ORIGINAL ARTICLE

Evaluation of In Vitro Susceptibility of Cefepime-Tazobactam against Clinical Isolates of *Escherichia coli, Klebsiella pneumoniae* and *Proteus mirabilis*. A Cross Sectional Study

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ABSTRACT

Introduction: Gram negative pathogens have acquired resistance to third and fourth generation cephalosporins due to their indiscriminate use and production of ESBL and AmpC and so a successful method to get rid of this problem is to use Novel β- lactam / β- lactamase inhibitor combinations (BL-BLI) like cefepime-tazobactam (CPT) for treatment of infections with Gram negative bacteria like *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis*. **Objective:** To evaluate invitro susceptibility of cefepime-tazobactam against clinically significant isolates of *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis*. **Results:** The present study was conducted to evaluate invitro susceptibility of cefepime-tazobactam against Gram negative bacteria where a total of 170 isolates of *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis* were tested by disc diffusion method and E-test where 74.03% of *Escherichia coli* isolates, 100% of *Proteus mirabilis* isolates were sensitive but only 43.39% of *Klebsiella pneumoniae* isolates were sensitive to cefepime-tazobactam. **Conclusion:** This study gives insight into invitro susceptibility of cefepime-tazobactam against clinical isolates of *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis* where this drug showed good sensitivity against *Escherichia coli* and *Proteus mirabilis* isolates but low sensitivity rate was seen against *Klebsiella pneumoniae* isolates to confirm which further multicenteric studies are required.

KEY WORDS: Cefepime-Tazobactam (CPT), ESBL, AmpC, Disc diffusion method, E-test

Introduction

Gram negative pathogens such as members of Enterobacteriaceae (especially ESBL and AmpC producers) and Non fermenters have acquired several drug resistant mechanisms to get rid of the effect of antibiotics and became an important role in both community acquired and hospital acquired infections [1]. β–Lactam antibiotics were being used against these pathogens where indiscriminate use of 3rd and 4th generation cephalosporins has led to development of sophisticated resistance mechanisms against these drugs by production of Extended spectrum β-Lactamases (ESBL's) and AmpC which lead to the use of carbapenem group of antibiotics against these pathogens and there is need to reduce the usage of carbapenems to combat resistance against this group of antibiotics [2].

As ESBL producing strains are highly prevalent in India leaving many antibiotics ineffective against these organisms, a successful method to get rid of these plasmid coded β–Lactamases is to use combination of β–Lactam antibiotic with an β–Lactamase inhibitor (BL-BLI) which may provide an effective measure to overcome this problem [2, 3] because these β–Lactamase inhibitors when administered alone do not have any antimicrobial effect, but when co-administered with β–Lactam antibiotic they act to bind and inactivate β–Lactamases and give the partner antibiotic an opportunity to overcome hydrolysis by those enzymes and potentiate the activity of the antibiotic by directly binding to the penicillin binding proteins (PBP's) of the bacteria and leading to inhibition of cell wall synthesis [4, 5].

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Cefepime, a 4th generation cephalosporin was approved by FDA for clinical use in 1996 for treatment of various infections of respiratory tract, skin & soft tissue, intra abdominal infections etc. Cefepime unlike other cephalosporins has a positively charged substitution in its nucleus which makes it a zwitterion with a neutral charge facilitating it to penetrate the bacterial cell wall. As cefepime resistance is seen among Gram negatives via production of β–Lactamases and use of cefepime alone in Gram negative infections is a debatable issue and also may lead to treatment failures. Cefepime-Tazobactam (CPT) which is a novel BL-BLI combination, which is approved by Drug Controller General of India (DCGI) for treatment of various infections with Gram negative bacteria and is expected to increase the susceptibility of Gram negative bacteria by overcoming the resistance mechanisms like AmpC & OXA by cefepime and ESBL's by tazobactam [6, 7, 8].

This study was undertaken at our institute in department of microbiology after attaining Institutional Ethics Committee (IEC) approval to evaluate the invitro susceptibility of various clinical isolates of *E. coli*, *K. pneumoniae* and *P. mirabilis* against cefepime-tazobactam.

Materials And Methods

The present study was a cross sectional observational study conducted between March 2024 to February 2025 in the department of microbiology, Dr. Pinnamaneni Siddhartha Institute of Medical Sciences and Research Foundation, China Avutapalli, Andhra Pradesh which is a tertiary care centre after obtaining Institutional Ethics Committee (IEC) approval. Reg no- Faculty/1016/23 dated 01/12/2023 (CDSCO Reg no: ECR/804/Inst/AP/2016-RR-19 and DHR Reg no: EC /NEW/Inst/2021/2140).

Inclusion Criteria

All the specimens like blood, urine, pus, swabs, sputum etc sent to microbiology laboratory for culture and sensitivity testing from various OPD's and IPD's of various departments from our attached General and Superspeciality hospital during study period showing clinically significant growth of *E. coli*, *K. pneumoniae* and *P. mirabilis* were included in the study.

Exclusion Criteria

Repetitive samples and samples showing growth of bacterial isolates other than *E. coli*, *K. pneumoniae* and *P. mirabilis* including Gram negative non-fermenters were excluded from the study.

Sample Design

A total of 170 non duplicate strains of *E. coli*, *K. pneumoniae* and *P. mirabilis* isolates from various clinical samples like blood, urine, pus, swabs, sputum etc. which were identified by Gram's stain, catalase test, oxidase test, motility, biochemical tests, amino acid utilization tests and sugar fermentation tests [9-12] were collected and further processed by antibiotic susceptibility testing by Kirby Bauer disc diffusion method on Mueller Hinton agar (MHA) by routine antibiotics along with cefepime (30µg) and cefepime-tazobactam discs (30/10 µg) (Himedia Labs, Mumbai, India) recommended by CLSI [13] and the results were interpretated and tabulated as Sensitive(S), Intermediate(I), Resistant(R) as per CLSI guidelines and these were further subjected to cefepime tazobactam by E-test on Mueller Hinton agar and were interpretated as Sensitive (S)(≤ 2 µg/ml), Intermediate (I)(4-8µg/ml) and Resistant (R)(≥ 16 µg/ml) according to CLSI guidelines [13].

Study Variables

The MIC (Minimum Inhibitory Concentration) of cefepime-tazobactam against clinically significant isolates of *E. coli*, *K. pneumoniae* and *P. mirabilis* from various samples and their cut off range is based on CLSI guidelines by Epsilometer-test (E-test) using E-strips (Himedia Labs, Mumbai, India) with MIC's ranging from 0.016 to 256 µg/ml and interpretated as Sensitive (S) if MIC is ≤ 2 µg/ml, Intermediate (I) if MIC is 4-8 µg/ml and Resistant (R) if MIC is ≥ 16 µg/ml for *E. coli*, *K. pneumoniae* and *P. mirabilis* isolates.

Study Procedure

A total of 170 non duplicate strains of *E. coli*, *K. pneumoniae* and *P. mirabilis* isolated from various clinical samples like blood, urine, pus, swabs etc. were identified upto species level by standard phenotypic tests like colony morphology, hemolysis, lactose fermentation, Gram's stain, catalase test, oxidase test, motility test, indole test, nitrate test, TSI, urease test, amino acid utilization tests and sugar fermentation tests as per CLSI guidelines [9-12]. All these isolates were tested for their susceptibility against routine antibiotics by Kirby Bauer disc diffusion method using MHA including cefepime (30µg) and cefepime-tazobactam (30/10 µg) discs (Himedia Labs, Mumbai, India) and the results were noted and tabulated as Sensitive (S) ≥25mm, Intermediate (I) 19-24mm, Resistant (R) ≤18mm as per CLSI guidelines [13]. ESBL and AmpC production were detected in these strains by Double disc synergy test. The test strain with 0.5McFarland turbidity was lawn cultured onto MHA plate and discs of cefotaxime (30µg) and cefotaxime-clavulanic acid (30/10µg) (Himedia Labs, Mumbai, India) were placed 24mm apart (distance measured from center to center of discs) and incubated at 35-37°C for 18-24hrs and interpretated as ESBL producers if the zone diameter around cefotaxime-clavulanic acid is ≥ 5mm than cefotaxime [13, 14]. AmpC production was detected by the same procedure where cefotaxime (30µg) and cefotaxime-cloxacillin (30/200µg) (Himedia Labs, Mumbai, India) were used and placed 24mm apart after lawn culture of test strain and

interpretated as AmpC producers if the zone diameter around cefotaxime-cloxacillin disc is ≥ 5mm than cefotaxime disc zone diameter [13, 15]. All the strains (including ESBL and AmpC producers) [12, 13, 16-18] were subjected to Epsilometer test (E-test) along with Kirby-Bauer disc diffusion method using E-strips of cefepime-tazobactam with MIC's ranging from 0.016-256 µg/ml (Himedia Labs, Mumbai, India) where the inoculum was prepared using 3-4 colonies of test strain and were emulsified in normal saline in a test tube and turbidity was compared to that of 0.5Mc Farland standard and turbidity was adjusted accordingly and inoculation was done on MHA plate with a sterile swab dipped into the inoculum and streaked over entire surface of MHA and then E-strips of cefepime-tazobactam were applied onto agar surface and the plates were incubated at 35-37^{o}C for 18-24hrs and were then interpretated as Sensitive (S)(≤ 2 µg/ml), Intermediate (I)(4-8µg/ml) and Resistant (R)(≥ 16 µg/ml) for *E. coli*, *K. pneumoniae* and *P. mirabilis* isolates according to CLSI guidelines [13]. ATCC strains *Escherichia coli* - 25922, *Klebsiella pneumoniae* – 27736 were used as controls.

Methodology Flow Chart

Samples - blood, urine, pus, swabs etc. → Gram's stain → Inoculation onto Sheep Blood agar and MacConkey agar → Incubation at 35-37^{o}C /18-24hrs → Reading the plates → Colony morphology, Hemolysis, Lactose fermentation → Gram's stain → Gram negative bacilli → Subculture onto Sheep Blood agar and MacConkey agar → Incubate at 35-37^{o}C /18-24hrs standard biochemical tests → Amino acid utilization tests → Sugar fermentation tests Identification upto species level → Detection of ESBL and AmpC production → Antibiotic susceptibility testing by Kirby-Bauer disc diffusion method on MHA with routine antibiotics recommended by CLSI along with cefepime (30µg) and cefepime-tazobactam discs (30/10 µg) (Himedia Labs, Mumbai, India) → Interpretated as Sensitive (S) ≥25mm, Intermediate (I) 19-24mm, Resistant (R) ≤18mm according to CLSI guidelines → All strains including ESBL and AmpC producers subjected to Epsilometer test (E-test) by E-strips of cefepime-tazobactam (Himedia Labs, Mumbai, India) with MIC's ranging from 0.016 to 256 µg/ml → Interpretated as Sensitive (S) if MIC is ≤ 2 µg/ml, Intermediate (I) 4-8 µg/ml and Resistant (R) ≥ 16 µg/ml for *E. coli*, *K. pneumoniae* and *P. mirabilis* isolates → Data was collected and tabulated in microsoft excel sheet → Descriptive statistics were used to represent the variables → proportion of isolates of *E. coli*, *K. pneumoniae* and *P. mirabilis* which were Sensitive, Intermediate and Resistant to cefepime-tazobactam were tabulated and expressed in the form of numbers and percentages.

Statistical Analysis

The collected sensitivity data of *E. coli*, *K. pneumoniae* and *P. mirabilis* were tabulated in Microsoft excel sheet and analysed and descriptive statistics were used to represent the variables. The proportion of isolates of *E. coli*, *K. pneumoniae* and *P. mirabilis* which were Sensitive, Intermediate and

Resistant to cefepime-tazobactam were expressed in the form of numbers and percentages.

Results

Table 1: Number of isolates from various clinical samples

S. No	Name of the organism	No. of isolates
1	*E. coli*	104 (61.17%)
2	*K. pneumoniae*	53 (31.17%)
3	*P. mirabilis*	13 (7.64%)
4	Total	170 (100%)

Table 2: Number of ESBL, Non ESBL and AmpC producers

S. No	ESBL Producers	Non ESBL Producers	AmpC Producers	Total No. of isolates
1	30 (17.65%)	140 (82.35%)	10 (5.88%)	170 (100%)

Table 3: Antibiotic susceptibility of various isolates to cefepime (CPM) and cefepime-tazobactam (CPT) based on disc diffusion method

S. No	Name of the organism	Name of the antibiotic					
		Cefepime			Cefepime-Tazobactam		
		Sensitive	Intermediate	Resistant	Sensitive	Intermediate	Resistant
1	*E. coli*	28 (26.92%)	22 (21.15%)	54 (51.92%)	66 (63.46%)	11 (10.57%)	27 (25.96%)
2	*K. pneumoniae*	17 (32.07%)	2 (3.77%)	34 (64.15%)	21 (39.62%)	3 (5.66%)	29 (54.71%)

S. No	Name of the organism	Name of the antibiotic					
		Cefepime			Cefepime-Tazobactam		
		Sensitive	Intermediate	Resistant	Sensitive	Intermediate	Resistant
3	*P. mirabilis*	11 (84.61%)	-	2 (15.38%)	13 (100%)	-	-

Table 4: Susceptibility pattern of various isolates to cefepime–tazobactam based on E-test

S. No	Name of the organism	Cefepime-Tazobactam		
		Sensitive	Intermediate	Resistant
1	*E. coli*	77(74.03%)	-	27 (25.96%)
2	*K. pneumoniae*	23(43.39%)	-	30(56.60%)
3	*P. mirabilis*	13(100%)	-	-

Table 5: Showing susceptibility pattern of cefepime–tazobactam in ESBL, Non ESBL & AmpC producers based on E-test

S. No	Name of the antibiotic	ESBL Producers (30 isolates)	Non ESBL Producers (140 isolates)	AmpC producers (10 isolates)
1	Cefepime- Tazobactam	23 (76.66%)	90 (64.28%)	6(60%)

Table 6: Susceptibility pattern of various isolates to cefepime–tazobactam in ESBL & AmpC producers based on disc diffusion method and E-test

S. No	Name of the organism	ESBL producers (30)	Cefepime-Tazobactam		AmpC producers (10)	Cefepime-Tazobactam	
			Disc diffusion method	E-test		Disc diffusion method	E-test
1	*E. coli*	23 (76.66%)	14 (60.86%)	19 (82.60%)	5 (50%)	4 (80%)	4 (80%)
2	*K. pneumoniae*	5 (16.66%)	2 (8.69%)	2 (8.69%)	4 (40%)	-	-
3	*P. mirabilis*	2 (6.66%)	2 (100%)	2 (100%)	1 (10%)	1 (100%)	1 (100%)

Discussion

There is increasing concern regarding development of multidrug resistance (MDR) especially in Gram negative bacteria globally which is complicated by absence or non availability of newer antibiotic regimens for treatment of such infections. So, now there is increased interest among clinicians in newer combination drugs such as cefepime–tazobactam (CPT) which can be used to treat various infections caused by certain Gram negative bacteria such as uncomplicated and complicated urinary tract infections (UTI's), skin and soft tissue infections, intra abdominal infections, severe lower respiratory tract infections etc [2] and due to lack of studies regarding its efficacy and adverse reactions in case of pregnancy and lactation, it cannot be commented.

High prevalence of ESBL producers among hospital and community acquired infections also lead to carbapenem resistance due to various mechanisms where the main mechanism is production of carbapenemase enzyme. So, as an alternative, β-Lactam and β-Lactamase inhibitor (BL-BLI) combination drugs are being widely used and they proved to be effective drugs like cefepime-tazobactam [17].

Cefepime (CPM) is a semi synthetic , broad spectrum, fourth generation cephalosporin which has good activity against many Gram negative and Gram positive bacteria and is also effective against Gram negative isolates which

are ESBL and AmpC producers due to its 3 [1] side chain. Tazobactam is a good β-Lactamase inhibitor (BLI) which provides inhibitory action against a wide range of β-Lactamases which includes group-1 cephalosporinases and group 3 metallo β-Lactamases (MBL'S). Combination of cefepime-tazobactam (BL-BLI) was found to be very effective in treatment of Gram negative infections especially with ESBL and AmpC producers [11, 17].

The present study was conducted at our institute to evaluate the invitro susceptibility of cefepime-tazobactam against clinically significant isolates of *E. coli, K. pneumoniae* and *P. mirabilis* where a total of 170 (100%) isolates were tested out of which *E. coli* were 104 (61.17%), *K. pneumoniae* were 53 (31.17%) and *P. mirabilis* were 13 (7.64%) [Table. 1]. All the isolates were being tested for antibiotic susceptibility with routine antibiotics along with cefepime (30µg) and cefepime-tazobactam (30/10 µg), (Himedia labs, Mumbai, India) by disc diffusion method and E-test for cefepime-tazobactam for all the isolates including ESBL and AmpC producers according to CLSI guidelines [13].

ESBL production was noted in 17.65% of isolates and AmpC in 5.88% [Table. 2] correlating with findings of Smita Sood [19] (26.90%), David N. Livermore et al [16] (22.76%), Abdul Ghafur et al [20] (24%) for ESBL production where as high prevalence rates were reported by Ramanpreet Kaur et al [1] (60%), Susan M et al [14] (67.8%), Biswas S et al [21] (52.41%), Mohanty S et al [22] (68.78%), Meghna S et al [15] (62%). AmpC producers were 5.88% in our study correlating with findings of Mona Wassef et al [23] (5.8%) and high prevalence rates of ≥40% were also reported by Thean Yen Tan et al [24], Peter Getzlaff S et al [25], Roopshree S et al [26], Madhumati B et al [27].

By disc diffusion method for cefepime-tazobactam susceptibility, 63.46% of *E. coli*, 39.62% of *K. pneumoniae* and 100% of *P. mirabilis* isolates [Table. 3] were sensitive correlating with findings of Kalavani Ramakrishnan et al [2] who showed 83% of *E. coli*, 82% of *K. pneumoniae* and 91% of *P. mirabilis* isolates were sensitive. Our findings also correlate with Susan M et al [14] who showed that 86.9% of *E.coli* isolates were sensitive, Smita Sood et al [19] showed that 95.14% of *E .coli*, 82.8% of *K. pneumoniae* and 75% of *P. mirabilis* isolates were sensitive, Roshini Agarwal et al [11] who showed 86.2% of *E. coli* isolates were sensitive, Rammurugan N et al [28] who showed that 90% of *E. coli* and 100% of *P. mirabilis* isolates were sensitive. In our study invitro susceptibility of *K. pneumoniae* for cefepime-tazobactam tested by disc diffusion method was low (39.62%) correlating with findings of Vivek Bhat et al [29] (45.3%), Roshini Agarwal et al [11] (42.7%) and Rammurugan N et al [28] (42%). By E-test, 60% of AmpC producers were sensitive [Table. 5] in our study, correlating with findings of Burcu Isler et al [6](97%) and David M. Livermore et al [16] (100%). Overall, by E-test 74.03% of *E. coli*, 100% of *P. mirabilis* isolates were sensitive to cefepime-tazobactam but only 43.39% of *K. pneumoniae* isolates [Table. 4] were sensitive in our study, correlating with findings of Helio S Sader et al [17] who showed 99.5% of *E. coli* and 99.8% of *P. mirabilis* isolates were sensitive, Rammurugan N et al [28] who showed 90% of *E. coli* isolates, 45% of *K. pneumoniae* and 100% of *P. mirabilis* isolates were sensitive, Helio S Sader et al [30] who showed 99.1% of *E. coli,* 87.7% of *K. pneumoniae* and 100% of *P. mirabilis* isolates were sensitive.

Conclusion

This study gives an insight into invitro susceptibility of cefepime-tazobactam against clinically significant isolates of *E. coli*, *K. pneumoniae* and *P. mirabilis*. According to our experience cefepime-tazobactam showed good invitro activity against clinically significant isolates of *E.coli* and *P. mirabilis*. Low invitro susceptibility was noted among *K. pneumoniae* isolates which to confirm requires further multicenteric studies. Further invitro and in vivo studies are needed to assess the actual effectiveness of this novel combination against various Gram negative isolates, especially against ESBL and AmpC producers. Research is also going on with various novel combinations of BLI'S with cefepime regarding their effectiveness against various Gram negative and Gram positive bacteria like Cefepime–Zidebactam, Cefepime-Taniborbactam and Cefepime–Enmetazobactam.

Limitations of the study:

Limited number of isolates of *E. coli*, *K. pneumoniae* and *P. mirabilis* isolated from different samples were included in the study, which may be considered as a drawback of the study. Further multicenteric studies including invitro and in vivo studies are required to assess the actual effectiveness of cefepime-tazobactam against various Gram negative bacteria especially *K. pneumoniae* which is a cause of multiple infections in hospital as well as in the community. Further studies may enlighten the clinicians in order to include cefepime-tazobactam as a therapeutic agent in Gram negative infections especially with *E. coli*, *K. pneumoniae* and *P. mirabilis*.

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