ARTICLE

The Addition of Ceftriaxone to Oral Therapy Does Not Improve Outcome in Febrile Children With Urinary Tract Infections

P. Chris Baker, MD; Douglas S. Nelson, MD; Jeff E. Schunk, MD

Objective: To determine whether the addition of a single dose of ceftriaxone sodium to a 10-day course of trimethoprim and sulfamethoxazole hastens urine sterilization or resolution of clinical symptoms in febrile children with urinary tract infections.

Design: Prospective, single-blind, randomized study.

Setting: Tertiary care children's hospital emergency department.

Patients: Febrile children aged 6 months to 12 years with a presumptive urinary tract infection based on history, physical examination, and urinalysis findings.

Interventions: A history was taken, a physical examination and urinalysis and culture were performed, and a white blood cell count and erythrocyte sedimentation rate were obtained. Children were randomized to receive an intramuscular dose of ceftriaxone then 10 days of trimethoprim-sulfamethoxazole (IM+PO group) or oral trimethoprim-sulfamethoxazole alone (PO group). After receiving study medication, patients were discharged from the hospital to return in 48 hours for a follow-up evaluation and urine culture. Treatment failure was defined as the persistence of a positive culture at 48 hours or the need for hospital admission for intravenous rehydration or antibiotic therapy.

Results: Sixty-nine children were enrolled, 34 in the IM+PO group and 35 in the PO group. The 2 groups were similar at the initial visit with respect to age, sex, clinical degrees of illness, white blood cell count, and erythrocyte sedimentation rate ($P>.05$). At the 48-hour follow-up visit, there were no differences between the 2 treatment groups in resolution of vomiting, fever, general appearance, abdominal tenderness, and hydration state ($P>.05$). There were 9 treatment failures, 4 in the IM+PO group and 5 in the PO group ($P=.93$).

Conclusion: The addition of a single dose of intramuscular ceftriaxone to a 10-day course of oral trimethoprim-sulfamethoxazole for urinary tract infection with fever resulted in no difference at 48 hours in the urine sterilization rate, degree of clinical improvement, or subsequent hospital admission rate.

Arch Pediatr Adolesc Med. 2001;155:135-139

From the Department of Pediatrics, University of Utah School of Medicine, and the Emergency Department, Primary Children's Medical Center, Salt Lake City.

URINARY TRACT infections (UTIs) are common in children, with an 11-year cumulative incidence of 1% in boys and 3% in girls.[1] Short-term complications in infants can include bacteremia and meningitis, and potential long-term sequelae can include renal scarring and nephropathy.[2] It is presumed that prompt initiation of antibiotic therapy can help prevent these sequelae.

Patient age, clinical appearance, reliability of care providers, and whether the patient has cystitis or pyelonephritis can affect therapy choice.[3] Accurate determination of the anatomic site of infection is difficult in children because they often lack the classic localizing signs and symptoms that allow cystitis and pyelonephritis to be differentiated. Radionuclide scanning might allow this distinction to be made, but this examination is not commonly performed in clinical practice. It might be more clinically relevant to categorize children with UTIs based on the presence or absence of fever because patients with fever are more likely to have upper UTI.

Optimal therapy has not been determined for the subset of pediatric patients with UTI and fever. It has been shown that ceftriaxone sodium with oral therapy effectively treats children with UTI and fever, and ceftriaxone is commonly used as an adjunct to oral therapy at our institution.[4] However, it has not been determined whether the addition of ceftriaxone to a standard 10-day course of oral antibiotics is more efficacious than oral therapy alone.

PATIENTS AND METHODS

A prospective, randomized, single-blind study was conducted in the Emergency Department at Primary Children's Medical Center, Salt Lake City, Utah, a tertiary care children's hospital with an annual emergency department census of 30 000 patients. Patients were enrolled between September 1, 1996, and March 31, 1998. Patients were initially enrolled if they were aged 6 months to 12 years, had a temperature greater than 38.0°C, and were diagnosed as having a UTI based on presenting history, physical examination, and urinalysis findings. Patients were excluded if they had a known urologic anomaly, were taking antibiotics, had allergies to study medications, or were clinically unstable. Patients were subsequently included in the final study sample if they had a positive urine culture (as defined later) and were reexamined in 2 days.

At the initial visit, a history was taken, a physical examination and urinalysis were performed, and the following data were collected: white blood cell (WBC) count with differential, erythrocyte sedimentation rate (ESR), and urine culture. Enrolled patients received 10 days of oral trimethoprim-sulfamethoxazole, using a twice-daily 5 mg/kg per dose of the trimethoprim portion. Patients were randomized to receive an intramuscular injection of ceftriaxone, 50 mg/kg (IM+PO group), or no initial intramuscular therapy (PO group). The patient's nurse blindly selected opaque envelopes containing group assignment from a bin. The study medications were provided free as a result of a study grant from Roche Pharmaceuticals, Denver, Colo. Physicians caring for the patients were unaware of study group assignment. At the 48-hour follow-up visit, another clinical assessment, urinalysis, and urine culture were performed. The physician caring for the patient at the follow-up visit usually was not the physician who cared for the patient at the first visit and was aware only that the patient was enrolled in the study. In addition, all patients received a bandage on their thigh regardless of receiving an intramuscular injection.

At the time of revisit, drug adverse effects and compliance were ascertained. Signs or symptoms were attributed to a drug adverse effect if they appeared since treatment began. Compliance was calculated by comparing the number of doses reportedly given to the patient and the number expected in the interval period if dosing instructions had been followed.

A positive urine culture was defined in accordance with published guidelines as single-organism growth of greater than 1×10^5 colony-forming units per high-power field (CFU/HPF) from a clean-catch urine specimen or greater than 1×10^4 CFU/HPF from a catheterized urine sample.[5] Treatment failure was based on microbiologic and clinical criteria and was defined as the persistence of bacterial growth in the follow-up urine culture after 48 hours of treatment or the subsequent need for hospital admission. The decision to admit was left to the discretion of the attending emergency physician, who was blinded to treatment group.

The Mann-Whitney *U* test was used to compare nonparametric continuous data. χ^2 Analysis or the Fisher exact test was used to compare nominal data between groups. Differences were considered statistically significant at $P<.05$ in all analyses. The 95% confidence intervals (CIs) for proportions were calculated using standard statistical techniques.

The hospital's investigational review board approved the study. Written informed consent was obtained from the patients' caregivers at initial enrollment.

We sought to determine whether the addition of a single dose of ceftriaxone to a 10-day course of trimethoprim and sulfamethoxazole impacts 48-hour urine sterilization rates or the need for subsequent hospitalization in children with UTI and fever. We also attempted to identify any clinical and laboratory factors associated with treatment failure.

RESULTS

During the study period, 87 febrile patients were enrolled with a presumptive diagnosis of UTI. Fourteen patients subsequently had no growth in their urine cultures and 4 did not return for follow-up (1 in the PO group and 3 in the IM+PO group; none were eventually hospitalized). The remaining 69 patients constitute the study group. Thirty-five patients were randomized to the PO group and 34 to the IM+PO group. Eight patients seen in the emergency department during the study met entrance criteria but were not enrolled (6 refused enrollment and 2 were not petitioned).

The treatment groups had similar demographic and clinical characteristics (**Table 1**). No differences were seen in clinical measures of initial illness severity. *Escherichia coli* was isolated from the urine culture in 31 (89%) of the PO group and 28 (82%) of the IM+PO group. No difference in *E coli* antibiotic susceptibility patterns was noted between treatment groups: 74% for trimethoprim-sulfamethoxazole(n=26) and 100% for ceftriaxone (n=35). Other organisms isolated were *Proteus mirabilis, Klebsiella pneumoniae,* and *Staphylococcus saprophyticus.*

Overall, there were 9 (13%; 95% CI, 9%-17%) treatment failures: 5 (14%; 95% CI, 8%-30%) from the PO group and 4 (12%; 95% CI, 5%-27%) from the IM+PO group. This failure rate was not different between the 2 groups ($P>.05$). Three of 4 failures in the IM+PO group and 4 of 5 in the PO group were due to bacterial growth in the 48-hour urine cultures. Of those 7 microbiologic failures, 3 were due to lack of antibiotic sensitivity. The other 2 failures, one from each group, resulted from persistent vomiting and inability to take oral medications. Neither of these patients had a positive 48-hour urine culture.

Clinical condition was reassessed at 48 hours in all study patients. There were no significant differences between the 2 treatment groups regarding frequency of vomiting, well appearance, normal hydration, or abdominal tenderness. The average temperature at 48 hours was not different between the PO group (37.3°C) and the IM+PO group (37.2°C) ($P>.05$, by *t* test). All patients were contacted by telephone 1 month after their initial visit. None had repeated infections or hospitalizations.

Table 1. Demographic and Initial Clinical Characteristics of Children in the 2 Treatment Groups*

	PO Group (n = 35)	IM + PO Group (n = 34)	*P*
Age, mean, y	3.8	3.6	.37
Girls	30 (86)	32 (94)	.27
Illness >24 h	26 (74)	25 (74)	.96
Vomiting	21 (60)	18 (53)	.51
Temperature, mean, °C	39.2	39.5	.36
Well appearance	24 (69)	24 (71)	.31
Abdomen tender	16 (46)	15 (44)	.91
Intravenous fluids given	3 (9)	5 (15)	.25
WBC count, mean, $\times 10^9$/L	16.8	16.3	.96
ESR, mean, mm/h	39	45	.21
Escherichia coli cultured	31 (89)	28 (82)	.38
E coli sensitivity			
Trimethroprim-sulfamethoxazole	26 (74)	24 (71)	.93
Ceftriaxone	35 (100)	34 (100)	.97
Growth at 48 h	4 (11)	3 (9)	>.99
Need hospital admission	5 (14)	4 (12)	>.99
Medication compliance	34 (97)	33 (97)	>.99

*Data are given as number (percentage) of patients except where indicated otherwise. PO indicates oral trimethoprim and sulfamethoxazole only; IM + PO, intramuscular ceftriaxone and oral trimethroprim-sulfamethoxazole; WBC, white blood cell; and ESR, erythrocyte sedimentation rate.

Table 2. Clinical Factors in Patients Who Failed Outpatient Treatment and Those Who Did Not*

	Failures† (n = 9)	Nonfailures (n = 60)	*P*
Age, mean, y	3.8	3.7	.95
Boys	6 (67)	7 (12)	<.001
Temperature, mean, °C	39.0	39.3	.25
Vomiting	7 (78)	34 (57)	.26
Well appearance	1 (11)	12 (20)	.60
Abdomen tender	7 (78)	26 (43)	.08
WBC count, mean, $\times 10^9$/L	23.3	16.4	.001
ESR, mean, mm/h	37	42	.96
Urinalysis results			
Nitrites positive	5 (56)	34 (57)	.98
LES >1+	7 (78)	41 (68)	.60
Pyuria >10 WBC/HPF	9 (100)	43 (72)	.15
Bacteriuria >1+	6 (67)	47 (79)	.30

*Data are given as number (percentage) of patients except where indicated otherwise. WBC indicates white blood cell; HPF, high-power field; ESR, erythrocyte sedimentation rate; and LES, leukocyte esterase.
†Failure is based on microbiologic and clinical data as outlined in the "Patients and Methods" section.

The 9 patients who failed outpatient therapy are compared with those whose therapy was successful (**Table 2**). Those failing outpatient treatment were more likely to be boys (67% [n=6] vs 12% [n=7]; $P<.001$) and had higher WBC counts (23.3×10^9/L vs 16.4×10^9/L; $P=.001$). No abnormalities on initial urinalysis were associated with treatment failure.

Signs and symptoms thought to be adverse effects of medication use occurred in 9% of the PO group (3 patients) and 11% (4 patients)of the IM+PO group. This difference was not statistically significant ($P=.96$). Adverse effects consisted of diarrhea and new-onset vomiting, except for some injection site (noncellulitis) erythema at 48 hours in 1 patient in the IM+PO group. Compliance with medication instructions for both groups was 97% at 48 hours.

In an effort to identify a subset of patients that might benefit from the addition of a single intramuscular dose of ceftriaxone, patients were divided to examine subsets with greater degrees of illness. When only patients having a WBC count greater than 20×10^9/L were analyzed (n=16) there was no significant difference in failure rates between the PO and IM+PO groups. Similarly, when only patients with an ESR greater than 40 mm/h were considered (n=18), there was no difference in failure rates between treatment groups. However, when the subset of patients with initial temperature greater than 39°C (n=30) was considered, there were no failures in the IM+PO group compared with 27% in the PO group (n=4) ($P<.05$, by Fisher exact test).

COMMENT

This study compares treatment regimens in febrile children with culture-proven UTI. Rather than performing studies to determine the anatomic location of the UTI, we chose a more practical and universally available clinical grouping based on the presence of fever. Within the study population of febrile children aged 6 months to 12 years with UTI, most can be successfully treated as outpatients. In this study, the addition of a single dose of ceftriaxone at the initiation of outpatient oral therapy did not decrease the failure rate when failure was defined on a microbiologic basis or as the need for hospital admission.

The presenting clinical and laboratory characteristics of the patients in this study were similar to those in 2 recent studies comparing antibiotic regimens for children with UTIs: Dagan et al[6] compared oral cefixime therapy with oral trimethoprim-sulfamethoxazole therapy in children aged 6 months to 13 years and Hoberman et al[7] compared oral cefixime therapy with a regimen of initial 3 days of cefotaxime sodium therapy before beginning oral cefixime administration in children aged 1 to 24 months with UTIs. In our study, girls predominated (90%), as in the studies by Dagan et al[6] (88%) and Hoberman et al[7] (90%). This female gender propensity for UTI is well recognized.[8]

Most of our patients had high fevers on presentation, with a mean temperature of 39.3°C, identical to the mean presenting temperature of children in the study by Hoberman et al.[7] In the study by Dagan et al,[6] the mean initial temperature was lower (38.5°C), but fever was not an entrance criteria in that study. In addition, laboratory indicators such as mean WBC count and mean ESR were similarly elevated in all 3 studies. It has been shown that such significant elevations in these acute-phase reactants often correlate with the presence of pyelonephritis.[6] Hoberman et al[7] showed that those with such elevations in their acute-phase reactants were more likely to have pyelonephritis than simple cystitis. We might infer that many of our patients had pyelonephritis because their presenting mean WBC counts and ESRs were moderately elevated.

Escherichia coli was isolated from 84% of the urine specimens (n=59), consistent with the other pediatric and adult UTI studies.[3-8] Susceptibility to trimethoprim-sulfamethoxazole was 72%, similar to the 85% rate of susceptibility in the study by Hoberman et al[7] but less than the 100% rate found in the study by Cox[9] completed 10 years earlier. Despite in vitro resistance, some antibiotics are concentrated by the kidney, allowing greater in vivo activity. In our study, the urine was sterilized in 48 hours despite in vitro antibiotic resistance in all but one instance.

Treatment regimens using various combinations of oral and parenteral therapy have been used to treat UTIs in children. A previous study by Nelson et al[4] shows that intramuscular ceftriaxone was commonly used at the initiation of outpatient oral therapy for children with UTIs and fever. Similarly, in an adult study,[10] 80% of women with pyelonephritis treated as outpatients received a single parenteral antibiotic (usually gentamicin sulfate or ceftriaxone) at initiation of oral therapy. Dagan et al[11] showed this so-called parenteral-oral switch regimen of antibiotics to be effective for children with pneumonia. Parenteral antibiotics have presumed advantages compared with oral antibiotics and have been recommended in the past for young children with UTIs.[12,13] The American Academy of Pediatrics recommends the parenteral route for certain situations because it ensures optimal antimicrobial levels early in the illness.[8]

The theoretical rationale for the addition of parenteral ceftriaxone for outpatient treatment of UTI with fever is clear. Ceftriaxone provides excellent coverage for the typical urinary pathogens found in the pediatric age group and adds only a modest amount of risk to already low-risk therapy. Children with fever and UTI frequently vomit, and successful administration of oral medications cannot be ensured. Parenteral dosing provides guaranteed antibiotic coverage for the first day of therapy, after which oral medications might be better tolerated.

Despite these theoretical advantages, administration of a single dose of parenteral ceftriaxone at the initiation of oral antibiotic therapy for febrile children with UTIs showed no added benefit. Our study showed that the PO and IM+PO regimens had equal rates of clinical and microbiologic success. This lack of benefit from parenteral therapy of UTIs in children echoes the results obtained in a recent study by Hoberman et al[7] that used different antibiotics. In that study,[7] there was no difference in clinical or bacteriologic improvement between those receiving 14 days of oral cefixime and those receiving an initial 3 days of intravenous cefotaxime followed by 11 days of oral cefixime. Both treatment groups had fever defervesence and urine sterilization at 24 hours. Furthermore, the study by Hoberman et al[7] showed no difference in the amount of renal scarring 6 months after the initial infection.

The overall treatment failure rate (13%) in our study was similar between the 2 treatment groups. Pinson et al[10] showed that 12% of women with pyelonephritis returned for parenteral antibiotic treatment or hospital admission after receiving an initial parenteral dose of antibiotics preceding oral trimethoprim-sulfamethoxazole administration. Determining an acceptable failure rate depends on the disease, the potential complications, morbidity and suffering, and sequelae related to delays in efficacious therapy. A trial of outpatient oral therapy for febrile children with UTIs seems justified and safe. Only 3% (1/35) of the children in the PO group required subsequent hospitalization, and 11% (4/35) did not have sterile urine at 48 hours.

It would be ideal for the clinician to identify factors at presentation that could predict those who are at greater risk for outpatient treatment failure. Patients who failed outpatient therapy were significantly more likely to have a high WBC count and to be boys. Higher WBC counts might suggest increased risk for pyelonephritis, which would be more difficult to treat than cystitis. In support of this, Hoberman et al[7] showed that children with pyelonephritis had higher mean WBC counts and ESRs than those with cystitis. Similarly, the presence of fever with UTI has been accepted as a clinical marker for renal parenchymal involvement.[8] This might explain why the addition of ceftriaxone seemed to decrease the treatment failure rate in the subset of children with temperatures greater than 39°C. Our finding that boys failed outpatient therapy more often (66% vs 34%; $P<.001$) is surprising. Until more data exist on this topic, it is difficult to predict outpatient treatment failure based solely on any one presenting factor.

Limitations of this study included its single-blind design. We believed that double-blinding the study with an intramuscular placebo injection would hinder enrollment. There was no long-term patient follow-up, so the recurrence rate is not known and therefore could not be compared between treatment groups. We also were unable to correlate treatment response with anatomic anomalies because imaging studies were not part of the study protocol. Our results might be more useful if the anatomic site of infection were known (cystitis vs pyelonephritis). However, accurate determination of anatomic site is difficult, expensive, and impractical at initiation of therapy. Although a renal parenchymal radionuclide scan would have better defined patients with pyelonephritis to confirm our suspicions that treatment of upper tract infection fails more than does its lower tract counterpart, this would have been more involved. There is good evidence that information easily obtainable at the initial visit (WBC count and ESR) can be correlated with site of UTI.[7] Last, our results show no difference in low rates of adverse outcomes between 2 treatment groups, and therefore the study is limited by sample size. A power analysis based on our sample size suggests that this study achieved a 75% power to detect a true difference of 30% in treatment failure rates.

In conclusion, most febrile children older than 6 months with UTI and fever can be successfully cared for as outpatients. The addition of a single dose of ceftriaxone at the initiation of outpatient oral antibiotic therapy did not impact the need for hospital admission or urine sterilization within 48 hours. Patients with treatment failure were more likely to be boys and had higher WBC counts. Our data suggest that children with a temperature greater than 39°C would be more likely to benefit from initial ceftriaxone dosing, but further investiga-

tion of this subpopulation is needed to clarify this issue. Overall, our data indicated that in febrile children with UTI, the 2 study regimens sterilized the 48-hour urine in 90% of the cases. Additional investigation is needed to determine whether a shorter course of antibiotics (with or without the addition of intramuscular ceftriaxone) would be as efficacious as longer regimens in febrile children with UTI.

Accepted for publication September 11, 2000.

This study was supported by a grant from Roche Pharmaceuticals.

Presented in part at the annual meeting of the Ambulatory Pediatric Association, New Orleans, La, May 1998.

Corresponding author and reprints: P. Chris Baker, MD, 101 Marion Ave, Sausalito, CA 94965 (e-mail: suzannaz@pacbell.net).

REFERENCES

1. Winberg J. Epidemiology of symptomatic urinary tract infections in childhood. *Acta Paediatr Scand Suppl.* 1974;252:1-20.
2. Bachur R, Caputo G. Bacteremia and meningitis among infants with urinary tract infections. *Pediatr Emerg Med.* 1995;11:280-284.
3. Shapiro ED. Infections of the urinary tract. *Pediatr Infect Dis J.* 1992;11:165-168.
4. Nelson DS, Gurr MB, Schunk JE. Management of febrile children with urinary tract infections. *Am J Emerg Med.* 1998;16:643-647.
5. Hellerstein S. Urinary tract infections: old and new concepts. *Pediatr Clin North Am.* 1995;42:1433-1457.
6. Dagan R, Einhorn M, Lang R, et al. Once daily cefixime compared with twice daily trimethoprim/sulfamethoxazole for treatment of urinary tract infection in infants and children. *Pediatr Infect Dis J.* 1992;11:198-203.
7. Hoberman A, Wald E, Hickey RW, et al. Oral versus initial intravenous therapy for urinary tract infections in young febrile children. *Pediatrics.* 1999;104:79-86.
8. 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;4:843-852.
9. Cox C. Cefixime versus trimethoprim-sulfamethoxazole in treatment of patients with acute, uncomplicated lower urinary tract infections. *Urology.* 1989;34:322-326.
10. Pinson AG, Philbrick JT, Lindbeck MD. ED management of acute pyelonephritis in women: a cohort study. *Am J Emerg Med.* 1994;12:271-278.
11. Dagan R, Syrogiannopoulos G, Ashkenazi S, et al. Parenteral-oral switch in management of pediatric pneumonia. *Drugs.* 1994;47(suppl 13):43-51.
12. McCracken GH Jr. Options in antimicrobial management of urinary tract infections in infants and children. *Pediatr Infect Dis J.* 1989;8:552-555.
13. Givner LB. Therapy of acute pyelonephritis from hospital to home. *Semin Pediatr Infect Dis.* 1990;1:349-362.

Books Received for Review

Mehler PS, Andersen AE, eds. *Eating Disorders: A Guide to Medical Care and Complications*. Baltimore, Md: JHU Press; 1999. 241 pp. ISBN 0-8018-6277-9.

Kendall PC. *Childhood Disorders*. Philadelphia, Pa: Psychology Press Ltd; 2000. 229 pp. ISBN 0-86377-609-4.

Osborne RE, Lafuze J, Perkinis D. *Case Analysis for Abnormal Psychology: Learning to Look Beyond the Symptoms*. Philadelphia, Pa: Psychology Press Ltd; 2000. 200 pp. ISBN 0-86377-584-5.

Turecki S, Tonner L. *The Difficult Child*. 2nd ed. New York, NY: Bantam Books; 2000. 302 pp. ISBN 0-553-38036-2.