Oral Versus Initial Intravenous Therapy for Urinary Tract Infections in Young Febrile Children

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ABSTRACT. *Background.* **The standard recommendation for treatment of young, febrile children with urinary tract infection has been hospitalization for intravenous antimicrobials. The availability of potent, oral, third-generation cephalosporins as well as interest in cost containment and avoidance of nosocomial risks prompted evaluation of the safety and efficacy of outpatient therapy.**

Methods. **In a multicenter, randomized clinical trial, we evaluated the efficacy of oral versus initial intravenous therapy in 306 children 1 to 24 months old with fever and urinary tract infection, in terms of short-term clinical outcomes (sterilization of the urine and defervescence) and long-term morbidity (incidence of reinfection and incidence and extent of renal scarring documented at 6 months by ^{99m}Tc-dimercaptosuccinic acid renal scans). Children received either oral cefixime for 14 days (double dose on day 1) or initial intravenous cefotaxime for 3 days followed by oral cefixime for 11 days.**

Results. **Treatment groups were comparable regarding demographic, clinical, and laboratory characteristics. Bacteremia was present in 3.4% of children treated orally and 5.3% of children treated intravenously. Of the short-term outcomes, 1) repeat urine cultures were sterile within 24 hours in all children, and 2) mean time to defervescence was 25 and 24 hours for children treated orally and intravenously, respectively. Of the long-term outcomes, 1) symptomatic reinfections occurred in 4.6% of children treated orally and 7.2% of children treated intravenously, 2) renal scarring at 6 months was noted in 9.8% children treated orally versus 7.2% of children treated intravenously, and 3) mean extent of scarring was ~8% in both treatment groups. Mean costs were at least twofold higher for children treated intravenously ($3577 vs $1473) compared with those treated orally.**

Conclusions. **Oral cefixime can be recommended as a safe and effective treatment for children with fever and urinary tract infection. Use of cefixime will result in substantial reductions of health care expenditures.**

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Received for publication Sep 2, 1998; accepted Feb 1, 1999.

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Pediatrics **1999;104:79–86;** ***urinary tract infection, acute pyelonephritis, therapy.***

ABBREVIATIONS. UTI, urinary tract infection; APN, acute pyelonephritis; IV, intravenous; VCUG, voiding cystourethrogram; DMSA, dimercaptosuccinic acid; VUR, vesicoureteral reflux.

Management of urinary tract infection (UTI) requires early diagnosis and prompt antimicrobial treatment to minimize renal scarring that results from acute pyelonephritis (APN).[1,2] Most pediatric textbooks and review articles recommend that young children be hospitalized, at least initially, to receive intravenous (IV) antibiotics.[3–6] However, oral therapy, if effective in treating the acute infection and preventing the development of scars, would preclude both the costs and risks associated with hospitalization. We therefore undertook a multicenter, randomized clinical trial to compare the efficacy of oral antibiotic alone versus initial treatment with IV antibiotic followed by oral antibiotic, in young children with fever and UTI.

METHODS

Enrollment and Eligibility Criteria

The study was conducted at Children's Hospital of Pittsburgh, Columbus Children's Hospital, Fairfax Hospital for Children, and Children's Hospital, Boston, after approval by the Institutional Review Board at each of these participating institutions. Children aged 1 to 24 months were considered eligible if they 1) had a rectal temperature of ≥38.3°C at presentation or within 24 hours, and 2) were suspected to have a UTI because of the presence of pyuria (≥10 white blood cells per cubic millimeter in an uncentrifuged urine sample) and bacteriuria (≥1 Gram-negative rod per 10 oil immersion fields in a Gram-stained smear of uncentrifuged urine).[7] Final eligibility required that there be a positive urine culture (≥50 000 colony-forming units[CFU]/mL, single pathogen) from a specimen obtained by catheter. Children were excluded if they had 1) a negative urine culture, 2) hypersensitivity to cephalosporins, 3) Gram-positive cocci on the stained urine, 4) an unequivocal alternative source for fever (eg, meningitis), 5) a history of UTI or abnormalities of the urinary tract, 6) received a systemic antimicrobial within 48 hours, or 7) an underlying chronic disease. Eligible children who were judged by the examining physician to be severely ill (eg, systolic blood pressure <60 mm Hg, or capillary refill >3 seconds) were excluded from randomization. However, such children received the same evaluation and monitoring of health status as the remainder of the study children.

Entry Laboratory Observations

The enhanced urinalysis was performed according to a standardized protocol. Uncentrifuged urine was drawn into a

Neubauer hemocytometer by capillary action. White blood cells were counted on one side of the chamber and multiplied by 1.1 to obtain a total cell count per cubic millimeter. Smears were prepared by using 2 drops of uncentrifuged urine on a sterile slide within a standardized marked area of 1.5-cm diameter, air-dried, and Gram-stained.[7,8] Blood was sent for white blood cell count, Wintrobe erythrocyte sedimentation rate, and nephelometric C-reactive protein and aerobic and anaerobic blood culture in Bactec vials. Quantitative urine cultures and antimicrobial susceptibility testing were performed following standardized procedures.

Assignment to Treatment

Subjects were randomized at each site within strata based on age (1–12 or 13–24 months) and duration of fever (<48 or ≥48 hours).

Initial IV Treatment

Children assigned to IV treatment were hospitalized and treated with cefotaxime (Claforan; 200 mg/kg/d, in four divided doses) for 3 days or until the child had been afebrile (rectal temperature, <38°C) for 24 hours, whichever was longer. Subsequently, children received oral cefixime (Suprax; 8 mg/kg, once daily) to complete a 14-day course, followed by prophylaxis with cefixime (4 mg/kg, once daily) for 2 weeks until a voiding cystourethrogram (VCUG) was performed.

Oral Treatment

Children assigned to oral treatment received cefixime for 14 days. On day 1, 16 mg/kg cefixime was given in the emergency department. Subsequently, a daily dose of 8 mg/kg was given for 13 days with two exceptions. First, children between 4 and 8 weeks of age assigned to oral treatment were admitted to the hospital initially to monitor their progress; they received cefixime in the same dosages and were discharged to complete 14 days of cefixime when clinically improved and afebrile. Second, children assigned to oral treatment whose vomiting precluded administration of cefixime were observed for up to 4 hours; oral or IV fluids were given in addition to a trial dose of cefixime. Thereafter, children were either discharged to complete 14 days of cefixime or admitted for fluid therapy (IV or oral) and continued treatment with cefixime until adequate hydration was achieved. After treatment, children were placed on prophylaxis with cefixime as described above.

Evaluation of the Index Episode

A repeat physical examination and urine culture were performed at ~24 hours (18–30 hours). Subsequent evaluation of inpatients was made both on daily rounds and by contacting parents 48 hours after discharge and at 10 days after study entry. Parents of children treated orally were contacted by telephone at 48 hours and 10 days after study entry. All telephone contacts followed a standard protocol. A follow-up outpatient visit was conducted at ~14 days for all children.

Imaging Studies

^{99m}Tc-Dimercaptosuccinic acid (^{99m}Tc-DMSA) renal scans were performed at entry and again 6 months later, using an IV dose of 5 mCi ^{99m}Tc-DMSA per 1.73 m^2 body surface area. APN was defined as focal or diffuse areas of decreased uptake without evidence of cortical loss. Scarring was defined as decreased uptake associated with loss of the contours of the kidney or cortical thinning with decreased volume. If the initial scan showed scarring, outcome scans were classified as changed (more scarring) or not changed. The degree of scarring was assessed quantitatively by outlining the scarred area and calculating its ratio to the total area of the kidney. Scans were interpreted independently by two physician investigators (M.C., M.M.) who were unaware of the child's treatment assignment.[9] Discrepancies were resolved by discussion between the evaluators.

A renal ultrasonogram was performed on the same day as the DMSA scan, and a VCUG at ~4 to 5 weeks. Vesicoureteral reflux (VUR) was graded according to the International Reflux Study Committee.[10] Children with VUR of at least grade 2 were maintained on prophylaxis with either trimethoprim-sulfamethoxazole (5 mg/kg) or nitrofurantoin (2 mg/kg) once daily for 11 months or until the reflux was ≤ grade 1.

Assessment of Compliance

A urine sample obtained at the 2-week visit or at the time of the VCUG was tested by using a bioassay for cefixime. Any detectable cefixime was regarded as evidence of compliance.

Long-Term Follow-Up

All children were followed for 6 months. A history of fever or other signs or symptoms compatible with UTI were elicited during standardized monthly phone calls and interim visits. Specimens for routine urine culture were obtained at 3 and 6 months after entry and at the time of any febrile illness. Children experiencing reinfections were treated, using the same route of administration (oral or IV) to which they had been randomized initially. After a second episode of UTI, children were maintained on prophylaxis, as described above, for 6 months.

Cost of Therapy

The cost of therapy (IV versus oral) was compared on a sample of 40 children enrolled at Pittsburgh by selecting every fifth child per treatment group. Cost included the initial emergency department visit, radiographic studies, repeat urine cultures, and outpatient and inpatient hospital care, and was calculated by multiplying hospital charges for each service by the variable cost to charges. Total cost-to-charge ratios were obtained from the hospital's Medicare Cost Report.

Statistical Analysis

It was estimated that ~30% of children with UTI treated with IV antimicrobials would have renal scarring of some degree at 6 months.[11] To detect an absolute difference of 15% in the incidence of renal scarring between children treated orally (45%) compared with those treated intravenously, at an α value of .05 (one-tailed) and with a power of .80, 128 children per treatment group were needed. An intention-to-treat analysis was used to assess the effectiveness of treatment. For categorical variables, χ^2 or Fisher's exact test were used; for continuous variables, an independent t test was used. To explore for differences in outcome between treatment groups, multiple independent predictor variables (eg, degree of VUR and extent of APN at entry) and their interaction were evaluated in logistic regression models. All statistical assumptions were met for each of the inferential tests used. An α value of .05 was considered to be statistically significant.

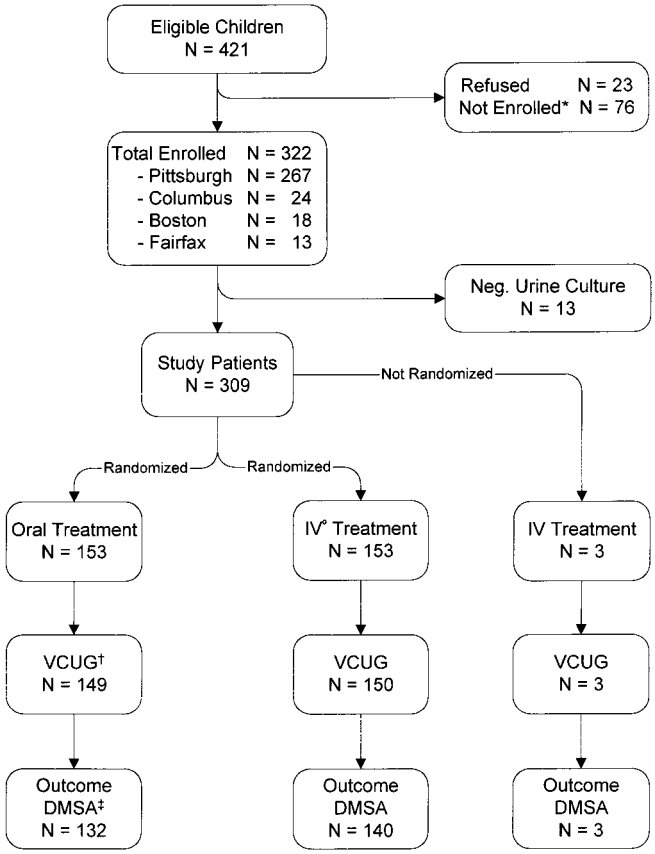
RESULTS

Enrollment and Subject Characteristics

A total of 421 children were eligible for enrollment between January 1992 and July 1997. Enrollment continued throughout the entire study period only at Pittsburgh. Figure 1 describes enrollment and adherence to protocol of all patients eligible for the trial. Demographic and clinical characteristics of children who were randomized are described in Table 1. No significant differences were found between treatment groups.

Imaging Studies

Results of the renal ultrasonogram performed within 48 hours (to be reported elsewhere) did not modify management and were similar in both treatment groups. Table 2 shows results of the initial DMSA renal scan and the VCUG. Although no statistically significant differences between treatment groups were found, a slightly higher incidence of APN at entry was noted among children treated orally compared with those treated intravenously. Only 1 child was noted to have renal scarring at entry. Four of 5 children with grade 4 VUR received



* Not enrolled: investigator unavailable or not notified, prior antibiotics, language barrier, primary care provider refused or out-of-state residence
° IV: intravenous
† VCUG: voiding cystourethrogram
‡ DMSA: Tc^{99}mDimercaptosuccinic acid renal scan

Fig 1. Enrollment and follow-up of children eligible for study.

oral therapy (see Table 2). Children with evidence of APN on initial DMSA renal scan had significantly higher acute-phase reactants (white blood cell count, erythrocyte sedimentation rate, and C-reactive protein) than children with normal initial scans and presumed cystitis (Table 3).

Bacterial Pathogens

Escherichia coli was isolated from the urine of 298 children, *Klebsiella pneumoniae* from 3 children, *Proteus mirabilis* from 3 children, and *K oxytoca* and *Pseudomonas aeruginosa* from 1 child each. Approximately 40% of urinary pathogens were resistant to ampicillin/amoxicillin, 5% were resistant to trimethoprim-sulfamethoxazole, 17% were resistant to cephalexin, two pathogens were resistant to gentamicin, one pathogen was resistant to cefuroxime, and one pathogen was resistant to cefixime.

Short-Term Outcomes

The urine was sterile in all children (291) who had urine cultures obtained within 24 hours of initiating antimicrobial therapy. Defervescence occurred at almost identical times in both treatment groups (Table 4). Only 1 child was unable to tolerate cefixime because of persistent vomiting, and treatment was changed to IV therapy. Bacteremia was documented in 13 children; 5 received oral therapy and 8 received IV therapy. *E coli* was isolated in 12 children and *Streptococcus pneumoniae* from 1 child. Data regarding clinical and laboratory characteristics of children with and without bacteremia are presented in Table 5. Although the clinical appearance of children with and without bacteremia was indistinguishable, children with bacteremia tended to be younger, had a longer duration of fever before administration of antimicrobials and had relatively higher acute-phase reactants than children with negative blood cultures. All children with bacteremia had a repeat blood culture performed within 24 hours that was sterile.

Long-Term Outcomes

The incidence of reinfection was not significantly different in children treated orally compared with

TABLE 1. Distribution of Demographic, Clinical, and Laboratory Characteristics According to Mode of Therapy

Characteristic	Oral Therapy (n = 153)	Intravenous Therapy (n = 153)	P
Age, mo			
Mean (SD)	8.8 (5.9)	8.3 (5.6)	.36
4–7 wk, n (%)	4 (2.6)	9 (5.9)	
8 wk to 11 mo, n (%)	108 (70.6)	100 (65.4)	.31
12–24 mo, n (%)	41 (26.8)	44 (28.8)	
Sex			
Female, n (%)	136 (88.9)	137 (89.6)	1.0
Race			
White, n (%)	114 (74.5)	110 (71.9)	
Black, n (%)	26 (17.0)	34 (22.2)	.39
Other, n %	13 (8.5)	9 (5.9)	
Males circumcised, n (%)	3 (17.6)	7 (43.7)	.14
Temperature at presentation, °C			
Mean (SD)	39.3 (1.0)	39.3 (1.0)	.64
Highest temperature within 24 h, °C			
Mean (SD)	39.7 (0.8)	39.7 (0.8)	.91
Duration of fever, h			
Mean (SD)	48.4 (48.4)	46.5 (45.4)	.39
Peripheral white blood cell count, $\times 10^3/mm^3$			
Mean (SD)	19.7 (7.4)	21.0 (8.6)	.68
Erythrocyte sedimentation rate, mm/h			
Mean (SD)	38.8 (18.1)	40.7 (17.8)	.14
C-reactive protein, μg/mL			
Mean (SD)	9.0 (7.8)	8.6 (10.0)	.96
Positive blood culture, n (%)	5 (3.4)	8 (5.3)	.62

TABLE 2. Results of DMSA Renal Scan (Performed Within 48 Hours of Study Entry) and of VCUG (Performed at 4 Weeks) According to Mode of Therapy

Imaging Results	Number (%) of Subjects		P
	Oral Therapy (n = 153)	Intravenous Therapy (n = 153)	
Initial DMSA renal scan			
Normal	51 (33.3)	64 (41.8)	
Acute pyelonephritis	100 (65.3)	87 (56.9)	.16
Renal scars	0 (0)	1 (0.7)	
Not interpretable	2 (1.3)	1 (0.7)	
Extent (% renal parenchyma, mean)	31.8	29.9	.47
VCUG			
Normal	88 (59.1)	96 (64.0)	
Grade 1 VUR	15 (10.1)	10 (6.7)	
Grade 2 VUR	21 (14.1)	20 (13.3)	
Grade 3 VUR	21 (14.1)	23 (15.3)	.52
Grade 4 VUR	4 (2.7)	1 (0.7)	
Grade 5 VUR	0 (0)	0 (0)	
Not obtained	4	3	

Abbreviations: DMSA, ^{99m}Tc–dimercaptosuccinic acid; VCUG, voiding cystourethrogram; VUR, vesicoureteral reflux.

TABLE 3. Mean Acute-Phase Reactants According to Results of Initial DMSA Renal Scan

Initial DMSA Results	n	PWBC ($\times 10^3/mm^3$)	ESR (mm/h)	CRP (μg/mL)
Acute pyelonephritis	186	22.2	47.5	11.9
Cystitis	111	17.3	28	3.8

Abbreviations: PWBC, peripheral white blood cells; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.
All comparisons, $P < .05$; Wilcoxon rank sum test.

children treated intravenously (5.3% vs 8.5%; P = .28). Symptomatic reinfections (fever, pyuria, and positive urine culture) occurred in 7 children treated orally and in 11 children treated intravenously during the 6-month follow-up period. Episodes of asymptomatic bacteriuria (positive urine culture in the absence of fever and pyuria) occurred in 1 child treated orally and in 2 children treated intravenously (see Table 4).

There was no significant difference between treatment groups in the incidence of new renal scarring, when we included all children, only those who completed the study, or only those with documented APN at entry. In a similar manner, there was no significant difference between treatment groups in extent (severity) of scarring (see Table 4). All children whose initial scan was normal had normal scans at follow-up. Three children were deemed too sick to be

TABLE 4. Clinical Course, Incidence, and Extent of Renal Scarring at 6 Months According to Mode of Therapy and Degree of VUR

Outcomes	Oral Therapy (n = 153)	Intravenous Therapy (n = 153)	P
Defervescence, h			
Mean (SD)	24.7 (23.2)	23.9 (23.3)	.76
Reinfection, n (%)			
None	132 (86.3)	134 (87.6)	
Symptomatic (UTI)	7 (4.6)	11 (7.2)	.28
Asymptomatic (ABU)	1 (0.7)	2 (1.3)	
Lost to follow-up	13 (8.5)	6 (3.9)	
Outcome DMSA renal scan			
Time performance, mo			
Mean (SD)	6.8 (1.5)	6.9 (1.9)	.70
Normal, n (%)	117 (76.5)	129 (84.3)	
Renal scarring, n (%)	15 (9.8)	11 (7.2)	.21
Not obtained, n (%)	21 (13.7)	13 (8.5)	
Incidence of renal scarring in children with APN, % (CI)	16.9 (9.1–24.6)	13.6 (6.1–21)	.18
Extent, % renal parenchyma			
Mean (SD)	7.9 (2.7)	8.6 (5.6)	.41
Scarring according to degree of VUR, n (%)			
No VUR	4/75 (5.3)	6/90 (6.7)	
Grade 1 VUR	2/14 (14.3)	2/8 (25)	
Grade 2 VUR	1/19 (5.3)	2/20 (10)	
Grade 3 VUR	5/20 (25)	1/21 (4.8)	.37
Grade 4 VUR	3/4 (75)	0/1 (0)	
Grade 5 VUR	0 (0)	0 (0)	

Abbreviations: VUR, vesicoureteral reflux; UTI, urinary tract infection; APN, acute pyelonephritis; CI, 95% confidence interval; DMSA, ^{99m}Tc–dimercaptosuccinic acid; ABU, asymptomatic bacteriuria.

TABLE 5. Distribution of Demographic, Clinical, and Laboratory Characteristics According to Results of Blood Culture

Characteristic	Blood Culture Negative (n = 288)	Blood Culture Positive (n = 13)	P
Age, mo			
Mean (SD)	8.5 (5.7)	5.4 (4.4)	.025
4 wk to 6 mo, n (%)	134 (46.5)	10 (76.9)	
7–11 mo, n (%)	74 (25.7)	2 (15.4)	.12
12–24 mo, n (%)	80 (27.8)	1 (7.7)	
Sex			
Female, n (%)	256 (88.9)	12 (92.3)	.89
Race			
White, n (%)	212 (73.6)	8 (61.5)	
Black, n (%)	55 (19.1)	4 (30.8)	.47
Other, n (%)	21 (7.3)	1 (7.7)	
Highest temperature within 24 h, °C			
Mean (SD)	39.7 (0.8)	39.6 (0.9)	.72
Duration of fever before antibiotics, h			
Mean (SD)	47.2 (46.7)	65.8 (52.7)	.18
Duration of fever after antibiotics, h			
Mean (SD)	24 (23)	25.7 (23.7)	.79
Peripheral white blood cell count, $\times 10^3/mm^3$			
Mean (SD)	20.3 (7.8)	24.9 (10.1)	.04
Erythrocyte sedimentation rate, mm/h			
Mean (SD)	40.1 (17.8)	46.1 (17.9)	.38
C-reactive protein, μg/mL			
Mean (SD)	8.8 (8.9)	12.4 (10.4)	.19
APN on initial DMSA scan, n (%)	178 (62.2)	10 (83.3)	.22
VCUG			
No VUR, Grade 1–2 VUR, n (%)	234 (81)	11 (85)	.76
Grade 3–5 VUR, n (%)	54 (19)	2 (15)	
Scarring on outcome DMSA scan, n (%)	26 (10.2)	0 (0)	.61
Symptomatic reinfections, n (%)	16 (6)	3 (23.1)	.05

Abbreviations: APN, acute pyelonephritis; VCUG, voiding cystourethrogram; DMSA, ^{99m}Tc–dimercaptosuccinic acid.

randomized and were removed from study analyses; all had normal outcome scans. The incidence of scarring was identical in children aged <1 year and those aged 1 to 2 years (19 of 198 vs 8 of 74; P = .84), but the duration of fever before initiating treatment was shorter in younger children compared with older children (43 ± 40 vs 57 ± 60 hours, respectively; t test for unequal variances, P = .07). Slightly higher, but not significantly different, incidences of scarring were noted among children who presented for care after at least 24 hours of fever compared with those who presented sooner (19 of 159 vs 9 of 99; P = .29), and among children who defervesced beyond 36 hours of initiating treatment compared with those

who defervesced more promptly (8 of 57 vs 76 of 190; $P = .32$). Renal scarring was significantly more likely to occur in children with VUR than in those without VUR (16 of 107 vs 70 of 165; $P < .03$). When independent predictor variables and their interaction were evaluated by using logistic regression models to determine their influence on scarring, only the degree of VUR was associated significantly with a higher incidence of scarring irrespective of the mode of treatment ($P = .007$).

Compliance

Cefixime was detectable in 159 (85%) of 186 children for whom a urine specimen was available; there was no difference between groups.

Cost of Therapy

Charges and costs of therapy according to treatment modality are presented in Table 6. In the context of our study, charges and costs for inpatient therapy were at least twofold higher than those for outpatient therapy.

DISCUSSION

Our study showed equivalent efficacy of oral cefixime and IV cefotaxime for treatment of young children with fever and UTI. At present in the United States, UTI in young children is treated by one of three regimens, ie, oral therapy for the entire treatment period, parenteral (IV or intramuscular) therapy for the entire period, or a combination of oral and parenteral therapy.[6,12] Previous studies have assessed the treatment of adults and children with fever and UTI with oral antimicrobials. However, these studies have been limited by their lack of evaluation of long-term outcomes,[13–15] lack of comparisons with standard IV therapy,[14–16] and use of relatively insensitive imaging methods, ie, intravenous pyelogram, to detect renal scars.[16]

If we had followed existing guidelines for the evaluation of febrile children, which recommend screening boys for UTI only when aged <6 months,[17] 18 (55%) of 33 boys would not have been identified. Most boys in this study were uncircumcised (23 of 33, 70%), which contrasts with the rate of circumcision in our population (~85%). The small number of male subjects precluded statistical analysis of the association of circumcision status and response to treatment.

Only 3 children were deemed too sick to be randomized and only 1 child was unable to tolerate oral antibiotics because of vomiting. Children with UTI and bacteremia were clinically indistinguishable from children with UTI and negative blood cultures. The low incidence of bacteremia associated with UTI (13 of 298, 4%), and its clearance within 24 hours of initiating oral or IV therapy, prompts us to question the necessity for obtaining routine blood cultures in children with fever who are found to have pyuria on the enhanced urinalysis. In addition, all urine cultures obtained after 24 hours of therapy were sterile, and all but one bacterial isolate recovered from the urine was susceptible to a third-generation cephalosporin. Thus, routine performance of a repeat urine culture when adequate susceptibilities are documented may also be unnecessary. If children are treated with oral therapy, it may be prudent to administer the initial double dose in the outpatient setting to ensure compliance and tolerability, and to maintain close contact with families during the initial phase of therapy. Unfortunately, the unique resistance pattern of Gram-negative organisms in different geographic areas, together with our administration of a double dose of cefixime on day 1, may preclude generalization of study findings to other antimicrobials. With regard to duration of therapy, the recommended standard at the time we initiated our study (1992) consisted of a 14-day course of antimicrobials. Duration of therapy was, therefore, not extended for study purposes. However, in 1999, within the context of a nearly universal desire to limit the use of antimicrobials, we believe a 10-day course of antibiotics is adequate therapy for APN.

Previous studies have identified infants aged <1 year as a group at particularly high risk for renal scarring.[16,18] A more recent report did not confirm this view,[19] but its findings were limited by performance of outcome scans only 2 months after the index infection.[20] Our results also indicate that children aged <1 year were not at higher risk for scarring than those aged between 1 and 2 years. Younger children may have benefited more from earlier diagnosis than older children, as demonstrated by a relatively shorter duration of fever before initiating therapy. Our findings are consistent with the prevailing opinion that scarring is more common when there is either a delay in initiating treatment or when there is a sluggish response to therapy. However, none of these findings achieved statistical significance.

We examined our results to determine if the apparent differences between treatment groups, in incidence of scarring among children with grades 3 and 4 VUR (see Table 4), were statistically significant. It was unfortunate that the randomization schema allocated 4 of the 5 children with grade 4 VUR (3 of whom developed scarring) to oral treatment. Although 8 of 24 children treated orally and only 1 of 22 children treated intravenously developed renal scarring, there was no significant difference in any

TABLE 6. Charges and Costs of Therapy and Follow-Up Imaging Studies According to Treatment Modality

	Charges (Costs, $)	
	Oral Therapy ($n = 20$)	Intravenous Therapy ($n = 20$)
Clinic visit	56 (56)	0 (0)
Emergency department	106 (80)	281 (213)
Laboratory	803 (284)	1,073 (380)
Hospital room	0 (0)	1,747 (1034)
Nursing	0 (0)	1,071 (634)
Medications	70 (66)	570 (374)
Miscellaneous	37 (26)	82 (57)
Renal ultrasound	477 (177)	477 (177)
Voiding cystourethrogram	391 (145)	391 (145)
2 DMSA renal scans	1,690 (629)	1,690 (629)
Total	3,630 (1463)	7382 (3577)

Abbreviation: DMSA, ^{99m}Tc–dimercaptosuccinic acid.

other outcome, specifically, defervescence, incidence of reinfection and extent of scarring. However, 1) our study was not designed and had no power to compare the incidence of renal scarring between small subgroups of children, 2) logistic regression analysis of the entire trial's results excluded treatment as a variable associated with scarring, and 3) the scars identified were relatively small and their long-term implications are unknown. Accordingly, the apparent difference in outcome between treatment groups observed in children with grade 3 and grade 4 VUR was almost certainly caused by chance alone. Furthermore, although the presence and degree of VUR significantly increased the likelihood of renal scarring, documented VUR was not a requisite for scarring.

The incidence of renal scarring reported here is lower (26 of 272, 9.6%) than the 30% previously reported in studies that used DMSA scans to determine outcome.[21–23] The relatively low incidence and small extent of scars in our study may have resulted from the active surveillance for and treatment of UTI in young children with fever that is the practice at participating institutions.[24] The fact that only 1 child had a scar demonstrated on the initial scan, rather than the 11% reported in previous studies,[21] validates the appropriateness of the inclusion and exclusion criteria used to select a group of children with bona fide first-time UTI. The independent, blinded, and contemporaneous interpretation of scans at the end of the study by physicians who 1) are experts in nuclear medicine, 2) used stringent definitions, and 3) were later asked to reach a consensual diagnosis gives us confidence in the final interpretation of the study's primary outcome. The requirement for agreement between interpretations also contributed to the lower rate of scarring because the ultimate rate of positive scans was lower than that reported by a single physician in the context of clinical care.[25]

The long-term implications of small scars identified with renal scintigraphy are unknown. Investigators with studies that reported the association of scarring early in life with the development of hypertension, preeclampsia, renal insufficiency, and end-stage renal disease decades later used intravenous pyelograms, a method substantially less sensitive than DMSA scanning, and almost certainly observed children with extensive rather than minimal parenchymal damage.[26,27] A recent report of women with scarring confirmed that renal function was reasonably well preserved and that the incidence of hypertension was lower than has been reported previously.[28]

Our cost analysis for initial IV therapy of UTI compared with oral therapy was consistent with a 1996 report from the National Association of Children's Hospitals and Related Institutions (average length of hospitalization, 3.65 days; average adjusted charges, $5692). Although cefixime is more expensive than trimethoprim-sulfamethoxazole, its effectiveness against almost all common urinary pathogens may reduce treatment failure and costs associated with repeat treatment. Because follow-up imaging studies accounted for approximately one-half the costs of outpatient therapy, further refinement of the appropriateness of the various imaging techniques will render additional savings. Although this study did not measure other outcomes, it seems plausible to us that outpatient management may have been less traumatic psychologically to the child, less disruptive to the family, and less likely to be associated with nosocomial infection.

As we study the long-term effects (if any) of small renal scars, outpatient management of young children with fever and UTI with oral cefixime can be recommended as a safe and effective treatment that will result in substantial reductions of health care expenditures. Aggressive surveillance for infection of the urinary tract in young febrile children leads to early diagnosis and excellent outcome with either oral or IV therapy with third-generation cephalosporins.

ACKNOWLEDGMENTS

This study was supported by the Biomedical Research Support Grant Program, Division of Research Resources, the General Clinical Research Center Grants at Children's Hospital of Pittsburgh (M01-RR00084), and Children's Hospital, Boston, both from the National Institutes of Health, Bethesda, MD, and by Lederle/Wyeth-Ayerst Laboratories.

We thank Kenneth D. Rogers, MD, for his mentorship and thoughtful advice in the design, conduct, and analysis of the study and in the preparation of this manuscript. We also thank Julia Kearney, BS, William Barson, MD, Mark Mentser, MD, Deborah Miller, RN, and Christopher W. Murray, PhD; the housestaffs at Children's Hospital of Pittsburgh, Columbus Children's Hospital, Children's Hospital, Boston, and Fairfax Hospital for Children; nurses, nurse practitioners, and physician assistants at each of the respective emergency departments; and the staff of the Central Laboratories at Children's Hospital of Pittsburgh for their invaluable assistance.

Two of the authors (A.H. and E.R.W.) have received grants from Wyeth Ayerst Laboratories and are members of its speakers' bureau.

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CHILD SOLDIERS

Virtually unnoticed in the catalog of horrors emanating from Sierra Leone's brutal civil war is the forcible conscription of children, some as young as 7 years old. Kidnapped by rebel forces or drawn into the government's army, they are forced to become soldiers, human shields, spies, porters, and sex slaves.

By some estimates, children now make up between 40% and 50% of the insurgents' total force strength of around 15 000. On the government side, officials admit, children compose one fifth of the 25 000-strong Civil Defense Forces. In Africa, child soldiers have fought or are fighting in Angola, Liberia, Mozambique, Rwanda, the Sudan, Congo and Uganda, as well as Sierra Leone. There are now an estimated 300 000 child soldiers worldwide, a figure that has increased by one sixth during the last 3 years.

Goodwin J. *The New York Times*, February 14, 1999

Noted by JFL, MD

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