A network meta-analysis of the efficacy of inhaled antibiotics for chronic Pseudomonas infections in cystic fibrosis


CRD summary
This review concluded that inhaled tobramycin (powder or solution), colistin and aztreonam lysine were comparable in their effectiveness for treating chronic Pseudomonas aeruginosa lung infection in people with cystic fibrosis. The limitations of the review, uncertainty around trial quality, and the small number of trials informing the network meta-analysis, means the conclusions should be treated with caution.

Authors' objectives
To compare the efficacy of the inhaled antibiotics tobramycin, colistimethate sodium (colistin) and aztreonam lysine for treating chronic Pseudomonas aeruginosa lung infection in cystic fibrosis.

Searching
MEDLINE, MEDLINE in Process, EMBASE and The Cochrane Library were searched for studies published in English to October 2010; search terms were reported. Further studies were identified that were published after the search was conducted; the source was not reported. Conference abstracts from 2009 and 2010 were identified from BIOSIS Previews and four relevant societies.

Study selection
Randomised controlled trials (RCTs) that compared inhaled tobramycin, colistin, aztreonam lysine for inhalation, amikacin or ciprofloxacin to each other or placebo in patients with cystic fibrosis aged at least six years with chronic P. aeruginosa infection, were eligible for inclusion. Studies had to use an approved antibiotic formulation, and the licensed dose, for inhalation (detailed in the paper). Outcomes of interest were percent change from baseline in forced expiratory volume in 1 second (FEV₁)% predicted and P. aeruginosa sputum density, the proportion of patients with use of additional anti-P. aeruginosa antibiotics and respiratory hospitalisations.

Across the studies, the mean age ranged from 11 to 32 years, mean baseline FEV₁% predicted ranged from 49.9% to 63.6% and half the studies recruited treatment-naïve populations. The drugs evaluated were tobramycin, colistin and aztreonam lysine; dosing regimens varied across studies.

Two reviewers independently selected studies for the review.

Assessment of study quality
Study quality was assessed in terms of blinding, the use of an intention-to-treat analysis and data imputation methods.

The authors did not state how many reviewers assessed study quality.

Data extraction
Data for the changes in FEV₁% predicted, P. aeruginosa sputum density and exacerbations (including standard errors) were extracted or calculated.

The authors did not state how many reviewers extracted data.

Methods of synthesis
Data extracted on efficacy and safety of the interventions were included in Bayesian network meta-analysis models with non-informative priors. Fixed-effect and random-effects models were used. The model was used to produce differences in outcomes (relative treatment effects) between each of the interventions included, with 95% credible intervals (CrI) as the measure of uncertainty surrounding the point estimates. This was used to suggest the probability of each intervention being the better treatment. Analyses included models for: all available study data; subgroups of studies; and/or investigating study level covariates (age, baseline FEV₁% predicted, prior study drug exposure).
Results of the review
Eleven RCTs were included (2,197 participants; range 32 to 520); eight compared to placebo and three to active comparators. Of the 11 RCTs, eight were double-blind and three were open label. Nine RCTs analysed the treated population, five with no imputation of missing data, three used last observation carried forward, and one didn’t report on imputation; two RCTS used a per protocol population. Duration of follow-up ranged from four to 24 weeks. The base case analysis included a network of seven RCTs; four RCTs were excluded due to a lack of chronic infection in all patients, differing naïve/exposed status, and patients only with mild FEV₁ impairment.

Tobramycin (powder or 300mg solution in 4mL or 5mL), colistin and aztreonam lysine all showed improvement in the change from baseline in FEV₁ % predicted at four weeks over placebo, tobramycin powder and 300mg in 5mL solution significantly so. The tobramycin preparations, colistin and aztreonam lysine showed comparable improvements in efficacy at four weeks. The difference for tobramycin powder was -0.55 (95% CrI -3.5 to 2.4) compared to the 300mg in 5mL solution, -0.64 (95% CrI -7.1 to 5.7) compared to the 300mg in 4mL solution, 3.64 (95% CrI -1.0 to 8.3) compared to aztreonam lysine, and 5.77 (95% CrI -1.2 to 12.8) compared to colistin. Results for the other comparisons and a range of scenario analyses were also reported.

Results for *P. aeruginosa* sputum density at four weeks were variable and subject to high degrees of uncertainty. There were insufficient data to produce reliable results for percentage change from baseline in FEV₁ % predicted at 20 weeks, *P. aeruginosa* sputum density at 20 weeks, respiratory hospitalisation and anti-*P. aeruginosa* antibiotic use at 24 weeks.

Authors’ conclusions
All studied antibiotics have comparable efficacies for the treatment of chronic *Pseudomonas aeruginosa* lung infection in cystic fibrosis.

CRD commentary
The review addressed a clear research question with reproducible inclusion criteria. Several relevant sources were searched and attempts were made to identify unpublished studies. Only studies published in English were included, so there was no attempt to address potential for language bias. Study selection was conducted in duplicate, but it was unclear whether similar methods to reduce error and bias were used during data extraction and the quality assessment. Some appropriate criteria were used to assess included study quality, but the assessment did not fully explore potential biases. Appropriate methods of synthesis were used, although some studies were excluded from the analysis post hoc that seemed to meet the a priori inclusion criteria. The review was funded by the manufacturer of one of the drugs being evaluated.

Given the limitations of the review, the uncertainty around the quality of the included trials, and the small number of trials informing the network meta-analysis, the conclusions should be treated with caution.

Implications of the review for practice and research
**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that future research needed to: consider study design and population differences; investigate potential effect modifiers to understand their impact on outcomes and their relative importance, for example chest computed tomography to characterize structural lung abnormalities at baseline; include a more homogenous population regarding age, baseline FEV₁ % predicted and inclusion of either chronically- or non-chronically-infected patients. They also stated that the major study design difficulty was in controlling for exposure status as most patients will have prior exposure to several antibiotics. Clinicians and researchers need to align the approach to study design, population selection and the most relevant comparative outcomes.

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