Monotherapy or aminoglycoside-containing combinations for empirical antibiotic treatment of febrile neutropenic patients: a meta-analysis

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Authors' objectives
To compare the efficacy of antibiotic monotherapy with that of combination therapy including an aminoglycoside for empirical treatment of febrile neutropenic cancer patients.

Searching
MEDLINE was searched from January 1966 to December 2000, using the keywords given in the review. This was supplemented by a manual search of the bibliographies of pertinent studies and reviews. Only studies reported in the English language were included.

Study selection
Study designs of evaluations included in the review
Only randomised clinical trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
The inclusion criteria specified that the studies had to be comparisons between any single drug antibiotic regimen and any aminoglycoside-containing antibiotic combination. The studies included in the review were of a large number of different regimens. The monotherapy regimens utilised cephalosporins (ceftazidime, cefoperazone, cefepime), carbapenem (imipenem meropenem) or a fluoroquinolone (ciprofloxacin, ofloxacin), in various doses and regimens. The aminoglycoside-combination regimens usually consisted of a combination of two antibiotics, although it consisted of three antibiotics in a small number of studies. The full list of regimens was given in the paper. Glycopeptides were never included as part of the combination therapy.

Participants included in the review
Cancer patients suffering from febrile neutropenia were included.

Outcomes assessed in the review
The primary outcome was the failure of antibiotic therapy, defined as an inadequate clinical response, i.e. modification of initial regimen required or death. The end points were analysed separately for febrile episodes overall and febrile episodes arising in bacteraemic episodes.

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
The quality of the studies was rated according to a 19-item score that covered the study design, data analysis and presentation of results. Two reviewers performed the quality assessment, and any disagreements were resolved by consensus.

Data extraction
Two of the authors, blinded to the bibliographic details of the studies, independently extracted the data. The data extraction was cross-checked.

The data extracted included: the number and age of patients; drugs and their regimens; underlying disease; the degree and duration of neutropenia; adverse effects; the numbers of successes, failures and deaths in each group; and the
number of exclusions and withdrawals.

**Methods of synthesis**

How were the studies combined?
The studies were combined in a meta-analysis. The odds ratios (ORs) were calculated using the fixed-effect model of Mantel-Haenszel, as modified by Peto, and the random-effects model of DerSimonian and Laird (see Other Publications of Related Interest nos.1-3).

How were differences between studies investigated?
Heterogeneity was tested using the chi-squared test, taking a p-value of 0.1 as the significance level. Where significant heterogeneity was detected, the random-effects model was used for pooling.

**Results of the review**

Twenty-nine trials involving 4,795 episodes of febrile neutropenia (range per trial: 27 to 958) were included.

The quality scores for the studies included in the review ranged from 0.16 to 0.7 (mean 0.42); the individual scores were listed in the review.

The pooled estimate of effect was marginally in favour of the monotherapy regimens: the OR was 0.88 (95% confidence interval, CI: 0.78, 0.99) when using a fixed-effect model or 0.87 (95% CI: 0.75, 1.01) when using a random-effects model. The test for heterogeneity was not statistically significant (p=0.20).

Subgroup analyses found similar findings for beta-lactam monotherapy versus beta-lactam plus aminoglycoside, cephalosporin monotherapy, and carbapenem monotherapy; i.e. the pooled estimate slightly favoured monotherapy but did not always quite attain statistical significance, particularly if the random-effects model was used.

When only studies of patients with severe neutropenia were included in the meta-analysis, the overall ORs were 0.91 (95% CI: 0.77, 1.09) and 0.92 (95% CI: 0.79, 1.08) when using the random-effects and fixed-effect models, respectively, and neither was statistically significant. When only studies of patients aged over 14 years were pooled, the random-effects and fixed-effect ORs were 0.82 (95% CI: 0.67, 0.99) and 0.82 (95% CI: 0.69, 0.97), respectively.

When only treatment of bacteraemic episodes were pooled, the random-effects and fixed-effect ORs were 0.72 (95% CI: 0.54, 0.95) and 0.70 (95% CI: 0.54, 0.92), respectively.

A sensitivity analysis that included only the higher quality studies reported random-effects and fixed-effect ORs of 0.94 (95% CI: 0.81, 1.09) and 0.94 (95% CI: 0.82, 1.07), respectively, i.e. the treatment difference was not statistically significant. The exclusion of various studies due to the choice of comparators, methodology, size and so on, had small effects on the findings. A cumulative analysis using a fixed-effect model also found a very slight treatment benefit of monotherapy, which achieved borderline statistical significance.

**Authors' conclusions**

Monotherapy has been as effective as aminoglycoside-containing combinations for empirical treatment of febrile neutropenia.

**CRD commentary**

This review addressed an appropriate question using clearly defined inclusion and exclusion criteria. The search strategy was rather limited with only one electronic database being searched. It is probable that studies were missed. The authors discussed publication bias but they did not try to evaluate it. The conduct of the review was well reported, and the independent duplication of the quality checks and data extraction will have minimised any bias within the review. The results of the quality assessment were used appropriately in a sensitivity analysis, thus strengthening the reliability of the overall findings. The individual study details were adequately presented, and the results were pooled appropriately using established meta-analytical techniques.
Overall, the authors' conclusions are fully supported by the review’s findings, although the possibility that some studies may have been missed from the review should be borne in mind.

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

Practice: The authors state ‘Our findings do not support the indiscriminate use of empiric combination therapy as routine treatment for febrile neutropenic patients’.

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

**Bibliographic details**


**PubMedID**

11937423

**Other publications of related interest**


**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Aminoglycosides /administration & dosage /therapeutic use; Anti-Bacterial Agents /therapeutic use; Bacteremia /drug therapy /etiology; Drug Therapy, Combination; Fever /drug therapy /etiology; Humans; Neoplasms /complications /drug therapy; Neutropenia /drug therapy /etiology; Odds Ratio; Randomized Controlled Trials as Topic; Treatment Outcome

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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.