

# Evaluating Sensitivity and Resistance Pattern of Cefazolin and Ceftriaxone Against Different Pathogenic Organisms- A Comparative In-Vitro Analysis

Feroza Perveen<sup>1</sup>, Syed BaqirShyum Naqvi<sup>2</sup>, Asif Khaliq<sup>3</sup>

## Abstract

**Objectives:** To evaluate the zone of inhibition and sensitivity pattern of cefazolin and ceftriaxone against selected pathogenic organisms.

**Methodology:** This was an invitro experimental study that was conducted on clinical isolates of *Escherichia coli*, *Klebsiella* spp., *Proteus* spp., *Pseudomonas aeruginosa* and *Staphylococcus aureus* from urine and pus samples. These samples were collected from four pathological laboratories in Karachi and tested against two commonly used cephalosporins; cefazolin and ceftriaxone from the period of 1st January-27th February 2011. The resistant pattern was determined by disc diffusion method (Kirby-Bauer test). The data was analyzed by Statistical Package for Social Sciences version 19. Mean  $\pm$  SD used for continuous measurements whereas frequencies and percentages were used for categorical variables. Independent sample t-test was applied to see antibiotic sensitivity pattern in urine and pus samples.

**Results:** The results of this study reveal that *Escherichia coli* are the most common uropathogen that was present in more than 35% of samples. The zone of inhibition of Ceftriaxone is greater than Cefazolin for all types of clinical isolates. Moreover, the sensitivity pattern of Ceftriaxone for all the clinical isolates was greater 90.25%, 85.72%, 100%, 75% and 85% to *Escherichia coli*, *Klebsiella* spp., *Proteus* spp., *Pseudomonas aeruginosa*, *Staphylococcus aureus* respectively than does Cefazolin. The pathogenic organisms present in urine were more susceptible to ceftriaxone. The p-value obtained after applying independent sample t-test for ceftriaxone was 0.012. Therefore, a significant difference in the sensitivity pattern of ceftriaxone for pathogens present in urine and pus samples.

**Conclusion:** Ceftriaxone is more effective than cefazolin in most of the cases and there is clear difference in their zone of inhibition. Moreover, resistance to cefazolin develops more easily than for Ceftriaxone. Continuous surveillance, public awareness and health care education can decrease the irrational use of these antibiotics.

**Keywords:** Pathogenic organisms, Resistance, Sensitivity, Zone of Inhibition, Cefazolin, Ceftriaxone, efficacy.

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## Introduction

Antibiotic resistance is one of the major health care concerns worldwide. One of the main reasons for increased antibiotic resistance is irrational prescription and use<sup>1</sup>. This ever-growing issue not only threatens public health, but also significantly impact on economic growth of country by prolonging

recovery time, delayed hospitalizations, specialized care and expensive medicines for patients<sup>2</sup>. The Centers for Disease Control and Prevention (CDC) estimated that in the USA over 35,000 individual expire out of more than 2.5 million antibiotic-resistant infectious diseases annually<sup>3</sup>. Although to optimize use of antimicrobials in 2015, the World Health Organization (WHO) has launched a Global Action Strategy to practice evidence based prescribing through low-cost, rapid and effective diagnostic tools<sup>4</sup>. However, antibiotic resistance is a growing challenge for effective infectious diseases treatment.

<sup>1</sup>Department of Pharmacy, Aga Khan University

<sup>2</sup>Department of Pharmaceutics, University of Karachi

<sup>3</sup>Department of Pediatrics and Child Health, Aga Khan University

**Correspondence:** Dr. Feroza Perveen  
Department of Pharmacy, Aga Khan University

**Email:** feroza.parveen@yahoo.com

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The  $\beta$ -lactam antibiotics, penicillin and cephalosporin are commonly prescribed by the physicians in countries like Pakistan which accounts for 64.5%<sup>5</sup>. Cephalosporins like ceftriaxone and cefazolin is widely use in urinary tract and other infections<sup>6</sup>.

Globally urinary tract infections (UTIs) are among the most common public health problem. UTIs are most frequent infection in lower and lower middle-income countries (LMIC) as compared to other developed countries. UTIs are expected to cause higher adverse outcome with high morbidity, it may be due to less access to medical facilities in LMIC. The Urinary tract infections are very common infections in Pakistan and are caused by different types of bacteria. Around 60% of samples have *Escherichia coli* in their urine sample. Other pathogens in the UTI sample were *Proteus*, *Enterococcus*, *Pseudomonas*, *Staphylococcus* and *Klebsiella*. Another study conducted in Saudi Arabia reported that UTIs are the second foremost infections predominately in females<sup>7</sup>. In UTI infections, often antibiotic treatment is started empirically before the availability of urine culture and susceptibility testing. Appropriate antibiotic use in UTI may improve patient outcome, reduce hospital length of stay and healthcare costs.

After UTI, surgical site infections are the second most common nosocomial infections. Surgical site infection (SSI) has now become a major public health issue and challenge for clinician's worldwide<sup>8</sup>. Regardless the prophylactic use of antibiotics and advancement in surgical techniques, surgical SSI remained a foremost influential factor of morbidity and mortality. Shadowing of SSI is very important to make an appropriate choice of antibiotics to curtail these infections. Pus formation is the foremost sign of surgical site infection. Predominant pathogens for pus infections are *Escherichia coli*, *Klebsiella*, *Pseudomonas* and *Staphylococcus aureus*<sup>9</sup>.

Within the clinical and hospital setting, cefazolin and ceftriaxone are highly prescribed cephalosporins for treating different infections. Al-

though, it is evident that both the antimicrobial agents are effective against *Escherichia coli*, *Staphylococcus aureus*, *Proteus* Species, *Klebsiella pneumonia* and *Pseudomonas aeruginosa*, but the therapeutic efficacy in terms of antimicrobial resistance and sensitivity pattern for urine and pus samples were not evaluated in-vitro. Therefore, we aim to compare the therapeutic efficacy of both of these antimicrobials for common pathogenic organisms present in urine and pus. We conducted this study to evaluate the zone of inhibition and sensitivity pattern of cefazolin and ceftriaxone against selected micro-organisms.

Antibiotics are used for the prevention and treatment of bacterial infections. Antibiotic resistance develops when bacteria modify in response of these medicines' usage. These bacteria may infect animals and humans. The infection caused by resistant bacteria is more difficult to treat as compared to non-resistant bacteria. Antibiotic resistance leads to increased hospital length of stays, increased mortality, and health care costs. There is an urgent need to make strategies to rationalize antibiotics prescribing and usage trend. Without change in behavior, even after development of new antibiotics, antibiotic resistance will remain a major concern globally<sup>10</sup>.

Cephalosporins are among the most commonly prescribed  $\beta$ -lactam antibiotics. Because of it is generally well-tolerated, easy to administer and has broad range of coverage. Cephalosporins are bactericidal in nature and the mechanism of action is inhibition of bacterial wall synthesis<sup>11</sup>.

Cefazolin is 1st-generation parenteral cephalosporins effective against most of gram-positive cocci. It also has good coverage against most strains of *Escherichia coli*, *Klebsiella pneumonia* and *Proteus mirabilis*<sup>11</sup>.

Ceftriaxone is a 3rd generation cephalosporin available in parenteral form used to prevent and treat bacterial infections. It has wide spectrum against gram negative bacteria with some coverage against gram positive bacteria which make it most

commonly consumed antibiotic. Rational use of ceftriaxone with appropriate indication impact on patient outcome<sup>11</sup>.

This study was a comparative in-vitro analysis with the objective of evaluating the sensitivity and resistance pattern of selected antibiotics i.e., Cefazoline and Ceftriaxone, against different clinical isolates.

### Material and Methods

This was an in-vitro experimental study done at Department of Pharmaceutics, University of Karachi, in which convenient sampling technique was used to collect the samples of patients. These samples were collected from four different pathological laboratories located in Karachi from 1st January - 27th February 2011. In this study, two commonly used cephalosporin i.e., cefazolin and ceftriaxone were choose for evaluating the resistance pattern of different clinical isolates of pathogenic bacteria (*Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa* and *Proteus spp*).

In order to carry out the procedure, the inoculum was prepared by touching the top of the colonies with sterile wire loop and suspending in a tube containing broth with different isolates. All the test tubes containing inoculum were then incubated for 2-6 hours until turbidity appears, equal to Macfarland turbidity standard at 37°C. As per the instructions of manufacturer the media was prepared and sterilized. Media was poured into sterile Petri dish about 20-25 ml in each plate. To ensure the uniformity in depth of medium care should be taken to pour the media on a level surface on the plates then plates were allowed to solidify. Sterile swabs were dipped into a broth suspension of organism then the swab was streaked evenly over the surface of medium in three different directions, rotating the plates approximately 60 degrees to confirm that the distribution is even. The appropriate antimicrobial disc of cefazolin and ceftriaxone were placed on the agar surface with the help of sterile forceps. To ensure each disk in contacts with the agar disk must

be lightly pressed and once in place should not move. Each disc was placed in a way that it was about 15 millimeters from the edge of plate and no closer to each other than 25 millimeters from disc to disc.

After disc application within 30 minutes, the plates were inverted and incubated at 37 degrees centigrade for 24 hours. Plates were then examined to ensure the growth, after 18-24 hours was measured the zone of inhibition in millimeter (mm).

Inclusion criteria was pathological isolates containing *Escherichia coli*, *Klebsiella Spp.*, *Proteus Spp.*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* were selected for the study to determine the sensitivity and resistant pattern of Cefazolin and Ceftriaxone.

In a disk diffusion test, one can visualize a series of concentric rings extending out from the disk, each representing a declining concentration of antibiotic. Theoretically, there are concentric areas in the agar where the antibiotics concentration exactly matches those concentrations produced in the broth dilution test.

It should now become clear that there is theoretically a point away from the disk in the diffusion test that exactly matches the "break point" in the broth dilution test. It is exactly this distance that is taken as the "sensitive" zone diameter.

The fallacy of "zone vs. no zone" method of reading disk diffusion test is that the presence of a zone of growth inhibition around a disk indicates that the organism is "sensitive"; however, if the zone is too small, the organism may be "sensitive" only at a very high concentration of antibiotics beyond that which can be achieve in the blood or at the site of infection even using maximum dosage. In a practical sense, the organism is "resistant" even though a zone of growth inhibition is present<sup>12</sup>.

The composition of agar was uniformly controlled from batch to batch so that the microorganism used in quality control testing give virtually identical reactivity from one lot of medium to the next. It is also important that medium be poured to

a uniform depth of 4 mm in the agar dish. If the medium is thinner than this, the antibiotic tends to diffuse from the disc to the greater extent in a lateral direction, increasing the zone sizes; agar deeper than 4 mm, result in more of the antibiotic diffusing downward, with a tendency to artificially narrow the zone of growth inhibition. If the suspension of organism is lighter than the MacFarland No.1 standard, the tube must be re incubated once again. If the turbidity of the organism suspension exceeds that of the standard, sterile saline can be added until the two matches. It is suggested that the swab be streaked in at least three directions, turning the plates at approximately 60-degree angles after each streak. Manufacturers of antibiotic disk must carefully control the concentration of antibiotics within each disk, to within 60 to 20 percent of the stated content, under guidelines established by the Food and Drug Administration. Disk may be purchased in individually packaged vial or in special cartridges designated to fit in to automatic dispensers. All disks not in current use should be stored in a 20°C freezer. Those currently in use should be kept in the refrigerator, preferably in a closed chamber with a desiccant. Disk should be allowed to warm to room temperature before placing on the agar surface. Because the antibiotic concentration may be altered during storage, it is important that all disks be tested with a suitable quality control organism of known reactivity each time the procedure is performed. All vials and cartridges containing antibiotic disks must possess a clearly printed label indicating the exact concentration of antibiotic within the disks and the date of expiration. Laboratory personnel must take care not to use any disks that have exceeded their designated expiration dates. Using incubator with CO<sub>2</sub> should be avoided because carbonic acid can form on the moisturized surface of the agar, resulting in a drop in pH. The growth of some organism is inhibited in an acidic pH, tending to false narrow the zones of the growth inhibition. In laboratories with a small workload where only a CO<sub>2</sub> incubator is available, it is acceptable to place the susceptibility plates in a candle or anaerobic, sealing the lid to

prevent access of the CO<sub>2</sub> with the incubator. Although with some of the more rapidly growing organism the zone of inhibition may be apparent within as early as 4 hours and reasonably accurate preliminary interpretations can be made, the recommended standard method requires that all final measurements should be made at exactly 18 hours. Even most of the slower growing species have developed sufficiently by 18 hours, that an accurate measurement should be made. If interpretation is delayed beyond 18 hours, alterations in the zone's diameter may occur from drying of agar, deterioration, or overgrowth of the bacterial colonies.

The data was entered in excel and analyzed using SPSS version 19. Continuous measurements are presented in Mean ± SD. Categorical variables are presented in frequencies and percentages. Independent sample t-test was applied to see the antibiotic sensitivity pattern in pathological urine and pus samples.

## Results

Out of 100 pathogenic samples of clinical isolates from urine and pus, 66 were of urine and rest of 34 was of pus sample. Among these samples, highest number of samples contain *Escherichia coli* 41% (41) followed by *Staphylococcus aureus* 20% (20), *Klebsiella pneumonia* 14% (14), *Pseudomonas aeruginosa* 20% (20) and *proteus* species 5% (5).

Table 1 is showing zone of inhibition of cefazolin and ceftriaxone of all pathogenic microbes in urine and pus sample. Zone of inhibition of ceftriaxone is higher than does the zone of inhibition of cefazolin for all the clinical isolates except *Pseudomonas aeruginosa*. The detail regarding different microbes for cefazolin and ceftriaxone is presented in Table I.

**Table 1.** Cefazolin and Ceftriaxone zone of inhibition against urine isolates (N=100).

Organism Name*	Cefazolin (mean ± SD)	Ceftriaxone (mean ± SD)
Escherichia coli	22.93 ± 5.12	29.48 ± 5.11
Staphylococcus aureus	26.72 ± 3.13	30.91 ± 4.44
Proteus Species	22.5 ± 2.88	29.6 ± 4.27
Klebsiella pneumonia	25.85 ± 2.17	31.13 ± 2.79
Pseudomonas aeruginosa	31.93 ± 6.74	25.25 ± 3.80

In general, the zone of inhibition of both cefazolin and ceftriaxone was higher in urine sample, but when statistical test were applied. It showed significant difference in the therapeutic efficacy, i.e., Zone of inhibition of ceftriaxone and thus we conclude that all the organism showed great sensitivity against ceftriaxone than does cefazolin.

Table 2 shows the sensitivity and resistance pattern of Cefazolin and Ceftriaxone against Escherichia coli, Klebsiella species, Proteus species, Pseudomonas aeruginosa and Staphylococcus aureus.

**Table 2.** Sensitivity and Resistance Pattern of Cefazolin and Ceftriaxone against Urinary Isolates N=100\*.

Name of Organism	N	Cefazolin		Ceftriaxone	
		Sensitivity	Resistance	Sensitivity	Resistance
Escherichia coli	41	33 (80.49)	8 (19.51)	37 (90.25)	4 (9.75)
Klebsiella spp.	14	11 (78.58)	3 (21.42)	12 (85.72)	2 (14.28)
Proteus spp.	5	4 (80)	1 (20)	5 (100)	0 (0)
Pseudomonas aeruginosa	20	14 (70)	6 (30)	15 (75)	5 (25)
Staphylococcus aureus	20	15 (80)	4 (20)	16 (85)	3 (15)

\*Sensitivity and resistance represented in n (%)

Table 3 shows the p-value obtained after applying independent sample t-test was 0.171 for cefazolin. This value is greater than the value of  $\alpha$  (0.05). Therefore, we fail to reject null hypothesis and conclude that there is no difference in the sensitivity pattern of cefazolin for pathogenic urine and pathogenic pus sample. While the p-value for ceftriaxone obtained after applying independent sample t-test was 0.012. This value is less than the value of  $\alpha$  (0.05). Therefore, we reject null hypothesis and conclude that there is significant difference in the sensitivity pattern of ceftriaxone for patho-

genic urine and pathogenic pus sample. The pathogenic organisms present in urine are more susceptible to antibiotic ceftriaxone.

**Table 3.** Antibiotic sensitivity pattern in pathological urine and pus samples (N=100).

Antibiotic name	Sample collected type	Sample	Mean ± SD	F-value	t	df	p-value
Cefazolin	Urine	66	21.1 ± 10.1	14.33	1.379	98	0.171
	Pus	34	17.6 ± 14.7				
Ceftriaxone	Urine	66	27.0 ± 9.6	6.04	2.559	98	0.012*
	Pus	34	21.1 ± 12.9				

### Discussion

Globally antibiotic resistance and its rapid spread is the most prevalent public health issue. UTIs affect the individual quality of life and result in considerable public health and economic burdens. UTIs cost approximately \$3.5 billion per year alone in the United States<sup>13</sup>.

In this study, highest numbers of pathogenic sample identified were of Escherichia coli, i.e., 41% isolated from urine and pus specimens. Escherichia coli is the most common bacterial uropathogen in the urine. The high prevalence of Escherichia coli in urine sample is also supported by other studies as well<sup>14,15</sup>.

It becomes very important to regularly monitor the resistance patterns of uropathogens, So that antibiotic therapy guidelines can be improved to help physicians in managing UTIs with least therapeutic failures<sup>14</sup>.

In this study there were 80.49% clinical isolates of Escherichia coli that were sensitive to Cefazolin. This result is in confirmation with the work of Yoshifusa Abe et al<sup>16</sup>. They reported that cefazolin is effective in more than 80% of pediatric population with their first febrile UTI. Although they recommended that cefazolin need to be switched to appropriate antibiotics when fever is not subsided within 72 hrs. This shows that cefazolin can be appropriate choice for those UTI patients who are not critically ill. In recent study 2019, Uppala et al also reported promising results of cefazoline in urinary tract infection<sup>17</sup>. These findings shows that to de-

crease antibiotics drug resistance third-generation cephalosporins can be reserved for serious cases. Therefore, more judicious approach is required to prescribe this antibiotic considering short and long-term outcomes and health of patients.

Furthermore, in our study we found that there was significant difference in the sensitivity pattern of ceftriaxone against urine and pus samples as compared to cefazolin. It means that pathogenic organisms were more susceptible to ceftriaxone. The results were in consistent with the previous work done by Chang-Teng et al<sup>18</sup>. They found remarkable coverage of ceftriaxone in urinary tract infection in young children. Ceftriaxone is still found to be effective and safe in UTI infections<sup>19</sup>. Ceftriaxone needs to be prescribed as per updated antibiotic guidelines in UTI infections in order to prevent multidrug resistance. The present situation is alarming, otherwise an effective antibiotic ceftriaxone may fail to treat simple infections.

The resistance to uropathogens is increasing against cefazolin and ceftriaxone day by day. The causes of antimicrobial resistance in developing countries are complex and associated with many factors like lack of diagnostic facilities and health professionals training, practices of inappropriate prescription and inadequate patient education<sup>20</sup>. In developed countries UTI tends to be recover very quickly due to readily health care access and appropriate antibiotic therapy on time and this could decrease the morbidity rate as compared to developed world.

Pakistan is one of LMIC country, self-medication is common practice in population they treat themselves without proper visit and follow-up to physicians. They stop therapy when they feel better without completing the regimen. There is lack of practice of intravenous to per oral (IV to PO) switch after loading dose when patient can tolerate the oral formulation. This along with Self-medication are the precipitating factors to develop drug resistance. Limited laboratory screening, irrelevant diagnostic testing and shortage of antimicrobial drugs may results in ineffective treatment.

There is a need for policy to avert the dispensing of antibiotics over the counter and self-medication which need to be regulated by the government. Strong coordinated action is required among different stakeholders to handle antibiotic resistance<sup>21</sup>. Moreover, the community awareness about the irrational use of antibiotics could also help minimizing the damage. Furthermore, continuous medical education and orientation programs are required to be conducted for medical practitioners as a routine practice to know more about updated antibiotic guidelines and the impact of irrational use of antibiotic on the health and cost of therapy.

Our study highlights the immediate attention as well as the future planning is required to preserve the antimicrobial activity of these antibiotics otherwise these antibiotics will lose their efficacy and could cause a threat to human health. In addition, similar studies need to be conducted periodically on large scale to see the current resistance pattern of clinical pathogens against different antimicrobial agents. So, that the therapy guidelines for antibiotics can be updated to improve patient outcomes and minimal antibiotic misuse.

The current study reveals that ceftriaxone has excellent antimicrobial activity against *Escherichia coli* and *Proteus spp.*, good effectiveness against *Klebsiella spp.*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* as compared to cefazolin. The use of antibiotic must be restricted, and continuous monitoring can decrease the drug resistance.

## Conclusion

Ceftriaxone is more effective than Cefazolin in most of the cases and there is a clear difference in their zone of inhibition. Moreover, resistance to Cefazolin develops more easily than does Ceftriaxone. Persistent surveillance and antibiotic sensitivity testing could help in preventing treatment failures.

## Conflict of Interest

Authors have no conflict of interest and no grant/funding from any organization.

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