Efficacy and safety of ceftriaxone for uncomplicated gonorrhoea: a meta-analysis of randomized controlled trials

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CRD summary
The authors concluded that better efficacy, for uncomplicated gonorrhoea, was found for ceftriaxone 250mg versus cefixime 400mg, and for ceftriaxone 125mg versus spectinomycin 2g. Unexplained statistical variation, potential reporting bias, and a high risk that bias could have affected the pooled results, mean that the authors' conclusions may not be reliable.

Authors' objectives
To compare and evaluate the efficacy and safety of ceftriaxone, versus four other antibiotics, for the treatment of uncomplicated gonorrhoea.

Searching
Six databases, including The Cochrane Library and MEDLINE, were searched to August, 2011; search terms were reported.

Study selection
Eligible studies were randomised controlled trials (RCTs) that assessed ceftriaxone in patients with uncomplicated gonorrhoea. It appears that the eligible comparators were cefotaxime, spectinomycin, and cefixime. The primary outcomes were the cure rate and the side-effect rate.

In the included trials, the patient age ranged from 16 to 60 years. Most trials were conducted in the USA; others were conducted in Germany, India, Thailand, or Kenya. The daily doses for ceftriaxone were 125mg or 250mg, and for cefixime they were 400mg or 800mg, for spectinomycin the dose was 2g, and for cefotaxime it was 500mg.

Two reviewers selected trials for inclusion; disagreements were resolved through discussion.

Assessment of study quality
Trial quality was assessed, using the Cochrane approach, for the adequacy of description of randomisation, allocation concealment and blinding of patients, investigators, outcome assessors, and data analysts. Each item was rated yes (low risk of bias), no (high risk of bias), or unclear (unclear or unknown risk of bias).

Two reviewers independently assessed trial quality; the authors did not state how any disagreements were resolved.

Data extraction
The cure rate (cure was defined as a negative culture for Neisseria gonorrhoeae), clinical response rate, and side-effect rate for each group (treatment or control) were extracted to calculate odds ratios, with 95% confidence intervals.

Two reviewers independently extracted the data; the authors did not state how any disagreements were resolved.

Methods of synthesis
Odds ratios and 95% confidence intervals from the individual trials were pooled using random-effects models. Statistical heterogeneity was assessed using $\chi^2$ and $I^2$. Sensitivity analyses were performed by repeating the meta-analyses, using a fixed-effect model. Predefined subgroup analyses were performed by antibiotic dose.

Results of the review
Thirteen RCTs were included in the review (2,557 patients). Eight trials were unclear on their randomisation method, six were unclear about blinding and seven were not blinded. All 13 trials were unclear about allocation concealment. Attrition rates ranged from none to 46% for the intervention groups and from none to 35% for the control groups.

Cure rates: No statistically significant difference, in the overall cure rate, was found between ceftriaxone and...
cefotaxime, cefixime, or spectinomycin. Low statistical heterogeneity was found in the meta-analyses for cefotaxime ($I^2=1\%$) and cefixime ($I^2=6.4\%$); medium heterogeneity was found in the meta-analysis for spectinomycin ($I^2=43\%$).

**Side-effects**: The rate of side-effects was statistically significantly higher with ceftriaxone, than with cefotaxime (OR 1.87, 95% CI 1.14 to 3.08; four trials). No statistical heterogeneity was found ($I^2=0$). No statistically significant difference was found between the rates for ceftriaxone and cefixime. Medium statistical heterogeneity was found ($I^2=52\%$).

**Subgroup and sensitivity analyses**: The cure rate was statistically significantly higher for ceftriaxone 250mg than for cefixime 400mg (OR 1.77, 95% CI 1.11 to 2.80, three trials; $I^2=0$), and for ceftriaxone 125mg than for spectinomycin 2g (OR 3.44, 95% CI 1.08 to 10.90; two trials; $I^2=56\%$). No other statistically significant differences in the rates of side-effects or cure, were found. The analyses with the fixed-effect model yielded similar results to those using the random-effects model.

**Authors’ conclusions**
The evidence revealed that ceftriaxone 250mg was more effective than cefixime 400mg, and ceftriaxone 125mg was more effective than spectinomycin 2g, for uncomplicated gonorrhoea. The difference in cure rate between ceftriaxone 250mg and cefotaxime 500mg favoured ceftriaxone, but was not significant and ceftriaxone had more side-effects than cefotaxime.

**CRD commentary**
The review question was clear, but the inclusion criteria were not; this may have been due to the fact that the web tables could not be accessed. Relevant databases were searched and attempts were made to minimise error and bias, during the review process. Basic trial information was presented. The quality assessment criteria seem to have been appropriate; all trials were at a high or unclear risk of bias. Trial quality was not used to interpret the pooled results of the main analyses (for example, by sensitivity analyses for different biases), nor were they used to add context to the review conclusions.

Moderate or high levels of statistical heterogeneity were reported for some of the subgroup analyses, notably for those that included trials with high attrition rates (up to 37%). The reasons for attrition were unclear. A discrepancy between the text and figure labelling made it difficult to ascertain the accuracy of the results reported in the text. The authors acknowledged that selective reporting may have been present, given that not all trials reported adverse event and clinical response data.

Substantial and unexplained statistical variation, potential reporting bias, and a high risk that bias could have affected the pooled results, mean that the authors' conclusions may not be reliable.

**Implications of the review for practice and research**
**Practice**: The authors stated that this review’s conclusions were consistent with the gonorrhoea treatment guidelines of the World Health Organization, the Centers for Disease Control and Prevention, the UK and Europe, but most of the trials were conducted at least 10 years ago, and their results might not still be valid.

**Research**: The authors stated that further randomised controlled trials of ceftriaxone for uncomplicated gonorrhoea were needed.

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**Bibliographic details**

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Adolescent; Adult; Anti-Bacterial Agents /adverse effects /therapeutic use; Cefixime /therapeutic use; Ceftriaxone /adverse effects /therapeutic use; Gonorrhea /drug therapy; Humans; Middle Aged; Odds Ratio; Randomized Controlled Trials as Topic; Spectinomycin /therapeutic use; Treatment Outcome