

Aerolized antibiotics for the treatment of Ventilator Associated Pneumonia: A new era!

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SUMMARY. The increasing rate of ventilator-associated pneumonia (VAP) caused by multidrug-resistant pathogens warrants the development of new treatment strategies. Carefully engineered delivery systems are undergoing evaluation to test the hypothesis that aerosolized administration of antibiotics will provide high local concentrations and fast clearance, which in turn may improve efficacy and decrease the risk of microbial resistance. Recent studies indicate that aerosolized delivery systems for specially formulated antibiotics yield high local concentrations with rapid clearance and low systemic exposure. Preliminary clinical studies reveal that aerosolized delivery of antibiotics is well tolerated and active, when combined with intravenous antibiotics. No single aerosolized antibiotic is likely to provide broad-spectrum activity against both Gram-negative and Gram-positive bacteria. Large multicenter trials are needed to determine whether preliminary findings will translate to improved clinical activity and decreased microbial resistance in VAP patients, and to optimize the use of aerosolized antibiotics. *Pneumon 2014, 27(1):87-93.*

INTRODUCTION

The most common infection in the Intensive Care Unit (ICU) is ventilator-associated pneumonia (VAP). It is a type of infection characterized by increased morbidity and mortality, especially when adequate therapy is not administered in a timely manner, meaning it should be active against the causative pathogen and administered in the correct dosage, or when it is caused by multi-drug resistant (MDR) pathogens.^{1,2}

During the last decade, several methods have been proposed in order to attain the optimal antibiotic concentration at the site of infection. Specifically, the correct and accurate application of antibiotic pharmacokinetic/pharmacodynamic properties, the continuous infusion administration (of β -lactams, carbapenems and piperacillin/tazobactam) and the adminis-

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tration of maximum doses to overcome resistance were particularly emphasized. Nevertheless, the outcome of patients with VAP was not improved. In case the causative agent was an MDR pathogen, the clinical failure of treatment is common due to the poor distribution of the intravenously administered antibiotic to atelectatic pulmonary regions and the failure to achieve therapeutic concentrations. The subtherapeutic concentrations may often lead to prolonged antibiotic administration, which may result to increased selective resistance pressure and the emergence of resistant strains.^{3,4}

Treatment with inhaled antibiotics is popular in patients with cystic fibrosis, while it has been increasingly used during the last decade in mechanically ventilated patients. However, administration protocols are heterogeneous (different administration methods, use of various administration devices, dosages and durations of therapy). Thus, the results of this kind of treatment are not deemed satisfactory up to now to be proposed as routine treatment.⁵ In this review, there will be a reference to the "philosophy" of inhaled antibiotics administration, to the methods according to which it is applied and to the studies that support it so far.

INHALED ANTIBIOTICS

There is a large amount of experience regarding the administration of inhaled antibiotics in patients with cystic fibrosis and *Pseudomonas spp.* chronic infection. It seems that with this method high antibiotic concentrations may be attained at the site of infection with compromising the drug safety and the incidence of adverse events.⁶ However, no study has proved the effectiveness of this treatment so far in ICU patients. There are several factors that may have an important role in its application including the choice of the antibiotic that will be administered

as an aerosol, the administration device, the diameter of aerosol particles etc.^{6,7}

Antibiotics for inhaled use

The ideal preparation of inhaled antibiotic should have no preservatives, be non-hyperosmotic, have a practically neutral pH and contain at least 30 mEq of permeant anions (mainly chlorides) to avoid causing cough or bronchospasm (Table 1).⁸ In case the antibiotic does not contain the aforementioned anions, such as ceftazidime in the study of patients with VAP, the patient should be sedated with propofol before the administration in order to avoid cough and bronchospasm.

Antibiotics that have been used as inhaled are:

1. Colistin or Colistimethate (Colistin Methanosulfate), which is an inactive prodrug of colistin, is activated by slow hydrolysis and releases formaldehyde bisulfite. Colistin (also known as polymyxin E) consists of tightly interconnected cationic peptides that act as "detergents" on the bacterial outer membrane of Gram-negative pathogens, but may damage mammalian airways and alveoli.^{9,10} Colistin doses differ from country to country. In the USA, available preparations contain the active substance and not the prodrug, thus administering 150 mg of antibiotic, which are equivalent to 390 mg in the European Union. Pharmacokinetic study of colistin is cumbersome, because since receiving the specimen under study the drug continues to convert to its active form, thus not permitting the measurement of drug levels in vivo.¹¹
2. Aminoglycosides, which have been used in patients with cystic fibrosis to treat chronic infections due to *Pseudomonas spp.* and other Gram-negative pathogens. Their activity (dose-dependent), when administered as inhaled antibiotics, is better compared to antibiotics acting against the bacterial wall (e.g. cephalosporins),

TABLE 1. Technical terms regarding the use of inhaled antibiotics

Technical terms	Definitions
Hygroscopic increase	Increase in the size of inhaled particles due to water absorption from the humidified environment
Permeant anions	Anions that may readily penetrate the cellular membrane (e.g. Cl ⁻)
Sputum competition	Active binding of mucin with an antibiotic, which inhibits the antibiotic's biological action. It is more intense with aminoglycosides
Air flow difference	The air flow in the ventilator circuit, which is continuous, helps to prevent reinhalation of the exhaled gases, «flushes» the tubes and minimizes the condensation of particles in the tube

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because higher endobronchial concentrations may be attained, which are characterized by short half-life.¹² Their most important disadvantages are a) the need for high antibiotic doses (>25 times greater than minimum inhibitory concentration (MIC)) to attain bactericidal concentrations due to the competitive action with sputum (Table 1) and b) the fact that the administration of high antibiotic doses as monotherapy against highly resistant Gram-negative pathogens has not been studied adequately.¹³

3. Cephalosporins, which have been used in patients with VAP and aztreonam (monobactam) that has been used in patients with cystic fibrosis; both patient populations were infected with Gram-negative pathogens.¹⁴ The activity of cephalosporins that are administered as inhaled antibiotics depends on the amount of time their concentration lies above the MIC (that is the reason why they are administered >4 times per day; in a study, ceftazidime was administered every 3 hours) and the airway clearance rate.¹⁴
4. Carbapenems, which cause allergic reactions. The inhaled doripenem trial was interrupted in phase II.^{15,16}
5. Fosfomycin, which is a phosphonic acid with activity against both Gram-positive and Gram-negative pathogens. It is always administered in combination with other antibiotics, because the emergence of resistance is rapid when administered as monotherapy. It has been co-administered mostly with aminoglycosides, namely with tobramycin for the treatment of chronic endobronchial infections due to *Pseudomonas* and methicillin-resistant *Staphylococcus aureus* (MRSA) in patients with cystic fibrosis. Recently, then combined administration with amikacin was studied in a phase I trial including patients with VAP.^{17,18}

ADMINISTRATION DEVICES OF INHALED ANTIBIOTICS

Most nebulizers transport the inhaled antibiotics to the airways, but not to the pulmonary parenchyma. The site of drug deposition depends on the size of the particles that are being transported. The particle size is expressed by the mass mean aerodynamic diameter (MMAD) (Figure 1).¹⁹ For the drug particles to be propelled to the pulmonary parenchyma, they must have a diameter of 3 mm MMAD. However, jet nebulizers deliver particles with a diameter of 5 mm MMAD, thus the antibiotic deposition to the pulmonary parenchyma is problematic. Further-

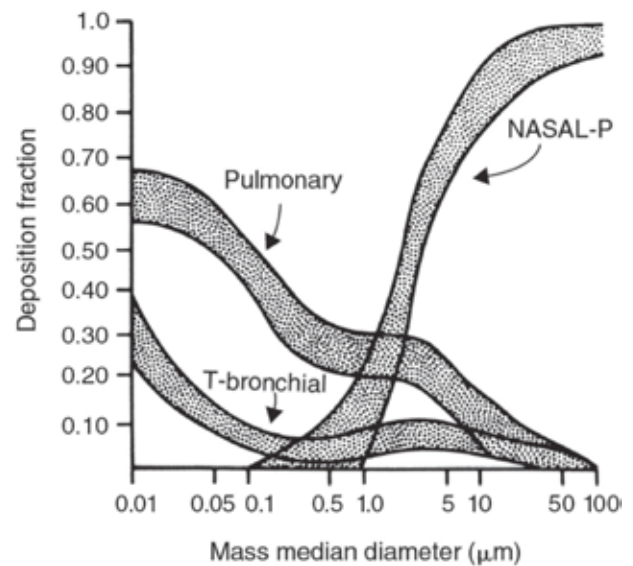


FIGURE 1. Particle deposition as a function of particle diameter in various regions of the lung. The nasopharyngeal region consists of the nose and throat; the tracheobronchial (T-bronchial) region consists of the windpipe and large airways; and the pulmonary region consists of the small bronchi and the alveolar sacs. Source: Task Group on Lung Dynamics (1996). *Health Physics*. 12: 173

more, the deposition is influenced by the humidity in the ventilator circuit that increases the hygroscopic environment of the endotracheal tube (in intubated patients) (Table 1).¹⁹ A simple example is the placement of a jet nebulizer to the proximal end of the ventilator and the administration of 300 mg of tobramycin solution: the mean tracheal concentration is 900 mg/g. The treatment of an infection caused by a Gram-negative pathogen with an MIC >32 mg/ml is impossible, since a concentration 25 times higher is needed to overcome the competitive action with sputum.²⁰

These problems led to the manufacturing of two special devices, namely of PDDS (Nektar Bayer Pulmonary Drug Delivery System) and of PARI (Investigational eFlow Inline Nebulizer System). PDDS is a disposable device that is placed at the upper part of the circuit's "Y" of the ventilator and consists of a vibrating plate of a nebulizer that delivers the administered drug during inspiration. The nebulizer goes off by a separate device that is pressure sensitive. The particles delivered to the pulmonary parenchyma are approximately 4.7 mm MMAD when the circuit is not humidified. In a pharmacokinetic study in which inhaled amikacin sulfate was administered twice

a day in a dose of 400 mg and PDDS was used, the initial mean concentration in the sputum was 11900 mg/ml, but the total mean concentration was less than 6400 mg/ml, thus showing the changes observed in the antibiotic concentration when using these devices.¹² The drug delivery time was 50 min. Bronchospasm was recorded as an adverse event, because the antibiotic preparation which was administered did not contain permeant anions.¹² PARI is a multifunctional device, which is placed at the inspiratory arm of the circuit, while a vibrating ejector made from stainless steel is placed at the same axis with the air flow and operates continuously. The nebulizer's inspiratory end acts as a spacer where the antibiotic aerosol is collected during expiration and discharged during expiration. Circuit humidification may be operated, because it does not particularly affect the hygroscopic environment, although the particle diameter increases from 2.8 mm to 3.2. However, this increase does not prevent the particles' propulsion to the pulmonary parenchyma, since it remains adequately short (≤ 3.0 mm). PARI device was used in a phase I trial including patients with VAP receiving a combination of

amikacin hydrochloride and fosfomycin (300 mg and 120 mg respectively). The administration of this combination yielded initial maximum mean tracheal concentrations of 12.390 mg/ml with a range from 6.910 to 17.000 mg/ml in a total nebulization time of 12 min and without any adverse events.¹⁸

In conclusion, both devices have the ability to propel and deliver high concentrations of antibiotics to the pulmonary parenchyma in patients with VAP. PARI device can be used many times in the same patient and does not require opening and closing of the ventilator circuit before and after the treatment which helps in preventing superinfections.

CLINICAL TRIALS ON THE ADMINISTRATION OF INHALED ANTIBIOTICS IN PATIENTS WITH VAP

All clinical trials regarding the administration of inhaled antibiotics were non-inferiority or superiority and single-centered trials. None was able to indicate a clear message regarding the use of inhaled antibiotics, as they

TABLE 2. Recent clinical trials studying the administration of inhaled antibiotics in patients with VAP – General characteristics

Trial	Design	Number of patients	Treatment	Outcome (inhaled vs. control)
Arnold ²³	Single-centered retrospective	93	Adjunct administration of inhaled colistin or tobramycin vs. IV antibiotics	30-day mortality 0 vs. 18% (p= 0.03 Kaplan–Meier curve, log rank)
Lu ¹⁴	Prospective randomized	40	Inhaled ceftazidime and amikacin vs. IV ceftazidime and amikacin	Clinical success 70 vs. 55% Superinfections 15 vs. 15% 28-day mortality 10 vs. 5%
Lu ²⁴	Prospective comparative observational non-randomized	165	Inhaled colistin ± IV aminoglycosides vs. IV β-lactams + aminoglycosides or quinolones	Clinical success 67 vs. 66% Superinfections 6 vs. 13% Mortality 16 vs. 23%
Niederman ¹²	Double-blind randomized	69	Inhaled amikacin (q12 h, q24 h) or placebo each with IV antibiotics	Antibiotic concentrations 50 vs. 17% Success 94 vs. 75 vs. 88%
Korbila ²⁵	Retrospective single-centered cohort study	121	Inhaled colistin ± IV colistin vs. IV colistin	Clinical success 76% vs. 61% In-hospital mortality 40% vs. 44%
Montgomery ¹⁸	Double-blind randomized phase I	4	Escalating doses of inhaled amikacin and fosfomycin	Concentrations - Amikacin >98 times MIC ₉₀ <i>P. aeruginosa</i> - Fosfomycin >68 times MIC ₉₀ MRSA

IV= intravenous, MIC₉₀ = Minimum Inhibitory Concentration for 90% of strains, MRSA= methicillin-resistant *Staphylococcus aureus*, q= every, VAP= Ventilator Associated-Pneumonia.

TABLE 3. Recent clinical trials studying the administration of inhaled antibiotics in patients with VAP – Special characteristics

Trial	Number of patients	Pathogens	Treatment	Dose of administered antibiotics and comments
Arnold ²³	93	<i>Pseudomonas aeruginosa</i> or <i>Acinetobacter baumannii</i>	Adjunct administration of inhaled colistin or tobramycin vs. IV antibiotics	Colistin 150mg or tobramycin 300mg q12 for >15–20min Nebulizers: Airlife, CareFusion, San Diego, California, USA (particle size 1–5mm) They had been placed at the inspiratory arm at a distance of 30 cm from the endotracheal tube Humidification was interrupted during treatment Patients receiving colistin (n=9) or tobramycin (n=10) were more severely ill (p=0.004) and had more MDR infections (p <0.001) than patients receiving IV antibiotics (n=74)
Lu ¹⁴	40	<i>P. aeruginosa</i>	Inhaled ceftazidime and amikacin vs. IV ceftazidime and amikacin	Nebulizers: Aeroneb Pro, AeroGen Corporation, Galway, Ireland or AeroGen Treatment duration >30 min Ceftazidime 15 mg/kg q3 h for 8 days, Amikacin 25 mg/kg per day for 3 days IMPORTANT: Control group received only inhaled antibiotics Resistant <i>P. aeruginosa</i> emerged only in the group receiving IV antibiotics Inhaled antibiotics caused the obstruction of the expiratory filter in 3 out of 20 patients due to the high administered doses and the increased frequency of administration
Lu ²⁴	165	<i>P. aeruginos</i> ή <i>A. baumannii</i>	Inhaled colistin ± IV aminoglycosides vs. IV β-lactams + aminoglycosides or quinolones	Colistin 400mg for 60 min q 8h for 7–19 days Nebulizer: AeroGen Control group : more MDR pathogens
Niederman ¹²	69	<i>P. aeruginos</i> ή <i>A. baumannii</i>	Inhaled amikacin (q12 h, q24 h) or placebo each with IV antibiotics	Amikacin 400mg q12h or q24 h) with PDDS preparation Main trial scope: concentrations >25 times MIC (256 mg/ml) This concentration was defined as amikacin concentration in tracheal aspirates > 6400mg/ml and $AUC_{asp}/T_{MIC} >100$ on day 1
Korbila ²⁵	121	<i>A. baumannii</i> ή <i>P. aeruginosa</i> ή <i>K. pneumoniae</i>	Inhaled colistin ± IV colistin vs. IV colistin	The mean ± SD daily dose of inhaled colistin was 2.1 ± 0.9 million IU. Siemens Servo Ventilator 300 Control group: more blood transfusions, more polymyxin-only susceptible pathogens, fewer days of iv colistin treatment
Montgomery ¹⁸	4	Enterobacteriaceae, <i>P. aeruginosa</i> , <i>Acinetobacter</i> spp. MRSA	Escalating doses of inhaled amikacin and fosfomycin	Nebulizer PARI Each patient received 3 doses of amikacin 50 mg/ml and fosfomycin 20 mg/ml in 24h. Day 3 : patients were randomized to receive two doses of amikacin και fosfomycin or placebo in 2h 15min after the first dose Amikacin concentrations in tracheal aspirates were 178 times higher than MIC ₉₀ (16mg/ml) and Fosfomycin concentrations were 54 times higher than MIC ₉₀ (32mg/ml)

q= every, MIC= Minimum Inhibitory Concentration, AUC= area under the curve, MIC₉₀ = Minimum Inhibitory Concentration for 90% of strains.

do not suggest a standard nebulization method and diameter of propelled particles, and highlight significant differences between the populations under study due to methodological problems regarding the control group.^{12-14,21-25} Their research hypothesis is based on a) the assumption that there is no difference between the groups under study when the trial is a superiority trial in favor of inhaled treatment or b) the assumption that experimental treatment is inferior to standard treatment when it comes to a non-inferiority trial. In case statistically significant differences are found, these are more evident in trials that have been designed to prove superiority of the treatment under control, especially if the patient sample is small. In trials that were designed to demonstrate non-inferiority, the final conclusion is a cause of criticism, because confidence intervals are broad. Generally, all studies to date result in that inhaled antibiotics is an adjunct to conventional systemic therapy especially in patients with MDR pathogens or VAP patients who do not respond to treatment (Table 2 and 3).²¹⁻²⁵

In conclusion, the increasing incidence of VAP by MDR pathogens apparently causes, or even require, the more substantial use of inhaled antibiotics, because it seems to improve patient outcomes and reduce the emergence/spread of antimicrobial resistance, as high concentrations of antibiotics are propelled to the site of infection without requiring long-term therapy. The use of inhaled antibiotics is promising but has not yet been established.

BIBΛIOΓΡΑΦΙΑ

- Iregui M, Ward S, Sherman G, et al. Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. *Chest* 2002; 122:262–268.
- Bekaert M, Timsit JF, Vansteelandt S, et al. Attributable mortality of ventilator associated pneumonia: A reappraisal using causal analysis. *Am J Respir Crit Care Med* 2011; 184:1133–1139.
- Sievert DM, Ricks P, Edwards JR, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009–2010. *Infect Control Hosp Epidemiol* 2013; 34:1–14.
- Kiem S, Schentag JJ. Interpretation of antibiotic concentration ratios measured in epithelial lining fluid. *Antimicrob Agents Chemother* 2008; 52:24–36.
- Ehrmann S, Roche-Campo F, Sferrazza Papa GF, et al. Aerosol therapy during mechanical ventilation: an international survey. *Intensive Care Med* 2013; 39:1048–1056.
- Ramsey BW, Pepe MS, Quan JM, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic fibrosis inhaled tobramycin study group. *N Engl J Med* 1999; 340:23–30.12.
- McCoy KS, Quittner AL, Oermann CM, et al. Inhaled aztreonam lysine for chronic airway Pseudomonas aeruginosa in cystic fibrosis. *Am J Respir Crit Care Med* 2008; 178:921–928.
- Eschenbacher WL, Boushey HA, Sheppard D. Alteration in osmolarity of inhaled aerosols cause bronchoconstriction and cough, but absence of a permeant anion causes cough alone. *Am Rev Respir Dis* 1984; 129:211–215.
- VanDevanter DR, Rose LM, Sprugel KH. 28-day inhalation toxicology of polymyxin E1, the major active component of colistin, in rats and dogs (poster P236). Presented at European Cystic Fibrosis Congress, June 6–9, 2001, Vienna, Austria.
- McCoy KS. Compounded colistimethate as possible cause of fatal acute respiratory distress syndrome. *N Engl J Med* 2007; 357:2310–2311.
- Coulthard K. Maximizing the efficacy and safety of colistimethate therapy. *Pediatr Pulmonol* 2008; 43:193–195.
- Niederman MS, Chastre J, Corkery K, et al. Bay41-6551 achieves bactericidal tracheal aspirate amikacin concentrations in mechanically ventilated patients with Gram-negative pneumonia. *Intensive Care Med* 2012; 38:263–271.
- Montgomery AB, Rhomberg P, Abuan T, Jones R. Synergistic effects for a combination of amikacin and fosfomycin against selected resistant Gram negative pathogens (abstract 43023 and poster). *Am J Respir Crit Care Med* 2013; 187:A3236.
- Lu Q, Yang J, Liu Z, et al. Nebulized ceftazidime and amikacin in VAP caused by Pseudomonas aeruginosa. *Am J Respir Crit Care Med* 2011; 184:106–115.
- Sorbello A. Doripenem safety review. 2013. Available at www.fda.gov/ohrms/dockets/ac/08/slides/2008-4364s1-05-FDA.
- Hilas O, Ezzo DC, Jodlowski TZ. Doripenem (doribax), a new carbapenem antibacterial agent. *Pharm Ther* 2008; 33:134–180.
- Trapnell BC, McColley SA, Kissner DG, et al. Fosfomycin/tobramycin for inhalation in patients with cystic fibrosis with pseudomonas airway infection. *Am J Respir Crit Care Med* 2012; 185:171–178.
- Montgomery AB, Vallance S, Abuan T, et al. A randomized double-blind placebo-controlled dose-escalation phase 1 study of aerosolized amikacin and fosfomycin delivered via the PARI investigational eFlow Inline nebulizer system in mechanically ventilated patients (abstract 42767 and poster 42767). *Am J Respir Crit Care Med* 2013; 187:A3236.
- Miller DD, Amin MM, Palmer LB, et al. Aerosol delivery and modern mechanical ventilation: in vitro/in vivo evaluation. *Am J Respir Crit Care Med* 2003; 168:1205–1209.
- Clark R, Heslet L, Abtonsens K, Donehower B. Evaluation of the disposition and safety of tobramycin solution for inhalation in ventilator associated pneumonia or tracheobronchitis patients (poster). Presented at American Thoracic Society International Conference 2003, Seattle, WA.
- Abu-Salah T, Dhand R. Inhaled antibiotic therapy for ventilator-associated tracheobronchitis and ventilator-associated pneumonia: an update. *Adv Ther* 2011; 28:728–747.
- Wood GC. Aerosolized antibiotics for treating hospital-acquired and ventilator-associated pneumonia. *Expert Rev Anti Infect*

- Ther 2011; 9:993–1000.
23. Arnold HM, Sawyer AM, Kollef MH. Use of adjunctive aerosolized antimicrobial therapy in the treatment of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* ventilator-associated pneumonia. *Respir Care* 2012; 57:1226–1233.
 24. Lu Q, Luo R, Bodin L, et al. Efficacy of high-dose nebulized colistin in ventilator-associated pneumonia caused by multi-drug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. *Anesthesiology* 2012; 117:1335–1347.
 25. Korbila IP, Michalopoulos A, Rafailidis PI, et al. Inhaled colistin as adjunctive therapy to intravenous colistin for the treatment of microbiologically documented ventilator-associated pneumonia: a comparative cohort study. *Clin Microbiol Infect* 2010; 16:1230-1236.