Long-term antibiotics for the prevention of recurrent urinary tract infection in children: a systematic review and meta-analysis

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CRD summary
This review assessed efficacy and safety of long-term prophylactic antibiotics on recurrent urinary tract infection in children. The authors concluded that there was no evidence that prophylactic antibiotics were associated with a reduction in recurrent urinary tract infection. This conclusions was consistent with the evidence presented and is likely to be reliable.

Authors' objectives
To evaluate the efficacy and safety of long-term prophylactic antibiotics for recurrent urinary tract infection in children.

Searching
PubMed, EMBASE, and the Cochrane Library were searched up to November 2009, with no language restrictions. Search terms were reported. Reference lists of retrieved papers and reviews were searched.

Study selection
Randomised controlled trials (RCTs) and quasi-RCTs that assessed long-term antibiotic prophylaxis versus placebo or no treatment, in children (less than 18 years of age) without a major predisposing cause (such as neurological or skeletal disease), were eligible for inclusion. Long-term prophylaxis was defined as antibiotics administered daily for at least two months.

The primary outcome was the proportion of patients experiencing at least one recurrence of symptomatic urinary tract infection, confirmed by bacterial growth in the urine, in combination with signs or symptoms of a urinary tract infection while undergoing treatment. The secondary outcomes were risk of repeat positive urine culture, the rate of new or deteriorated renal scarring, and any reported adverse events during and after treatment. The frequency and method of urine collection for urinary tract infection outcomes were reported.

The included trials evaluated various antibiotic prophylaxis, although it was usually co-trimoxazole or nitrofurantoin, with varied dosing schedules; the duration of antibiotic prophylaxis varied from 10 weeks to 24 months.

The definition for initial urinary tract infection varied across the trials that reported this. All but one trial included patients with vesico-ureteric reflux. About three-quarters of the participants were female, with a range of mean ages from 8.3 months to 8.7 years.

Two reviewers independently applied the inclusion criteria and selected studies but how disagreements, if any, were resolved was not reported.

Assessment of study quality
The quality of the included trials was assessed on allocation concealment, standardisation and blinding of outcome assessment, intention-to-treat analysis and losses to follow-up.

Two reviewers independently assessed quality and resolved disagreements by discussion among the reviewers.

Data extraction
Two reviewers independently extracted outcomes data for calculating relative risk (RR), with 95% confidence intervals (CI). Where applicable, authors of the included trials were contacted for additional data. Discrepancies were resolved by discussion among the reviewers.
Methods of synthesis
Relative risk and 95% confidence intervals were combined in a meta-analysis using a fixed-effect model; a random-effects model was used when heterogeneity was significant. Statistical heterogeneity between trials was assessed by the Cochran’s Q and $\Gamma^2$ statistics.

Sensitivity analysis was performed on various factors to determine the robustness of the results. Sub-group analyses were performed to evaluate clinically significant heterogeneity in the included trials.

Publication bias was assessed by the Begg's adjusted rank correlation test for funnel plot asymmetry and Egger’s regression asymmetry test.

Results of the review
Eleven RCTs met the inclusion criteria (n=2,046 children). Three RCTs adequately concealed allocation, two RCTs did not conceal allocation and it was unclear whether allocation was concealed in six RCTs. Only two RCTs were double blind, five RCTs were not blinded and only radiological outcome assessors were blinded in three RCTs. Five RCTs performed intention-to-treat analysis; it was unclear in the remaining RCTs. Losses to follow-up were generally low (0 to 22%) at six months to four years of follow-up.

The effect of antibiotic prophylaxis on recurrence of symptomatic urinary tract infection was not statistically significantly different from placebo or no treatment (RR 0.83 95% CI 0.66 to 1.05; seven trials; n=1,717 children), with no apparent heterogeneity between the trials ($\Gamma^2=0\%$).

Antibiotic prophylaxis significantly reduced repeat positive urine culture compared with placebo or no treatment (RR 0.50, 95% CI 0.34 to 0.74; 11 trials; n=2,046 children), but heterogeneity was significant ($\Gamma^2=76\%$).

There was no significant difference in new or deteriorated renal scars between antibiotic prophylaxis and placebo or no treatment (RR 0.95, 95% CI 0.51 to 1.78; seven trials; n=1,093 children), with no heterogeneity between the trials ($\Gamma^2=0\%$).

Three trials reported on adverse events, and recorded very low event rates (2 to 7.3%), which were mainly mild.

Sensitivity and subgroup analyses did not change the findings on recurrence of symptomatic urinary tract infection, except on the level of trial quality; adequately concealed studies showed statistically significant reduction in recurrent symptomatic urinary tract infection (RR 0.68, 95% CI 0.48 to 0.95; number of studies not stated). A subgroup analysis on patients without vesico-ureteric reflux demonstrated non-significant reduction in risk of repeat positive urine culture (P=0.17), although there was significant heterogeneity between the studies ($\Gamma^2=62\%$).

There was no evidence of publication bias.

Authors’ conclusions
There was no evidence that prophylactic antibiotics were associated with a significant reduction in the incidence of recurrent urinary tract infection or new renal damage in children.

CRD commentary
This review addressed a well-defined question in terms of participants, interventions, outcomes, and study design. The search included appropriate databases, but no attempts were made to retrieve unpublished studies, so some relevant data might have been missed. The results showed no evidence of publication bias. To minimise bias and errors during the review process, two reviewers independently selected trials, extracted data, and assessed the quality of the included trials.

The quality of included trials was assessed, and was used in interpreting the results of the review. The characteristics of the individual trials were presented. Appropriate methods were used to pool the data, although the number of trials and participants contributing to certain analyses was not always provided. Also, the authors did not distinguish between trials using placebo and trials where the control group received no treatment, which made it difficult to
interpret individual trial results. Potential sources of heterogeneity were explored and reported. Sub-group analyses did not demonstrate significant variation between the trials. Sensitivity analyses demonstrated that the results were robust to changes in the factors considered. Although there was clinical variation, statistical heterogeneity and methodological weaknesses in the included trials, the review process was robust.

The authors’ conclusion was consistent with the evidence presented and is likely to be reliable.

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

**Practice**: The authors suggested that the potential benefit of antibiotic in clinical practice should be weighed against the risk of the bacteria developing resistance against the drug given the lack of evidence in support of antibiotic use in the prevention of urinary tract infection.

**Research**: The authors stated that RCTs targeting patients with grade III to V vesico-ureteric reflux are needed, since the risk of renal damage high grade of vesico-ureteric reflux is four to six times greater than grade I or II and eight to 10 times greater than those without vesico-ureteric reflux. More details about such a trial (such as the rate of urinary tract infection and new scarring at different ages, gender and type of antibiotic) should be recorded and it should have sufficient power to detect significant differences.

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