Effectiveness of beta-lactam antibiotics compared with antibiotics active against atypical pathogens in non-severe community-acquired pneumonia: meta-analysis

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CRD summary
This review compared beta-lactam antibiotics with antibiotics active against atypical pathogens in the management of community-acquired pneumonia. The authors concluded that beta-lactam antibiotics should remain the first choice for the management of non-severe community-acquired pneumonia in adults. Generally, this was a well-conducted study and the authors' conclusions are likely to be reliable.

Authors' objectives
To systematically compare beta-lactam antibiotics with antibiotics active against atypical pathogens in the management of community-acquired pneumonia (CAP).

Searching
MEDLINE, EMBASE and the Cochrane CENTRAL Register were searched up to December 2003; broad search terms were stated. Conference abstracts were also searched, and registration authorities and pharmaceutical companies that had carried out trials on antibiotics active against atypical pathogens were contacted. The reference lists of review articles and retrieved studies were checked. The included studies were not restricted by date, language or publication status.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs) were included in the review.

Specific interventions included in the review
Monotherapy trials comparing antibiotics active against atypical pathogens (fluoroquinolones, macrolides and ketolides) with any beta-lactam antibiotic (penicillins and cephalosporins) were eligible for inclusion. Studies with the option of adding an antibiotic active against atypical pathogens to beta-lactam therapy were excluded. The drugs included in the review were azithromycin, ciprofloxacin, erythromycin, gatifloxacin, gemifloxacin, grepafloxacin, levofloxacin, moxifloxacin, sparfloxacin, telithromycin, temafloxacin and trovafloxacin. Most drugs were administered orally, with just two studies using intravenous administration initially.

Participants included in the review
Studies of adults with radiographically confirmed CAP were included in the review. Strict exclusion criteria in the included studies resulted in study populations that were younger and had a better prognostic risk profile than observational pneumonia cohorts. The mean age of the participants ranged from 41 to 61 years.

Outcomes assessed in the review
The primary outcome included in the review was failure to achieve clinical cure or improvement, as defined by each individual study. All-cause mortality was also included.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed studies for inclusion. Any disagreements were resolved through discussion.

Assessment of study quality
Only double-blind trials were eligible for inclusion, which means that studies were assessed according to blinding of the investigators, participants and outcome assessors. The authors did not state how the papers were assessed for validity, or
how many reviewers performed the validity assessment. However, as double-blinding was a criterion for inclusion, it appears that it might have been carried out at the screening stage by two independent reviewers, and disagreements resolved through discussion.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The number of participants not achieving clinical cure or improvement was extracted, as well as data for all-cause mortality. Where data were available for more than one time point, the earlier time point was used as the test of cure. Information about years of study, study size, mean age, whether an intention-to-treat (ITT) population was used, and the severity of the pneumonia (where available) was extracted for each study.

**Methods of synthesis**
How were the studies combined?
Study results for dichotomous outcomes were expressed as relative risks (RRs) with 95% confidence intervals (CIs), and were pooled using a fixed-effect model. For the primary analysis, the authors used the ITT or modified ITT populations (those with confirmed CAP who had received at least one dose of the study drug).

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared statistic. Subgroup analyses of the type of antibiotic and participants with atypical pathogen diagnoses (as defined by each study) were carried out. Sensitivity analyses were carried out to investigate the use of per protocol versus ITT analysis, and the effects of a study that included patients with nosocomial pneumonia on the results. For studies of fluoroquinolones, the results of published studies were compared with those of unpublished studies.

**Results of the review**
Eighteen double-blind RCTs (n=6,749) were included in the review.

All included studies blinded the investigators, participants and outcome assessors. No statistical heterogeneity between the studies was detected.

Based on all trials, there was no statistically significant difference between antibiotics active against atypical pathogens and beta-lactam antibiotics for the number of patients failing to achieve clinical cure or improvement (RR 0.97, 95% CI: 0.87, 1.07). There was also no difference between treatment groups in separate analyses of the studies on macrolides and ketolides (RR 0.81, 95% CI: 0.58, 1.14) or fluoroquinolones (RR 0.99, 95% CI: 0.88, 1.11).

There were no differences in all-cause mortality between treatment arms (RR 1.20, 95% CI: 0.84, 1.71).

The treatment effect was not altered when trials that did not use ITT or modified ITT analysis were excluded; it was also similar when a per protocol population was used. There was no difference in the result when a trial including a small proportion of patients with nosocomial pneumonia was excluded.

There was no significant treatment effect in patients with Mycoplasma pneumoniae (13 studies) or Chlamydia pneumoniae (7 studies). However, the failure rate from antibiotics active against atypical pathogens in patients with legionella was statistically significantly lower than that from beta-lactam antibiotics (RR 0.40, 95% CI: 0.19, 0.85; 10 studies).

**Authors’ conclusions**
There was little evidence to support the use of antibiotics active against atypical pathogens in all-cause non-severe CAP. Although these antibiotics were superior in the management of patients later shown to have legionella-related pneumonia, this pathogen was rarely responsible for pneumonia within the included trials. Beta-lactam antibiotics should remain the first choice for the management of non-severe CAP in adults.
CRD commentary
The authors set out a clear objective at the beginning of the review, with inclusion criteria defined in terms of the participants, interventions, outcomes and study design. Appropriate sources were searched, and the authors did not restrict the search by date, language or publication status; this helps to ensure relevant articles are not missed and reduces the risk of both language and publication bias. Two reviewers independently assessed studies for inclusion. However, it was unclear whether the same procedures were used for the data extraction. Only double-blind, randomised trials were included in the review, but quality appears to have been assessed only in terms of blinding. Relevant study details were presented, and the statistical combining of the studies seems appropriate. Statistical heterogeneity was assessed, and known differences between studies were investigated in sensitivity and subgroup analyses. Generally, this was a well-conducted study and the authors’ conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that beta-lactam antibiotics should remain the first choice in the initial management of non-severe CAP in adults.

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

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Other publications of related interest
This additional published commentary may also be of interest. Marrie TJ. Review: antibiotics active against atypical pathogens do not improve community acquired pneumonia more than beta lactam antibiotics. Evid Based Med 2005;10:115.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.