Do high doses of quinolones decrease the emergence of antibacterial resistance: a systematic review of data from comparative clinical trials
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CRD summary
This review concluded that there is limited evidence to support or reject the use of high doses of quinolones to reduce the development of antimicrobial resistance. Despite the lack of any assessment of study validity, the authors’ cautious conclusions appear to be reliable given the limited amount of data from quite different studies and study populations.

Authors’ objectives
To assess whether high doses of quinolones decrease the emergence of antimicrobial resistance.

Searching
PubMed and the Cochrane CENTRAL Register were searched up to June 2006; the search terms were reported. In addition, the reference lists of studies, meta-analyses and guidelines were screened for other studies. The searches were restricted to articles written in English, French, German, Italian, Spanish, Czech and Greek.

Study selection
Studies were assessed for relevance according to the following inclusion criteria: a randomised controlled trial (RCT) or non-randomised controlled trial comparing the emergence of resistance in patients with documented infections, treated with different daily doses of quinolones, using the same administration route. The secondary outcomes of interest included clinical or bacteriological failure and any toxicity or withdrawal due to toxicity. Studies had to compare a minimum of two different doses of quinolones and involve at least one patient in whom the causative pathogen persisted during or after treatment. Studies where the drug dosage was adjusted, where quinolones now withdrawn from the market were used, or where patients were infected with mycobacteria or brucella, were excluded. The included studies assessed patients with a variety of infections, such as pneumonia, urinary tract infections, genital infections, typhoid, and skin and soft tissue infections; the specific bacteria involved also varied. The types of quinolones included ciprofloxacin (100 to 2,000 mg), levofloxacin (300 to 750 mg), moxifloxacin (200 to 400 mg) and fleroxacin (200 to 600 mg). The durations of therapy varied from a single dose to 3 months, but were usually equivalent for each study group or dependent on the severity of the infection.

Two reviewers assessed the relevance of studies.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Two reviewers independently extracted the proportion of patients in whom bacterial resistance developed, and any discrepancies were resolved through consensus or with a third reviewer. The incidences of bacterial or clinical failure, toxicity and withdrawals due to toxicity were also extracted. The authors appear to have used intention-to-treat data. For each study, the data from the intervention groups were compared using Pearson’s χ² test or Fischer’s exact test (p<0.05 denoted statistical significance).

Methods of synthesis
The studies were pooled in a narrative synthesis using summary data tables.

Results of the review
Twelve studies (n=2,979 intention-to-treat) were included in the review: 8 RCTs and 4 non-randomised controlled trials.

Five of the studies showed some development of resistance, but no statistically significant differences were reported.
between patients in different dose groups (3 studies). Similarly, no statistically significant differences in secondary outcomes were observed between different dose groups.

Authors’ conclusions
There is limited evidence from the trials reviewed with which to support or reject the use of high doses of quinolones to reduce the development of antimicrobial resistance.

CRD commentary
This review answered a clear review question, but there may be some risk of publication and language bias given that restrictions were placed on the language of publication and that only two databases were searched. Some attempts were made to reduce the risk of error and bias in the review methods, but the absence of any assessment of study validity makes it difficult to assess the reliability of the data. The wide variety of patient populations and interventions make it difficult to compare the data and form any reliable conclusions. The authors also acknowledged a number of other limitations regarding the study data, including the variation in the time period over which the studies were conducted, given the recent increases in bacterial resistance and the existence of alternative causes of therapeutic failure. However, given the limited amount of data from quite different studies and study populations, the authors’ cautious conclusions appear to be reliable.

Implications of the review for practice and research
Practice: The authors stated that evidence from clinical trials does not support or reject the data from laboratory studies, which suggest that higher doses of quinolones reduce the development of antimicrobial resistance.

Research: The authors stated that further comparative clinical studies are required to compare different doses of quinolones in real patient settings.

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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.