Short compared with standard duration of antibiotic treatment for urinary tract infection: a systematic review of randomised controlled trials

M Michael, E M Hodson, J C Craig, S Martin, V A Moyer

METHODS

Search strategies
Randomised and quasi-randomised controlled trials were identified from MEDLINE (1966 to February 2001), EMBASE (1988 to February 2001), and the Cochrane Controlled Trials Register (Cochrane Library Issue 1, 2001) without language restriction. The optimally sensitive strategies of the Cochrane Collaboration to identify randomised controlled trials were combined with subject headings and textwords for urinary tract infection and duration of treatment and limited to the paediatric age range (full details available on request). Reference lists of review articles, relevant trials, nephrology textbooks, and abstracts of scientific meetings were also searched. Two reviewers reviewed trials independently for study eligibility and extracted trial data.

Inclusion criteria
Randomised or quasi-randomised trials were selected if they involved children aged 3 months to 18 years with culture proven symptomatic UTI, and compared short term therapy (2–4 days) against standard therapy (7–14 days). To eliminate possible heterogeneity owing to the efficacies of different antibiotics, only studies that used the same antibiotic in both short and standard duration arms were included. The primary outcomes of interest were persisting clinical symptoms at the end of treatment, significant bacteriuria (colonies > 10⁵ organisms per ml of urine) at completion of therapy (0–7 days after completing treatment), and recurrent UTI after treatment (10 days or more after completing treatment). Secondary outcomes sought were compliance with medication, development of resistant organisms, costs, and side effects of therapy.

Abbreviations: Cl, confidence interval; RCT, randomised controlled trial; RR, relative risk; UTI, urinary tract infection
<table>
<thead>
<tr>
<th>First author, Year, Country, Source</th>
<th>Patients entered</th>
<th>Patients evaluated</th>
<th>Inclusion criteria</th>
<th>Antibiotics used</th>
<th>Outcomes</th>
<th>Length of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wientzen, 1987, USA, OPD</td>
<td>57</td>
<td>52</td>
<td>Symptomatic UTI. Children with ≥3 UTI in previous year excluded. Age 0.25–16 y. MSU*, SPA†, bag‡ samples.</td>
<td>Amoxycillin 4 days versus 10 days</td>
<td>UTI any time after treatment</td>
<td>12 months</td>
</tr>
<tr>
<td>Lohr, 1981, USA, OPD</td>
<td>55</td>
<td>49</td>
<td>Girls with symptomatic UTI. Age 2–18 y.</td>
<td>Nitrofurantoin 3 days versus 10 days</td>
<td>UTI 0–7 days after treatment</td>
<td>6 months</td>
</tr>
<tr>
<td>Helin, 1981, Sweden, OPD</td>
<td>43</td>
<td>43</td>
<td>Symptomatic UTI. Age 0.25–16 y. Bag, MSU samples.</td>
<td>Trimethoprim/sulphadiazine 4 days versus 10 days</td>
<td>UTI at end of treatment</td>
<td>12 months</td>
</tr>
<tr>
<td>Zaki, 1986, Kuwait, Not stated</td>
<td>55</td>
<td></td>
<td>Symptomatic UTI. Children with UTI in previous 6 months excluded. Age 0.5–13 y. Collection method not stated.</td>
<td>(a) Nalidixic acid 3 days versus 10 days</td>
<td>UTI 2–3 days after treatment</td>
<td>3 months</td>
</tr>
<tr>
<td>Madrigal, 1988, Costa Rica, OPD</td>
<td>104</td>
<td>90</td>
<td>Symptomatic UTI. Children with recurrent UTI excluded. Age 0.25–12 y. MSU, SPA, catheter urine samples.</td>
<td>TMP/SMX 3 days versus 7 days</td>
<td>UTI 10–12 days after therapy</td>
<td>44 days</td>
</tr>
<tr>
<td>CSG, 1991, Denmark, OPD</td>
<td>333</td>
<td></td>
<td>Girls with symptomatic &amp; asymptomatic UTI. Age 1–15 y. MSU samples.</td>
<td>(a) Sulphamethizole 3 days</td>
<td>UTI 1–10 days after treatment</td>
<td>80 days</td>
</tr>
<tr>
<td>Jojart, 1991, Hungary, Not stated</td>
<td>132</td>
<td></td>
<td>Symptomatic &amp; asymptomatic UTI. Children with UTI &gt;3 months earlier could be re-entered to other therapy. Age 1.5–9 y. Collection method not stated.</td>
<td>(a) Nitrofurantoin 3 days versus 14 days</td>
<td>UTI at 28–36 days after treatment</td>
<td>36 days</td>
</tr>
<tr>
<td>Gaudreault, 1992, Canada, ED</td>
<td>45</td>
<td>40</td>
<td>Symptomatic UTI. Children with UTI in previous 6 months excluded. Age 2.5–18 y. MSU samples.</td>
<td>Trimethoprim/sulphadiazine 3 days versus 10 days</td>
<td>UTI at end of treatment</td>
<td>38 days</td>
</tr>
<tr>
<td>Johnson, 1993, USA, OPD</td>
<td>48</td>
<td>37</td>
<td>Symptomatic UTI. Age 1–13 y. MSU, SPA, catheter samples.</td>
<td>Amoxicillin/clavulinic acid 3 days versus 10 days</td>
<td>UTI 4 days after treatment</td>
<td>33 days</td>
</tr>
<tr>
<td>Kornberg, 1994, USA, ED &amp; OPD</td>
<td>38</td>
<td>25</td>
<td>Symptomatic UTI. UTI in last 30 days excluded. Age 2–11 y. MSU, catheter samples.</td>
<td>Cefuroxime 2 days versus 10 days</td>
<td>UTI 3–5 days after treatment</td>
<td>15 months</td>
</tr>
</tbody>
</table>

*Mid stream urine or clean catch urine collection. †Suprapubic bladder aspiration urine collection. ‡Strap-on bag urine collection. §Trimethoprim/sulphamethoxazole. ¶Third group of study by Copenhagen Study Group not included in results. OPD, outpatient department; ED, emergency department.
Quality assessment
Two reviewers (MM and EH) assessed study quality without
blinding to author or source using the criteria of the Cochrane
Renal Group. Discrepancies were resolved through discussion.
Quality items assessed were allocation concealment, intention
to treat analysis, completeness of follow up, and blinding of
participants, investigators, and outcome assessment since
these may bias the underlying treatment effect. 11

Statistical analysis
For dichotomous outcomes the relative risks (RR) with 95%
confidence intervals (CI) were calculated in RevMan12
for individual studies and the summary statistics were calculated
using a random effects model. The random effects model takes
into account between study variability as well as within study
variability. A fixed effects model was also used to test the
robustness of the analysis and for outliers. Heterogeneity was

discussed.

Table 2 Quality of included trials comparing short with standard duration antibiotic
therapy for lower UTI

<table>
<thead>
<tr>
<th>First author</th>
<th>Allocation concealment</th>
<th>Percent lost to follow up</th>
<th>Blinding of participants and investigators</th>
<th>Blinding of outcome assessment</th>
<th>Intention to treat analysis</th>
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</thead>
<tbody>
<tr>
<td>Wientzen26</td>
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<td>Not stated</td>
<td>Not stated</td>
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<tr>
<td>Lohr23</td>
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<td>Yes</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>Helin26</td>
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<td>0</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>Zakic25</td>
<td>Unclear</td>
<td>0</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>Madrigal22</td>
<td>Unclear</td>
<td>14</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>CSG21*</td>
<td>Yes</td>
<td>21</td>
<td>No</td>
<td>Not stated</td>
<td>Not stated</td>
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<tr>
<td>Joart20</td>
<td>Unclear</td>
<td>34</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>Gaudreault19</td>
<td>Unclear</td>
<td>11</td>
<td>No</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>Johnson18</td>
<td>Yes</td>
<td>23</td>
<td>No</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>Kornberg27</td>
<td>Unclear</td>
<td>16</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
</tbody>
</table>

* Copenhagen Study Group of urinary tract infections in children.

Figure 1 Meta-analyses showing the summary and individual trial relative risks (95% CI) for (A) persistence of urinary tract infection at the end of treatment (8 data sets) and (B) recurrence of infection 10 days to 15 months (12 data sets) after treatment with short duration or standard duration of antibiotics. Trials are shown ordered by study weights. No heterogeneity was shown using Cochran’s Q statistic (x2). The test statistic Z indicates that there were no significant differences between short and standard durations of antibiotic therapy.
analysed using Cochran’s Q statistic with an α of 0.1 used for statistical significance. Subgroup analysis was planned based on study quality, patient type (age, finding of abnormal radiological findings), and intervention (type of antibiotic used) as we postulated that the relative treatment effect could vary with these factors.

RESULTS

Trial characteristics

Of 636 titles and abstracts screened, 14 studies were identified by full text review as randomised controlled trials (RCT), which compared short course to standard duration of oral antibiotic treatment. Three studies were subsequently excluded as two13,14 compared different antibiotics in the short and standard duration groups, and the third15 compared one day treatment with 10 day treatment. A fourth trial16 was excluded as significantly more patients (32 of 59) with pyelonephritis were included in the seven day group compared with the three day group (11 of 58) (χ² = 15.65, df = 1; p < 0.001), which strongly suggested non-random allocation. Thus ten trials were included in the systematic review.17-26

Table 1 summarises trial characteristics. Two trials19,20 had four arms and were treated as separate trials. Hence there were 12 data sets for analysis. Seven trials20,22,23,25,26 used ≥ 10⁵ organisms/ml to define UTI. Two trials17,21 used < 10⁵ organisms/ml and three trials22,23,24 used <10⁴ organisms/ml to define cure of UTI; the remaining studies used ≥10⁴ organisms/ml to define persistent bacteriuria. In two trials25,26,28 urine specimens obtained by strap on bags were excluded. Only one trial22 recorded persisting symptoms at the end of therapy. Two trials included children with asymptomatic UTI.23-25 No trial specified whether recurrent UTIs were symptomatic or asymptomatic. All trials excluded children with acute pyelonephritis (diagnosed on the basis of fever of 38°C or above with or without symptoms of loin pain, chills, vomiting, or toxic appearance) or known renal tract abnormalities. Three trials22,23,24 examined the occurrence of resistant organisms in children with persistent or recurrent UTI.

Study quality

Although 910 children entered the trials, outcomes were evaluated in only 652 children. Trial investigators excluded 168 children from analysis because of loss to follow up, deviation from protocol, non-compliance, or other reasons. Ninety one children were excluded from the meta-analyses because there was no long duration comparison group.22 Problems in trial design and reporting were common (table 2). Randomisation was adequately concealed in two studies20,21; in the remaining studies sufficient information was not provided to determine whether allocation was adequately concealed.

Study outcomes

As results from random and fixed effects models did not differ, only results from the random effects model are reported. After standard duration therapy, the prevalence of bacteriuria after treatment varied from 0% to 23% (median 10%, mean 14%), while that of recurrent UTI varied from 5% to 50% (median 28%, mean 24%). There were no significant differences (fig 1) in the frequency of bacteriuria at 0–7 days after completing treatment (eight data sets; RR 1.06, 95% CI 0.64 to 1.76) or in the number of UTIs during 10 days to 15 months follow up (12 data sets; RR 1.01, 95% CI 0.77 to 1.33) between short and standard duration therapy. Analyses comparing different durations of follow up showed no differences in outcomes, so follow up data from 10 days to 15 months were combined. In the one study27 that reported the outcome of symptomatic UTI, symptoms persisted in three of 12 children treated for two days, but in none of 13 children treated for 10 days. However, the authors did not state at what time during or after treatment this assessment was made.

No significant differences (fig 2) between short and standard duration therapy were found in the number of children with urinary pathogens resistant to the treating antibiotic on in vitro sensitivity analysis in persistent bacteriuria (one study, RR 0.57, 95% CI 0.32 to 1.01; p = 0.06) and in recurrent UTI (three studies; RR 0.39, 95% CI 0.12 to 1.29; p = 0.12).
However, the summary relative risk reductions for the occurrence of resistant organisms were 43% and 61% for bacteriuria at the end of treatment and recurrent UTI respectively, suggesting a trend towards a fall in the number of children with resistant organisms following short course therapy. Three studies\textsuperscript{17–19 21 23–25} reported that compliance was satisfactory in both treatment groups, and one study\textsuperscript{20} reported that 28% (37/132) were excluded from evaluation because of non-compliance, but did not specify the treatment groups. No studies evaluated the costs of the treatment regimens. Adverse effects of antibiotics were not reported in sufficient detail to allow analysis. Of the seven trials\textsuperscript{18 21} that reported on adverse effects, only two studies\textsuperscript{21 23} reported in which groups the adverse effects occurred. Overall nine children suffered adverse effects: gastrointestinal disturbances (n = 6), dizziness (n = 1), or rash (n = 2).

In subgroup analyses, relative treatment effects with short and standard duration therapy did not differ with sulphonamide containing antibiotics or with non-sulphonamide based antibiotics or between children with and without abnormal renal tracts on imaging after treatment (table 3). Subgroup analysis based on other potential effect modifiers, such as study quality and patient age, was not possible because of the limited numbers of studies available.

**DISCUSSION**

In children with lower tract UTI there is no significant difference between short and standard duration antibiotic therapy for UTI at the end of treatment or in UTI recurrence rate 10 days to 15 months after treatment. Although there was no significant difference in the rate of bacteriuria at the end of treatment, the wide confidence intervals of the summary estimate (RR 1.06, 95% CI 0.64 to 1.76) indicate residual imprecision in the results. Ideally a further adequately powered trial is required. About 1–3% of unselected children treated for symptomatic UTI have UTI after 7–14 days of antibiotic treatment.\textsuperscript{7–10} To show a reduction in UTI after treatment from 3% to 2% or from 1% to 0.5% would require 8000 and 10 000 children, respectively, to be enrolled. Such a trial is highly improbable, so how should clinicians decide what treatment duration they should use? The relevance of the residual uncertainty to patient care depends on the risk of persistent infection with standard duration therapy. If the upper and lower limits of the 95% confidence intervals are used to define the best and worst case scenarios in 1000 children with a 1% risk of infection at the end of treatment for their first UTI, four fewer children or eight extra children would have UTI following short duration therapy compared with standard duration—a clinically unimportant difference (table 4). All trials included in this systematic review involved children with recurrent UTI; such children are known to be at a higher risk of UTI at the end of treatment compared with children with their first infection.\textsuperscript{11} If the risk of infection following treatment is 14% with standard duration therapy, as in the included trials, then 50 fewer or 110 extra children would have UTI following short duration therapy—a difference that is clinically important. In populations with recurrent UTI and a higher risk of UTI at the end of treatment, the possible harms (delay in resolution of symptoms) of not clearing the infection would have to be weighed against the possible benefits (reduced resistance to treating antibiotics, reduced adverse effects of antibiotics, improved compliance, and reduced costs) of using a short course of therapy.

Data on the development of resistant organisms were reported in only three trials. In view of the increasing prevalence in UTI of organisms resistant to commonly used antibiotics,\textsuperscript{21} the possible trend towards a reduction in the

<table>
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<tr>
<th>Table 3</th>
<th>Effects of short and standard duration therapy for UTI based on antibiotics used and associated urinary tract abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subgroup</td>
<td>UTI at end of treatment</td>
</tr>
<tr>
<td>Antibiotic type</td>
<td></td>
</tr>
<tr>
<td>Sulphonamide group\textsuperscript{*}</td>
<td>0.80 (0.45 to 1.41)</td>
</tr>
<tr>
<td>Other antibiotics\textsuperscript{†}</td>
<td>1.72 (0.64 to 3.80)</td>
</tr>
<tr>
<td>Imaging studies\textsuperscript{‡}</td>
<td></td>
</tr>
<tr>
<td>Abnormality</td>
<td>0.71 (0.38 to 1.32)\textsuperscript{§}</td>
</tr>
<tr>
<td>No abnormality</td>
<td>0.99 (0.12 to 8.56)\textsuperscript{§}</td>
</tr>
</tbody>
</table>

Results presented as relative risk and 95% CI.

\textsuperscript{*Six studies (339 patients) using sulphonamides alone or in combination with trimethoprim.\textsuperscript{19–24}}

\textsuperscript{†Six studies (233 patients) using other antibiotics.\textsuperscript{17 18 20 23 25 26}}

\textsuperscript{‡Intravenous pyelogram and/or micturating cystourethrogram.}

\textsuperscript{§Two studies involving 154 children (60 with abnormal imaging).\textsuperscript{18 21}}

\textsuperscript{¶One study involving 70 children (12 with abnormal imaging).\textsuperscript{22}}

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Estimated risk for UTI 0–7 days following short duration antibiotic therapy in 1000 children, with different risks of UTI (using the summary RR of 1.06; 95% CI of 0.64 and 1.76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of UTI 0–7 days after standard duration therapy</td>
<td>Number with UTI after standard duration therapy</td>
</tr>
<tr>
<td>1%\textsuperscript{*}</td>
<td>10</td>
</tr>
<tr>
<td>3%\textsuperscript{†}</td>
<td>30</td>
</tr>
<tr>
<td>14%\textsuperscript{‡}</td>
<td>140</td>
</tr>
</tbody>
</table>

\textsuperscript{*Data from Craig et al.\textsuperscript{2}}

\textsuperscript{†Data from Winberg et al.\textsuperscript{1}}

\textsuperscript{‡Mean rate of UTI, 0–7 days after standard duration therapy from 8 data sets included in meta-analysis.\textsuperscript{17–19}}
number of children with resistant organisms following short duration therapy needs further study. It was not possible to determine whether short duration therapy offered any reduction in antibiotic related adverse effects. Detailed data on compliance with medications in each treatment group were not provided in any study. No study addressed whether using short course therapy reduced costs.

There are important limitations of this systematic review because of problems with the primary studies. Some information of most relevance to clinical care was not provided in these studies. None of the trials specified the time to symptom resolution after commencement of antibiotics and whether UTI at the end of treatment or UTI recurrence were associated with clinical symptoms. Two trials included both symptomatic and asymptomatic patients. Inclusion of these trials did not result in heterogeneity. It is now recommended that school age children with asymptomatic bacteriuria should not be treated with antibiotics as they are not at increased risk of impaired renal growth or deterioration in renal function when untreated, but are at increased risk of pyelonephritis following treatment. Children with pyelonephritis or known urinary tract pathology were excluded, so no recommendations on treatment duration can be made for such children, who comprise a large proportion of children under 5 years with UTI. Studies were generally small, included children from a wide age range, and were of suboptimal quality. Trials with inadequate allocation or blinding can exaggerate the efficacy of experimental treatment, and meta-analyses of poor quality trials can provide erroneous information on the benefits of therapy. Despite these methodological issues, no significant heterogeneity was shown between study results. Formal testing to exclude publication bias resulting from exclusion of some unpublished trials using funnel plots was not possible because of the small number of studies.

Combining inadequately powered trials in a meta-analysis can improve statistical power. However, this study has still not provided incontrovertible evidence that short duration (2–4 days) is better or worse than standard duration therapy (7–14 days) in eradicating childhood UTI because of residual imprecision. For most children with first UTI, who are at low risk (1–3%) of bacteriuria at the end of treatment with standard duration treatment, this statistical imprecision is of doubtful clinical significance. Therefore, based on these data, short duration of treatment is a reasonable option for children with lower tract UTI.

ACKNOWLEDGEMENTS

The authors wish to thank Narelle Willis, Coordinator of the Cochrane Renal Group, for her help with analysis using the Review Manager software. This work has been presented in part at the Annual Scientific Meeting of the Royal Australasian College of Physicians (Sydney, 2001) and at the 12th Congress of the International Pediatric Nephrology Association (Seattle, 2001).

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REFERENCES


