Effects of prolonged use of azithromycin in patients with cystic fibrosis: a meta-analysis
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CRD summary
This review found that azithromycin improved lung function in patients with cystic fibrosis, especially those colonised by *Pseudomonas*. Nausea and diarrhoea were more frequent with azithromycin. The small number of studies, possibility of missed studies and lack of details of the review process made the reliability of the authors’ conclusions unclear.

Authors' objectives
To investigate the efficacy and safety of azithromycin in patients with cystic fibrosis.

Searching
PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) were searched without language restrictions from inception to April 2008. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) that compared azithromycin treatment with placebo and assessed the effects of long-term treatment with azithromycin on pulmonary function tests, respiratory infections, antibiotic use and hospitalisations in patients with cystic fibrosis were eligible for inclusion.

The primary outcome of interest was lung function deterioration (percentage change in forced expiratory volume at one second (FEV1) and forced vital capacity (FVC). A number of secondary outcomes of interest included acute pulmonary exacerbations, additional courses of antibiotics, changes in inflammatory markers, frequency of newly positive sputum cultures, new hospitalisations, adverse effects and quality of life.

Patients in the included studies had a mean age of 18.5 years in the placebo group and 18.1 years in the azithromycin group. Half of the studies were in young adults and the rest in children. Patients were treated for 13 to 52 weeks. Some of the included patients were colonised with *Pseudomonas*. The included regimens were 250mg daily or three times a week where weight was less than 40kg and 500mg daily or three times a week where weight was more than 40kg.

Study selection was performed independently by two reviewers. Disagreements were resolved by consensus.

Assessment of study quality
Methodological quality was assessed using the Jadad scale of randomisation, blinding, withdrawals and dropouts) to give a quality score out of five.

The number of reviewers who assessed study quality was not reported.

Data extraction
Mean differences (MDs) or risk ratios (RRs) and 95% confidence intervals (CIs) were extracted. Where data for patients colonised with *Pseudomonas* were available these were extracted separately where possible.

The number of reviewers who extracted outcome data was not reported.

Methods of synthesis
Mean differences or risk ratios were pooled using a random-effects model. Heterogeneity was assessed using X^2 and I^2 tests. The Egger regression method was used to assess publication bias. Patients with *Pseudomonas* were pooled separately. Studies were pooled at all time points and one to three months and six to 12 months follow-up.

Results of the review
Four RCTs were included in the review (n=368). All of the trials had a Jadad score of 4 (no further details were reported).

Azithromycin was associated with a significant increase in FEV$_1$ (MD 3.53%, 95% CI 0.00 to 7.07; four RCTs) and FVC compared with placebo (MD 4.24%, 95% CI 2.02 to 6.45; four RCTs). There was some heterogeneity for FEV1 (I$^2$ 38%) and none for FVC. For FVC the difference between groups was not significant in trials with a low proportion of $Pseudomonas$.

No significant FEV$_1$ or FVC changes were found at one to three months follow-up.

Large amounts of heterogeneity meant studies could not be combined for secondary efficacy outcomes. Three trials reported a significant decrease in the number of antibiotic courses (no further details were reported).

The risk of gastrointestinal effects was higher with azithromycin (RR 1.72, 95% CI 1.33 to 2.21). The main side effects reported were nausea (RR 2.04, 95% CI 1.19 to 3.45) and diarrhoea (RR 2.12, 95% CI 1.10 to 4.08), which were significantly higher with azithromycin than with placebo.

There was no evidence of publication bias (p=0.31).

**Authors' conclusions**
Azithromycin improved lung function in patients with cystic fibrosis, especially in those colonised by $Pseudomonas$. Nausea and diarrhoea were more frequent with azithromycin.

**CRD commentary**
The research question was supported by clear inclusion criteria. Searches were conducted without date and language restrictions. Only two databases were searched, so relevant studies may have been missed. No specific attempts were made to locate unpublished studies, so publication bias was possible; the small number of studies meant that tests for publication bias may not have been reliable. Study selection was performed by two reviewers, which reduced risks of error and bias; it was unclear whether similar steps were taken for quality assessment and data extraction. Study quality was assessed and reported, but there was no reporting of items that were not fulfilled and allocation concealment was not assessed. Meta-analysis appeared appropriate. Heterogeneity was assessed.

The small number of studies, possibility of missed studies and lack of details of the review process made the reliability of the authors’ conclusions unclear.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that more studies were needed to investigate the appropriate time to initiate therapy, the best dosing regimen and the subgroup of patients that would benefit most.

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