

## Comparing ceftriaxone and cefazolin for treatment of adult acute pyelonephritis; A clinical trial

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### ABSTRACT

**Background:** Urinary tract infection (UTI) is a major health concern worldwide. The present study was aimed to compare drug resistance to ceftriaxone and cefazolin in adult patients with acute pyelonephritis.

**Patients and methods:** For this clinical trial, patients with fever plus either dysuria, frequency, flank pain or flank tenderness were enrolled. Having performed urinalysis (U/A), urine culture (U/C) and antibiogram, they were randomly assigned in two groups: ceftriaxone 1gr twice a day or cefazolin 1gr trice a day. Three days later, urine was re-evaluated and patients were categorized as clinical and microbiological responders. Chi-square test and Fisher's exact tests were used, when appropriate. Statistical significance was defined as  $p < 0.05$ .

**Results:** Study population included 59 females and 27 males. *Escherichia coli* was the most frequent isolated pathogen (86.0%). Dysuria, flank pain and flank tenderness was more frequent among non-*E. coli*-infected than *E. coli*-infected subjects, however, the difference was solely significant for flank tenderness ( $p = 0.008$ ). Clinical response was observed in 86.1%, 11.6%, and 2.3% of patients 3, 4, and 5 days following the therapy, respectively, however, there was no significant difference between ceftriaxone and cefazolin group. Totally, 93% of patients became culture negative. Rate of microbiological response did not differ significantly between groups.

**Conclusion:** The results demonstrated that clinical and microbiological responses of patients with acute pyelonephritis are not always compatible. Meanwhile, first and third generation cephalosporins have similar efficacy for treatment of uncomplicated patients.

**Keywords:** *Pyelonephritis, Ceftriaxone, Cefazolin.*

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### INTRODUCTION

Urinary tract infections (UTIs) are among the most prevalent infectious diseases and are the cause of more than 7 million physician visits in the United States each year. These infections are diagnosed in 1% to 3% of school-aged girls and in 2% to 8% of pregnant women. Symptomatic

infections in upper urine system are unusually prevalent in pregnancy, while 20%-30% of pregnant women with asymptomatic bacteriuria complicated with pyelonephritis (1). Almost, all of women have at least one episode of UTI in their lifetime (2), however, 25% of women experience symptomatic UTI for one time in their life (3). Furthermore, 10% of men and 30% of women aged >60 years have bacteriuria among whom 30% develop pyelonephritis (4). The following

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complications have been reported after pyelonephritis: renal scar, papillary necrosis, urethral stenosis, inter-renal abscess, perinephric abscess, emphysematous pyelonephritis and chronic renal infections (1,3).

Totally, 80% of acute infections in patients without catheter, urologic disorders and stone, caused by *E. coli* (1). *Proteus*, *klebsiella* and *enterobacteria* are seen more frequently among patients with urologic anomalies, stone and stasis. *Serratia* and *pseudomonas* have important role in nosocomial infections with catheters. Gram-positive organisms, such as *staphylococcus*, and *enterococci* are unusual (1). First and third generation cephalosporins are widely used for treatment of adults pyelonephritis (1,2). Prior investigators have reported different frequency for isolated uropathogens and different sensitivity and resistance to antibiotics (5-11). Nevertheless, *E.coli* was by far the most common uropathogen (6,9,11). Resistance to ceftriaxone was ranged between 1% to as high as 24% and 27.6% (5,7,11).

The present study was aimed to compare the efficacy and safety of ceftriaxone and cefazolin in a group of Iranian adults with acute uncomplicated pyelonephritis.

## PATIENTS and METHODS

This single-blinded clinical trial was performed in Vali-e-Asr hospital in Birjand between September 2006 and September 2008. Patients aged >14 years old with fever plus either dysuria, frequency, flank pain or flank tenderness were enrolled. The following exclusion criteria were applied at baseline: septic shock or septicemia, use of antibiotics in the recent 72 hours, structural or functional abnormalities of the urinary tract, persistent Foley catheterization, anaphylaxia to cephalosporins and penicillins, pregnancy, and known immunocompromised state. Moreover, patients with negative initial urine culture were excluded.

Having explained our aim, our patients were requested to fill an informed consent, then 10cc middle urine sample was collected by midstream clean-catch, and sent to laboratory for urine analysis (U/A), culture (U/C) and antiobiogram in usual temperature. All urine analysis and cultures were achieved by an expert microbiologist in agar and EMB media. A positive culture was defined as isolation of an uropathogen in quantities of  $>10^5$  colony forming units (CFU). Pyuria was defined as  $>10$  leukocytes/  $\text{mm}^3$  of urine.

Patients were randomly allocated into 2 groups. One group received intravenous ceftriaxone 1gr every 12 hours and the other group received cefazolin 1gr every 8 hours.

Physical examinations were achieved carefully. Body temperature was measured sublingually twice a day while dysuria, frequency, flank pain and flank tenderness were assessed once a day.

Urine analysis and culture were re-evaluated 3 days following the therapy and when patients became afebrile. Meanwhile, when patients became afebrile intravenous antibiotics were changed to oral cephalixin 500mg/qid or cefixime 200mg/bid and continued till day 14<sup>th</sup>. However, if signs and symptoms were not resolved after 72 hours, intravenous antibiotic would continue until he/she became afebrile unless antibiogram revealed resistance to the prescribed antibiotic.

Patients who became afebrile after 72 hours were classified as clinical responders and those with negative urine culture after 72 hours were categorized as microbiologic responders.

Data were analyzed using SPSS software (version 11.0, SPSS Inc., Chicago, USA) and chi square, t-test and Fisher's exact test were used, when appropriate.  $P<0.05$  was set as the significant level.

## RESULTS

Totally, 93 patients were enrolled among whom 7 were excluded due to urine stone (3 cases),

prostate hyperplasia (2 cases) and nosocomial infections (2 cases). Of 86 patients, 27 (31.4%) were males and 59 (68.6%) were females. Patients were equally assigned in either ceftriaxone or cefazolin group. Mean age of patients did not differ between the ceftriaxone and cefazolin group ( $38.9 \pm 14.3$  vs.  $37.5 \pm 13.9$  years,  $p=0.63$ ). Totally, 74 (86.0%) were infected with *Escherichia coli*, however, the remaining 12 patients were infected with *klebsiella* ( $n=9$ ), and *enterococcus* ( $n=3$ ). Of 74 *E. coli*-infected subjects, 37 (50%) belonged to ceftriaxone group.

Dysuria, frequency, flank pain and flank tenderness were more frequent among non-*E. coli*-infected than *E. coli*-infected subjects, however, the difference was solely significant for flank tenderness ( $p=0.008$ ). Table 1 compares clinical and paraclinical findings between *E. coli*- and non-*E. coli*-infected subjects.

**Table 1.** Comparison of clinical and paraclinical findings between *E.coli*- and non-*E.coli*-infected subjects

Findings	<i>E.coli</i> -infected (n=74)	Non- <i>E.coli</i> -infected (n=12)	P value
Chill	34(45.9)	5(41.7)	0.78
Flank pain	36(48.6)	8(66.7)	0.25
Flank tenderness	16(21.6)	7(58.3)	0.008
Dysuria	32(43.2)	6(50.0)	0.66
Frequency	23(31.1)	4(33.3)	0.88
Bacteriuria	59(79.7)	11(91.7)	0.29
WBC cast	15(20.3)	5(41.7)	0.11
Nitrit	20(27.0)	7(58.3)	0.03

Totally, clinical response was observed in 86.1% of patients, however, 11.6% and 2.3% became afebrile on days 4 and 5, respectively. Patients receiving ceftriaxone averagely became afebrile after  $2.63 \pm 0.95$  days in comparison with  $2.77 \pm 0.81$  days in cefazolin group ( $p=0.47$ ). Totally, 93% revealed to be microbiologic responders. Of 3 non-responders to ceftriaxone, 2 were infected with *Klebsiella pneumoniae* and one with *enterococcus*.

Totally, 89.2% ( $n=33$ ) of *E. coli*-infected and 100% ( $n=6$ ) of non-*E. coli*-infected subjects showed clinical response to ceftriaxone, however, these figures were 86.5% ( $n=32$ ) and 50% ( $n=3$ ) for cefazolin group, respectively (table 2).

Surprisingly, 60 (69.8%) and 52 (60.5%) patients represented in vitro sensitivity to ceftriaxone and cefazolin, respectively ( $p=0.2$ ). Table 3 compares in vitro sensitivity to cefazolin and ceftriaxone.

**Table 2.** Comparison of clinical and microbiologic response to ceftriaxone and cefazolin

	Ceftriaxone (n=43)	Cefazolin (n=43)	p-value
Clinical response	39(90.7)	35(81.4)	0.21
<i>E.coli</i> -infected (n=37)	33(89.2)	32(86.5)	0.2
Non <i>E. coli</i> -infected (n=6)	6(100)	3(50.0)	0.18
Microbiologic response	40(93.0)	40(93.0)	1

**Table 3.** Comparison of in vitro sensitivity to cefazolin and ceftriaxone

	Ceftriaxone (n=86)	Cefazolin (n=86)	p
Total (n=86)	60(69.8)	52(60.5)	0.2
<i>E.coli</i> -infected (n=74)	51(68.9)	41(55.4)	0.09
Non <i>E.coli</i> -infected (n=12)	9(75)	11(91.7)	0.59

Agreement between clinical response and in vitro sensitivity was 51.2% in both treatment groups. However, 9.3% of patients who did not respond clinically to ceftriaxone were sensitive to in vitro antibiotic whereas 39.5% of clinical responders were resistant to in vitro antibiotic. However, 11.6% of patients who did not respond clinically to cefazolin were sensitive to in vitro antibiotic whereas 30.2% of clinical responders were resistant to in vitro antibiotic (NS). Thus, drug resistance agreement to ceftriaxone and cefazolin were 51.2% and 58.2%, respectively.

## DISCUSSION

In our study, *E. coli* was isolated from urine samples of 86% of patients, a finding that was in agreement with other studies (1,12,13).

Marcus, Ghiro and Wells have reported *E. coli* as the etiologic agent in 60%, 89.9% and 67.7% of their samples, respectively (14,15,5). In a study conducted by Arrieta on 204 patients with urinary tract infections, 80% were *E. coli*- and *klebsiella*-positive (16), however, Talan and Wing reported *E.coli* in 90% and 79.5% of their patients (17,18).

In our setting, clinical response was found in 86.1% of patients, however, 11.6% and 2.3% became afebrile on days 4 and 5, respectively. Patients receiving ceftriaxone averagely became afebrile after  $2.63\pm 0.95$  days in comparison with  $2.77\pm 0.81$  days in cefazolin group (NS). Indeed, 89.2% (n=33) of *E.coli*-infected and 100% (n=6) of non-*E.coli*-infected subjects showed clinical response to ceftriaxone, however, these figures were 86.5% (n=32) and 50% (n=3) for cefazolin group, respectively. Similarly, Wing et al and Sanchez-Ramos et al did not find a significant difference between ceftriaxone and cefazolin group when considering period after which patients became afebrile (18,19). Nevertheless, afebrile state after 72 hours was reported as low as 7.3% in Bogdanov and 15% in Ghiro study to as high as 85% in Marcus study (7,14,15).

Furthermore, 93% of our patients revealed to be microbiologic responders. Of 3 non-responders to ceftriaxone, 2 were infected with *Klebsiella pneumoniae* and one with *entrococcus*. This finding is in agreement with others (15).

Totally, 60 (69.8%) and 52 (60.5%) patients represented in vitro sensitivity to ceftriaxone and cefazolin, respectively. Inappropriate prescription and misuse of antibiotics are probable causes of high resistance to these agents. In a study conducted by Marcus 15% of *Klebsiella* strains were resistant to cefazolin (14), however, Ramson et al have not reported significant differences between treatment failure of ceftriaxone and cefazolin group (19).

Carrie et al demonstrated 22.6% in vitro and 7.5% in vivo resistance to first generation cephalosporins (20).

In conclusion, clinical and microbiological responses of patients with acute pyelonephritis are not always compatible. Meanwhile, first and third generation cephalosporins have similar efficacy for treatment of uncomplicated patients.

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