In vitro Activity of Ceftolozane/Tazobactam for the Treatment of Complicated Urinary Tract Infections by Escherichia coli in the Era of Antibiotic Resistance “Rejuvenate the mystery”

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Authors’ contributions

This work was carried out in collaboration among all authors. The concept of study, data analysis, drafting, and finalizing of the results were done by author LF. The article was critically reviewed and finally drafted by author AA. Finally reviewed and approved by author SNA. Laboratory/instrument based work was performed under the supervision of author MAUK and assisted by authors SM and HA. All authors read and approved the final manuscript.

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ABSTRACT

Background: Urinary tract infections are found to be commonest bacterial infections across the globe. Various studies have demonstrated high prevalence rate of UTIs in Pakistan. Multiple broad spectrum antibiotics are being used for the treatment of UTI but the resistance by the pathogen against these drugs is increasing worldwide. As the resistance in the organisms is increasing day by day, and it is now hallmark and matter of concern for clinicians to treat uropathogenic E. coli, so there is a pertinent need to explore new sensitive antibiotics or alternative options to manage the disease.

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Aims: To determine the pathogen burden and susceptibility pattern of ceftolozane/tazobactam against MDR E. coli isolates from clinical specimens of urinary tract infections in Karachi.

Study Design: It was an in-vitro clinical study.

Study Settings: The study was conducted in department of Pharmacology, Baqai Medical University and isolates were collected from Microbiology laboratory of Karachi.

Methodology: On the basis of identification methods, one hundred and fifty (150) strains of E. coli were isolated from 650 specimen of urine. Clinical isolates were identified by standard and specific microbiological methods. The antibiotic susceptibility pattern was determined by Kirby Bauer Disc diffusion method. Samples were processed as per procedures defined by Clinical and Laboratory Standards Institute (CLSI) guidelines 2018.

Results: Out of 150 isolates of E. coli, 95 (63.3%) were MDR E. coli. Majority of the cases were obtained from age group 61-80 year (32.6%). Highest sensitivity was seen by ceftolozane/tazobactam (96%) followed by ceftriaxone (88%). Least sensitivity was observed with Imipenem (13.70%). However increased trend of resistance was seen among all empirical used drugs.

Keywords: In vitro activity; ceftolozane/tazobactam; UTI; MDR E. coli.

1. INTRODUCTION

Urinary tract infections (UTI) are the most common bacterial infections encountered in hospitals worldwide [1,2]. After gastrointestinal and respiratory tract infections in developing countries UTI rank at third position [3]. The major etiologic agent of community acquired (80-90%) as well as nosocomial acquired uropathogenic infections (30-50%) is E. coli [4].

Studies conducted in different regions of Pakistan have shown high prevalence rate of UTI [5,6]. Despite UTI is curable but due to multidrug resistant strains, treatment failure and complications are major cause of morbidity and mortality in hospitals. According to Muoneke V et al. about 150 million people are reported with UTI each year, it is estimated that in united states alone approximately 100,000 patients with UTI are admitted in hospitals per year [7]. If it is diagnosed earlier and managed properly UTI rarely leads to complications, but if it remained undiagnosed the organism may reach to kidneys and will lead to serious consequences such as permanent kidney damage (pyelonephritis), urethral stricture from recurrent urethritis and sepsis a life threatening infection [8].

UTI may be reported at any stage of life, particularly young and healthy females are more prone to develop UTI. This may be due to anatomical variation, hormonal changes, use of contraceptive pills, longtime catheterization and decreased frequency of urination during pregnancy [9]. Multiple broad spectrum antibiotics are being used for the treatment of UTI but the resistance by the pathogen against these drugs is increasing worldwide [10,11].

Injudicious and irrational use of empirical antibiotics and lack of surveillance program regarding antibiotics is major cause of emergence of resistance [11].

To the best of our knowledge there is no current data available in Pakistan for the use of 5th generation Cephalosporin antibiotic in infections. As the resistance in the organisms is increasing day by day, and it is now hall mark and matter of concern for clinicians to treat uropathogenic E. coli, so there is a pertinent need to explore new sensitive antibiotics or alternative options to manage the disease. The aim of the study is to determine the prevalence of E. coli in population of Karachi and to evaluate the sensitivity of ceftolozane/tazobactam (C/T) a novel “5th generation Cephalosporin” antibiotic against E. coli.

2. MATERIALS AND METHODS

It was a preclinical, experimental in-vitro study, conducted from January 2019 to June 2019 at Baqai Medical University Karachi. Urine Samples were collected from in-door and out-door patients using non probability technique. Total 1700 suspected UTI patients from first day of life to more than 80 years of age of either sexes were included in this study. Patients were educated regarding the aims of the study by an informed consent form. After their agreement as a participant in study detailed history was recorded on a questionnaire. The clean catch midstream urine samples were collected from participants into a wide mouthed sterile container and were sent to Microbiology Lab for culture and sensitivity. All the samples were processed as per microbiological procedures CLSI Guideline
2018. Urine was inoculated on CLED (cysteine-lactose and electrolyte-deficient) agar. CLED agar is a differential culture medium for isolating and enumerating bacteria in urine from the suspected cases of urinary tract infections. Urine was mixed by rotating the container. With the help of sterile calibrated wire loop, urine was inoculated on MacConkey's agar and the plate was incubated aerobically at 35-37°C overnight, then growth of organism was checked on plate, colony count greater than 100000/ml signified the bacterial growth.

2.1 Antibiotic Sensitivity Test

The antibiotic sensitivity was performed for confirmed pathogenic E. coli by the standard Kirby Bauer’s disc diffusion method and the results were interpreted by the Clinical and Laboratory Standards Institute (CLSI, 2018). Antibiotic discs with different concentrations such as gentamycin (10 ug), amoxicillin (30 ug), ciprofloxacin (5 ug), cotrimaxazole (30 ug), ceftriaxone (30 ug), imipenem (10 ug), moxifloxacin (10ug), C/T (30/10 ug) and cefaclor (30 ug) were tested. Before determination of the results, plates were incubated for 16-24 h at 35°C. The antibiotics were concluded either sensitive or resistant after the measurement of zones of growth inhibition around each antibiotic disc, the procedure were carried out in accordance to CLSI guidelines (2018).

2.2 Statistical Analysis

Data was analyzed by using Statistical Package for Social Sciences (SPSS) version 21. Descriptive analysis for numerical variables were mentioned as Mean with standard deviation. Frequencies and percentages were calculated for categorical variables. Gender, age group and specimen distribution were men 55(36.6%) were non MDR E. coli and 55 (36.6%) were non MDR E. coli. MDR E. coli were predominant in females 55 (57.8%) as compared to males, 40 (42.1%) as shown in Table 1.

Table 1. Showing frequency of MDR and Non MDR strains in males and females

<table>
<thead>
<tr>
<th>Total samples</th>
<th>MDR</th>
<th>Non MDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>55 (57.8%)</td>
<td>30 (54.5%)</td>
</tr>
<tr>
<td>Male</td>
<td>40 (42.1%)</td>
<td>25 (45.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>n = 95</td>
<td>n = 55</td>
</tr>
</tbody>
</table>

The mean age of study participants was 54 years with the standard deviation of 20. Majority of the MDR E. coli cases were reported from age group 61-80 years that was 31 (32.6%) as shown in Table 2.

Table 2. Frequency of MDR E.coli in different age groups

<table>
<thead>
<tr>
<th>Age</th>
<th>MDR</th>
<th>NON MDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month – 20 years</td>
<td>10 (10.3%)</td>
<td>8 (14.5%)</td>
</tr>
<tr>
<td>21 - 60 years</td>
<td>25 (26.3%)</td>
<td>24 (43.6%)</td>
</tr>
<tr>
<td>41 - 80 years</td>
<td>31 (32.6%)</td>
<td>16 (29.0%)</td>
</tr>
<tr>
<td>61 – 80 years</td>
<td>19 (20%)</td>
<td>7 (12.7%)</td>
</tr>
<tr>
<td>80 years and above</td>
<td>10 (10.5%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

MDR E. coli showed increased resistance to almost commonly used antibiotics. Highest resistance was observed with imipenem (86.3%) followed by amoxicillin (85.20%), gentamycin is (80%), cotrimaxazole (72%), ciprofloxacin (65%), cefaclor(61.0%), moxifloxacin (30%), ceftriaxone (12%) and least resistance was observed against C/T that was 4% . The resistance pattern against antibiotics is shown in Fig. 1.

4. DISCUSSION

UTI is a common clinical condition encountered in both the community and health care associated settings. Dromigny et al. reported that among all the causative agents of UTI, E. coli is responsible for about 77-90% of the cases and it is found that the presence of E. coli in gut is a primary source of UTI [12,13]. In our study the prevalence of E. coli was found to be 23%. However in multiple studies conducted in different regions of Pakistan has shown marked prevalence of E. coli. In a study conducted in Kohat and Gilgat the prevalence was found to be 41% and 47.7% respectively [14,15]. Even though this trend is not only prevalent in Pakistan but it has shown high frequency rate around the globe. Studies in Nepal, Kashmir, South India, Uganda has shown a marked increase in frequency of UTIs due to E. coli [16,17,18,19].
Fig. 1. Antibiotic susceptibility pattern of MDR E. coli

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Sensitivity (%)</th>
<th>Resistance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem</td>
<td>13.70</td>
<td>86.30</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>14.80</td>
<td>85.20</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>Co-trimazazole</td>
<td>28</td>
<td>72</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>Cefclor</td>
<td>39</td>
<td>61</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>Ceftrixone</td>
<td>88</td>
<td>12</td>
</tr>
<tr>
<td>C/T</td>
<td>96</td>
<td>4</td>
</tr>
</tbody>
</table>
In this study, out of n=95 (63.3%) MDR strains of *E. coli*, females were more frequently affected 55 (57.8%), as compared to males 40 (42.1%). These finding are parallel to the studies conducted in Gilgat, Nepal and South India [20,21,22]. It is suggested that female patients in age group 41-60y, suffer from post-menopausal changes such as estrogen loss, thinning of epithelium and decrease in vaginal flora that may be a cause of high incidence of UTI particularly in this age group [23,24], in our study also found the high prevalence of UTI in elderly females. With a marked variation MDR *E. coli* to a certain level was found to have sensitivity to almost all the tested antibiotics, the highest sensitivity (96%) was associated with ceftolozane/tazobactam followed by ceftriaxone(86%), along with that resistance pattern was shown to be highly significant to most commonly used drugs such as imipenem (86.30%), amoxicillin (85.20%), gentamycin (80%), cotrimoxazole (72%), ciprofloxacin (65%), cefaclor (61.10%) and moxifloxacin (30%).

A study published in Spain showed that gentamicin was thought to be first-line drug in treatment of UTIs, but the resistance to gentamicin was reported [25] and results are in accordance to our study. Findings of our study showed high resistance to beta lactam antibiotics such as amoxicillin, cotrimaxazole, imipenem, and cefaclor, this trend was escalating day by day in our country and also around the globe [26,27,28,29].

Higher resistance in MDR *E. coli* against penicillin and cephalosporins indicates that these may have been misused in health care settings. Quinolones, especially ciprofloxacin have been used for *E. coli* infections in recent past. In the present study however *E. coli* were highly resistant to ciprofloxacin (65%) Ullah. A. et al reported the same in Kohat [30].

The increasing frequency of cross-resistance between beta-lactamases and fluoroquinolones has become a major concern globally [31]. The Study for Monitoring Antimicrobial Resistance Trends (SMART) has reported that fluoroquinolones may no longer be effective as first-line therapy for UTI in hospitalized patients [32]. Ceftolozane/Tazobactam was observed as highly sensitive (96%) drug for MDR *E. coli* in our study. It is a novel 5th generation cephalosporin with well-established beta lactamase inhibitors and effective against MDR strains as well as also effective for ESBL *E. coli*. Phase II and III trials have shown high efficacy and good tolerability in complicated UTI when compared with standard therapy [33]. Clinical trial was conducted which showed higher efficacy when compared to levofloxacin [34]. As we are running out for the antibiotics for the treatment of Uropathogenic *E. coli* so the therapeutic use of C/T should be reserved only for severe and life threatening infections.

5. CONCLUSION

UTI due to MDR *E. coli* may be difficult to treat because of high resistance to commonly used empirical antibiotics. C/T is an appropriate antibiotic to treat UTIs caused by MDR *E. coli*. Continuous surveillance of multidrug resistant organisms and antimicrobial stewardship needed in order to prevent treatment failure and reduce selective pressure. These findings will help in choosing more suitable treatment options for UTI patients in this region of Pakistan.

6. LIMITATIONS

The study was confined to one setup only and with that we were just able to encounter the population that visited our OPD.

7. SUGGESTIONS

The same kind of study should be conducted with collaboration of multiple setups of Karachi to identify the invading organism in large sample size and to validate the effective treatment options for resistant organisms.

CONSENT

Consent was taken on a preformed proforma that enclosed the demographic data and patient’s agreement for participation in study.

ETHICAL APPROVAL

The study was approved by Research Ethics Committee of Ziauddin University.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES


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