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


Authors' objectives
To carry out a meta-analysis of randomised controlled trials (RCTs) of azithromycin compared with other antibiotics, in the treatment of lower respiratory tract infections including acute bronchitis, acute exacerbation of chronic bronchitis and community-acquired pneumonia.

Searching
MEDLINE and EMBASE were searched for RCTs published from 1990 to 21 March 2000, using the textword and MeSH 'azithromycin'. The Cochrane Controlled Trials Register was also examined for additional studies.

Study selection
Study designs of evaluations included in the review
RCTs were included.

Specific interventions included in the review
Trials that assessed the use of azithromycin in the treatment of acute bronchitis, acute exacerbation of chronic bronchitis and community-acquired pneumonia were included.

In the studies of acute bronchitis, 4 studies used a 3-day azithromycin regimen and one study used a 5-day regimen. The comparator drugs were co-amoxiclav (n=2), clarithromycin (n=2) and roxithromycin (n=1).

In the studies of acute exacerbation of chronic bronchitis, 11 studies used a 3-day azithromycin regimen and 2 studies used a 5-day regimen. The comparator drugs were amoxicillin (n=1), co-amoxiclav (n=6), cefaclor (n=2), clarithromycin (n=2), dirithromycin (n=1) and roxithromycin (n=1).

In the studies of community-acquired pneumonia, 8 studies used a 3-day azithromycin regimen and 7 studies used a 5-day regimen. All the adult studies used a total dose of 1,500 mg azithromycin, except for one where 3,000 mg were used. In the paediatric studies, where mentioned, the maximum dose of azithromycin used was also 1,500 mg. The comparator drugs were erythromycin (n=6), roxithromycin (n=2), josamycin (n=2), clarithromycin (n=3), cefaclor (n=2), co-amoxiclav (n=2) and benzylpenicillin (n=1).

Participants included in the review
The review included patients with acute bronchitis, acute exacerbation of chronic bronchitis and community-acquired pneumonia. In the studies of acute bronchitis, all the participants were adults. Their mean ages ranged from 43 to 57 years, and the proportion of men ranged from 47 to 59%. In the studies of acute exacerbation of chronic bronchitis, all the participants were adults. Their mean ages ranged from 45 to 66 years, and the proportion of men ranged from 55 to 86%. In the studies of community-acquired pneumonia, 10 studies were in adult populations while 4 studies were conducted exclusively in paediatric patients. The proportion of male participants in the studies ranged from 44 to 77%.

Outcomes assessed in the review
The primary outcome was the clinical failure rate in patients receiving azithromycin versus the comparator antibiotics. The authors selected the day closest to day 10 as the time for evaluating the clinical outcome; all the studies evaluated the primary outcome between days 6 and 21. Relapses at the time of primary evaluation were counted as failures.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.
Assessment of study quality
Validity was not systematically assessed. However, the authors report whether eligible studies used an appropriate randomisation method and made adequate efforts to conceal treatment allocation, and details of blinding.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

The data extracted included information on the study population, the types and diagnosis of eligible infections, the efficacy and safety outcomes, and the study design characteristics.

Methods of synthesis
How were the studies combined?
The pooled odds ratios (ORs), risk ratios, risk differences and 95% confidence intervals (CIs) for clinical failures were calculated for each lower respiratory infection of interest. The authors used both the fixed-effect model of Mantel and Haenszel (see Other Publications of Related Interest no.1) and the random-effects model of DerSimonian and Laird (see Other Publications of Related Interest no.2). For the evaluation of toxicity, the authors pooled and compared the rates of discontinuations due to side-effects for each agent, across all cases of lower respiratory tract infection. The study-specific rates were weighted first by the sample size of each study. Weighting by the inverse of the fixed-effect or random-effects variance yielded qualitatively similar results.

Publication bias was investigated using funnel plots.

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

Subgroup analyses were carried out to identify differences in the efficacy when different comparator antibiotics were used, and for different types of community-acquired pneumonia. Analyses based on source of funding were also conducted.

Results of the review
Five studies (1,372 participants) of acute bronchitis, 13 studies (1,342 participants) of acute exacerbation of chronic bronchitis, and 15 studies (1,664 participants) of community-acquired pneumonia were eligible for inclusion in the meta-analysis.

Acute bronchitis.
There was no significant heterogeneity between the studies. There was no statistically-significant difference between azithromycin and the comparators (random-effects OR 0.84, 95% CI: 0.54, 1.31). The results obtained using the fixed- and random-effect models were similar.

Acute exacerbation of chronic bronchitis.
The combined estimate (random-effects OR 0.64, 95% CI: 0.31, 1.32) showed no statistically-significant difference between azithromycin and its comparators. There was significant between-study heterogeneity, with one particular outlier study favouring the comparator arm. This study also included cases with radiographic failures and had unusually low efficacy rates for azithromycin-treated cases of Streptococcus pneumoniae and Haemophilus influenzae, without reporting antibiotic susceptibility profiles of the isolates. The sensitivity analysis, after removing the outlier, resulted in a statistically-significant reduction of clinical failures in azithromycin-treated patients (random-effects OR 0.50, 95% CI: 0.30, 0.82; fixed-effect OR 0.47, 95% CI: 0.31, 0.74). There was no significant between-study heterogeneity in the remaining 12 studies.

Community-acquired pneumonia.
There was no significant between-study heterogeneity. A significant reduction in the risk of clinical failures was noted with azithromycin therapy (random-effects OR 0.63, 95% CI: 0.42, 0.95). The results obtained using the fixed- and random-effects models were similar.

There were limited data from double-blind studies and their pooled results were inconclusive. The random-effects OR was 1.50 (95% CI: 0.51, 4.43) for acute bronchitis, 0.75 (95% CI: 0.32, 1.75) for acute exacerbations of chronic bronchitis, and 1.12 (95% CI: 0.32, 3.88) for community-acquired pneumonia.

There was no evidence of publication bias for any of the three conditions of interest. Analyses based on the source of funding showed no significant differences between the subgroups.

Adverse events.

Data on discontinuation due to side-effects per study arm were available in 33 trials. Overall, there were 23 discontinuations due to adverse events among 3,487 patients receiving azithromycin (discontinuation rate 0.7%). The discontinuation rates for the other antibiotics were 4.0% for co-amoxiclav, 0.9% for clarithromycin, 2.2% for erythromycin and 2.8% for cefaclor. The side-effects that led to the discontinuation of azithromycin included gastrointestinal trace side-effects (n=8), rash (n=3), paraesthesia (n=1), hyperkinesia and urticaria (n=1), and unstated reasons (n=10). Data on severe-grade side-effects per study arm were only available in 16 trials. Twelve of them stated that there were no severe side-effects with azithromycin, and only 4 mentioned some severe side-effects.

**Cost information**

None, although the authors highlighted the increased cost of azithromycin as a treatment.

**Authors’ conclusions**

The meta-analysis indicated that, compared with other commonly used antibiotics, azithromycin offered no significant advantages for bronchitis, but may be more effective in community-acquired pneumonia. However, the authors concluded that these results should be interpreted with caution as there were limitations in the designs of several of the studies. The majority of the trials were open-label, which may have introduced bias. In addition, several patients with acute bronchitis had to be excluded from the data synthesis because of inextricable information.

**CRD commentary**

The authors stated their review question and inclusion criteria clearly, also referring readers to a companion meta-analysis of azithromycin in upper respiratory tract infections (see Other Publications of Related Interest no.3). The literature search was adequate, although the authors did not report any attempts to identify unpublished or grey literature. The authors demonstrated that there was no evidence of publication bias for all three conditions of interest.

The validity of the individual studies does not appear to have been systematically assessed. The authors did not report details as to how decisions were made in relation to the study selection and data extraction processes, such as how many of the reviewers were involved, whether the studies were examined independently, and whether the reviewers were blinded to source.

The study details tabulated were adequate and were supplemented by narrative discussion. Heterogeneity was statistically assessed, and the authors presented results from random-effects and fixed-effect models. Subgroup analyses were performed, based on the type of comparator antibiotic, different types of community-acquired pneumonia, and the source of funding for the individual studies.

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Overall, this was a well-conducted systematic review and the authors’ conclusions appear to be justified.

**Implications of the review for practice and research**
Practice: The authors state that the absolute benefit of azithromycin treatment amounts to an estimated one failure prevented per 50 patients with community-acquired pneumonia. These figures need to be considered in conjunction with both the tolerability profile and the increased cost of this regimen, in order to determine whether azithromycin should be a first-line antibiotic for lower respiratory infections.

Research: The authors state that careful meta-analyses and well-designed (preferably double-blinded and adequately powered) large trials should be encouraged in the field of antimicrobial chemotherapy in general.

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