

## ORIGINAL ARTICLE

## Short-term effectiveness of ceftriaxone single dose in the initial treatment of acute uncomplicated pyelonephritis in women. A randomised controlled trial

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**Objective:** To compare the short-term effectiveness of ceftriaxone single dose followed by cefixime with a standard treatment of acute uncomplicated pyelonephritis in women.**Methods:** An open, prospective, and randomised trial of women with acute uncomplicated pyelonephritis was performed. Group A were given a daily intravenous dose of 1 g ceftriaxone; group B: ceftriaxone 1 g intravenous single dose followed by oral cefixime. When urine culture was received, both groups completed a 10 day treatment based in sensitivity studies. Only women with positive initial urine culture were included. After three days of treatment, clinical and bacteriological efficacy was assessed. Clinical response was classified as "cured" if acute symptoms (fever, urinary syndrome and flank pain) were settled. Bacteriological response was classified as: eradication, or no eradication.**Results:** Of 144 eligible patients, urine culture was positive in 54 of 72 (75%) women in group A and 51 of 72 (71%) in group B. There were no significant differences between groups in resolution of acute symptoms. Clinical cure was observed in 49 of 54 (91%) patients in the group A and in 47 of 51 (92%) patients in the group B ( $p = 0.68$ ). After three days of treatment urine culture was negative for all patients. No adverse effects were observed in either of the groups.**Conclusion:** These data suggest that a intravenous single dose of ceftriaxone followed by oral cefixime is both effective and safe for the initial treatment of acute uncomplicated pyelonephritis in women. This regimen could be useful in managing selected patients with pyelonephritis as outpatients.

Uncomplicated acute pyelonephritis is defined as an infection of renal parenchyma that occurs in women with otherwise normal urinary tract and absence of compromised immune system. It is extremely common, particularly among sexually active women with approximately 250 000 acute cases occurring each year in the United States.<sup>1</sup> Based on current medicine textbooks and recent reviews of the topic, admission and use of combined parenteral antibiotics has been considered the standard treatment.<sup>2-4</sup> When resolution of acute symptoms is achieved (short-term effectiveness), these women are usually discharged with an antibiotic treatment based on sensitivity studies to avoid relapses (long term effectiveness).<sup>5</sup> However, after reviewing hospitalised adult female patients with pyelonephritis, Safrin *et al* found that immunocompetent women without underlying illness might be treated as outpatients, resulting in potential savings.<sup>6</sup> Despite there being few controlled treatment trials on this subject, some studies have stated that initial parenteral dose loading antibiotic monotherapy in the emergency department (ED) followed by oral therapy is as effective as traditional treatment when assessing long term effectiveness.<sup>7-9</sup> Unfortunately, short-term effectiveness has not been analysed and the question of whether these patients could safely be discharged from the ED remains unclear. Moreover, with such a new approach, it is important to choose an antibiotic regimen with both well demonstrated efficacy in pyelonephritis and long half life to administer once daily. Neither of these conditions has completely been achieved in those previous studies, because of either the increasing resistance of uropathogens to trimethoprim-sulfamethoxazole over the past few years<sup>10</sup> or the use of at least twice daily antibiotic therapy.

In some bacterial infections, the efficacy of monotherapy with third generation cephalosporins has been established in well designed clinical trials.<sup>11,12</sup> Ceftriaxone and cefixime are

widely used third generation cephalosporin antibiotics that have a broad spectrum of bactericidal activity in vivo and in vitro against aerobic Gram positive and Gram negative bacteria.<sup>13,14</sup> They are distinguished from other third generation cephalosporins by their comparatively long half life, so once daily administration is recommended.

The aim of this study is to assess the short-term effectiveness of parenteral ceftriaxone single dose followed by oral treatment with cefixime, and compare it with a standard three day treatment of parenteral ceftriaxone in the initial treatment of uncomplicated acute pyelonephritis in women.

**METHODS****Study design**

This was a prospective, randomised, open trial, which was conducted at the Emergency and Infectious Diseases Departments of an adult tertiary care hospital with 135 000 ED visits per year. The study was performed between September 1996 and January 1998. The study protocol was approved by the ethics committee of the hospital and written informed consent was obtained from all patients.

**Patients**

The inclusion criteria were: women between 18 and 75 years, with presumptive diagnosis of uncomplicated acute pyelonephritis based on a temperature  $>38.0^{\circ}\text{C}$ , urinary syndrome, flank pain, and pyuria (defined as presence of leucocytes  $>8/\text{ml}$  in urinary analysis).

The exclusion criteria consisted of: pregnancy or nursing, presence of urinary catheter, antibiotic treatment in the

**Abbreviations:** AST, aspartate aminotransferase; ALT, alanine aminotransferase; MIC, minimal inhibitory concentration

**Table 1** Patient characteristics at baseline. Results are expressed as mean (SD) values or frequency (percentages)

|   | Group A (n=54) | Group B (n=51) | Mean or proportion difference (95% CI) | p    |
|---|----------------|----------------|--|------|
| Age (y) (mean (SD))                             | 34.9 (15.5)    | 32.7 (14.9)    | 2.2 (-3.7 to 8.1)                      | 0.46 |
| Previous infections                             | 27 (50)        | 24 (47)        | 3 (-1.6 to 22)                         | 0.84 |
| Symptoms duration (days) (mean (SD))            | 3.2 (1.9)      | 3.5 (2.1)      | -0.3 (-1.1 to 0.5)                     | 0.44 |
| Chills  | 48 (89)        | 41 (80)        | 9 (-5 to 22)                           | 0.28 |
| CRP (mg/dl) (mean (SD))                         | 7.1 (5.9)      | 9.8 (12.7)     | -2.7 (-6.5 to 1.1)                     | 0.16 |
| Leucocyte count ( $\times 10^9/l$ ) (mean (SD)) | 12.6 (4.0)     | 11.9 (3.2)     | 0.7 (-0.7 to 2.1)                      | 0.33 |
| AST (U/l) (mean (SD))                           | 24.7 (8.3)     | 27.1 (14.1)    | -2.4 (-6.8 to 2)                       | 0.29 |
| ALT (U/l) (mean (SD))                           | 27.1 (13.4)    | 29.1 (19.8)    | -2 (-8.5 to 4.5)                       | 0.55 |
| Creatinine (mg/dl) (mean (SD))                  | 0.8 (0.2)      | 0.8 (0.1)      | 0 (-0.1 to 0.1)                        | 1.00 |

CRP, C reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

preceding seven days, renal impairment (creatinine  $>2$  mg/dl), urinary tract infection in the preceding 30 days, known functional or structural abnormalities of the urinary tract, known hypersensitivity to cephalosporins. Additionally, patients were further excluded if urine culture was sterile.

Before starting treatment, history of previous urinary tract infections and duration of symptoms and signs (temperature, chills, flank pain and urinary syndrome) were obtained and physical examination was performed. Patients who satisfied the inclusion criteria were admitted and randomised to one of two treatment regimens: group A: ceftriaxone 1 g intravenously once daily until the urine culture was received. Group B: ceftriaxone 1 g single dose intravenously, followed by oral treatment with cefixime 400 mg once daily until the urine culture was received. Then, a 10 day oral antibiotic treatment based on sensitivity studies was completed in both groups. The randomisation process was based on computer generated numbers.

During the hospitalisation no treatments were given that could not have been accomplished at home (apart from intravenous antibiotics in group A).

The patients were discharged when both urine culture was received and they remained afebrile for 24 hours. A follow up visit was scheduled after completion of a 10 day oral treatment.

## Laboratory procedures

### Laboratory variables

At admission, the acute inflammatory response was assessed with C reactive protein, and total white blood cell count. Other laboratory variables as serum creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were also measured both at admission and after the three days of treatment was begun, and used to assess the safety. Any significant change from baseline was noted.

### Urine culture

Voided midstream urine specimens for culture were obtained at admission and after three day treatment was begun. Examination included identification of pathogens, quantification and susceptibility testing. Bacteriuria was defined as  $>10^5$  CFU/ml urine. Bacteria were classified as being resistant to ceftriaxone if minimal inhibitory concentration (MIC) was  $>6$  mg/l. The MIC used for cefixime was 2 mg/l.

### Blood culture

Two blood specimens for aerobic and anaerobic culture were performed at admission. Examination included identification of pathogens and susceptibility testing.

### Assessment of efficacy

The patients were evaluated daily from the admission to the discharge. The short-term effectiveness was assessed by means of both clinical and bacteriological response. The clinical response after three days of treatment, based on the duration of temperature, urinary syndrome and flank pain, was

classified as follows: "cured": resolution of all these clinical symptoms and signs; "improved": normalisation of temperature but persistence of either urinary syndrome or flank pain; "failure": no normalisation of temperature; development of shock at any time; or death.

The bacteriological response after three days of day treatment was classified as: eradication: eradication of the infecting strain. No eradication: persistence of the infecting strain.

### Assessment of safety

Patients who had received at least one dose of the study drugs were included in the safety analysis. Knowledge of adverse events was obtained from spontaneous reports and also by asking the patients for any complaint.

### Statistics

Results were analysed using the SPSS and INSTAT statistical packages. Categorical variables were expressed as percentages and quantitative variables as mean (SD). Comparison between groups was carried out by two ways. Firstly, proportions and means differences with 95% confidence intervals were obtained, and statistical significance was accepted if 95% confidence intervals excluded the value 0. Secondly, categorical variables were compared using the  $\chi^2$  analysis or Fisher's exact test, as appropriate. Quantitative variables were compared using the unpaired Student *t* test with the Welch's approximation if variances were not equal, which was ascertained by Levene's test. Statistical significance was defined as  $p < 0.05$ .

## RESULTS

### Patients characteristics

During the study period, 144 women presenting with presumptive diagnosis of uncomplicated acute pyelonephritis were recruited: 72 received ceftriaxone once daily, and 72 patients received ceftriaxone single dose followed by oral cefixime. The initial urine culture was negative in 39 (27%) women, so 105 patients were entered into efficacy evaluation (54 from the group A and 51 from the group B). Before treatment began, the two groups were well matched with regard to age, history of previous urinary tract infections, duration of symptoms and signs, and laboratory variables (table 1).

### Microbiological findings

The distribution of pathogenic bacteria among the patients in the two study groups is shown in table 2. *Escherichia coli* was the commonest pathogen in urine cultures. Bacteriemia was present in 26 of 105 patients, 14 of 54 from the group A and 12 of 51 from the group B ( $p = NS$ ). *E coli* was grown from all positive blood cultures.

No isolates were classified as resistant to ceftriaxone or cefixime.

**Table 2** Distribution of pathogenic bacteria among two groups. Urine and blood cultures isolates (percentages shown in parentheses)

|                     | Group A (n=54) |               | Group B (n=51) |               |
|---------------------|----------------|---------------|----------------|---------------|
|                     | Urine culture  | Blood culture | Urine culture  | Blood culture |
| <i>E coli</i>       | 54 (100)       | 14 (25.9)     | 48 (94.1)      | 12 (23.5)     |
| <i>P mirabilis</i>  | –              | –             | 2 (3.9)        | –             |
| <i>K pneumoniae</i> | –              | –             | 1 (2)          | –             |

**Table 3** Clinical and bacteriological outcome of the two treatment groups at the third day. Results are expressed as mean (SD) values or frequency (percentage)

|                         | Group A (n=54) | Group B (n=51) | Mean or proportion difference (95% CI) | p    |
|-------------------------|----------------|----------------|--|------|
| Duration (days)         |                |                |  |      |
| Fever                   | 1.6 (0.7)      | 1.7 (0.8)      | –0.1 (–0.4 to 0.2)                     | 0.50 |
| Urinary syndrome        | 1.3 (0.6)      | 1.5 (0.9)      | –0.2 (–0.5 to 0.1)                     | 0.19 |
| Flank pain              | 2 (1.3)        | 2.3 (1.1)      | –0.3 (–0.8 to 0.2)                     | 0.21 |
| Clinical outcome        |                |                |  |      |
| Cured (%)               | 49 (91)        | 47 (92)        | –1 (not calculable)                    | 1.00 |
| Improved (%)            | 3 (6)          | 3 (6)          | 0 (not calculable)                     | 1.00 |
| Failure (%)             | 2 (4)          | 1 (2)          | 2 (not calculable)                     | 1.00 |
| Bacteriological outcome |                |                |  |      |
| Eradication (%)         | 54 (100)       | 51 (100)       | –                                      | –    |
| No eradication          | –              | –              | –                                      | –    |

### Efficacy assessment

The resolution of acute symptoms was achieved in both groups and no significant differences were observed in the duration of the temperature, the urinary syndrome and flank pain.

The clinical response after the three day treatment was not significantly different between both groups. Three patients from each group were classified as “improved” because of persistence of flank pain. Two patients from the group A and 1 patient from the group B were classified as “failure” because of persistence of temperature. All of them finally recovered when a oral antibiotic based on sensitivity studies was begun.

The bacteriological response was the eradication in all cases from both groups. The efficacy assessment is shown in table 3.

The patients were hospitalised 3.4 (0.3) days in group A compared with 3.3 (0.3) days in group B ( $p=NS$ ). At the 10 day follow up visit, none of them made any complaint related to either the illness or the treatment.

### Safety assessment

No adverse effect was reported for any patient or increase in the serum parameters detected in the treatment groups.

### DISCUSSION

The aim of this trial was to show the short-term effectiveness of an intravenous single dose of ceftriaxone followed by once daily oral cefixime, and compare it with a standard regimen in the initial treatment of acute uncomplicated pyelonephritis in women. Successful clinical and bacteriological response was achieved in both treatment groups at the same time. The data demonstrate that the proposed regimen with oral third generation cephalosporins is efficient, and therefore could be used by emergency physicians as the initial treatment of these patients, when sensitivity studies based on urine cultures are not yet available.

Hospitalisation and administration of combined parenteral antibiotics have constituted the traditional treatment of acute pyelonephritis. This approach continues to be the standard of

care recommended.<sup>2-4</sup> When appropriately treated, the majority of patients hospitalised with pyelonephritis have a favourable outcome. With the advent of third generation cephalosporins that have demonstrated their efficacy in well designed clinical trials,<sup>11,12</sup> an intravenous monotherapy regimen with such antibiotics in hospitalised patients has been considered a valid alternative approach.<sup>15</sup> However, more interestingly, the question has been raised as to whether hospitalisation is necessary for all patients with acute pyelonephritis.<sup>6</sup> Unfortunately, prospective studies in the literature investigating this practice are scarce. In a randomised trial, 120 haemodynamically stable pregnant women were either treated as outpatients with two doses of ceftriaxone followed by 10 days of oral cephalexin, or were hospitalised to receive intravenous cefazolin until they were afebrile for 48 hours and then were discharged. Clinical and bacteriological responses were assessed one week after completion of treatment with similar success rates in both groups.<sup>7</sup> Another prospective but uncontrolled study was conducted by Ward *et al* in which 44 patients with mild to moderate acute pyelonephritis were given two intravenous doses of trimethoprim-sulfamethoxazole at a 12 hour dosing interval in an ED observation unit, followed by a 10 day course of the same antibiotic orally. All patients included did well clinically with a bacteriological cure rate of more than 90%, although percentage of drop out reached 33%.<sup>8</sup> Finally, Millar *et al* have published that outpatient treatment with oral cephalexin is effective and safe in selected pregnant women with pyelonephritis when compared with inpatient management with parenteral cefazolin.<sup>9</sup>

Overall, these studies have shown the usefulness of such therapeutic regimens when the eradication of infecting bacteria is assessed. However, data about early clinical outcome have not been reported. In addition, trimethoprim-sulfamethoxazole treatment is less common because of increased bacteriological resistance, allergy, and poor compliance. A recent study conducted by Talan *et al* has partly resolved this issue, demonstrating that a seven day ciprofloxacin regimen achieves greater bacteriological and clinical

cure rates than a 14 day trimethoprim-sulfamethoxazole regimen in women with acute uncomplicated pyelonephritis treated as outpatients.<sup>16</sup> The clinical cure rate assessed after three days of antimicrobial treatment (short-term effectiveness), was higher in the ciprofloxacin group. However, the duration of acute symptoms was not shown, and the study design did not allow the determination of whether or not those patients would have fared better as inpatients. It is important to show that symptoms resolution in inpatients and outpatients is similar in order to assure effective relief of symptoms when an outpatient regimen is selected. Otherwise, physicians will prefer to admit these patients to avoid clinical failures and re-attendance. This study was designed specifically to simulate outpatient treatment after an initial parenteral antibiotic dose in group B. Treatment was not given during hospitalisation that could not have been accomplished at home. Under these conditions, the results suggest that women with acute uncomplicated pyelonephritis might be treated safely in an outpatient setting with oral antibiotics.

*E coli* was the commonest organism isolated in our study, similar to other studies.<sup>17</sup> Antibiotic resistance is increasing<sup>10</sup> and the usefulness of any antibiotic treatment may be reduced. In our study the bacteria were not resistant to ceftriaxone or cefixime.

Nevertheless, this study has two limitations that should be discussed. Firstly, patient acceptability to an oral antibiotic regimen was good, but it might not have been if patients had been discharged from ED. Secondly, the study was limited to only those patients with bacteriologically proven pyelonephritis. The inclusion of patients who clinically appear to have pyelonephritis when bacteriological assessment is unavailable would be more relevant to ED physicians. However, we felt that it was important to ensure all patients had infections.

In conclusion, our study suggests that the cost and inconvenience of hospitalisation in otherwise healthy women with acute uncomplicated pyelonephritis may be avoided. A larger controlled trial of our treatment regimen is required to confirm our findings. The safety of the proposed regimen would encourage this practice. With the continued emphasis on cost effectiveness, the ED will probably be a pivotal area for the initiation of new therapeutic approaches that change infectious disease management. Therefore, in acute uncomplicated pyelonephritis, there would be no apparent disadvantage in beginning the treatment with a parenteral loading dose of ceftriaxone in ED followed by an outpatient regimen with oral cephalosporin if a close follow up, perhaps including home nursing visits, was assured after discharge from the ED.

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