Short-course versus conventional length antimicrobial therapy for uncomplicated lower urinary tract infections in children: a meta-analysis of 1279 patients

Tran D, Muchant D G, Aronoff S C

Authors' objectives
To compare the efficacy of single-dose, short-course and standard-course antimicrobial therapy for uncomplicated childhood cystitis.

Searching
MEDLINE was searched from 1966 to 1999 using the MeSH keywords and textwords 'urinary tract infection' and 'antibiotic course'. The following filters were applied: English language, human research, all children (0 to 18 years), and randomised controlled trials. The bibliographies of each article were handsearched for additional relevant studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Comparisons of short-course (single dose 4 days) and conventional-course (at least 5 days) antimicrobial therapies were eligible for inclusion. The short courses in the included studies ranged from a single dose to 4 days’ treatment, while a long course ranged from 5 to 14 days. Various antimicrobial agents were tested.

Participants included in the review
Studies were eligible for inclusion if all the participants were aged less than 18 years. The initial infection had to be documented by urine culture and at least one subsequent culture obtained. In addition, there had to have been some attempt to separate upper from lower tract infection, by any clinical, laboratory or imaging criteria. Culture was defined as either 100,000 colony-forming units of a single organism per mL of clean catch urine, or any bacterial growth from a catheterised specimen or bladder aspirate. In the included studies, the age ranged from less than one year to 18 years. The bacteriological criteria for establishing infection of the urinary tract were uniform among the studies.

Outcomes assessed in the review
The primary outcome was defined as the cure rate, i.e. one minus the proportion of treatment failures (out of the number of patients completing the protocol). Definitions of cure, relapse and reinfection varied between the included studies.

How were decisions on the relevance of primary studies made?
All potentially relevant studies were retrieved on the basis of the titles and abstracts, although the authors do not state how potentially relevant studies were selected. Two independent investigators then reviewed the 'Methods' section of each study and applied the selection criteria. The investigators were blinded to the journal of publication, authors, institution, and the magnitude and direction of the results. The selection criteria included: study design; age; attempt to separate upper urinary tract infection from cystitis, or to exclude upper tract infections; documentation of infection; and treatment failures. Any disagreements were resolved by consensus.

Assessment of study quality
The authors do not generally report the method used to assess validity, or how the validity assessment was performed. However, it was reported whether the analysis was by intention-to-treat, and whether the observers were blinded.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

The data extracted from the included studies were: the number of participants; age range; the duration of short- and long-course therapy; the cure rates with short- and long-course therapy; drugs used; whether the analysis was by intention to treat; and whether the observers were blinded.

Methods of synthesis
How were the studies combined?
The authors describe both an analysis of pooled data and a meta-analysis. The cure rates for the short- and long-course therapy, and the differences and variances in cure rates between the groups, were calculated within each study. The mean cure rate and its standard deviation (SD) were calculated from pooled data for the short courses and long courses. The mean absolute difference (and its SD) between the short- and long-course cure rates for each study were calculated for the pooled data. The latter was chosen for the meta-analysis because it enabled calculation of the number-needed-to-treat (NNT).

How were differences between studies investigated?
Heterogeneity was tested statistically in the meta-analyses. In cases where heterogeneity was statistically significant (P<0.05), a random-effects model was used (see Other Publications of Related Interest).

Five subgroups of studies were identified post hoc: (1) same antimicrobial agent used in both treatment groups; (2) single-dose compared with conventional length therapy; (3) more than a single dose compared with conventional length therapy; (4) amoxicillin used in both treatment groups; and (5) trimethoprim/sulfamethoxazole used in both treatment groups.

Results of the review
Twenty-two RCTs (n=1,279) were included.

Twelve of the 22 included trials used intention to treat analysis, and only one attempted to blind both the observers and participants.

Analysis of pooled data.

The pooled cure rate was 88.5% (SD 7.4) for conventional length antimicrobial therapy and 78.8% (SD 13.5) for single-dose/short duration therapy, based on all 22 studies. The pooled difference was 9.8% (SD 10.3). The cure rates, and the difference in cure rates between the two regimens, were not affected by the inclusion of studies that did not match antimicrobial agents in both treatment groups.

Meta-analysis.

When all 22 trials were pooled there was significant heterogeneity between the studies (P=0.01). A random-effects meta-analysis showed an absolute difference in the cure rate of 6.38% (95% confidence interval, CI: 1.88, 10.89), in favour of longer treatment. The NNT was 16 (95% CI: 9, 53).

There was significant heterogeneity between the 17 trials (n=832) that used the same drug in both treatment groups (P=0.01). A random-effects meta-analysis showed an absolute difference in the cure rate of 7.92% (95% CI: 2.09, 13.8), in favour of longer treatment. The NNT was 13 (95% CI: 6, 35).

There was no difference between the treatment groups in the subgroup meta-analyses of studies wherein a single-dose was compared with conventional length therapy (9 trials, n=383), or more than a single dose was compared with conventional length therapy (13 trials, n=896).

Heterogeneity between the 5 trials (n=193) that used amoxicillin in both treatment groups was not statistically significant (P=0.6). A fixed-effect meta-analysis showed an absolute difference in the cure rate of 13.0% (95% CI: 4.0,
in favour of longer treatment. The NNT was 8 (95% CI: 5, 25).

There was significant heterogeneity between the 6 trials (n=310) that used trimethoprim/sulfamethoxazole in both treatment groups (P=0.004). A random-effects meta-analysis showed no significant difference in the cure rate (6.24%, 95% CI: -3.74, 16.2).

Cost information
The authors estimated the cost of preventing a single trimethoprim/sulfamethoxazole short-course treatment failure to be approximately $30 for a child of 20 kg.

Authors' conclusions
Single-dose amoxicillin is inadequate therapy for uncomplicated cystitis in childhood. Three days of trimethoprim/sulfamethoxazole appears to be as effective as conventional length courses of the drug.

CRD commentary
This review addressed a clear question in terms of the participants, intervention and comparators, and it defined the primary outcome of interest. The search for studies was not comprehensive, consisting of a search of one database that was restricted to English language publications, and the bibliographies of the retrieved articles. The potential for publication and language bias in the review should be borne in mind. While it is unclear how the titles and abstracts were screened for relevance, full papers that were retrieved were assessed by two independent reviewers using explicit selection criteria. The reviewers attempted to further minimise bias at this stage by blinding the selectors to the source and results of each study. The processes used to assess validity and to extract the data were not described. The included studies were presented clearly in tabular format, although no details of the participants were given, other than their age. The cure rate in each treatment group is shown for each study, enabling the reader to make some judgement about the variation in treatment effect between trials. It is difficult to tell from the description of the pooling and meta-analysis given in the report, whether or not the analyses were conducted using appropriate methods. Pooling appears to have produced simple averages, while key elements of the meta-analysis such as weighting are not mentioned. The meta-analysis software used was EPIMETA, but details of this were not found by the writer of this abstract at the website given by the review's authors. The authors used a random-effects meta-analysis when statistical heterogeneity was evident, without exploring possible reasons for it. Calculation of the NNT from pooled heterogeneous studies is of questionable clinical relevance. Study quality, as far as it was assessed, was not taken into account when interpreting the findings.

The authors' conclusions are based on subgroups of trials and should be interpreted with some caution. The amoxicillin trials were small and of doubtful methodological quality. Similarly, the trimethoprim/sulfamethoxazole trials also showed significant heterogeneity of effect.

Implications of the review for practice and research
Practice: The authors state that short-course antimicrobial therapy for childhood cystitis is less effective than therapy of conventional duration, but that a 3-day course of trimethoprim/sulfamethoxazole appears to be an effective alternative to the standard course of therapy.

Research: The authors state that there are insufficient data available to determine the efficacy of short-course amoxicillin.

Bibliographic details

PubMedID
Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Adolescent; Amoxicillin /therapeutic use; Anti-Infective Agents, Urinary /therapeutic use; Child; Child, Preschool; Cystitis /drug therapy; Drug Administration Schedule; Humans; Infant; Penicillins /therapeutic use; Time Factors; Trimethoprim, Sulfamethoxazole Drug Combination /therapeutic use; Urinary Tract Infections /drug therapy

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.