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Inhaled Antibiotics in the ICU (Michael S. Niederman)



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Introduction

Inhaled antibiotics have been available for use in patients with a wide range of respiratory infections, but their role in mechanically ventilated patients has not been routine, and has been primarily as adjunctive salvage therapy for difficult infections. With the emergence of multidrug-resistant (MDR) pathogens as a cause of lower respiratory tract infection in the ICU, the need for new therapeutic approaches is acute. Inhaled antibiotics address this need in a variety of ways. They can be effective against emerging MDR pathogens, including *Pseudomonas aeruginosa*, *Acinetobacter* spp, and the Enterobacteriaceae, primarily because they achieve high local concentrations at the site of infection. In addition, they do so without increasing the risk of systemic drug toxicity. Although the concept of inhaled antibiotics is not new, the technology of drug delivery has improved in recent years, while the availability of systemic antibiotics that are effective against MDR pathogens has declined, and there are few new drugs being developed for infection with gram-negative pathogens.

Historical Perspective

Topical antimicrobial therapy for ICU patients was popularised in the 1970s with a series of investigational interventions to prevent ventilator-associated pneumonia (VAP) (Klick et al. 1975). Although the intervention was successful in preventing many pneumonias, the patients who did develop pneumonia, in spite of this effort, were infected with highly resistant organisms, and the resulting infections had a high mortality, so that the net effect was no change in ICU death rate. The observation about the emergence of resistance was so concerning that interest in using topical antibiotics for pneumonia in the ICU declined rapidly. Since then, usage has been primarily sporadic and anecdotal, being applied in situations of infection with MDR pathogens, but never as routine adjunctive therapy of VAP (Hamer 2000).

For example, one recent report described a retrospective, matched case-control study of 43 patients in Greece with MDR VAP, treated with either IV colistin alone or combined aerosol and IV colistin. The population included 77% of patients having *A. Baumannii* as the pathogen. Although there was a trend to more clinical cure with adjunctive aerosol therapy, there was no difference in mortality, clinical success or bacterial eradication (Kofteridis et al. 2010). Other investigators have applied aerosol therapy as a last ditch salvage effort for patients with MDR pathogens, who were either failing systemic therapy, or who had infection with pathogens that were not susceptible to any available therapy. In these reports, some patients did recover, suggesting a role for aerosol therapy in this dire circumstance (Hamer 2000). In addition, some investigators have shown the efficacy of inhaled therapy for patients with ventilator-associated tracheobronchitis (Palmer et al 2008).

In all of these early studies the aerosol was delivered by either routine nebulisation, a jet nebuliser, an ultrasonic nebuliser, or no specific delivery system was specified. In general, all of these approaches were inefficient, sometimes with little drug getting into the patient, and even less being delivered to the distal lung, at the alveolar site of infection. Recently, nebulisation techniques have improved, with a better understanding of how to optimise delivery to ventilated patients, and these developments have opened up new possibilities for aerosol therapy of VAP.

New Understanding to Improve Aerosol Delivery to the Lung

Attention to delivery of aerosolised antibiotics to the infected lung has prompted investigators to define the optimal criteria for drug selection and drug delivery. The drug that is used must have high intrinsic activity against the most resistant pathogens causing respiratory infection. At the same time a limited systemic absorption from the respiratory site could minimise systemic toxicity. With both of these considerations in mind, recent studies have focused on inhaled use of aminoglycosides and colistin.

In considering how to deliver antibiotic to the lung, there are several issues that are relevant for mechanically ventilated patients with pneumonia. First, a delivery device should be able to generate small particles (< 5 microns) that are capable of reaching the alveoli, and not just depositing in the upper airway. In addition, whatever device is selected should be positioned in the ventilator circuit to maximise retention by the patient while minimising environmental contamination, which occurs if delivery is coordinated with the inspiratory cycle. In addition, it is important to consider whether an inhaled antibiotic can penetrate the pneumonic lung, or whether the presence of consolidation will prevent the deposition of antibiotic at the most affected site.

Deposition of inhaled agents in pneumonic lung is possible, but is not as effective as in non-consolidated tissue.

Goldstein and colleagues studied piglets with bronchopneumonia from *E. coli* intrabronchial instillation, who were treated with amikacin given by an ultrasonic nebuliser (Goldstein et al. 2002). In the study 38% of the nebulised dose was retained in the lung, with higher concentrations in the lung areas that were less severely affected by the pneumonia. However, when lung concentrations were compared for aerosolised versus intravenous therapy, more drug was delivered, even to the severely bronchopneumonic area, with aerosol therapy than with intravenous therapy. However, there was more systemic drug absorption from the pneumonic area than from the non-pneumonic areas. Thus, the findings of this study suggested a utility for aerosol therapy, even for pneumonic lung, provided that serum levels were monitored to avoid too much systemic absorption.

Rouby and colleagues have conducted a number of animal and human studies of aerosol therapy of pneumonia, and have suggested ways to optimise drug delivery to the lung in mechanically ventilated patients (Rouby et al. 2012). They have generally advocated for the use of a new type of vibrating mesh plate nebuliser, rather than a jet nebuliser, although they have also suggested some value with the use of an ultrasonic nebuliser. Vibrating mesh plates are able to generate a uniform particle size, keeping all the particles less than 5 microns. In the studies by Rouby et al., the nebuliser is placed in the inspiratory limb, before the Y connector, and it can be synchronised with inspiration, so that at least 60% of the reservoir dose is deposited in the lung. In selecting the nebulised dose, they recommend using the systemic dose of the antibiotic, plus the amount of drug that is

estimated to deposit in the tubing and expiratory filter. They also recommend using a tidal volume of 7-9 cc/kg, in a controlled ventilatory mode, with the patient sedated, using constant inspiratory flow, at a 1:1 inspiratory to expiratory ratio. They suggest using an inspiratory pause of at least 20% of the duty cycle, and to do the nebulisation with the heat moisture exchange filter removed.

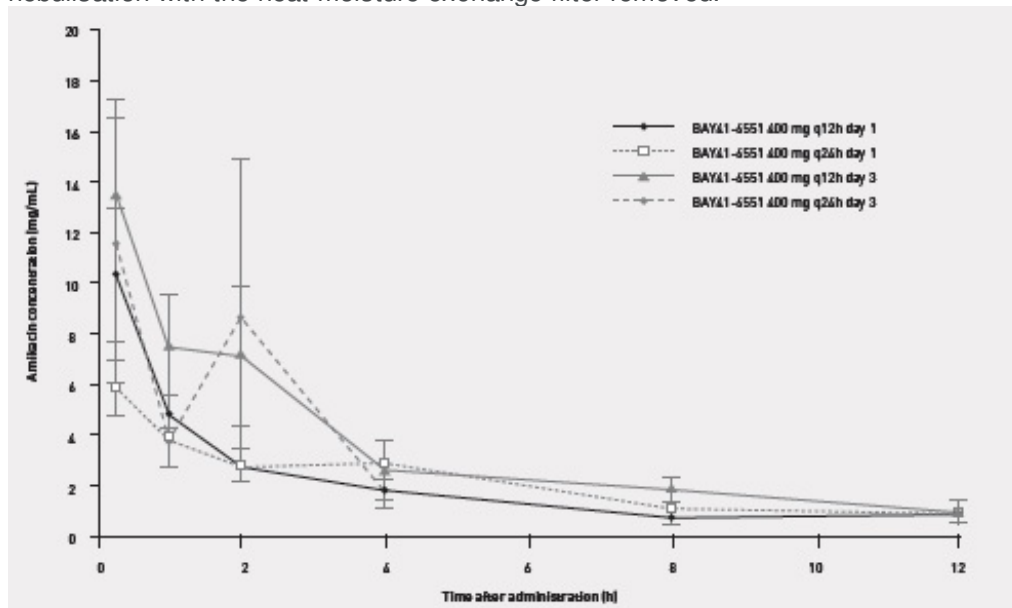


Figure 1. Tracheal aspirate amikacin concentrations (mean + standard error) over time on day 1 and day 3 (all treated patients). Values are for all treated patients with tracheal aspirate amikacin concentrations at the relevant time point. q12h every 12h, q24h every 24 h

With kind permission from Springer Science+Business Media: *Intensive Care Medicine*, BAY41-6551 achieves bactericidal tracheal aspirate amikacin concentrations in mechanically ventilated patients with Gram-negative pneumonia, Vol. 38, 2012, 263-71, Michael S. Niederman, Jean Chastre, Kevin Corkery, James B. Fink, Charles-Edouard Luyt, Miguel Sánchez García, figure 2.

We have recently completed a trial of nebulised amikacin for patients with gram-negative ventilator associated pneumonia (VAP), using a vibrating mesh plate nebuliser, and our delivery method was not exactly the same as specified by Rouby et al. In our study, the nebuliser was placed distal to the Y connector, before the origin of the endotracheal tube, and delivery was only in the inspiratory cycle (Niederman et al. 2012). Delivery was coordinated by a pressure control module that sensed the pressure in the inspiratory limb of the ventilator tubing, and delivery could be optimised by stopping nebulisation in the last 25% of the inspiratory cycle, to 'wash in' the inhaled agent to the deep lung. Using this method, any mode of ventilation was allowed, and patients did not need sedation to facilitate drug delivery. In the study, 71% of the patients were on assist-control ventilation, with the rest being on pressure support. The goal of the delivery system was to achieve a tracheal aspirate concentration of amikacin of > 6400 micrograms/ml (> 25 times an MIC of 256 micrograms/ml). Using a dose of 400 mg amikacin every 12 hours, this high concentration was achieved in 50% of the patients. Tracheal concentrations were higher after twice daily administration than after once daily administration. Tracheal concentrations were higher at day 3 than on day 1, but at both times serum concentrations remained < 10 micrograms/ml, and generally much lower than this level, with a mean of 3.16 micrograms/ml (see Figure 1).

Recent Findings With Inhaled Antibiotics

With the advent of new aerosol delivery methods, it is necessary to re-evaluate the efficacy and trial design of inhaled antibiotics for patients with gram negative pneumonia, treated with mechanical ventilation. When an inefficient nebuliser is used, along with too low a dose, efficacy is unlikely. For example, in one study of 100 patients with gram-negative pneumonia, a jet or ultrasonic nebuliser of 75 mg of colistin was added to systemic therapy, every 12 hours, with no benefit on clinical outcome (Rattanaumpawan 2010). Future trials may need to consider endpoints other than cure or mortality. These trials should probably focus on a patients with an enhanced risk of infection with MDR gram-negatives, use aerosol as an adjunct to systemic therapy, and look at endpoints such as early failure, without adjunctive aerosol therapy, and the ability of aerosol therapy to lead to clinical success with the use of less systemic therapy, than without adjunctive aerosol. Some of these ideas have been tested in recent trials.

One recent study has shown the value of inhaled high dose colistin in treating pneumonia caused by MDR

pathogens. In this study 43 patients with ventilator-associated pneumonia (VAP) caused by *Acinetobacter baumannii* or *Pseudomonas aeruginosa* were treated with high dose inhaled colistin (5 million units every 8 hours with a vibrating mesh plate nebuliser) either with or without (n=28) systemic antibiotics. The clinical cure rate was 67%, virtually identical to the success in treating 122 patients with VAP caused by sensitive strains of the same pathogens, that had been treated exclusively with intravenous antibiotics (Lu et al 2012). In areas of confluent pneumonia, the use of aerosolised colistin led to an increase in thoracic gas volume.

In another study by the same group of investigators, a randomised comparative trial was conducted in 20 patients with sensitive or intermediate strains of *P. aeruginosa* who were treated with inhaled amikacin plus inhaled ceftazidime, and a group of 20 patients with similar organisms who were treated with only intravenous ceftazidime plus intravenous amikacin or ciprofloxacin (Lu et al. 2011). After 8 days both groups had similar rates of treatment success, but acquired antibiotic resistance only occurred in those getting intravenous therapy. There were 4 patients with intermediately sensitive organisms who had bacterial eradication from the use of only aerosol therapy. Drug delivery by aerosolisation was efficient, with over 60% of the nebulised dose being retained in the lung. This study suggested that aerosol therapy alone, and not just as adjunctive therapy, was effective to treat VAP, although the use of this approach is not likely to be widespread.

In another recent study Niederman et al. examined whether the use of adjunctive aerosolised amikacin could have a clinical benefit other than clinical or microbiologic cure rates (Niederman et al. 2012). In a randomised trial of 69 mechanically ventilated patients with gram-negative pneumonia (with more than half having either *P. aeruginosa* or *Acinetobacter* spp), amikacin was given with a vibrating mesh plate nebuliser at either 400 mg twice daily, 400 mg once daily, or a placebo was given via aerosol. All patients received systemic antibiotics, and at the end of a week, in this blinded trial, the patients receiving the highest dose of amikacin were receiving less systemic therapy than the patients receiving either placebo or lower dose amikacin. In addition, systemic therapy was escalated (more or broader spectrum agents used) in 14% of the high dose inhaled amikacin patients, 38% of the lower dose inhaled amikacin patients and in 58% of those receiving inhaled placebo. Clinical failure was defined by serial measurement of the Clinical Pulmonary Infection Score, with failure defined as a rise >2 points at day 3, a failure to fall by >1 point at day 5 or >2 points at day 7. By this definition, there were fewer failures with the amikacin twice daily dosing than with other regimens (see Figure 2). Thus, the use of adjunctive aerosol therapy had the benefit of leading to less systemic antibiotic exposure, by leading to a more rapid clinical response than in those patients receiving only systemic antibiotics, and leading to less clinical failure, suggesting a possible role for aerosol therapy to reduce systemic antibiotic exposure in the ICU therapy of pneumonia.

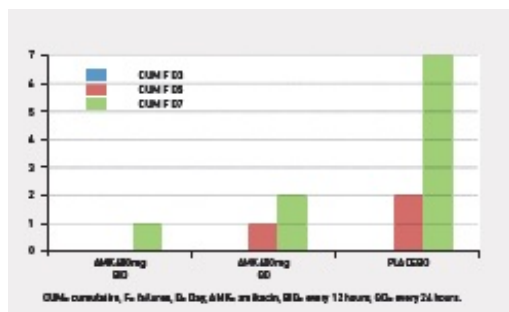


Figure 2. Cumulative number of clinical failures at day 3, day 5 and day 7 for each of 3 treatment groups. Clinical failure was defined by serial measurement of the Clinical Pulmonary Infection Score.

Is it Time for Routine Use of Inhaled Antibiotics as Adjunctive Therapy for VAP?

Based on recent findings, it may be time to re-evaluate the use of aerosolised antibiotics in the ICU for therapy of lower respiratory tract infection. While they may be useful as adjunctive therapy of pneumonia caused by MDR pathogens, they may also have a role as routine adjunctive therapy, to reduce the duration of systemic antibiotic therapy of pneumonia. Chastre et al. have demonstrated that 8 days of antibiotic therapy may be as effective as 15 days in VAP, but when nonfermenting gram-negatives are present, 8 days of therapy may lead to more microbiologic failures (Chastre et al 2003). The use of routine adjunctive aerosol therapy may address this issue by providing more 'up-front' therapy, thereby permitting short duration of systemic therapy, even for non-fermenting gram-negatives.

More data are needed to determine if nebulised antibiotics should be used routinely in the therapy of gram-negative pneumonia in ventilated patients. If the data are positive, we may be able to extend this approach to non-ventilated patients, since the same aerosol technology is becoming available for this population as well. Other targets of aerosol therapy in the ICU are patients with ventilator-associated tracheobronchitis, which may

be a predecessor of VAP, and which may be effectively treated with topical tracheobronchial antibiotics, without the use of systemic therapy. In the conduct of future studies, it is also important to evaluate the efficacy of current inhaled agents on gram-positive pathogens, where they may have efficacy, or it may be necessary to combine the current agents with another agent active against MDR gram-positives such as methicillin-resistant *S. aureus*, since many patients have mixed gram-negative and gram-positive infections.

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