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Efficacy of Cefepime/Enmetazobactam (Cipenmet) in Piperacillin-Tazobactam Resistant Urinary Tract Infections: A Cross-Sectional Study

Dr. Shivani B. Hambarde[1], Dr. Manjushree V. Mulay[2], Dr. Jayshree Pohekar[3], Dr. Anupama Wyawahare[4], Ms. Mishra J K[5]

[1]Junior resident, [2]Professor & Head of Department, [3]Assistant Professor, [4]Professor, [5]Assistant Professor

Department of Microbiology, MGM Medical college & hospital, Chh. Sambhajinagar, MGMIHS, Navi Mumbai, Maharashtra, India

Corresponding author: Dr. Manjushree V. Mulay

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ABSTRACT:

Introduction: Urinary tract infections (UTIs) are among the most common bacterial infections, with rising resistance to conventional antimicrobials such as piperacillin tazobactam. Carbapenem resistance further complicates management, necessitating evaluation of novel agents.

Aim: To assess the efficacy of cefepime/enmetazobactam (Cipenmet) in piperacillin tazobactam resistant UTIs and estimate the prevalence of resistance among Enterobacterales isolates.

Methods: A cross sectional study was conducted on 600 urine specimens, of which 288 yielded Enterobacterales. Among these, 153 isolates were resistant to piperacillin tazobactam; 65 isolates resistant to both piperacillin tazobactam and ceftriaxone were included. Antimicrobial susceptibility was tested using CLSI guidelines, including Cipenmet and carbapenems.

Results: Klebsiella pneumoniae (48%) and Escherichia coli (45%) were the predominant isolates. Catheterization was present in 80% of cases. Carbapenem resistance was observed in 54% of isolates, while Cipenmet resistance was higher at 66%. A strong correlation was noted between Cipenmet and carbapenem resistance ($\chi^2 = 38.79$, $p < 0.001$).

Conclusion: Cipenmet demonstrated limited efficacy in this cohort, with resistance strongly associated with carbapenem resistance. These findings highlight the urgent need for continued surveillance and exploration of alternative therapeutic strategies.

Introduction

Urinary tract infections (UTIs) remain one of the most common bacterial infections encountered in clinical practice, affecting millions of individuals worldwide each year[1]. The burden is particularly significant in hospitalized patients, where catheterization and prolonged antibiotic exposure predispose to complicated and resistant infections[2]. Among the causative agents, *Enterobacterales* such as *Escherichia coli* and *Klebsiella pneumoniae* dominate, but their rising resistance to conventional antimicrobials poses a major therapeutic challenge[3].

The widespread use of β-lactam/β-lactamase inhibitor combinations, such as piperacillin-tazobactam, has historically provided effective coverage against multidrug-resistant Gram-negative organisms. However, increasing resistance to this regimen has been reported globally, limiting its utility in severe infections[4]. Carbapenems, once considered the last line of defense, are now compromised by the emergence of carbapenem-resistant *Enterobacterales* (CRE), which are associated with high morbidity, mortality, and limited treatment options[5].

In response to this growing crisis, novel agents such as Cipenmet (a combination of cefepime and enmetazobactam) have been developed. This drug aims to restore activity against resistant strains by combining a fourth-generation cephalosporin with a potent β-lactamase inhibitor[6]. Early studies suggest promising in vitro activity against extended-spectrum β-lactamase (ESBL)-producing and carbapenem-resistant isolates, but clinical data remain limited[7].

Given the rising prevalence of multidrug-resistant UTIs and the urgent need for effective alternatives, the present

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study was undertaken to evaluate the susceptibility pattern and clinical efficacy of Cipenmet in patients with UTIs resistant to piperacillin-tazobactam. This investigation also sought to estimate the prevalence of piperacillin-tazobactam resistance among *Enterobacterales* isolates in a tertiary care setting, thereby contributing to the growing body of evidence on novel therapeutic strategies for resistant infections.

Aim & Objectives

Aim

To study the efficacy of novel drug Cipenmet (Cefepime/Enmetazobactam) in cases of Urinary tract infection patients which are resistant to piperacillin tazobactam combination.

OBJECTIVES –

1. To study the susceptibility pattern and efficacy of novel drug Cipenmet in cases of Urinary tract infection patients.
2. To estimate the prevalence of piperacillin tazobactam resistant isolates in cases of Urinary tract infection patients.

Material and Methods

Present study is a cross-sectional prospective study conducted at tertiary care hospital. Institutional ethics committee permission was taken prior to commencement of present study. A total of 600 urine specimens were collected and processed under strict aseptic precautions. Of these, 288 yielded Gram-negative bacterial isolates belonging to the Enterobacterales group. Antimicrobial susceptibility testing revealed that 153 of these isolates were resistant to piperacillin-tazobactam. From this subset, 65 isolates that demonstrated concurrent resistance to both piperacillin-tazobactam and ceftriaxone fulfilled the inclusion criteria and were finally enrolled for detailed evaluation in the present study.

The prevalence of piperacillin-tazobactam resistance among Enterobacterales isolates was found to be 153 out of 288 (53%). This indicates that more than half of the Gram-negative urinary pathogens in our cohort exhibited resistance to this commonly used β-lactam/β-lactamase inhibitor combination.

Study was explained to all participants and written informed consent was obtained from all.

Inclusion Criteria

All Enterobacterales isolated from urine specimens(Age group 19-60 years) from cases of UTI which are resistant to Piperacillin tazobactam & Ceftriaxone will be included in study.

Exclusion Criteria

Duplicate isolates from same patient will be excluded.

Procedure

Urine specimens were collected from patients under strict aseptic precautions, either through midstream clean-catch technique in non-catheterized individuals or directly from catheter ports in catheterized patients. Samples were transported promptly to the microbiology laboratory and processed within two hours of collection to minimize contamination and bacterial overgrowth.

Primary isolation of organisms was performed on Cystine Lactose Electrolyte Deficient (CLED) agar and MacConkey agar, followed by incubation at 37°C for 18–24 hours. Colonies were identified based on morphology, Gram staining, and standard biochemical reactions. Where necessary, automated identification systems (such as VITEK 2) were used for confirmation.

Antimicrobial susceptibility testing was carried out using the Kirby–Bauer disk diffusion method on Mueller–Hinton agar, in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines. The antibiotics tested included piperacillin-tazobactam, carbapenems (ertapenem, imipenem, meropenem), Ceftriaxone and the novel combination Cipenmet (cefepime/enmetazobactam). Minimum inhibitory concentrations (MICs) were determined for Cipenmet using broth microdilution where required.

Patient demographic details (age, gender, admission area) and clinical parameters (catheterization status, treatment response) were recorded systematically. For antimicrobial susceptibility profiling, isolates were tested against carbapenems (ertapenem, imipenem, meropenem) and Cipenmet (cefepime/enmetazobactam) using the Kirby–Bauer disk diffusion method. Resistance and susceptibility were recorded as frequencies and percentages

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Fig 1: Cipenmet A. Resistant B. Susceptible

Statistical analysis

For statistical analysis, categorical variables were expressed as frequencies and percentages. Associations between Cipenmet susceptibility and clinical outcomes were assessed using the Chi-square test, with a p-value <0.05 considered statistically significant.

Observation and Result

Table 1: Demographic Profile

Sr No	Variables	Number of cases n	Percentage %
1	**Age (Years)**		
	a. ≤20	4	6 %
	b. 21–40	30	46 %
	c. 41–60	31	48 %
2	**Gender**		
	a. Male	36	**55 %**
	b. Female	29	**45 %**
Total N (%)		**65**	**100 %**

The study enrolled 65 patients with urinary tract infections resistant to piperacillin-tazobactam. The majority of participants were in the 41–60 years age group (31 cases, 48%), followed closely by those aged 21–40 years (30 cases, 46%), while only 4 patients (6%) were younger than 20 years. Gender distribution showed a slight male predominance, with 36 males (55%) compared to 29 females (45%).

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Table 2: distribution of admission Area

Sr No	Area	Number of cases n	Percentage %
1	Various wards	52	**80 %**
2	Various ICUs	13	20 %
Total N (%)		**65**	**100 %**

Most patients were admitted in various wards (52 cases, 80%), while a smaller proportion were from ICUs (13 cases, 20%), reflecting that resistant UTIs were more common in general ward patients than in critical care settings

Table 3: Distribution of Enterobacterales Isolates

Sr No	Species	Number of isolates (n)	Percentage (%)
1	Klebsiella pneumoniae	30	48 %
2	Escherichia coli	29	45 %
3	Enterobacter cloacae complex	3	4 %
4	Klebsiella aerogens	3	4 %
Total N (%)		**65**	**100 %**

Among the Enterobacterales isolates, Klebsiella pneumoniae (30 isolates, 48%) was the most frequently encountered pathogen, followed closely by Escherichia coli (29 isolates, 45%). Less common isolates included Enterobacter cloacae complex (3 isolates, 4%) and Klebsiella aerogens (3 isolates, 4%). This highlights that Klebsiella and E. coli together accounted for more than 90% of resistant UTI cases, underscoring their clinical significance.

Table 4: Distribution of Cases according to catheterization

Sr No	catheterization	Number of cases n	Percentage %
1	catheterized	52	**80 %**
2	Non- catheterized	13	20 %
Total N (%)		**65**	**100 %**

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A striking observation was that 80% of patients (52 cases) were catheterized, while only 20% (13 cases) were non-catheterized. This suggests a strong association between catheterization and multidrug-resistant UTIs, consistent with the known risk of catheter-associated infections.

Table 5: Distribution of Cases according to antimicrobial susceptibility

Sr No	antimicrobial	Resistant n (%)	Susceptible n (%)	Total n (%)
1	CRE (Ertapenem, Imipenem, Meropenem)	35 (54 %)	30 (46 %)	65 (100 %)
2	Cipenmet (Cefepime/Enmetazobactam)	43 (66 %)	22 (34 %)	65 (100 %)

Resistance to carbapenem resistance (CRE) was observed in 35 isolates (54%), leaving 30 isolates (46%) susceptible. When tested against the novel drug Cipenmet (Cefepime/Enmetazobactam), 43 isolates (66%) were resistant, while 22 isolates (34%) remained susceptible. Cipenmet showed less efficacy compared to carbapenems with overall resistance rate alarmingly high.

Table 6: Correlation of Cipenmet susceptibility & outcome

Sr No	Cipenmet	CRE		Total n (%)	Chi square	P value
		Resistant n (%)	Susceptible n (%)			
1	**Resistant**	35 (54 %)	8 (12 %)	43 (66 %)	38.79	< 0.001 (S)
2	**Susceptible**	0 (0 %)	22 (34 %)	22 (34 %)		
Total N (%)		35 (54 %)	30 (46 %)	**65 (100 %)**		

In the present study, a strong correlation was observed between Cipenmet susceptibility and carbapenem resistance among Enterobacterales isolates. Of the 65 isolates tested, 43 (66%) were resistant to Cipenmet, and within this group, 35 (54%) were concurrently resistant to carbapenems while 8 (12%) remained carbapenem-susceptible. Conversely, all 22 isolates (34%) that were susceptible to Cipenmet were also susceptible to carbapenems, with no overlap of resistance. Statistical analysis using the Chi-square test demonstrated a highly significant association ($\chi^2 = 38.79$, $p < 0.001$), confirming that Cipenmet resistance was strongly linked with carbapenem resistance in this cohort. These findings suggest that shared resistance mechanisms, such as carbapenemase production or efflux pump activity, may underlie the observed cross-resistance patterns."

Discussion

The demographic profile in the present study revealed that the majority of patients belonged to the 41–60 years age group (48%), with a slight male predominance (55%). Similar age clustering has been reported in resistant UTI cohorts by Gupta et al., where middle-aged adults formed the largest group of multidrug-resistant infections[8]. A study by Sharma et al. also noted higher prevalence in males, attributing this to increased catheterization and comorbidities[9]. Conversely, Patel et al. found female predominance in community-acquired resistant UTIs, highlighting that hospital-based cohorts differ significantly from community settings[10]. The

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mechanism underlying age and gender distribution likely relates to cumulative antibiotic exposure, comorbid illnesses, and catheter use in hospitalized males.

Admission area analysis showed that 80% of resistant UTI cases were from general wards, with only 20% from ICUs. This contrasts with findings by Singh et al., who reported higher rates of resistant Enterobacterales in ICU patients due to prolonged ventilation and invasive procedures[11]. However, Deshmukh et al. observed similar ward predominance, suggesting that resistant strains are now widely disseminated beyond critical care units[12]. A multicenter survey by Rao et al. also confirmed that resistant UTIs are increasingly encountered in general wards, reflecting community-to-hospital transmission dynamics[13]. The mechanism may involve cross-transmission via healthcare workers and environmental reservoirs, not limited to ICUs.

Species distribution in our study showed Klebsiella pneumoniae (48%) and Escherichia coli (45%) as dominant pathogens. This aligns with the work of Mehta et al., who found Klebsiella and E. coli accounting for over 85% of resistant UTIs[14]. Similarly, Banerjee et al. reported Klebsiella predominance in catheter-associated infections[15], while Das et al. highlighted E. coli dominance in community-acquired resistant UTIs[16]. The mechanism behind Klebsiella's predominance in hospital settings may be its ability to acquire plasmid-mediated resistance genes and persist in biofilms on catheters, whereas E. coli remains the leading community pathogen.

Catheterization was strongly associated with resistant UTIs in our cohort (80%). This finding is consistent with Kumar et al., who demonstrated that catheterized patients had a threefold higher risk of multidrug-resistant infections[17]. Joshi et al. similarly reported catheterization as the single most important risk factor for resistant Enterobacterales UTIs[18]. In contrast, Bhatia et al. found that even non-catheterized patients in long-term care facilities exhibited high resistance rates, suggesting environmental reservoirs[19]. Mechanistically, catheterization facilitates biofilm formation, protects bacteria from host immunity, and promotes horizontal gene transfer of resistance determinants.

Antimicrobial susceptibility testing revealed carbapenem resistance in 54% of isolates, while Cipenmet resistance was even higher at 66%. Comparable carbapenem resistance rates were reported by Chatterjee et al. (52%)[20] and Mukherjee et al. (57%)[21], while a lower prevalence was noted by Iyer et al. (40%)[22]. Regarding Cipenmet, our findings diverge from Carmeli et al., who demonstrated superior efficacy of cefepime/enmetazobactam in complicated UTIs[6]. Similarly, the ALLIUM trial reported Cipenmet as superior to piperacillin-tazobactam[7]. The discrepancy may be explained by local resistance mechanisms, including carbapenemase production, efflux pump overexpression, and porin mutations, which may also compromise Cipenmet activity.

Correlation analysis showed that Cipenmet resistance was strongly linked with carbapenem resistance ($\chi^2 = 38.79$, $p < 0.001$). This mirrors the findings of Farzana et al., who demonstrated overlapping resistance mechanisms in Enterobacterales[5]. A study by Tamma et al. also highlighted cross-resistance between novel β-lactam/β-lactamase inhibitor combinations and carbapenems[23]. Additionally, Logan et al. reported that efflux pump activity and carbapenemase genes often co-exist, leading to multidrug resistance[24]. Mechanistically, shared resistance determinants such as KPC, NDM, and OXA-type carbapenemases likely explain the observed correlation.

Conclusion

The present study highlights the alarming prevalence of multidrug resistance among Enterobacterales causing UTIs, with more than half of isolates resistant to piperacillin-tazobactam. Cipenmet, though promising in earlier trials, showed limited efficacy in our cohort, with two-thirds of isolates resistant. The strong correlation between Cipenmet and carbapenem resistance suggests shared mechanisms such as carbapenemase production, efflux pump activity, and porin mutations. Klebsiella pneumoniae and Escherichia coli remain the dominant pathogens, particularly in catheterized patients, underscoring the importance of infection control practices. These findings emphasize the need for judicious antibiotic use, routine surveillance, and further evaluation of novel agents to combat resistant UTIs in tertiary care settings.

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