Role of fluoroquinolones in the primary prophylaxis of spontaneous bacterial peritonitis: meta-analysis

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CRD summary
The authors concluded that daily oral fluoroquinolone prophylaxis reduced the risk of first episode spontaneous bacterial peritonitis, severe infection and mortality in patients with cirrhosis and low protein ascites. The review was generally well conducted, but in view of the small amount of evidence available, a degree of caution may be advisable in interpreting these conclusions.

Authors' objectives
To evaluate the use of fluoroquinolones as primary prophylaxis for spontaneous bacterial peritonitis in high-risk patients.

Searching
MEDLINE, EMBASE, the Cochrane Library and Web of Science were searched. Search dates varied among sources, but spanned 1955 to August 2008. Search terms were reported. The references of selected studies and reviews were handsearched, as were abstracts from meetings of the American Gastroenterological Association and the American Association for the Study of Liver Diseases, from 2007 onwards. The search had no language restrictions.

Study selection
Randomised controlled trials (RCTs) comparing fluoroquinolones with placebo for preventing a first episode of spontaneous bacterial peritonitis were eligible for inclusion. Included trials were required to be conducted among patients at high risk, defined as those with low protein ascites (ascitic fluid protein levels under 1.5 grams per decilitre). Trials of non-liver related ascites, or those in a post-transplant setting, were excluded. The primary review outcome was spontaneous bacterial peritonitis, defined as culture-negative neutrocytic ascites, positive ascitic fluid culture or positive ascitic fluid gram-stain. Secondary outcomes were severe infection (spontaneous bacterial peritonitis or bacteraemia) and all-cause mortality.

The mean age of patients in the included studies was 58 years, and 67% were men. The most common cause of liver disease (where reported) was alcoholic cirrhosis. The intervention group received daily oral norfloxacin (400 milligrams (mg)) or ciprofloxacin (500 mg), and controls received placebo. In one trial, the placebo group were allowed norfloxacin if hospitalised. Adverse effects were reported in the review. The included trials were conducted in Spain, France and Argentina. Mean duration of follow-up was 40 weeks (range 18 to 52 weeks) and 297 patient-years.

Studies were selected independently by two reviewers, with a check of selected studies by a third reviewer. Disagreements were resolved by consensus.

Assessment of study quality
Trial quality was evaluated using the Jadad scale, which measured adequacy of randomisation, blinding, and reporting of withdrawals and dropouts. Each trial was awarded a score out of a maximum of 3 points.

The authors did not state how many reviewers performed the assessment.

Data extraction
Peto odds ratios were calculated from the numbers of events in the control and intervention groups of each trial. Adverse events were reported descriptively.

Data were extracted independently by two reviewers, with a check of extracted data by a third reviewer. Disagreements were resolved by consensus.
Methods of synthesis
Trials were combined using a random-effects model to calculate pooled 95% Peto odds ratios and 95% confidence intervals. The results were checked using exact stratified methods. The number needed-to-treat to prevent one event was also calculated. Cochran’s Q test and the $I^2$ statistic were used to assess for heterogeneity. The Egger test was used to assess publication bias. A sensitivity analysis was conducted, omitting the trial that permitted ‘rescue’ antibiotics in the placebo group.

Results of the review
Four randomised controlled trials (RCTs) were eligible for the review (n=384 patients). Trials were of fair to good quality, with a mean Jadad score of 2.25 out of 3 points. One RCT was double-blinded and three were single-blinded. Two RCTs were reported as having adequate allocation concealment. All RCTs reported power size calculations and used intention-to-treat analysis.

The intervention group were significantly less likely than the placebo group to experience a first episode of spontaneous bacterial peritonitis (odds ratio 0.18, 95% confidence interval (CI): 0.09 to 0.35; number-needed-to-treat (NNT) 7, 95% CI: 4.7 to 10.6; four RCTs), a serious infection (odds ratio 0.18, 95% CI: 0.10 to 0.32; NNT 6, 95% CI: 3.8 to 7.7; four RCTs) or death (odds ratio 0.60, 95% CI: 0.37 to 0.97; NNT 12, 95% CI: 5.8 to 261.2; four RCTs). No serious adverse effect attributable to the intervention was reported.

Results of the exact method of analysis and of the sensitivity analysis were similar to the main analysis. No obvious publication bias or significant statistical heterogeneity were detected ($I^2=0\%$ in all cases).

Authors’ conclusions
Daily oral fluoroquinolone prophylaxis reduced the risk of first episode spontaneous bacterial peritonitis, severe infection and mortality in patients with cirrhosis and low protein ascites.

CRD commentary
The objectives and inclusion criteria of the review were clear and relevant sources were searched for published and unpublished studies, with no language restriction. Steps were taken to reduce the risk of reviewer bias and error in the processes of study selection and data extraction, by having more than one reviewer make decisions independently. It was unclear whether these precautions also applied to the process of validity assessment. While an appropriate tool was used to assess validity assessment, it was not clear whether the criteria were correctly interpreted. Appropriate methods were used to combine the trials, to check the robustness of results to a differing type of analysis, and to assess for heterogeneity and publication bias. As the authors noted, there were few relevant trials and sample sizes were small. The review was generally well conducted, but in view of the small amount of evidence available, a degree of caution may be advisable in interpreting the results.

Implications of the review for practice and research
Practice: The authors stated that prophylaxis with fluoroquinolones may be advisable in selected high-risk patients with cirrhosis.

Research: The authors stated that more research is needed on primary prophylaxis of spontaneous bacterial peritonitis, including the optimum duration of treatment and the management of drug resistance. They noted that the guidelines for managing high-risk patients with cirrhosis could be refined in light of the review findings, especially for patients awaiting transplant.

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