

# Inhaled antibiotics beyond aminoglycosides, polymyxins and aztreonam: a systematic review

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## OBJECTIVE

We sought to evaluate published evidence regarding clinical or microbiological outcomes related to the use of inhaled antibiotics other than aminoglycosides, polymyxins and aztreonam.

## METHODS

➤A systematic search was performed in the PubMed and Scopus databases by one investigator (KKT), from August to September 2014.

➤Eligible studies should involve the administration of inhaled or instilled antibiotics, either as monotherapy or combination therapy, by the inhalation route only or in conjunction with systemic antibiotic therapy.

➤Studies referring to the administration of inhaled aminoglycosides, polymyxins or aztreonam were included only if other types of inhaled antibiotics were administered concomitantly.

## RESULTS

### Inhaled fosfomycin

In a DB RCT, patients with cystic fibrosis and chronic *P. aeruginosa* LRTI received inhaled aztreonam and then randomized to receive a combination of inhaled fosfomycin and tobramycin or placebo. Patients who received fosfomycin and tobramycin combination showed significantly less decline in FEV<sub>1</sub> and FVC than patients who received placebo (mean change in FEV<sub>1</sub>: 0 ml vs. -136 ml p<0.001, mean relative change in FVC: -1.3% vs. -5.6% p=0.02). Other clinical outcomes such as requirement for other anti-pseudomonal antibiotics, hospitalizations or missed days at work or school during the study, were not significantly different between the examined antibiotic combination in either dose and the placebo group.

### Inhaled β-lactams

#### Prevention of ventilator-associated pneumonia (VAP)

Ceftazidime was associated with significant reduction in the frequency of VAP compared to placebo (3/20 vs. 11/20 p=0.021) in one study but not in another (21/53 vs. 24/52 p=0.5). This deviation could be attributed to differences in study populations.

Inhaled and intravenous ampicillin-sulbactam was associated with a reduction in viable counts of extensively drug-resistant *A. baumannii* in bronchial secretions cultures (from 10<sup>7</sup>-10<sup>8</sup> CFU/ml in day 1, to <10<sup>2</sup> CFU/ml) compared to administration of the same drug by the intravenous route only.

#### VAP treatment

There was no significant difference between the aerosolized combination of aerosolized ceftazidime and amikacin was compared to the intravenous administration of ceftazidime and either amikacin or levofloxacin, in mechanically ventilated ICU patients with *P. aeruginosa* VAP (14/20 vs. 11/20 p=0.33) or in the rate of negative bronchial secretions cultures at the same time (17/20 vs. 14/20 p=0.45)

#### Cystic fibrosis treatment

In 2 DB crossover RCTs, inhaled ceftazidime and the combination of carbenicillin and gentamicin were better than placebo in the management of chronic *P. aeruginosa* LRTI in patients with cystic fibrosis resulting in significantly higher mean Peak Expiratory Flow Rate (PEFR), Forced Expiratory Volume in 1 second (FEV<sub>1</sub>) and Forced Vital Capacity (FVC) values.

A significant decrease was observed in the number of hospital admissions due to exacerbations related to *P. aeruginosa*, compared to the number of admissions of the same patients in the year prior to the study (5 vs. 16 p<0.05). In neither study was the *P. aeruginosa* eradicated from the lower respiratory tract secretions.

#### Non cystic fibrosis-related bronchiectasis treatment

In a non-blinded RCT patients with bronchiectasis and chronic *P. aeruginosa* LRTI received either a combination of aerosolized ceftazidime and tobramycin or non antibiotic,. A significant decrease was recorded in the inhaled antibiotics group in the mean number of hospital admissions due to exacerbations (0.6 vs. 2.5 p=0.023) and the mean duration of hospitalization (13.1 days vs. 17.9 days p=0.033). Lung function assessed by FEV<sub>1</sub> and FVC was not statistically different between the groups (p>0.05).

### Inhaled vancomycin

A placebo controlled DB RCT investigated the therapeutic effect of aerosolized vancomycin and/or aerosolized gentamicin in mechanically ventilated ICU patients with culture-positive VAT. Patients on aerosolized antibiotics exhibited significantly decreased signs of respiratory infection at the end of treatment than at the beginning (mean initial Clinical Pulmonary Infection Score (CPIS): 6.89, mean final CPIS: 5.47 p=0.021) while in patients in the placebo group the difference was not significant. Furthermore, patients on aerosolized antibiotics had significantly lower possibility of requiring systemic antibiotics for new or persistent infections (8/19 vs. 17/24 p=0.042) whereas the mortality rates of the two groups did not deviate significantly.

In a DB RCT VAP patients at risk for multi-drug resistant (MDR) VAP, were treated with either aerosolized vancomycin and/or aerosolized aminoglycoside or with placebo. Concomitantly to inhaled therapy appropriate systemic antibiotics were administered. Patients receiving aerosolized therapy were more likely than those in the placebo group to have the pathogen eradicated from sputum cultures at the end of treatment (26/27 vs. 2/23 p<0.001), and significant clinical improvement as assessed by CPIS score (p<0.001). No significant difference was demonstrated regarding mortality or duration of mechanical ventilation.

### Inhaled fluoroquinolones

In a DB RCT in patients with cystic fibrosis and chronic *P. aeruginosa* LRTI aerosolized levofloxacin decreased the mean density of *P. aeruginosa* (-0.73 log<sub>10</sub> cfu/g vs. 0.23 log<sub>10</sub> cfu/g p=0.001) and improved FEV<sub>1</sub> values, (6.25% vs. -2.36% p=0.003). Moreover, a significant reduction in need for additional anti-pseudomonal antibiotics was observed compared to placebo.

In 2 DB RCTs inhaled ciprofloxacin reduced the density of various pathogens, including *P. aeruginosa*, in sputum cultures compared to the beginning of treatment. The respective reduction in the placebo group was significantly lower (mean: -3.62 log<sub>10</sub> cfu/g vs. -0.27 log<sub>10</sub> cfu/g p<0.001 and -4.2 log<sub>10</sub> cfu/g vs. -0.08 log<sub>10</sub> cfu/g p=0.002). Moreover, in both studies the aerosolized antibiotic group had significantly higher eradication rate of pathogens in sputum cultures than the placebo group.

## CONCLUSION:

Published evidence is heterogeneous with regard to antibiotics used, studied indications, patient populations and study designs. Therefore, although the currently available data is encouraging, no safe conclusion regarding effectiveness and safety of the drugs in question can be reached.