e-ISSN: 0975-1556, p-ISSN:2820-2643
Available online on www.ijpcr.com
International Journal of Pharmaceutical and Clinical Research 2025; 17(1); 26-29
Original Research Article

Response of Ceftriaxone Resistant Cystitis to Ceftriaxone- A Comparative Pilot Study

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Received: 29-10-2024 / Revised: 28-11-2024 / Accepted: 29-12-2024
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Conflict of interest: Nil

Abstract:
Response to Ceftriaxone was assessed in resistant uncomplicated E. coli UTI cases as Ceftriaxone concentrates more than 10-fold in urinary bladder. 30 subjects were selected out of which 18 were females and 12 males. 14 resistant cases responded with a follow up negative culture and lowering of urinary pus cells and WBC counts whereas 3 resistant cases failed to respond. Out of 4 non-growers, 3 responded to CTO. This brings promise of initial treatment of uncomplicated UTI with Ceftriaxone prior to arrival of culture results.

Keywords: Urinary Tract Infection: UTI; Ceftriaxone: CTO; MIC: minimal inhibitory concentration.

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Introduction

Urinary tract infections (UTI) are a very common human illness affecting 150 million people per year in the world and are known to be notoriously persistent.[1] As many as 50-80% of women in the general population acquire at least one UTI episode during their lifetime. Nitrofurantoin was the first tolerable and effective agent used in the treatment of UTI. The most common manifestation of UTI is acute cystitis (symptomatic infection of bladder) presenting with dysuria, urgency and hesitancy and is far more prevalent among women than among men in the age group of 1-50 years. However, it encompasses a variety of clinical entities including asymptomatic bateriuria, prostatitis and pyelonephritis. Risk factors include female gender, prior UTI, sexual intercourse, vaginal infection, and diabetes. Uncomplicated UTI refers to an infection in female that is confined to urethra or bladder.[2] Extension of infection beyond bladder as implicated by presence of fever or signs and symptoms of systemic illness or any UTI in males constitutes complicated UTI. UTI in patients with anatomic abnormalities, harboring stones or foreign bodies are also considered complicated.

Coliform bacteria's are responsible for most non-nosocomial uncomplicated UTIs with E. coli being the most common (75-90%).[3] They respond well to a variety of oral and IV antibiotics, however nosocomial infections are often due to more resistant pathogens often requiring parenteral antibiotics. Treatment of uncomplicated UTIs is often done empirically; however, complicated UTIs require use of cultures prior to initiation of antibiotic therapy. Presence of pyuria or a colony count of $>10^5$ /mL correlates poorly with the diagnosis. Tissue infections like pyelonephritis require 2 weeks of therapy whereas mucosal infection like urethritis require only 3 days of therapy. Recurrences are common with an average of 2.6 infections per year resulting in clustering of episodes. This may be due to sloughing of protective outer bladder epithelial layer in response to bacterial attachment during acute cystitis or due antibiotic related alteration of normal flora. Vaginal and periurethral mucosal cells from women with recurrent UTIs bind threefold more uropathogens than do mucosal cells without recurrent infection. Mutations in host innate immune response genes also have been implicated in recurrent UTIs.

The majority of men with UTI have functional or anatomic abnormality of the urinary tract, most commonly prostatic hypertrophy. Lack of circumcision increases the possibility of infection. Vaginal ecology is an important environmental factor affecting the risk of UTI in women; anatomic factors like distance of urethra from anus and functional abnormalities like inhibition of ureteral peristalsis and tone in pregnancy also contributes to increased UTI risk. In the majority of UTIs, bacteria establish infection by ascending from the urethra to the bladder. Hematogenous spread accounts for <2% of documented UTIs and usually results from bacteremia caused by relatively virulent organisms like Salmonella and S.aureus.

Adhesins such as P fimbriae and type 1 pilus are important in disease causation. Type 1 pilli are thought to play a key role in initiating cystitis by binding to mannose on the luminal surface of the bladder uroepithelial cells. There is a worldwide increase in the resistance of E. coli to specific antibiotics in common use. Resistance rates of >20% to TMP-SMX and >10% to ciprofloxacin have been documented.

Patients get admitted to our hospital wards with several symptomatic illnesses and are often found to harbor UTI apart from their primary cause of hospitalization. They need empiric treatment according to their potential diagnostic clues (PDC) prior to the availability of investigations and one of such treatment constitutes institution of parenteral Ceftriaxone which is a broad-spectrum antibiotic covering most of the common infective organisms. Ceftriaxone, a semisynthetic broad spectrum third generation cephalosporin group of antibiotic has an average concentration of 151 µg/mL in plasma, 30 minutes after a one-gram intravenous dose which falls to 43 µg/mL after 8 hours and to 28 µg/mL, 12 hours after the dose. The drug is excreted 33-67% in urine as unchanged form with an average urinary concentration of 995 µg/mL, 0-2 hours after a 1g I/V dose falling to 293 µg/mL after 8 hours and to 147 µg/mL, 12 hours after the dose.

Ceftriaxone resistance occurs when the MIC goes above 4 µg/mL, in E. coli and other aerobic bacterias.[4] Though the serum levels remain above 4 µg/mL, in a 12 hourly dosing, the actual concentration at the affected area is often lower due to protein binding, acidic milieu and other pharmacokinetic causes and the drug gets resistant. However, its urinary concentration is much higher than the plasma concentration, often by several folds as Ceftriaxone gets concentrated in the bladder and may prove effective when shown resistant at plasma concentrations. We aim to see whether E. coli in urine with an MIC>4 µg/mL to Ceftriaxone still responds to the drug at a higher bladder concentration.[5]

Aims and Objectives

1. To observe the clinical and lab response to therapy with Ceftriaxone in sensitive and resistant cases of female uncomplicated UTI and male UTIs not known to harbor anatomic defects or catheterized.
2. If the study suggests significant response to the resistant drug, we may suggest for its empiric use prior to the availability of its culture sensitivity report.

Materials and Methods

A. **Study Design:** We did a cross-sectional prospective study with a study period of 12 months (Feb 2023-Jan 2024). Patients getting admitted to the inpatient department of KPCMCH with symptoms of dysuria, urgency and hesitancy without known anatomic defects or instrumentation were included in the study after obtaining their consent.

- **Inclusion Criteria**
  1. Patients having dysuria, hesitancy, and urgency
  2. Age between 14 and 90 years
- **Exclusion Criteria**
  1. Symptoms with fever (fever means infection going above the bladder)
  2. Other systemic medical illness causing fever (will be confounding to the cause)
  3. UTIs caused by organisms other than E. coli
  4. Presence of pregnancy
  5. Known anatomic defects in the urinary tract
  6. Instrumentation and present catheterization within 2 weeks.

B. **Sample Size:** No definite result showing resistance among Ceftriaxone users in UTI is known. It varied from 4%-75% in one Indian study. In our pilot project we took 30 patients and evaluated for resistance outcome.

C. **Methods:** We checked for clinical parameters like pulse, BP and temperature and laboratory parameters like CBC, CRP and urine R/E and C/S. As they vary with time and condition, the parameters were checked at 8 AM prior to intake of any antibiotic. The parameters were rechecked after 72 hours following use of Ceftriaxone in a dose of 1 g twice daily for 3 days.

Response to Ceftriaxone was assessed for both sensitive and resistant cases. Resistant cases were those with either MIC≥4 µg/mL or inhibition at ≤13mm in disk diffusion assay. Growth of organisms other than E. coli was rejected.

Calculation

Quantitative values were compared by paired t test whereas qualitative assays were compared by chi square test. Responders were identified as those who had a negative urine culture after 3 days of CTO therapy.

Table 1: Comparison between responsiveness of CTO in sensitive, resistant and no growth cases

	Sensitive E. coli	Resistant E. coli	No growth	Total
CTO Responsive	8	14	4	26
CTO non-responsive	0	3	1	4

χ^2 =1.69, p=0.1925

Table 2: Comparison of urinary pus cells before and after CTO in CTO resistant and no growth cases that were found to respond

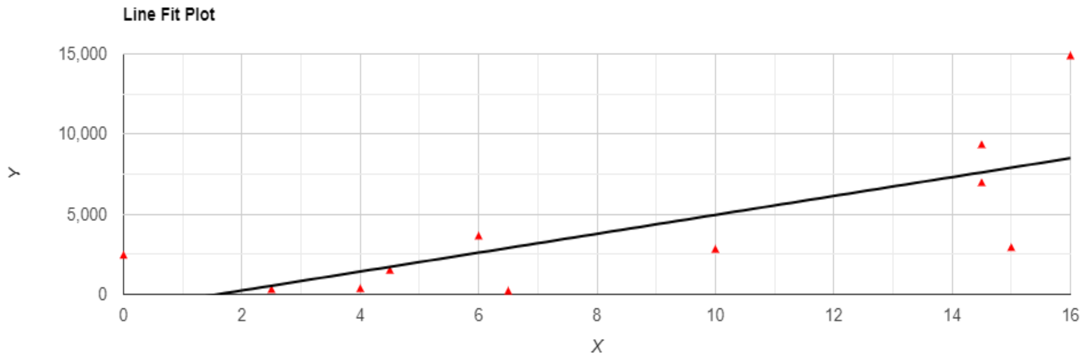
Average of urinary pus cells/hpf before CTO in CTO resistant and no growth responsive cases	Average of urinary pus cells/hpf after CTO in CTO resistant and no growth responsive cases
9	2.5
1.5	1.5
7	2.5
4	1.5
50	11
21	9
17.5	1.5
50	5
13	3
17.5	2.5
4	2.5
1.5	1.5
3.5	1.5
2.5	2.5
17.5	3
12.5	2.5
7.5	3.5
17.5	3

t value 3.1568, p=0.0033

Table 3: Comparison of WBC count before and after CTO in CTO resistant and no growth cases that were found to respond

WBC count before CTO in CTO resistant and no growth responsive cases	WBC count after CTO in CTO resistant and no growth responsive cases
3150	3000
7120	7480
9220	7770
8250	8000
9110	13850
7610	10500
22250	7420
11690	9540
14780	10720
10040	7170
5850	6770
8880	6490
3310	3000
14870	9780
14010	4720
15610	8690
12220	11910
9010	6250

t value 2.2824, p = 0.0356



r=0.7389, p=0.009384

Plot 1: Correlation between, "Reduction of pus cells" in x axis and "Reduction in WBC count" in y axis after CTO infusion for resistant UTI cases.

Discussion

A total number of 30 subjects were included in our study that had symptoms of uncomplicated UTI and included 18 females and 12 males; the youngest of them was 28 and oldest being 86. We got mainly an older population of average age 66 years because of the likelihood of getting admitted with minimal symptoms and chronic geriatric problems, thereby matching to our selection criteria.

The response to CTO was a positive one, though it failed to prove statistical significance (χ^2 =1.69, p=0.1925) we still had 14 responders to CTO originally marked resistant and only 3 of the initially resistant cases failed to respond. Amongst these 3, one developed fever and continued to grow E.coli in culture whereas others grew a mixed growth and enterococci in repeat cultures. One initial no growth grew Klebsiella in repeat culture.

We compared the WBC counts prior to and after 3 days CTO therapy and found a significant lowering of values in initially resistant and no responder cases (t=2.2824, p=0.0356); similarly average of urinary pus cells were compared and yielded highly significant values (t=3.1598, p=0.0033).

We further went to calculate the correlation coefficient between the decreases of WBC count and fall in urinary pus cells in resistant and non-growers and got the value of r=0.7389 after omitting the outliers which was highly significant p=.009384.

We presume that a higher concentration of CTO in bladder may come effective in resistant UTI cases; though we failed to prove significance statistically we had a large number of initially resistant cases responding to CTO and laboratory markers as WBC count and urinary pus cells contributed to significant reductions. Reductions in urinary pus cells correlated well decrease in WBC count. This may suggest use of CTO as initial empirical therapy for uncomplicated UTI cases prior to arrival of culture results. We recommend for a large-scale prospective study for the same in near future.

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