Impact of initial discordant treatment with beta-lactam antibiotics on clinical outcomes in adults with pneumococcal pneumonia: a systematic review

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CRD summary
This review concluded that initial discordant beta-lactam antibiotic monotherapy is not associated with a statistically significant increase in mortality, or clinical or bacteriological failure of treatment, compared with concordant monotherapy in adults with pneumococcal pneumonia. The conclusion should be treated with some caution, owing to limitations in the available data and weaknesses in how the review was conducted.

Authors' objectives
To compare the effectiveness of initial concordant beta-lactam monotherapy with discordant beta-lactam monotherapy in patients with pneumococcal pneumonia.

Searching
PubMed was searched from 1950 to 2005. Reference lists of relevant articles and reviews were also checked. The search terms were reported and there were no restrictions on language.

Study selection
Study designs of evaluations included in the review
Prospective studies were eligible for inclusion.

Specific interventions included in the review
To be eligible for inclusion, studies had to compare discordant beta-lactam antibiotic monotherapy with concordant monotherapy with the same beta-lactam antibiotic. Therapy was defined as concordant when the isolated Streptococcus pneumoniae was fully susceptible to the beta-lactam administered, based on in vitro susceptibility testing (2002 Clinical and Laboratory Standards Institute Guidelines), and discordant when the strain was resistant. The antibiotics used in the included studies were: ceftriaxone (1 to 2 g intravenously every 24 hours), cefotaxime (1 to 2 g intravenously every 6 hours), amoxillin-clavulanate (1 to 2 g intravenously every 8 hours, or 875/125 mg orally every 12 hours, or 2,000/125 mg orally every 12 hours), penicillin-procaine (1,200,000 units intramuscularly every 12 hours). Doses were not reported in one study which used penicillin and cefuroxime.

Participants included in the review
Studies of adult patients with culture-proven pneumococcal pneumonia were eligible for inclusion. Disease severity varied between the included studies.

Outcomes assessed in the review
Studies that reported all-cause mortality, clinical success or bacteriological success were eligible for inclusion. Clinical success was defined as the improvement or resolution of signs or symptoms of pneumococcal pneumonia. Bacteriological success was defined as the absence of all initial pathogens or clinical evidence of eradication in the absence of samples.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed the studies for relevance. It was not stated how any differences were resolved.

Assessment of study quality
The randomised controlled trials (RCTs) were assessed on whether there was randomisation, blinding and information on withdrawals and whether randomisation and blinding were appropriate. The authors did not state how the validity
assessment was carried out.

**Data extraction**
The authors did not state how the data were extracted for the review.

**Methods of synthesis**

How were the studies combined?
Pooled odds ratios and risk differences (RDs) and the respective 95% confidence intervals (CIs) were calculated using fixed-effect and random-effects models. Results of the fixed-effect analysis were reported if heterogeneity was not statistically significant. Data were not weighted because of the small sample number in the discordant groups.

How were differences between studies investigated?
Heterogeneity was investigated using a chi-squared test. Heterogeneity was considered significant at a p-value of less than 0.10. A sensitivity analysis of whether intermediately resistant strains were classified as concordant or discordant was also performed.

**Results of the review**
Six studies with a total of 946 participants with culture-proven pneumococcal pneumonia were included: 2 RCTs (n=92) and 4 prospective cohort studies (n=854).

The 2 RCTs were described as high quality since their mean score was 3.5 (maximum possible score of 5). The number of participants in the analysis receiving discordant beta-lactam was very small compared with concordant treatment: 42 versus 275 for mortality, 6 versus 42 for clinical success, and 3 versus 30 for bacteriological success.

There was no significant difference between discordant and concordant therapies for any of the outcomes: all-cause mortality (5 studies; RD -0.05, 95% CI: -0.23, 0.12), clinical success (3 studies; RD 0.07, 95% CI: -0.36, 0.50) and bacteriological success (2 studies; RD -0.18, 95% CI: -0.79, 0.42). The addition of data from intermediately resistant strains to either the concordant or discordant groups did not affect the overall findings. Fixed-effect data were reported for all outcomes.

**Authors' conclusions**
Treatment with discordant beta-lactam antibiotics is not associated with a statistically significant increase in mortality, or clinical or bacteriological failure of treatment, compared with concordant treatment.

**CRD commentary**
The inclusion criteria and search strategy used for this review were clearly stated, and details of the primary studies were provided. Despite there being no language restrictions, relevant studies might have been missed as only one database was searched. The quality of the RCTs was assessed, but the quality of the cohort studies is unclear. There is a considerable risk of bias in the data as the loss to follow-up appears to have exceeded 50% in 5 of the 6 included studies. The findings of this review were also limited by the low sample numbers in the discordant therapy group. In addition, study quality was not considered in the analysis. The authors made it clear that the data were not of sufficient quality to be used as a basis for change in practice, but their overall conclusion should be treated with some caution given the poor-quality data on which it is based and the limited searches that were conducted.

**Implications of the review for practice and research**
Practice: These data cannot be used as a basis for changes in the management of patients with pneumococcal infections.

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