Meta-analysis of randomized controlled trials on the comparative efficacy and safety of azithromycin against other antibiotics for upper respiratory tract infections


Authors' objectives
To compare azithromycin in the treatment of upper respiratory tract infections with other antibiotics that are typically administered in longer courses.

Searching
MEDLINE and EMBASE were searched from 1990 to 21 March 2000 using the textword and MeSH term 'azithromycin'. The Cochrane Controlled Trials Register was also searched. Papers published in English, French, German or Spanish were eligible, as were those published in any other language provided there was an English abstract that provided sufficient information for the planned meta-analysis.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) only were included.

Specific interventions included in the review
Comparisons of azithromycin with another antibiotic were eligible for inclusion in the review. The regimen of azithromycin in the included studies was not stated. The comparators were cefaclor, co-amoxiclav, clarithromycin, roxithromycin, amoxycillin, erythromycin, penicillin and penicillin V.

Participants included in the review
Studies of patients with acute otitis media, acute sinusitis or acute pharyngitis (including tonsillitis and pharyngotonsillitis) were eligible for inclusion in the review.

Outcomes assessed in the review
The primary outcome was the clinical failure rate at day 10 (or the nearest day) of treatment. Relapses by the day of evaluation were taken as failures. Data on bacteriological failures among culture-positive cases were also collected.

How were decisions on the relevance of primary studies made?
The inclusion criteria were independently applied by two investigators.

Assessment of study quality
Data were extracted on the method of random allocation, the adequacy of allocation concealment and masking. Each study was checked for compliance with these aspects of study quality. The validity of the studies was independently determined by two investigators.

Data extraction
The following information was extracted from each trial report (and separately for each condition of interest): year and language; the number of centres; location; company sponsorship; inclusion and exclusion criteria; the definition of condition of interest; treatment and comparators; patient demography; the number of patients randomised and in the analysis; clinical and bacteriological failure rates; the day of evaluation; the rates of toxicity; and severe side-effects.

Methods of synthesis
How were the studies combined?
Pooled odds ratios (ORs), risk ratios and risk differences, and their 95% confidence intervals (CIs) were calculated separately for the clinical failure rate in each infection studied. Both the Mantel-Haenszel fixed-effect models, and the random-effects models of DerSimonian and Laird (see Other Publications of Related Interest) were used. For the evaluation of toxicity, the rates of discontinuation due to side-effects were pooled and compared across all types of upper respiratory tract infections. Study-specific rates were weighted simply by the sample size of each study. Weighting by the inverse of the fixed-effect or random-effects variance was said to yield similar results, but these were not presented in the review.

**How were differences between studies investigated?**
Between-study heterogeneity was assessed using the chi-squared-based Q statistic.

**Results of the review**

**Acute otitis media:** there were 18 studies (19 comparisons) involving 3,421 patients (n in meta-analysis = 3,458).

Acute sinusitis: there were 10 studies (11 comparisons) involving 1,742 patients.

Acute pharyngitis: there were 14 studies (16 comparisons) involving 2,447 (n in meta-analysis = 2,603).

For the three types of infections, the quality of the studies was similar with one double-blind and one single blind study and the remainder unblinded or unknown. For clinical failure rates, there was no statistically-significant heterogeneity between the studies and the pooled estimates showed no difference between azithromycin and its comparators.

Acute otitis media: the random-effects OR was 1.12 (95% CI: 0.81, 1.54).

Acute sinusitis: the random-effects OR was 0.91 (95% CI: 0.60, 1.39). Acute pharyngitis: the random-effects OR was 1.07 (95% CI: 0.59, 1.94).

Fixed-effect ORs, risk ratios and risk differences were also reported in the review. Subgroup analyses according to the comparator drug were also conducted and reported.

Adverse events: data on discontinuations due to adverse events were available from 33 trials. The overall discontinuation rate from azithromycin was 0.8%, compared with 0.6% for penicillin or amoxycillin, 1% for clarithromycin, 1.3% for cefaclor, 1.9% for erythromycin, and 2.3% for co-amoxiclav.

**Authors’ conclusions**
Overall, azithromycin was safe and its shorter course was convenient, although the rationale for the longer courses used for its comparators is questionable. There were no clinically meaningful differences in its efficacy for upper respiratory infections in comparison with other antibiotics.

**CRD commentary**
This review addressed a clear and appropriate question regarding the efficacy and tolerability of azithromycin in upper respiratory tract infections. In addition, it used clearly defined inclusion and exclusion criteria. The literature search included the two most appropriate databases and a range of languages were accepted. It is possible that a small number of studies may have been missed. No assessment of publication bias was attempted. The methods adopted by the reviewers were described and appear to have been rigorous. Only RCTs were considered in this study and their quality was assessed. Generally, the quality of the RCTs found was limited by their lack of blinding. A good level of detail of the individual studies was presented in the review.

The meta-analyses performed were appropriate and the authors’ conclusions are consistent with the findings presented.

**Implications of the review for practice and research**
Practice: The authors state that ‘Short courses of azithromycin are as effective as longer courses of other antibiotics for
upper respiratory tract infections. Convenience of dosing should be balanced against the increased cost of this regimen (not assessed in this review) for the treatment of these common infections, where often no antibiotic may be indicated at all'.

Research: The authors did not state any implications for further research.

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