Efficacy of quinolone prophylaxis in neutropenic cancer patients: a meta-analysis

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Authors' objectives
To estimate the efficacy of quinolone antibiotics in preventing infection, fevers and deaths among cancer patients, who were neutropenic following chemotherapy.

Searching
MEDLINE was searched from 1966 to 1996 using the MeSH 'quinolones', 'human', 'random allocation', 'research design', 'placebos', 'bacterial infections' and 'leukopenia'. In addition, the authors searched for the following textwords: 'quinolone', 'neutropenia (and neutropenic)', 'prophylaxis', and the names of individual quinolones, i.e. 'ciprofloxacin', 'norfloxacin', 'ofloxacin', 'sparfloxacin' and 'perflaxacin'. Bibliographies of retrieved papers were examined for additional studies. Publications in any language were considered, and non-English papers were translated prior to inclusion in the review.

Study selection

Study designs of evaluations included in the review
Randomised controlled trials (RCTs) of prophylaxis with a quinolone versus a control arm with either no antibiotic or TMS prophylaxis.

Specific interventions included in the review
In the quinolone arm, the following interventions were used in various dosages, either alone or in combination: ofloxacin, norfloxacin, polymyxin B, ciprofloxacin, clotrimazole, acyclovir, nystatin, enoxacin, granulocyte colony-stimulating factor, and oral amphotericin B.

In the control arm, the following interventions were used in various dosages, either alone or in combination: no treatment, placebo, polymyxin B, clotrimazole, acyclovir, nystatin, granulocyte colony-stimulating factor, oral amphotericin B, and trimethoprim-sulfamethoxazole (TMS).

Participants included in the review
Participants were cancer patients who were neutropenic, or who were expected to become neutropenic following chemotherapy.

Outcomes assessed in the review
The outcomes measured were Gram-negative infection, Gram-negative bacteraemia, Gram-positive infection, Gram-positive bacteraemia, fungal infection, microbiologically-documented infection, clinically-documented infection, total infection, fever, and death due to infection.

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 authors performed the selection.

Assessment of study quality
The authors evaluated the included studies on their definition of neutropenia, their description of randomisation, blinding, and whether there was an intention-to-treat analysis. The authors do not state how the papers were assessed for validity, or how many of the authors performed the validity assessment.

Data extraction
Two infectious disease specialists independently extracted data for each trial, and any discrepancies were resolved.
through discussion and consensus.

**Methods of synthesis**

**How were the studies combined?**

Individual relative risk (RR) estimates for each outcome were pooled using a random-effects model. The results were presented as pooled RR estimates along with their 95% confidence intervals (CIs). A regression analysis was performed for quinolone-resistant bacteria.

**How were differences between studies investigated?**

The authors investigated the differences between blinding and unblinding in the primary trials for the outcomes of fever and clinically-documented infection. They also conducted sensitivity analyses by removing trials where they had used proportion data rather than count data, and by excluding a trial where the duration of neutropenia was unusually long; these did not change the results of the review.

**Results of the review**

Eighteen RCTs were included: 707 participants received prophylaxis with quinolones (ciprofloxacin, enoxacin, norfloxacin or ofloxacin), 334 received treatment with TMS, and 367 received no prophylaxis.

Compared with no prophylaxis, quinolones significantly reduced the incidence of Gram-negative bacterial infections (RR 0.21, 95% CI: 0.12, 0.37), microbiologically-documented infections (RR 0.65, 95% CI: 0.50, 0.85), total infections (RR 0.54, 95% CI: 0.31, 0.95) and fevers (RR 0.85, 95% CI: 0.73, 0.99).

Quinolone prophylaxis did not alter the incidence of Gram-positive bacterial, fungal, clinically-documented infections, or infection-related deaths.

Results were similar for trials that used TMS as the control regimen.

In those who used quinolones, the incidence of infections due to quinolone-resistant organisms was 3.0% (95% CI: 1.7, 5.2) for Gram-negative species and 9.4% ((95% CI: 5.3, 16.3) for Gram-positive species. The incidence of quinolone-resistant infections was no higher among quinolone recipients than controls.

Compared with unblinded trials, blinded trials found quinolones were less efficacious for fever.

**Authors’ conclusions**

Quinolone prophylaxis substantially reduced the incidence of various infection-related outcomes, but not deaths, in the patients.

**CRD commentary**

The authors conducted a very good review of the available literature, and addressed the issues of publication selection bias by translating and including non-English studies.

The inclusion criteria for the individual trials were stated, and the criteria for assessing the quality of the primary trials were listed. However, the authors did not state how judgements were made about the decision to include studies, or who reviewed the studies for the stated quality criteria.

The authors described their criteria or methods for the data extraction.

The authors did not discuss any differences found between the studies. Their pooling of the data using a random-effects model may imply that heterogeneity was found. However, a further analysis of treatments was conducted by the authors to check for any differences in the results between trials.

Although the authors could have given additional information regarding their investigation of differences between
primary studies and their role in the selection of the primary studies, their conclusions were supported by the data.

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

Practice: The authors state that the benefits for prophylaxis need to be assessed in the context of concern for the emergence of resistance with the continued use of antibiotics.

Research: The authors state that new regimens that prevent gram-positive infections are needed. In addition, further work is needed to clarify the impact of quinolones on the incidence and time of onset of fevers, and the subsequent effect on antibiotic usage, hospitalisation and cost.

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