A Meta-analysis of Randomized, Controlled Trials Comparing Short- and Long-Course Antibiotic Therapy for Urinary Tract Infections in Children

Ron Keren, MD, MPH, and Eugenia Chan, MD, MPH

ABSTRACT. *Background.* **Short-course antibiotic regimens, ranging in duration from a single dose to 3 days, are the current standard of care for the treatment of acute lower urinary tract infections (UTIs) in adult women. Despite multiple small randomized, controlled trials (RCTs) showing no difference in efficacy between short-course (≤3 days) and long-course (7–14 days) therapy in children, concerns about occult pyelonephritis and renal scarring have prompted standard recommendations of 7 to 14 days of antibiotics for UTIs in children.**

Objective. **To determine whether long-course antibiotic therapy is more effective than short-course therapy for the treatment of UTIs in children, and to explore potential sources of heterogeneity in the results of existing studies.**

Methods. **We searched online bibliographic databases (Medline and Cochrane Clinical Trials Registry) for RCTs comparing short- and long-course therapy for the treatment of UTI in children, and examined the references of all retrieved articles. Candidate studies for meta-analysis were restricted to RCTs comparing short-course (≤3 days) and long-course (7–14 days) outpatient therapy for acute UTI in children age 0 to 18 years. We excluded studies that were restricted to children with recurrent UTI or included children with asymptomatic bacteriuria. Sixteen studies met the inclusion criteria. Study quality was evaluated using a 9-item scoring system developed by the investigators. Data on the primary outcomes—treatment failure and reinfection rate—were extracted when available and reanalyzed based on intention to treat whenever possible. To determine whether anatomic level of infection (upper vs lower urinary tract) influenced the results, the meta-analysis was repeated on the subgroup of studies that attempted to restrict their participants to children with lower UTI. To determine whether there was a dose-response effect for the duration of short-course therapy, we performed separate subgroup analyses of studies of single-dose or single-day therapy and studies of 3-day therapy. To explore other potential sources of study result heterogeneity, such as study quality and patient age, we developed a random-effects regression model that included these variables as covariates.**

Results. **The pooled estimate for the relative risk (RR) of treatment failure with short-course antibiotic therapy was 1.94 (95% confidence interval [CI]: 1.19–3.15) and for the RR of reinfection was 0.76 (95% CI: 0.39–1.47). When** we excluded the 3 studies that did not attempt to restrict their participants to patients with lower UTI, the pooled RR of treatment failure was 1.74 (95% CI: 1.05–2.88) and of reinfection was 0.69 (95% CI: 0.32–1.52). For the subgroup of studies comparing single-dose or 1-day therapy to long-course therapy, the pooled RR of treatment failure was 2.73 (95% CI: 1.38–5.40) and of reinfection was 0.37 (95% CI: 0.12–1.18). For the subgroup of studies comparing 3-day therapy to long-course therapy, the pooled RR of treatment failure was 1.36 (95% CI: 0.68–2.72) and of reinfection was 0.99 (95% CI: 0.46–2.13). In the meta-regression, neither study quality nor mean participant age was significantly associated with the odds ratio of treatment failure or reinfection, in either the complete set of studies or the subset of studies restricted to patients with lower UTI.**

Conclusions. **In pooled analyses of published studies comparing long- and short-course antibiotic treatment of UTI in children, long-course therapy was associated with fewer treatment failures without a concomitant increase in reinfections, even when studies including patients with evidence of pyelonephritis were excluded from the analysis. Until there are more accurate methods for distinguishing upper from lower UTI in children, no additional comparative trials are warranted and clinicians should continue to treat children with UTI for 7 to 14 days.** *Pediatrics* 2002;109(5). URL: http://www.pediatrics.org/cgi/content/full/109/5/e70; *urinary tract infection, child, meta-analysis, antibiotic, treatment failure.*

ABBREVIATIONS. UTI, urinary tract infection; RCT, randomized, controlled trial; RR, relative risk; CI, confidence interval.

Short-course antibiotic regimens, ranging in duration from a single dose to 3 days, are the current standard of care for the treatment of uncomplicated lower urinary tract infections (UTIs) in women.[1] In addition to being effective, shorter treatment regimens are less expensive, improve adherence, have fewer side effects, and may prevent reinfections with resistant organisms.[2,3]

Despite the proven efficacy and advantages of short-course antibiotic treatment of lower UTI in adults, pediatricians have hesitated to extrapolate this practice to children for several reasons. By the time UTIs are identified in preverbal children, there is often upper tract involvement that cannot be reliably and easily distinguished from lower tract disease by clinical signs and symptoms or laboratory tests.[4–6] Compared with adults, young children are also more likely to have anatomic abnormalities and/or vesicoureteral reflux predisposing them to pyelonephritis. If pyelonephritis requires longer

course and possibly intravenous therapy,[1,7] then shorter course antibiotic treatment may not be appropriate for children.

These concerns are reflected in the American Academy of Pediatrics 1999 practice parameter on the management of children with UTIs, which recommended that infants and young children 2 months to 2 years of age receive a 7- to 14-day antimicrobial course.[8] However, randomized, controlled trials (RCTs) over the last 25 years have not provided definitive evidence supporting this practice. In fact, most of these studies showed no statistically significant difference in efficacy between short- and long-course therapy, although most were limited by small sample size.

Using meta-analysis, we sought to: 1) increase our power to identify differences in efficacy between short- and long-course therapy and thus reduce the possibility of concluding that there is no difference when in fact there is a difference (type 2 error); 2) derive a more precise estimate of the comparative efficacy of short and long-course therapy; and 3) explore potential sources of heterogeneity of results in existing studies, such as inclusion of patients with upper UTI, duration of short-course therapy, participant age, and study quality.

METHODS

Identification of Trials

In April 2001, we used the National Library of Medicine's PubMed search engine to search Medline for all English-language, published studies comparing short- and long-course therapy for the treatment of acute UTI in children. We indexed by the MeSH terms "urinary tract infection" and "antibiotics" and limited the search to RCTs, children age 0 to 18 years, and humans. This search returned 159 articles, the titles and abstracts of which we reviewed for inclusion in the meta-analysis. We scanned the references of all retrieved articles as well as a recent practice guideline on the management of UTIs in children[8] and searched the Cochrane Library Web site for systematic reviews on treatment of UTI. We also contacted experts in the field to identify other published or unpublished trials. Overall, our literature search returned 53 articles evaluating different durations of therapy for the treatment of pediatric UTIs.

Inclusion and Exclusion Criteria

We restricted candidate articles for our meta-analysis to RCTs comparing short- (≤3 days) and long- (7–14 days) course outpatient therapy of acute UTI in children age 0 to 18 years. Although we limited our search strategy to pediatric patients, many of the studies identified by the search were of adult participants. After excluding these studies, as well as studies of inpatient therapy, 21 RCTs remained.[9–29] After detailed review of the 21 trials, we excluded studies that were restricted to children with recurrent UTI[13] or included children with asymptomatic bacteriuria,[26] and studies with short-course therapy duration longer than 3 days.[22,29] This left us with 17 RCTs all together.

Data Extraction

Using a standardized data extraction form, we independently extracted the following information from each of the RCTs: year of publication, sample size, setting, mean participant age, definition of UTI, attempt to distinguish lower from upper UTI, exclusion criteria, method of allocation, definitions of short and long-course, antibiotic(s) studied, follow-up period, treatment failure rate, and reinfection rate. Any disagreements were resolved by consensus after returning to the original publication. There was considerable variation in the outcomes reported and the terminology used to describe these outcomes. When possible, we reanalyzed the primary data using the following definitions for our outcome measures:

- *Treatment Failure* denotes either persistent infection or relapse. We defined persistent infection as failure to eradicate the organism as evidenced by continued positive urine cultures within 1 to 2 days of initiation of therapy, and relapse as initial bacteriologic cure followed by recurrence of symptoms and infection with the same organism (as determined by strain, biotype, or antibiotic sensitivity pattern) as before. The time frame for following patients for relapse varied across studies from 2 days to 3 months. For our analysis, we used 2 weeks after cessation of treatment as a clinically reasonable time period for counting recurrent infections as relapses. Recurrent infections beyond 2 weeks were considered reinfections.[14,21,29]
- *Reinfection* denotes initial bacteriologic cure followed by recurrence of symptoms and infection with a different organism. For studies unable to type organisms, we assumed that any recurrence >2 weeks after cessation of treatment represented infection with a new organism. We also assumed that the reinfection rate reflects the extent to which an antibiotic regimen leads to the emergence of resistant organisms in the host.

In many of the studies the results were not presented in a form amenable to extraction. For example, if the authors did not specify the timing of recurrences, we could not include their data in our pooled estimate of treatment failure because recurrent infection >2 weeks after cessation of treatment did not meet our definition of treatment failure. To reflect our interest in recurrences related to emergence of resistant organisms, we defined reinfection as recurrence with a new organism within a month of cessation of therapy or, when typing data were not available, as recurrence between 2 to 4 weeks after cessation of therapy. Therefore, in constructing our pooled estimate of the relative risk (RR) of reinfection, we excluded studies that followed patients <2 weeks, considered recurrences after 1 month as reinfections, or, in the absence of typing data, did not specify the timing of recurrences.

Quality Scoring

We developed a 9-item scoring system to evaluate the quality of the RCTs included in the meta-analysis. The items addressed the following methodologic issues: 1) exclusion of children with anatomic and/or functional urinary tract abnormalities, 2) attempt to distinguish lower from upper UTI by signs and symptoms (fever, vomiting, flank pain, and costo-vertebral angle tenderness) and/or laboratory tests (elevated white blood cell count, blood urea nitrogen, creatinine, erythrocyte sedimentation rate, and C-reactive protein), 3) UTI defined by symptoms and bacteriologic findings, 4) distinction made between persistent infection, relapse with the same organism and reinfection with a different organism, 5) placebo-control for the short-course arm, 6) blinding, 7) method of participant allocation to short and long-course groups, 8) intention to treat analysis, and 9) equal surveillance and duration of follow-up for treatment and control groups.

Statistical Analysis

Reanalyzing the data with intention to treat whenever possible, we calculated the RR of treatment failure and reinfection (with 95% confidence intervals [CIs]) for each individual study comparing short and long-course therapy. We used the Q test to test for heterogeneity of study results.[30] To obtain the pooled RRs with 95% CIs for treatment failure and reinfection, we used the random effects model of DerSimonian and Laird.[31] To determine whether the anatomic level (upper vs lower) of UTI affects the relative efficacy of short- and long-course therapy, we calculated pooled RRs for the subset of studies that attempted to restrict their participants to children with lower UTI. To determine whether there is a dose-response effect for the duration of short-course therapy, we calculated separate pooled RRs for the subset of studies that compared single-dose or single-day therapy with long-course therapy, and the subset of studies that compared 3-day therapy with long-course therapy.

To explore other potential sources of study result heterogeneity, such as study quality and the mean age of the sample, we developed a random-effects regression model[32] that included these variables as covariates. In the meta-regression, the dependent variable was the odds ratio for the outcome of interest

(treatment failure or reinfection) and the independent variables were study quality score and mean age of the sample. In interpreting the results of the meta-regression of mean sample age on the odds ratio of treatment failure, a negative regression coefficient for the mean sample age variable would suggest that as the mean age of a study sample increases, the relative odds of treatment failure with short-course antibiotics decreases. Similarly, a negative regression coefficient for study quality would suggest that as study quality increases, the relative odds of treatment failure with short-course antibiotics decreases.

We investigated the possibility of publication bias affecting our results using Begg's[33] and Egger's[34] tests and a funnel plot, which maps the log standard error against the log odds ratio of individual studies. All statistical analyses were performed using Stata 7.0 (Stata Corporation, College Station, TX).

RESULTS

Table 1 lists the studies included in the meta-analysis (in order of ascending sample size) as well as study characteristics such as sample size, duration and choice of antibiotic in each treatment arm, and the recalculated RRs of treatment failure and reinfection. The pooled estimate for the RR of treatment failure with short-course antibiotic therapy was 1.94 (95% CI: 1.19–3.15; Fig 1) and for the RR of reinfection was 0.76 (95%: CI 0.39–1.47; Fig 2). When we excluded the 3 studies that did not attempt to restrict their participants to patients with lower UTI, the pooled RR of treatment failure was 1.74 (95% CI: 1.05–2.88) and the pooled RR of reinfection was 0.69 (95% CI: 0.32–1.52). When we restricted the meta-analysis to the 11 studies comparing single-dose or

1-day therapy with long-course therapy, the pooled RR of treatment failure was 2.73 (95% CI: 1.38–5.40) and of reinfection was 0.37 (95% CI: 0.12–1.18). For the 5 studies comparing 3-day therapy with long-course therapy, the pooled RR of treatment failure was 1.36 (95% CI: 0.68–2.72) and of reinfection was 0.99 (95% CI: 0.46–2.13).

None of the studies included in the meta-analysis satisfied all of our quality criteria. In fact, only 1 study was placebo-controlled and double-blinded, and only 3 analyzed their results with intention to treat. However, in the meta-regression neither study quality nor mean participant age was significantly associated with the odds ratio of treatment failure or reinfection, in either the complete set of studies or the subset of studies restricted to patients with lower UTI.

A funnel plot of all the included studies suggested that publication bias was not present. Both the Begg's and Egger's tests for publication bias were not significant ($P = .54$ and $P = .22$, respectively), which corroborates this result.

DISCUSSION

In all but 2 of the previous RCTs of short- versus long-course therapy for UTI in children, there was no statistically significant difference in treatment failure rates. Most authors interpreted this failure to achieve statistical significance as evidence that short-course

TABLE 1. RCTs Comparing Short- and Long-Course Antibiotic Therapy for UTI in Children

| Study	Year	Sample Size*	Duration of Short Course	Duration of Long Course	Antibiotic	Treatment Failure RR (95% CI)	Reinfection RR (95% CI)
Bailey and Abbott[27]	1978	10	Single dose	7 d	TMP-SMX	1.33 (0.17–10.25)	†
Khan et al[16]	1981	16	3 d	10 d	Ampicillin, sulfisoxazole, or cephalexin	0.20 (0.01–3.61)	4.00 (0.56–28.40)
Stahl et al[21]	1984	26	Single dose	10 d	Amoxicillin	1.20 (0.34–4.28)	†
Fine and Jacobson[9]	1985	31	Single dose	10 d	Amoxicillin	2.34 (0.53–10.30)	†
Shapiro and Wald[15]	1981	35	Single dose	10 d	Amoxicillin	†	†
Repetto and MacLoughlin[28]	1984	37	Single dose	10 d	Cefotaxime (short); TMP-SMX, nalidixic acid, nitrofurantoin, cephalexin, gentamicin (long)	†	†
Gaudreault et al[17]	1992	40	3 d	10 d	TMP and sulfadiazine	1.00 (0.02–48.09)	2.00 (0.20–20.33)
Pitt et al[20]‡	1982	42	Single dose	7 d	TMP-SMX	2.50 (0.11–58.06)	†
Helin[24]	1984	43	3 d	10 d	cephalexin (short); nitrofurantoin (long)	2.53 (0.25–25.81)	†
Grimwood et al[23]	1988	45	Single dose	7 d	Gentamicin (short); TMP-SMX, amoxicillin, or cephalosporin (long)	2.80 (0.65–12.02)	0.16 (0.02–1.26)
Avner et al[12]	1983	49	Single dose	10 d	Amoxicillin	4.69 (1.13–19.51)	0.52 (0.15–1.85)
Lohr et al[14]	1981	50	3 d	10 d	Nitrofurantoin macrocrystals	1.28 (0.23–7.00)	†
Wallen et al[11]	1983	54	Single dose	10 d	Amikacin IM (short); sulfisoxazole (long)	†	†
McCracken et al[10]	1981	76	1 d	10 d	Cefadroxil	†	†
Nolan et al[18]‡	1989	90	Single dose	7 d	TMP or co-trimoxazole	10.45 (1.40–78.31)	†
Madrigal et al[19]	1988	218	Single dose and 3 d	7 d	TMP/SMX	†	1.39 (0.28–7.01)
Copenhagen[25]	1991	264	3 d	10 d	Sulfamethizole or pivmecillinam (short); sulfamethizole (long)	1.50 (0.68–3.32)	0.61 (0.30–1.25)

TMP-SMX indicates trimethoprim-sulfamethoxazole; IM, intramuscular.
* Sample size based on data extracted for meta-analysis and may differ from number reported in original study.
† Results reported in original study did not permit abstraction of data for redefined outcomes in meta-analysis.
‡ Study did not attempt to exclude children with upper UTI.

3 of 6

Fig 1. RR of treatment failure with short-course antibiotic therapy. Pooled RR = 1.94 (95% CI: 1.19–3.15).
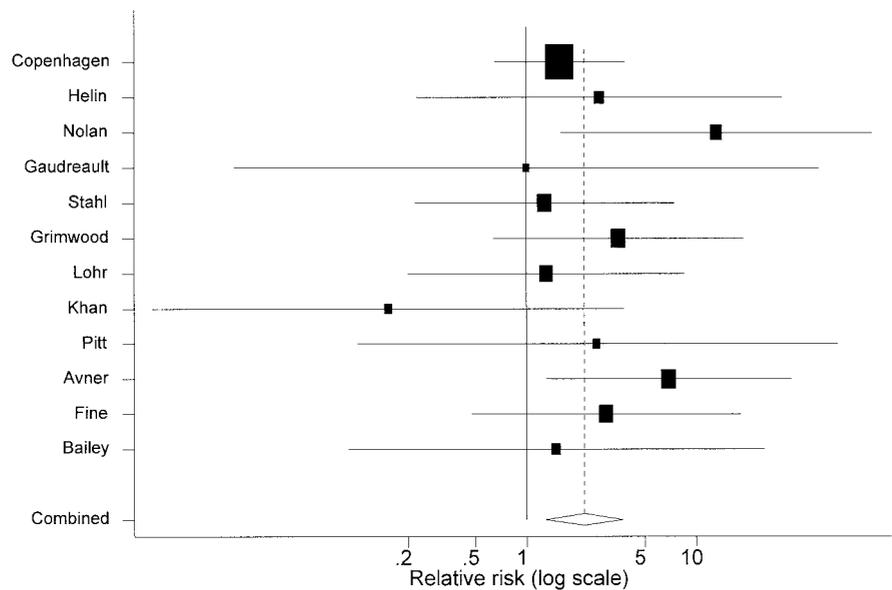
therapy was at least as effective as long-course therapy. An alternative explanation, however, as noted by Shapiro in a 1982 review,[35] is that there was a difference in efficacy but that these studies, because of small sample size, simply did not have the power to detect this difference. This explanation becomes more plausible when one looks at the best estimates of RR for each of the studies: All but 2 of them estimated the RR of treatment failure with short-course therapy as greater than 1.

Meta-analysis is perfectly suited to deal with such situations where there is an obvious trend in study results but each individual study lacks the power to show a statistically significant relationship. When we pooled the results of these nonsignificant studies, we gained sufficient power to show that short-course therapy was indeed associated with a statistically significant 94% increase in treatment failures compared with long-course therapy. Although there was a trend toward increased reinfections with long-course therapy, this result was not statistically significant.

When we pooled the results of the subgroup of studies that attempted to restrict their participants to patients with lower UTI, there was still a 74% increased risk of treatment failure with short-course therapy. The increased risk of treatment failure with short-course therapy in the larger group of studies may be explained, as previously discussed, by the presence of upper tract disease in children at the time of presentation with UTI. The residual increased risk of treatment failure with short-course therapy in the subset of studies that attempted to restrict participants to those with lower UTI suggests that either their methods for distinguishing upper from lower UTI were not accurate, or that cystitis in children also requires long-course treatment. The former explanation is entirely plausible, as the techniques used to distinguish upper from lower tract disease, such as the previously discussed signs and symptoms and/or laboratory tests, suffered from poor discrim-

inatory power.[35] However, the latter explanation cannot be ignored.

Subgroup analysis of studies comparing single dose and single day therapy with long-course therapy suggests that the RR of treatment failure is highest with single dose and single day therapy (RR = 2.73; 95% CI: 1.38–5.40). The pooled RR of treatment failure in the subgroup analysis of studies comparing 3-day and long-course therapy was lower but did not achieve statistical significance (RR = 1.36; 95% CI: 0.68–2.72). This may have been attributable to small sample size, as only 5 studies had data available for the subgroup analysis. However, it may also reflect a dose-response effect, with increasingly "longer" short-course therapy decreasing the probability of treatment failure. The limited number of studies and variation in duration of "short-course" therapy precluded identification of a duration of treatment threshold, above which longer duration of treatment does not improve outcomes.

In deciding which studies to include in the meta-analysis, we chose to use broad inclusion criteria, thus reducing the potential for inclusion bias. Although we did not reject any studies that met our initial entry criteria, we did not use data from studies when the reported results did not conform with the outcomes we defined a priori. Including data from studies that, for example, counted recurrent infections >1 month after treatment as treatment failures would have contradicted our a priori assumptions about treatment failure and reinfection. It is also important to note that our analysis included studies that excluded patients with resistant organisms. Because resistance is often relative and can be overcome with larger doses or longer courses of antibiotics, inclusion of such studies may bias the results toward the apparent effectiveness of short-course therapy. Thus, the risk of treatment failure with short-course therapy may actually be greater than that estimated in our meta-analysis.
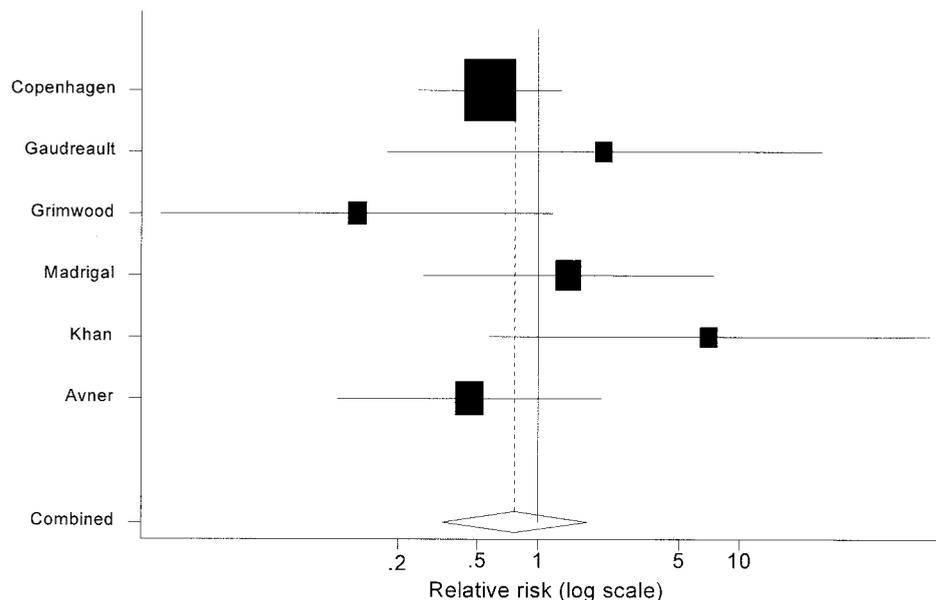
Although there was some variation in study de-

Fig 2. RR of reinfection with short-course antibiotic therapy. Pooled RR = 0.76 (95% CI: 0.39–1.47).

sign and quality, we did not exclude any studies for quality concerns alone. Determining the impact of study quality on meta-analysis results is important, but there is considerable controversy on how to do so.[36–38] We chose to use a cumulative quality score incorporating components of methodology common to all RCTs as well as items specific to trials of antibiotic therapy for UTI. The fact that the study quality score was not associated with outcomes in the meta-regression can be interpreted in 1 of 3 ways: There is no association of outcome with any of the components in the study quality score; there are associations with 1 or more components, but these components have so little weight that the effects are lost in the summary score; or associations with 2 or more components cancel out so that no association is found with the overall score.[37]

We had also hypothesized that the variation in mean participant age would explain some of the heterogeneity of study results. However, this was not borne out in our meta-regression. Our ability to discern a relationship between participant age and RR of treatment failure with short-course therapy may have been limited by the narrow range of mean participant age among the studies. With the exception of Fine's study of adolescent girls, the mean or median participant ages ranged from 4.2 to 8 years. We maintain our original hypothesis that older children, especially sexually active adolescent females with uncomplicated lower UTI, are likely to resemble their adult peers in their response to short-course antibiotics. However, in the absence of analyses stratified by age or studies with mean participant ages over a wider range of values, it is difficult to prove this hypothesis using meta-analysis.

This meta-analysis provides an empirical basis for the current widespread and recommended practice of treating pediatric UTIs with antibiotics for 7 to 14 days. Given our clinically and statistically significant results, we feel confident that no additional RCTs are needed at this time to address the question of whether short-course antibiotic therapy is sufficient for the treatment of UTI in children. It is possible that in the future there will be a reliable and accurate bedside method for distinguishing upper from lower UTIs. For instance, recent preliminary studies suggest that measurement of serum procalcitonin may have better discriminatory ability than previous methods.[39] If and when more accurate tests are available to distinguish upper from lower UTI, another RCT to evaluate the effectiveness of short-course therapy for lower UTI may be warranted. To avoid the methodologic limitations of previous studies that we reviewed, we propose the following suggestions for the design and reporting of any future RCTs:

1. Participants should be randomly allocated using a random number table or random number generator and allocation sequences should be concealed from investigators and participants.
2. Any exclusions based on a priori criteria should occur before randomization, and an intention to treat analysis should be used in cases of loss to follow-up.
3. To avoid observation bias, both participants and investigators should be blinded to the treatment allocation assignment.
4. To blind both investigators and participants to the allocation assignment (short- vs long-course therapy), children randomized to short-course therapy should receive placebo doses to match the duration of the long-course regimen, after completing their short course of antibiotics.
5. Short and long-course treatment protocols should be appropriate for local antibiotic resistance patterns, but easily generalizable. Investigators may consider testing "longer" short-course antibiotic regimens (between 3 and 7 days duration) to identify a duration of therapy threshold for successful treatment of UTI.

6. Outcome measures and follow-up plans should be clearly defined. Urine cultures should be obtained 2 days after cessation of therapy to demonstrate eradication of the organism, and children should be followed for 1 month for any recurrence of symptoms. All recurrent infections should be typed to distinguish relapse from reinfection. Recurrences should be dated and reported in terms of days from cessation of therapy.

7. Results should be stratified and reported by age, sex, and suspected level of infection to detect effect modification.

REFERENCES

1. Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). *Clin Infect Dis*. 1999;29:745–758
2. Rubin RH, Fang LS, Jones SR, et al. Single-dose amoxicillin therapy for urinary tract infection. Multicenter trial using antibody-coated bacteria localization technique. *JAMA*. 1980;244:561–564
3. Anderson JD, Aird MY, Johnson AM, et al. The use of a single 1 g dose of amoxycillin for the treatment of acute urinary tract infections. *J Antimicrob Chemother*. 1979;5:481–483
4. Benador D, Benador N, Slosman D, Mermillod B, Girardin E. Are younger children at highest risk of renal sequelae after pyelonephritis? *Lancet*. 1997;349:17–19
5. Benador D, Benador N, Slosman DO, Nussle D, Mermillod B, Girardin E. Cortical scintigraphy in the evaluation of renal parenchymal changes in children with pyelonephritis. *J Pediatr*. 1994;124:17–20
6. Hoberman A, Wald ER, Hickey RW, et al. Oral versus initial intravenous therapy for urinary tract infections in young febrile children. *Pediatrics*. 1999;104:79–86
7. McCracken GH Jr. Options in antimicrobial management of urinary tract infections in infants and children. *Pediatr Infect Dis J*. 1989;8:552–555
8. American Academy of Pediatrics, Committee on Quality Improvement, Subcommittee on Urinary Tract Infection. Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. *Pediatrics*. 1999;103:843–852
9. Fine JS, Jacobson MS. Single-dose versus conventional therapy of urinary tract infections in female adolescents. *Pediatrics*. 1985;75:916–920
10. McCracken GH Jr, Ginsburg CM, Namasonthi V, Petruska M. Evaluation of short-term antibiotic therapy in children with uncomplicated urinary tract infections. *Pediatrics*. 1981;67:796–801
11. Wallen L, Zeller WP, Goessler M, Connor E, Yogev R. Single-dose amikacin treatment of first childhood *E coli* lower urinary tract infections. *J Pediatr*. 1983;103:316–319
12. Avner ED, Ingelfinger JR, Herrin JT, et al. Single-dose amoxicillin therapy of uncomplicated pediatric urinary tract infections. *J Pediatr*. 1983;102:623–627
13. Khan AJ, Kumar K, Evans HE. Single-dose gentamicin therapy of recurrent urinary tract infection in patients with normal urinary tracts. *J Pediatr*. 1987;110:131–135
14. Lohr JA, Hayden GF, Kesler RW, et al. Three-day therapy of lower urinary tract infections with nitrofurantoin macrocrystals: a randomized clinical trial. *J Pediatr*. 1981;99:980–983
15. Shapiro ED, Wald ER. Single-dose amoxicillin treatment of urinary tract infections. *J Pediatr*. 1981;99:989–992
16. Khan AJ, Kumar K, Evans HE. Three-day antimicrobial therapy of urinary tract infection. *J Pediatr*. 1981;99:992–994
17. Gaudreault P, Beland M, Girodias JB, Thivierge RL. Single daily doses of trimethoprim/sulphadiazine for three or 10 days in urinary tract infections. *Acta Paediatr*. 1992;81:695–697
18. Nolan T, Lubitz L, Oberklaid F. Single dose trimethoprim for urinary tract infection. *Arch Dis Child*. 1989;64:581–586
19. Madrigal G, Odio CM, Mohs E, Guevara J, McCracken GH Jr. Single dose antibiotic therapy is not as effective as conventional regimens for management of acute urinary tract infections in children. *Pediatr Infect Dis J*. 1988;7:316–319
20. Pitt WR, Dyer SA, McNee JL, Burke JR. Single dose trimethoprim-sulphamethoxazole treatment of symptomatic urinary infection. *Arch Dis Child*. 1982;57:229–231
21. Stahl GE, Topf P, Fleisher GR, Norman ME, Rosenblum HW, Gruskin AB. Single-dose treatment of uncomplicated urinary tract infections in children. *Ann Emerg Med*. 1984;13:705–708
22. Stansfeld JM. Duration of treatment for urinary tract infections in children. *Br Med J*. 1975;3:65–66
23. Grimwood K, Abbott GD, Fergusson DM. Single dose gentamicin treatment of urinary infections in children. *N Z Med J*. 1988;101:539–541
24. Helin I. Three-day therapy with cephalexin for lower urinary tract infections in children. *Scand J Infect Dis*. 1984;16:305–307
25. Short-term treatment of acute urinary tract infection in girls. Copenhagen Study Group of Urinary Tract Infections in Children. *Scand J Infect Dis*. 1991;23:213–220
26. Bailey RR, Abbott GD. Treatment of urinary-tract infection with a single dose of amoxycillin. *Nephron*. 1977;18:316–320
27. Bailey RR, Abbott GD. Treatment of urinary tract infection with a single dose of trimethoprim- sulfamethoxazole. *Can Med Assoc J*. 1978;118:551–552
28. Repetto HA, MacLoughlin GJ. Single-dose cefotaxime in the treatment of urinary tract infections in children: a randomized clinical trial. *J Antimicrob Chemother*. 1984;14:307–310
29. Wientzen RL, McCracken GH Jr, Petruska ML, Swinson SG, Kaijser B, Hanson LA. Localization and therapy of urinary tract infections of childhood. *Pediatrics*. 1979;63:467–474
30. Petitti DB. *Meta-Analysis, Decision Analysis, and Cost-Effectiveness Analysis: Methods for Quantitative Synthesis in Medicine*. New York, NY: Oxford University Press; 1994
31. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188
32. Berkey CS, Hoaglin DC, Mosteller F, Colditz GA. A random-effects regression model for meta-analysis. *Stat Med*. 1995;14:395–411
33. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50:1088–1101
34. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–634
35. Shapiro ED. Short course antimicrobial treatment of urinary tract infections in children: a critical analysis. *Pediatr Infect Dis*. 1982;1:294–297
36. Moher D, Jadad AR, Tugwell P. Assessing the quality of randomized controlled trials. Current issues and future directions. *Int J Technol Assess Health Care*. 1996;12:195–208
37. Juni P, Altman DG, Egger M. Systematic reviews in health care: assessing the quality of controlled clinical trials. *BMJ*. 2001;323:42–46
38. Clarke M, Oxman AD, eds. *Cochrane Reviewers' Handbook 4.0*. Oxford, England: Update Software; 1999
39. Gervaix A, Galetto-Lacour A, Gueron T, et al. Usefulness of procalcitonin and C-reactive protein rapid tests for the management of children with urinary tract infection. *Pediatr Infect Dis J*. 2001;20:507–511

Updated Information & **Services**	including high resolution figures, can be found at: http://pediatrics.aappublications.org/content/109/5/e70
References	This article cites 37 articles, 10 of which you can access for free at: http://pediatrics.aappublications.org/content/109/5/e70#BIBL
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): **Gastroenterology** http://www.aappublications.org/cgi/collection/gastroenterology_sub **Infectious Disease** http://www.aappublications.org/cgi/collection/infectious_diseases_sub
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.aappublications.org/site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: http://www.aappublications.org/site/misc/reprints.xhtml

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

A Meta-analysis of Randomized, Controlled Trials Comparing Short- and Long-Course Antibiotic Therapy for Urinary Tract Infections in Children
Ron Keren and Eugenia Chan

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/109/5/e70

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®