Respiratory fluoroquinolones for the treatment of community-acquired pneumonia: a meta-analysis of randomized controlled trials

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CRD summary
The authors concluded that fluoroquinolones were associated with greater treatment success than macrolides and β-lactams for severe community acquired pneumonia, but there was no evidence of benefit for mortality and further research was required. This overall conclusion seems reasonable, although should not be considered definitive as several factors (which included poor study quality) may have influenced the findings.

Authors’ objectives
To assess whether use of fluoroquinolones was associated with more advantages or disadvantages than use of macrolides or β-lactams in terms of mortality, resolution of pneumonia and adverse effects for adults with pneumonia.

Searching
PubMed, Current Contents, Scopus, EMBASE, ClinicalTrials.gov and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for the period 1980 to 2008 without language restrictions. Search terms were reported. Reference lists from relevant articles were scanned. Conference abstracts were excluded.

Study selection
Randomised controlled trials (RCTs) that compared a fluoroquinolone (as proposed in the 2007 Infectious Diseases Society of America and American Thoracic Society guidelines) to a combination therapy of macrolide and β-lactams or monotherapy (macrolide, ketolide or β-lactam) were eligible for inclusion. Studies were included only if patients had pneumonia diagnosed from a chest radiograph demonstrating new or progressive infiltrates or consolidation without effusion plus four of 11 specified signs and symptoms. Outpatients and in-patients were included, as were studies that used additional microbial agents. The primary outcome of interest was all-cause mortality. Other outcomes of interest were treatment success, duration of hospital stay and adverse events. Treatment success was defined as cure (resolution of all symptoms and signs of infection) or improvement (resolution of two or more baseline symptoms or signs of infection). Patients were excluded from the analysis if they had received any antibiotics for treatment of pneumonia 24 to 48 hours before enrolment unless the treatment had failed or the isolated pathogen was resistant to the antibiotic.

Fluoroquinolones evaluated in the included studies were levofloxacin, gemifloxacin and moxifloxacin. Both intravenous and oral administration were used. Most patients in the included studies had mild to moderate pneumonia; around one third of studies included only patients with severe or moderate to severe pneumonia. Participants were adult in-patients or outpatients; criteria for hospital admission varied between studies.

Two reviewers independently assessed studies for inclusion.

Assessment of study quality
Two reviewers independently assessed study quality. Studies were awarded one point for reporting details of each of randomisation, generation of random numbers, allocation concealment, double blinding and information on withdrawals. Maximum score was 5 points. Trials that scored more than 2 points were classed as good quality.

Data extraction
Numbers of events were extracted for each outcome. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated based on intention-to-treat data (patients who received at least one dose) and the clinically evaluable population (patients who completed treatment and for whom outcome could be assessed).

Two reviewers independently extracted data. Authors of the trials were contacted for additional data where necessary.
Methods of synthesis
The pooled odds ratio was calculated using a Mantel-Haenszel fixed-effect model where there was no statistically significant heterogeneity (p<0.1 using \( \chi^2 \) test); a DerSimonian-Laird random-effects model was used where there was heterogeneity. There was an overall pooling of studies (all fluoroquinolones compared to all comparators). Studies were subgrouped by: severity of pneumonia (severe or moderate and mild); presence of bacteraemic pneumonia; mode of therapy (intravenous or oral); patients who required hospital admission; type of fluoroquinolone; comparator treatment (monotherapy or combination therapy of \( \beta \)-lactam and macrolide); and patients with microbiologically confirmed pneumonia.

Sensitivity analyses were undertaken to assess the impact of study quality and source of funding. Publication bias was assessed using a funnel plot and Egger's test.

Results of the review
Twenty-three RCTs were included (n=7,885); 11 were classed as high quality and 12 as low quality. All of the results reported here were based on intention-to-treat data unless otherwise stated.

Mortality (18 RCTs):
Mortality ranged from 0% to 7% in the fluoroquinolone group and from 0.5% to 8% in the comparator antibiotics. There was no difference between fluoroquinolone and comparator in mortality (OR 0.85, 95% CI 0.65 to 1.12). There was no statistically significant heterogeneity.

Treatment success (15 trials):
Treatment was successful for 84.2% of patients in the fluoroquinolone group and 82.2% in the comparator group. Significantly more patients in the fluoroquinolone group had treatment success than in the comparison group (OR 1.17, 95% CI 1.00 to 1.36). Similar results were obtained from the analysis based on patients for whom outcome data were available at the end of the study. There was no statistically significant heterogeneity.

Significantly more patients who received fluoroquinolones had treatment success than the comparator group where pneumonia was severe (OR 1.84, 95% CI 1.02 to 3.29; seven RCTs), where intravenous therapy was used (OR 1.44, 95% CI 1.13 to 1.85; 11 trials) and where patients were admitted to hospital (OR 1.30, 95% CI 1.04 to 1.61; 15 RCTs), but not in subgroups of studies of patients with mild to moderate pneumonia or moderate to severe pneumonia, trials that used oral therapy or that included outpatients. Significantly more patients who received fluoroquinolones had treatment success compared to combination therapy (OR 1.39, 95% CI 1.02 to 1.90; seven RCTs), but not \( \beta \)-lactam or macrolide monotherapy. Other subgroups where there was no significant difference in effectiveness between fluoroquinolone and comparator were the patients with \textit{Streptococcus} pneumonia, bacteraemic pneumonia or bacteraemic pneumonia due to \textit{Streptococcus} pneumonia.

Analyses based on study quality and source of funding found that fluoroquinolones were not more effective than comparator in the subgroup of studies funded by pharmaceutical companies and in the subgroup of high-quality studies; although in the latter these studies were of patients with milder pneumonia. The authors stated that they did not find evidence of publication bias.

Adverse outcomes:
Fluoroquinolones were associated with significantly fewer adverse outcomes than comparator antibiotics (OR 0.86, 95% CI 0.78 to 0.96), although withdrawal due to adverse effects was similar in both groups. Most adverse outcomes were mild to moderately severe disturbances of the gastrointestinal tract.

Authors’ conclusions
Fluoroquinolones were associated with greater treatment success for severe forms of pneumonia, but there was no evidence of benefit for mortality and further research was required.
**CRD commentary**
There was a clearly stated review question and a number of relevant sources were searched without language restrictions and with some attempt to locate unpublished data. Study quality was assessed and taken into consideration in the analysis. Appropriate methods were used to minimise error and bias in the review processes. The analysis seemed appropriate and key clinical sources of possible variability in outcome were explored. However, the results of the subgroup analyses should not be considered definitive. There were a large number of variables investigated and confounding between these variables was likely. For example, the subgroup of higher quality trials also contained mainly patients with milder disease. The authors also drew attention to the possible influence on the findings of the mainly poor quality of trials including patients with more severe disease, variable definitions of severity used and the zero baseline resistance of the isolated pathogens to fluoroquinolones. The overall conclusion seems reasonable although a need for further research was identified.

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

**Practice**: The authors stated that fluoroquinolones may be considered for the treatment of community acquired pneumonia, in particular for more severe forms and for patients who require admission to hospital and initial intravenous treatment.

**Research**: The authors stated that an RCT was required that should include patients with severe community acquired pneumonia with or without bacteraemia.

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