Fluoroquinolones vs beta-lactams for empirical treatment of immunocompetent patients with skin and soft tissue infections: a meta-analysis of randomized controlled trials
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CRD summary
This review found that fluoroquinolones do not have substantial advantages over beta-lactams for the treatment of patients with skin and soft tissue infections. Overall, the authors’ conclusions reflect the evidence presented and appear appropriate. However, many of the included studies were conducted in the 1980s and 1990s and the results may not be applicable to current conditions.

Authors’ objectives
To compare the effectiveness and safety of fluoroquinolones and beta-lactams in the treatment of skin and soft tissue infections (SSTIs).

Searching
The authors searched PubMed, the Cochrane Controlled Trials Register and the reference lists of relevant articles for studies published between January 1980 and February 2006; the search terms were reported and there were no language restrictions. Conference abstracts were not searched.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for the review. Studies with fewer than 10 participants were excluded.

Specific interventions included in the review
Studies that compared a fluoroquinolone with a beta-lactam antibiotic were eligible for the review. The administration of concomitant antibiotics was not allowed, except for metronidazole or clindamycin for anaerobic bacteria and vancomycin for methicillin-resistant staphylococci. Trials that studied the role of fluoroquinolones and beta-lactams in prophylaxis or compared their effectiveness after the pathogen had been identified were excluded, as were trials of fluoroquinolones that had been withdrawn because of adverse effects. The included studies compared a range of intravenous or oral agents at various doses (details reported in the paper). Additional antibiotics were allowed in about one-third of the included studies. The treatment duration, where reported, ranged from 6 to 25 days.

Participants included in the review
Studies of patients with SSTIs were eligible for the review; studies of patients with febrile neutropenia were excluded. The participants in most of the included studies had SSTIs of varying types and degrees of severity; the participants in one study had diabetic foot infections. Where reported, the percentage of participants with diabetes in other studies ranged from 12 to 44%.

Outcomes assessed in the review
The studies were required to assess clinical (complete resolution or significant improvement of clinical signs) and/or microbiological (eradication of the pathogen) effectiveness. The secondary outcomes were clinical effectiveness for different types of infection, microbiological effectiveness for different pathogens, superinfections, adverse effects, withdrawals related to adverse effects and mortality.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed studies for possible inclusion. Any disagreements were resolved by consensus among all the reviewers.
Assessment of study quality
The studies were given a score of up to 5 based on details of randomisation, double-blinding, and description of withdrawals and drop-outs. Studies scoring 3 or more were regarded as good quality and those scoring 2 or less were regarded as poor quality. Two reviewers independently assessed validity.

Data extraction
Two reviewers independently extracted the data. Any disagreements were resolved by consensus among all the reviewers. Data on the numbers of events in each group were used to derive odds ratios (ORs) and 95% confidence intervals (CIs) for the main outcomes.

Methods of synthesis

How were the studies combined?
The studies were combined by meta-analysis using both the Mantel-Haenszel fixed-effect model and the DerSimonian and Laird random-effects model. Results from the latter model were used when there was heterogeneity among the studies.

How were differences between studies investigated?
Heterogeneity among the studies was investigated using both the I-squared statistic and the chi-squared test; for the latter a p-value of less than 0.1 was considered to represent significant heterogeneity. Bias due to small studies was assessed using a funnel plot. However, full results of these analyses were not reported. Clinical differences among the studies were investigated using a number of subgroup and sensitivity analyses.

Results of the review
Twenty RCTs (4,817 enrolled patients) were included.

The mean quality score of the included RCTs was 2.7 (range: 1 to 5) and 11 RCTs scored 3 or more (good quality). Across all studies, fluoroquinolones showed significantly higher clinical effectiveness compared with beta-lactams (treatment success 90.4% versus 88.2%; fixed-effect OR 1.29, 95% CI: 1.00, 1.66). No significant difference was found in analyses restricted to RCTs that did not allow concomitant administration of other antibiotics and to RCTs rated as high quality. RCTs of ciprofloxacin and of patients with mild to moderate infections also showed significantly better clinical effectiveness in the fluoroquinolone group. Microbiological effectiveness did not differ significantly (fixed-effect OR 1.19, 95% CI: 0.89, 1.59). Fluoroquinolones were associated with significantly higher rates of adverse effects compared with beta-lactams (19.2% versus 15.2%; fixed-effect OR 1.33, 95% CI: 1.13, 1.57). The results of various other analyses were reported in the paper.

Authors’ conclusions
The high rate of treatment success in both groups and the higher rate of adverse events associated with fluoroquinolones suggest that these agents do not have substantial advantages over beta-lactams for the treatment of patients with SSTIs.

CRD commentary
This review addressed a well-defined question and the inclusion criteria were clear. The authors searched a relatively limited range of sources and did not search for unpublished trials, so it is possible that some relevant studies might have been missed. No language restrictions were applied, thus minimising the risk of language bias. Measures were taken to reduce the risk of bias and error in the study selection and data extraction processes. The validity of the included studies was assessed using a standard method and the results were used in the analysis.

Details of the included studies were tabulated. Statistical heterogeneity was assessed but the results were not reported, although the meta-analysis results were mainly from the fixed-effect model, implying that heterogeneity was not present. The absence of full details makes it difficult to comment on the appropriateness of combining the studies by meta-analysis. Clinical differences between the studies were investigated using subgroup and sensitivity analyses. As the
authors noted, many of the included studies were conducted in the 1980s and 1990s and the results may not be applicable to current conditions, particularly the increasing importance of antibiotic resistance. Overall, however, the authors' conclusions reflect the evidence presented and appear appropriate.

Implications of the review for practice and research
The authors did not state any implications for practice or further research.

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