Fluoroquinolones in children with fever and neutropenia: a systematic review of prospective trials


CRD summary
The review concluded that fluoroquinolone antibiotics demonstrated excellent outcomes and short-term safety in low-risk children with fever and neutropenia, but experience in high-risk patients was uncertain. The review had some methodological issues and the quality of the evidence base was small and of variable quality, so caution is warranted when interpreting the authors’ conclusions.

Authors’ objectives
To determine the efficacy and safety of fluoroquinolones for children with fever and neutropenia.

Searching
EMBASE, MEDLINE, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1980 to March 2011 for articles published in English. Search terms were reported.

Study selection
Prospective studies of fluoroquinolones for the empiric treatment of fever and neutropenia in pediatric patients (aged less than 18 years) were eligible for inclusion. Conference proceedings were excluded, as were studies which did not report an infection outcome, and studies of prophylaxis, modification of empiric therapy, and definitive therapy. The primary outcome was treatment failure at 30 days. Secondary outcomes included 30-day overall mortality and infection-related mortality, treatment failure, recurrent infection, fever duration, sepsis, and adverse events.

The included studies considered ciprofloxacin monotherapy, other fluoroquinolone monotherapy, and combination fluoroquinolones therapy in low-risk fever and neutropenia pediatric patients. The mean/median age of patients ranged from five to 10.8 years. Most studies were in out-patients, but some were in in-patients. The absolute neutrophil count ranged from 21% to 65%, where reported. The proportion of patients with fever of unknown origin ranged from 25% to 88%. In some studies, most patients had leukaemia and lymphoma. The year of publication of included studies ranged from 1997 to 2009.

Two reviewers independently performed study selection for full-text papers; one reviewer screened titles and abstracts.

Assessment of study quality
Two reviewers independently assessed study quality using a modified version of a prognosis study quality tool, which appraised study participation, study attrition, confounding variables, and measurement of outcomes. Each quality item was rated as low, medium, or high risk of bias.

Data extraction
Two reviewers extracted data on infection outcomes and adverse events using a pre-defined form. Data were used to calculate risks and 95% confidence intervals (CIs).

Methods of synthesis
A random-effects meta-analysis was used to calculate risks and 95% confidence intervals. For RCT data, rate ratios (RRs) were calculated. All effects were weighted by inverse variance. Subgroup analysis was conducted by type of fluoroquinolone therapy.

Results of the review
Ten studies were included in the review (740 fever and neutropenia episodes). There were six randomised controlled trials (RCTs) and four prospective non randomised trials. Most studies had a low risk of bias for study participation and study attrition. However, all but one study was high risk for confounding; half of the studies were high risk of bias for measurement of outcomes.
The risk of treatment failure (including treatment modification) with all fluoroquinolones was 20% (95% CI 11 to 29; six studies). The risk of treatment failure (including treatment modification) in subgroups was 17% with ciprofloxacin monotherapy (95% CI 7 to 27; one study), 17% with other fluoroquinolone monotherapy (95% CI 2 to 31; two studies), and 24% with combination fluoroquinolones (95% CI 4 to 44; three studies).

For the six RCTs, there was no difference in treatment failure when antibiotic modification was included as a criterion for failure (RR 1.02, 95% CI 0.72 to 1.45) or when modification was excluded as a criterion for treatment failure (RR 1.79, 95% CI 0.72 to 4.42).

There were no reported cases of mortality or infection-related mortality. The rates of adverse events and sepsis were low.

**Authors’ conclusions**
Experience with fluoroquinolones demonstrated excellent outcomes and short-term safety in low-risk paediatric patients with fever and neutropenia, but experience in high-risk patients was uncertain.

**CRD commentary**
Inclusion criteria for the review were broadly defined. Three relevant databases were searched. There was potential for language bias, as only English articles were included. Publication bias was not assessed and could not be ruled out. Attempts were made to reduce the risk of reviewer error and bias throughout the review.

The quality of the evidence base was variable; most studies did not control for confounding factors. Study quality results were not presented for the individual studies, which made it difficult to assess the quality of the evidence. There were differences across the studies for setting, type of therapy, and fever and neutropenia characteristics. The authors acknowledged that many studies allowed a single dose of another antibiotic prior to fluoroquinolone therapy, which may have biased results. Random-effects meta-analysis was conducted, which appeared appropriate, although statistical heterogeneity was not reported fully. The lack of focus and detail on comparisons with other treatments made it difficult to evaluate the context of the authors’ conclusions.

The review had some methodological limitations, and the evidence base was small and of variable quality, so caution is warranted when interpreting the authors’ conclusions.

**Implications of the review for practice and research**
**Practice:** The authors stated that their results suggested that fluoroquinolones could be confidently used in low-risk children with febrile neutropenia as long as the local antimicrobial resistance patterns supported their use.

**Research:** The authors stated that further research was needed into the effects of fluoroquinolones in high-risk patients; this research should focus on the effects of other fluoroquinolone antibiotics, such as levofloxacin. Future research should also aim to monitor late arthropathies in children receiving fluoroquinolones for febrile neutropenia.

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