchial mucosa and the location of the pneumonia (7). Also, by using a higher air flow (10 liters per minute), the delivery time can be decreased while at the same time providing appropriate sized molecules (9).

Delivery Devices

There are multiple types of nebulizers currently on the market and amongst these; there is a wide range of variability with as much as a 10-fold difference in the amount of drug delivered. Most nebulizers are designed to deliver a MMAD between 1-5 microns. The major factors that influence nebulizers are: mass output, aerosol particle size, composition of inhaled gas, and presence of lung disease (10).

The main two types of devices are the jet nebulizers and ultrasonic nebulizers. Though the two devices are very different, both seem to deliver the solution within therapeutic levels. Eisenberg et al. compared three different nebulizers (1 ultrasonic, 2 jet nebulizers) and found therapeutic levels in >90% of the patients for all nebulizers (11). Minimal systemic drug levels were found in all patients. Miller et al. found that though nebulizers may be similar, there are certain variables that allow optimization of antibiotic administration. Humidifying the air decreases the amount of drug delivered to the patient secondary to water in the air causing the droplets to clump together and more readily attach to the wall of the tubing (5). Breath-actuated nebulization was found to administer a higher dose of antibiotic to the lung than did continuous nebulization (5).

<u>Jet nebulizers</u>

Jet nebulizers force compressed air through a small exit orifice into the ventilator circuit. The air passes by the reservoir of medication and begins to expand after exiting the orifice. This expansion then causes a vacuum that shears the medication away from the reservoir and up into the circuit. Droplets that are too large are blocked by baffles and fall back into the reservoir (4). Interestingly, as the solution is nebulized, the evaporation of the antibiotic causes the solution's temperature to cool down (10). This cooling of the solution coincides with the concentrating of the fluid from evaporative losses and both can affect the

nebulizers output and particle size (12,13). Other factors include the solution characteristics, volume, gas pressure, gas flow, and baffle design (4,14-16).

Ultrasonic nebulizers

Ultrasonic nebulizers, through the use of a piezoelectric crystal, generate a vibration which aerosolizes the drug (4,10). Similar to the jet nebulizers, there is a baffle to collect large particles. Unlike jet nebulizers, the particle size may be altered by changing the frequency with particle size being inversely proportional to crystal frequency. The output which is directly proportional to crystal amplitude may likewise be altered. Unfortunately, ultrasonic nebulizers generate heat within the solution which may potentially lead to drug degradation during aerosolization.

Drug Dosing

The data concerning drug dosing is limited to small retrospective studies and case reports as summarized in the attached table. Palmer et al. have published studies on the use of aerosolized vancomycin and/or gentamicin as well as amikacin for the treatment of ventilator-associated tracheobronchitis (7,8). Tobramycin is the only antimicrobial actually formulated for nebulization and comes pre-packaged in a standard dose of tobramycin 300 mg (17,18,10,20). Colistin (colistimethate sodium or Polymyxin E) has been reviewed in a number of small retrospective studies or case series. Dosing may be expressed as either million units or milligrams. The conversion is approximately 80 mg per 1,000,000 units (10,23-26).

An additional concern with the administration of amikacin, gentamicin, vancomycin, and colistin via nebulization is that the intravenous dosage forms are not buffered and contain preservatives such as phenol and bisulfites (10). The presence of these preservatives as well as the generally hypertonic nature of these antimicrobials contributes to the development of airway irritation, coughing and bronchoconstriction (10). To prevent bronchoconstriction, pretreatment with albuterol is recommended (10).

Aztreonam lysine has been utilized in cystic fibrosis patients for the treatment of *Pseudomonas aerginosa*. However, the use of aerosolized aztreonam for ventilator-associated pneumonia has not been studied. Further studies are needed to establish utilization of aerosolized aztreonam for ventilator-associated pneumonia treatment.

LITERATURE REVIEW

Palmer et al. conducted a single center, randomized, double-blind, placebo-controlled trial on the use of inhaled vancomycin (120 mg nebulized q 8 hours), gentamicin (80 mg nebulized q 8 hours), both, or placebo in critically ill mechanically ventilated patients. The primary endpoint was a reduction in indices of respiratory infection. Secondary outcomes included white blood cell (WBC) count, systemic antibiotic therapy, mortality, and ventilator days. Microbiologic assessments were conducted with weekly tracheal aspirate cultures and also assessed for the development of antimicrobial resistance. Forty-three patients were included (19 in the aerosolized group, 24 in the placebo group). A decrease in the number of patients meeting National Nosocomial Infection Survey criteria for VAP from 73.6% to 35.7% in the treatment group after 14 days of therapy was identified (p=0.05). From a microbiologic perspective, there was a significant decrease in the number of resistant organisms isolated on Gram-stain (p=0.0056). There was no difference between the groups with regard to WBC before and after therapy or in mortality at 28 days. Fewer patients in the aerosolized antibiotic group required systemic antibiotic initiation during the study as compared to the placebo group (p=0.042). There was also no significant difference in the number of patients weaned from mechanical ventilation (12/19 treatment group vs. 13/24 placebo group, p=0.052) or in ventilator-free days (p=0.069) though when non-surviving patients were removed, weaning from mechanical ventilation was significantly higher in the treatment group (80% vs. 45%, p=0.046) (7).

Mohr et al. conducted a retrospective, single center study reviewing patients who received aerosolized antibiotics for the treatment of Gram-negative VAP. Patients received either tobramycin (300 mg nebulized q 12 hrs, N=16) or amikacin (400 mg nebulized q 8 hrs or 1000 mg nebulized q 12 hrs, N=6) based on the organism's susceptibility profile for a mean of 7 days of treatment. No patient developed

nephrotoxicity. There was a statistically significant improvement in PaO_2/FiO_2 ratio at the completion of therapy ($p < 0.05$). Twelve of the 26 patients had no further episodes of VAP (17).

Hallal et al. conducted a randomized, placebo-controlled trial using nebulized vs. intravenous tobramycin in 10 mechanically ventilated surgical/trauma ICU patients with documented *P. aeruginosa* or *A. baumanii* VAP on BAL. Patients received either tobramycin (TOBI®) 300 mg nebulized q 12 hrs + placebo IV + β-lactam antibiotic IV or placebo nebulized treatment + tobramycin IV q 24 hrs + β-lactam antibiotic IV. Five patients were enrolled in each group; the primary outcome measure was resolution of pneumonia. All patients in the inhaled tobramycin group were cured as compared to 3/5 in the intravenous tobramycin group. Trends were seen toward lower positive end expiratory pressure (PEEP) and more ventilator-free days in the nebulized group, but did not reach statistical significance. The intravenous tobramycin group showed a non-significant increase in serum creatinine compared to the inhaled tobramycin group (18).

Kwa et al. conducted a retrospective review of all patients treated with nebulized colistin for nosocomial pneumonia at their institution. They evaluated 21 patients who received colistin 80mg nebulized q6-12h for a median of 14 days. Eighteen of the 21 patients met criteria for either clinical cure/improvement and 12 of the 21 patients met criteria for microbiologic cure at the end of therapy. Pneumonia was the cause of death in only 3 of the 10 patients who died. There was no significant change in renal function over the course of therapy for either patient and no symptoms of neurotoxicity were detected. One of the 21 patients developed bronchospasm which resolved with albuterol (25).

Louzon P, *et al.*performed a retrospective review of 24 patients treated with a total of 29 courses of nebulized colistin therapy. Twenty-one of the 24 patients were surgical patients. The majority of the patients received colistin 150mg nebulized q12h (one patient received q8h). The majority of the patients had multi-drug resistant *P. aeruginosa*, however some of the isolates demonstrated resistance to colistin. Overall, the colistin treatments were well tolerated. Three patients developed bronchoconstriction, 5 had symptoms of neurotoxicity, and 8 had changes in renal function (only one progressed to dialysis). Eight of the 29 had microbiologic cure based on subsequent cultures; eleven of the patients had persistently positive cultures and ten had no follow-up cultures. This study emphasized the importance of verifying antimicrobial susceptiblitiy (27).

Falagas *et al.* performed a meta-analysis of eight trials comparing the prophylactic administration of aerosolized antibiotics in the ICU. This study, including 5 randomized studies and 3 non-randomized studies, had a total of 1,877 patients. Treatment included both aerosolized antibiotics and instillation administered aerosolized antibiotics. The authors found that ICU-acquired pneumonia was less common in the prophylactic group but no difference in mortality was noted within the primary analysis of only randomized trials. Within the secondary analysis, which included the three non-randomized trials, the authors found no difference in the incidence of either VAP or mortality. However, fewer patients were noted to be colonized with P. aeruginosa and no serious drug toxicities were observed (28). In a more recent meta-analysis by Falagas *et al.*, the author examined aerosolized antibiotics as monotherapy. The authors identified seven articles for a total of 63 patients. It was noted that patients, receiving either aerosolized or endotracheally instilled antimicrobials agents, had clinical cure rates of 86% and bacteriological eradication of 85%. The authors admitted that the data was limited but suggested that aerosolized antibiotics were an option in certain cases and hoped the data would encourage clinicians to conduct more studies (29).Arnold et al. performed a retrospective, single-center cohort study comparing aerosolized antimicrobial therapy along with systemic antimicrobial therapy to systemic antimicrobial therapy alone for *Pseudomonas aeruginosa* and *Acinetobacter baumannii* ventilator-associated pneumonia. Ninety-three patients were included with 74 patients in the systemic antimicrobial therapy group alone and 19 patients in the adjunctive aerosolized antimicrobial therapy group. Of the adjunctive antimicrobial therapy group, 9 patients received inhaled colistin and 10 patients received tobramycin. The adjunctive aerosolized antimicrobial group had significantly higher APACHE II scores. With regard to treatment-related factors, mechanical ventilation duration ($p<0.001$), ICU stay ($p=0.001$), and hospital stay ($p=0.001$) were significantly shorter in the systemic antimicrobial therapy group compared to the aerosolized antimicrobial group. Thirtyday mortality was lower in the aerosolized antimicrobial group (0% vs 17%), but this was not found to be statistically significant ($p=0.063$). However, the Kaplan-Meier curves depicting 30-day survival were statistically greater in the aerosolized antibiotic group ($p=0.03$).

Additionally, increased survival was seen for the subgroup of patients with APACHE II scores >16 that received adjunctive aerosolized antibiotics (p=0.004). There were no differences in treatment outcome between the colistin and tobramycin groups. Several limitations to this study include the retrospective design, small sample size, and uneven distribution between the two groups (30).

Rattanaumpawan et al. conducted an open-label, randomized controlled study of adults with Gram negative ventilator-associated pneumonia. In the control group, 49 patients received systemic antibiotics with nebulized sterile normal saline. In the experimental group, 51 patients received systemic antibiotics and nebulized 75 mg colistin. Favorable clinical outcomes were seen in 51% of the colistin group and 53.1% in the control group which was not found to be statistically significant (p=0.84). However, patients in the aerosolized colistin group had significantly more favorable microbiological outcome compared to the control group (p=0.03). Limitations to this study included lack of standardization for systemic antibiotic choices and durations of therapy. The study concluded that while adjunctive colistin therapy appeared to be safe, it did not produce a beneficial effect with regard to clinical outcome (31).

Lu et al. completed a prospective, comparative phase II trial assessing aerosolized combination ceftazidime and amikacin compared to intravenous combination ceftazidime and amikacin. In the aerosolized group, 20 patients received eight aerosol administration of ceftazidime per day for 8 days with a single daily dose of amikacin for 3 days. In the intravenous group,20 patients received a bolus dose of ceftazidime followed by a continuous infusion over 8 days along with a daily dose of amikacin for three days. After 8 days of therapy, treatment with aerosolized antibiotics did not produce a significant difference in microbiological response, treatment failure or rate of superinfection development compared to intravenous therapy. Several limitations of the study include small study design and occurrence at a single center limiting generalizability. Additionally, 8 days of therapy is not sufficient to treat *Pseudomonas aeruginosa* pneumonia (32).

Palmer et al. performed a double-blind placebo-controlled study which compared the use of IV systemic antibiotics alone versus IV antibiotics plus aerosolized antibiotics to eradicate multi-drug-resistant organisms in the ICU. Patients were randomized to receive systemic antibiotics and either aerosolized vancomycin 120 mg every 8 hours for gram-positive bacteria, gentamicin 80 mg every 8 hours or amikacin 400 mg every 8 hours for gram-negative bacteria or placebo. If patients had both gram positive and gram-negative pathogens, they received both aerosolized vancomycin and an aminoglycoside. 18 patients received placebo compared to 24 patients who received aerosolized antibiotics. Of the aerosolized group, 10 patients received vancomycin, 12 received an aminoglycoside and 2 patients received combination vancomycin and an aminoglycoside. The primary outcome of the study was eradication of bacteria detected at randomization. In the aerosolized antibiotic group, 26 of 27 bacterial isolates were eradicated compared to only 2 of 23 patients in the placebo group (p=0.0001). The aerosolized antibiotic group was significantly more effective at eradicating multidrug-resistant organisms compared to placebo (14 out of 16 patients vs. 1 out of 11 patients, p<0.0001). Additionally, the APACHE II scores were higher at randomization in the aerosolized antibiotic group suggesting more effectiveness in more critically ill patients (p<0.0007). Total ventilator days (p=0.078) and mortality (p=0.43) were not significantly different between either group. Limitations of the study include the small study size and lack of formal quantitative cultures for the microbiological endpoints (33).

Valachi et al. undertook a meta-analysis and systemic evaluation of the efficacy and safety of aerosolized colistin in conjunction with systemic antibiotics for the treatment of VAP. Eight studies were included in the study with a total of 690 patients. For the primary outcome of clinical response, there was a statistically significant improvement in clinical response and microbiological eradication when aerosolized colistin was added to systemic therapy. There was no difference in overall mortality or nephrotoxicity in any of the studies. The study suggests aerosolized colistin may be a safe and effective adjunctive therapy for VAP (34).

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Aerosolized Antibiotic Dosing

Study	Type of Study	# of Pts	Age (y)	Major Characteristics	Dose (nebulized)	Duration
Palmer LB, et al.(2)	Double-blind, randomized, placebo-controlled	43	19-92	ICU, MV	Vanc 120mg/2mL q8 Gent 80mg/2mL q8	Max 14 days
Palmer LB, et al.(4)	Prospective, serial study, self-controlled	6	19-96	ICU, MV	Gent 80mg q8 Amikacin 400mg q8 Amikacin 400mg q12 (renal failure)	2-3 weeks
Mohr AM, et al.(8)	Retrospective chart review	22	21-78	ICU, MV	Tobra 300mg q12 Amikacin 400mg q8 Amikacin 400mg q12 Amikacin 1g q12	7-10 days
Davis KK, et al.(9)	Prospective open-label study	6	52-73	*MAC* treatment	Amikacin 15mg/kg/day	4-52 months
Hallal A, et al.(10)	Randomized, double-blind, double-dummy	10	23-72	ICU, MV, GN VAP	Tobra 300mg q12	14 days
Labiris NRC, et al. (11)	Open-label, single-dose, self-controlled	10	52 ± 21	CF or bronchiectasis	Gent 160mg x1	Single dose trial
Levine BA, et al. (12)	Prospective, randomized	30	34	Burn pts w/inhalation injury	Gent 80mg q8	10 days
Dhand R. (7)	Review article	N/A	N/A	N/A	Colistin 40mg q12 Colistin 80mg q12 Colistin 160mg q8 Tobra 300mg q12	Not provided
Hamer DH (13)	Case series	3	45-67	ICU, pneumonia	Colistin 150mg q12 Colistin 100mg q12	11-14 days
Holloway KP, et al. (14)	Retrospective chart review	2	15-77	ICU, GN VAP	Colistin 160mg	Not provided
Kwa ALH, et al. (15)	Retrospective chart review	21	61	ICU, MDR VAP	Colistin 80mg q6-12	14 days (2-36 days)
Michalopoulos A, et al. (16)	Retrospective chart review	8	60 yrs	MDR VAP	Colistin 40mg q6-8 Colistin 80mg q8 Colistin 120mg q8 Colistin 160mg q8	3-19 days
Arnold et al. (30)	Retrospective chart review	93	39-69	ICU, MDR VAP	Colistin 150 mg q12 Tobramycin 300 mg q12	2-14 days
Rattanaumpawan et al. (31)	Open label randomized control trial	100	52-88	ICU, MDR VAP	Colistin 75 mg q12	5-15 days
Lu et al. (32)	Prospective comparator study	40	43-77	ICU, MDR VAP	Ceftazidime 15 mg/kg q3h Amikacin 25 mg/kg q24 for 3 days	8 days
Palmer et al. (33)	Double-blind placebo-controlled study	42	35-80	ICU, MDR, VAP	Vancomycin 120 mg q8 Gentamicin 80 mg q8 Amikacin 400 mg q8	14 days

CF = cystic fibrosis
MAC = *Mycoplasma pneumoniae*
VAP = ventilator-associated pneumonia
GN = Gram-negative
MDR = multidrug resistant
ICU = intensive care unit
MV = mechanical ventilation

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