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Original Research Article

Comparison of in vitro activity of cefepime-enmetazobactam and other carbapenem-sparing agents for gram-negative uropathogens

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Abstract

Background: Urinary tract infections (UTIs) caused by Gram-negative bacteria are an emerging therapeutic concern due to resistance to third-generation cephalosporins associated with Extended-spectrum beta-lactamases (ESBLs). This study aimed to evaluate the in vitro activity of cefepime-enmetazobactam compared to other carbapenem-sparing agents against Gram-negative uropathogens.
Materials and Methods: A total of 139 non-duplicate third generation cephalosporins resistant Gram-negative bacterial isolates were recovered from urine samples of patients with UTIs between February and March 2025. Antimicrobial susceptibility testing was performed for cefepime-enmetazobactam, cefepime, cefoperazone-sulbactam, piperacillin-tazobactam, meropenem and fosfomycin. ESBL production and carbapenem resistance were determined as per CLSI guidelines.
Results: Among the 139 patients, females constituted 78.4% (n=109), and the most affected age group was 21–40 years (45.3%). *Escherichia coli* was the predominant isolate (67.6%), followed by *Klebsiella pneumoniae* (17.3%) and *Pseudomonas aeruginosa* (5.8%). ESBL production was detected in 29.5% (n=41), while carbapenem resistance was observed in 12.2% (n=17). Among all isolates, resistance to cefepime was 46% (n=64), followed by piperacillin-tazobactam (16.5%), cefoperazone-sulbactam (12.2%), and cefepime-enmetazobactam (13.7%). Cefepime-enmetazobactam demonstrated strong activity against ESBL producers (97.5%, n=40), however, had poor activity against carbapenem-resistant organisms (CRO). Among the 64 cefepime-resistant isolates, 45 (70.3%) were susceptible to cefepime-enmetazobactam, reflecting a significant restoration of susceptibility.
Conclusion: Cefepime-enmetazobactam displayed superior in vitro effect compared to other carbapenem-sparing agents, particularly against cefepime-resistant and ESBL-producing uropathogens. These findings highlight its potential as an effective substitute for carbapenems in the treatment of UTIs caused by ESBL producing Gram-negative bacteria.

Keywords: Cefepime-enmetazobactam, Carbapenem-sparing antibiotic, Extended-Spectrum β-Lactamase, Multidrug-resistance.

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1. Introduction

Urinary tract infection (UTI) is one of the commonest infections encountered in community as well as healthcare settings.[1] Gram-negative bacilli, particularly Enterobacterales such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus spp.*, along with *Pseudomonas aeruginosa* are the major uropathogens implicated in these infections.[1] Treatment of UTI has become challenging with the rising global burden of antimicrobial resistance among these organisms. Increasing prevalence of extended-spectrum β-lactamase (ESBL) among Gram-negative uropathogens have been reported worldwide.[2] Carbapenem antibiotics have long been employed as the mainstay for managing complicated UTIs caused by ESBL-producing uropathogens. However, the widespread use of carbapenems has resulted in

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the emergence of carbapenem-resistant organisms (CRO).[3] This has led to a therapeutic crisis marked by limited treatment options.[4] Consequently, there has been a growing emphasis on developing effective carbapenem-sparing alternative agents to preserve the efficacy of carbapenems and to control the resistance development.[5] Various beta-lactam/beta-lactamase inhibitor (BL/BLI) combinations such as piperacillin-tazobactam, cefoperazone-sulbactam, ceftolozane-tazobactam, and ceftazidime-avibactam, as well as non-carbapenem beta-lactams such as, cefepime and cephamycins have been employed as carbapenem-sparing agent in treatment of ESBL-producing pathogens.[4,5] However, the therapeutic outcomes achieved are often variable and limited. The beta-lactam agents differ highly in their stability against various types of beta-lactamase enzymes.[6] Likewise, the available beta-lactamase inhibitors cannot effectively inhibit all classes of beta-lactamases.[6] Furthermore, co-production of multiple ESBLs, AmpC and carbapenemase enzymes are common among Gram negative organisms.[7,8] Hence, effectiveness of these combinations is often compromised by complex resistance mechanisms.

Cefepime-enmetazobactam is a novel BL/BLI combination. It has shown promising activity against a wide range of ESBL-producing and multidrug-resistant Gram-negative bacilli.[9] It is currently recommended for treatment of complicated UTI and hospital-acquired as well as ventilator-associated pneumonia in United States and Europe.[10] Hence, the potential role of cefepime-enmetazobactam as an effective alternative in the treatment of urinary pathogens need to be examined in Indian context. This study was undertaken to evaluate the antibacterial action of cefepime-enmetazobactam as a carbapenem-sparing antibiotic in comparison with other agents—namely cefepime, cefoperazone-sulbactam, piperacillin-tazobactam and fosfomycin, against uropathogenic Gram-negative isolates.

2. Materials and Methods

This cross-sectional observational study was conducted at a tertiary care teaching hospital in South India from February to March 2025 after receiving approval from the Institute Ethical committee (Ethical approval number MGMCRI/2022/IRC/95/04/IHEC/37). The study aimed to evaluate the in-vitro antibiotic susceptibility of cefepime-enmetazobactam and compare with piperacillin-tazobactam, cefoperazone-sulbactam, cefepime, and fosfomycin against Gram-negative uropathogens.

All midstream or catheter urine samples received in the microbiology laboratory during the study period were processed using standard microbiological techniques. The inclusion criteria were urine samples with significant growth (colony count of $\geq 10^5$ CFU/ml) of gram negative uropathogens resistant to third generation cephalosporins and the exclusion criteria were duplicate isolates from the same patient and samples showing contamination, mixed growth and non-significant growth. The isolates were subjected to antibiotic susceptibility testing using the Kirby-Bauer disc diffusion method on Mueller-Hinton agar, following Clinical and Laboratory Standards Institute (CLSI) guidelines, 2025.[11] Cefepime-enmetazobactam (30/20 µg), piperacillin-tazobactam (100/10 µg), cefoperazone-sulbactam (75/30 µg), fosfomycin (200 µg), meropenem (10 µg), cefepime (30 µg), ceftazidime (30 µg), and cefotaxime (30 µg) discs were used. The antibiotic discs were procured from commercially available sources (Microexpress, Goa, India). Isolates resistant to third generation cephalosporins (ceftazidime and cefotaxime) and positive in phenotypic confirmatory test for ESBL (ceftazidime and ceftazidime-clavulanate combined disc test) were considered as ESBL producer and isolates resistant to meropenem were considered as Carbapenem-resistant organisms (CRO). Since the interpretive criteria for fosfomycin in CLSI guidelines is limited to *Escherichia coli*, it is not tested for other organisms. [11] The clinical breakpoints of cefepime-enmetazobactam recommended by FDA for Enterobacterales and *P. aeruginosa* were followed in this study.[12] Accordingly, the zone size of ≥21 mm and ≥18 mm were considered as susceptible and zone size of ≤20 mm and ≤17 mm were considered as resistant for Enterobacterales and *Pseudomonas aeruginosa* respectively. [12] Quality control strains viz. *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used to ensure validity of susceptibility testing.

3. Results

A total of 357 urine samples had significant growth of Gram-negative bacteria of which 139 isolates were third generation cephalosporin resistant and were included in the study. The demographic distribution of the patients showed a significant female predominance with 78.4% (n = 109) females and 21.6% (n = 30) males. Age-wise, individuals of 21–40 years were most commonly affected by UTI, accounting for 45.3% (n = 63), followed by individuals of 41–60 years (26.6%, n=37), over 60 years (23.7%, n=33), 11-20 years (2.2%, n=3) and children less than 10 years (2.2%, n=3).

The predominant uropathogen isolated was *Escherichia coli*, consisting 67.6% (n = 94) of the total isolates. This was followed by *Klebsiella pneumoniae* (17.3%, n = 24), *Pseudomonas aeruginosa* (5.8%, n = 8), *Citrobacter spp.* (5%, n = 7), *Proteus mirabilis* (2.2%, n = 3), *Enterobacter spp.* (1.4%, n = 2), and *Proteus vulgaris* (0.7%, n = 1). These findings are consistent with global patterns in UTIs, where *E. coli* remains the most common causative organism, especially in community-acquired infections.[1]

Resistance profiling of the isolates demonstrated a significant burden of drug-resistant pathogens. ESBL-producing organisms were found in 29.5% (n = 41) of cases, and carbapenem-resistance was found among 12.2% (n=17) **(Table 1).** The resistance pattern of these isolates to cefepime-enmetazobactam and other antibiotics are illustrated in **Table 2.**

Table 1: Species-wise distribution of uropathogenic gram-negative isolates

Isolates	ESBL producer	CRO isolates	Non-ESBL, non-CRO isolates
Escherichia coli	40	11	43
Klebsiella pneumoniae	1	5	18
Citrobacter spp.	-	1	6
Enterobacter spp.	-	-	2
Proteus mirabilis	-	-	3
Proteus vulgaris	-	-	1
Pseudomonas aeruginosa	-	-	8

Table 2: Resistance pattern of gram-negative uropathogens

	Total (%) (n=139)	Among ESBL producers (n=41)	Among CRO isolates (n=17)	Among non-ESBL, non-CRO isolates (n=81)
Cefoperazone-sulbactam	17 (12.2%)	1	14	2
Piperacillin-tazobactam	23 (16.5%)	3	14	6
Cefepime	64 (46%)	29	15	20
Cefepime-enmetazobactam	19 (13.7%)	1	15	3
Fosfomycin (among *E. coli* n=94)	9 (9.6%)	4	2	3

Among the 64 isolates that were resistant to cefepime, 45 isolates, viz. 28 ESBL producers and 17 non-ESBL, non-CRO isolates, were susceptible when tested against cefepime-enmetazobactam, indicating a notable reversal of resistance.

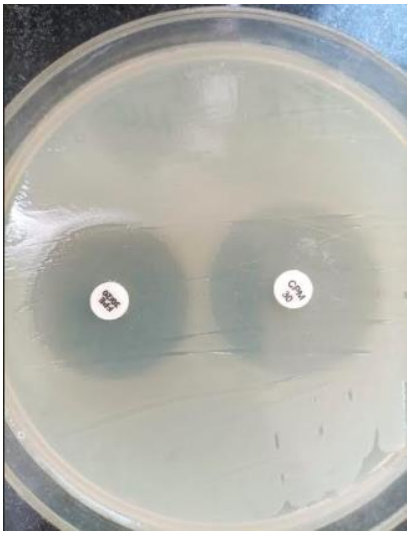

Figure 1: Antibiotic susceptibility test for cefepime-enmetazobactam by disc diffusion method. Enterobacterales with zone ≥21 mm was considered as susceptible and zone size ≤20 mm was taken as resistant as recommended by FDA.

4. Discussion

UTI represent a major cause of morbidity, particularly among women, the elderly, individuals with diabetes, urinary catheters or structural abnormalities of the urinary tract.[1] UTI affect approximately 21.8% to 31.3% of the population in India.[13] UTIs may range from simple cystitis to severe pyelonephritis and urosepsis, which may result in hospitalization and even mortality if not treated appropriately.[1] In our study, we found predominance of female patients (78.4%) with UTI, reflecting the well-established trend of higher UTI prevalence in women due to anatomical and physiological factors. *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa and Citrobacter spp* were the major uropathogens accounting for 67.6%, 17.3%, 5.8%, and 5% respectively.

Treatment of UTI is becoming increasingly difficult due to emergence of beta-lactamase producing multidrug resistant strains. ESBLs are a group of beta-lactamase enzymes that confer resistance to third generation cephalosporins and aztreonam.[14] CTX-M, TEM and SHV belonging to Ambler class A are the major ESBLs. Since these enzymes are inhibited by various BLI, such as clavulanate, tazobactam, avibactam, vaborbactam and relebactam, BL/BLI combinations are popularly used in treatment of ESBL-producing organisms.[15] However, Gram-negative pathogens are increasingly becoming resistant to these combinations owing to co-production of other beta-lactamases.[8] AmpC are inducible enzymes of Ambler class C which render third generation cephalosporins resistant after few days of treatment.[4] KPC and OXA are serine carbapenemases belonging to Ambler class A and class D respectively. NDM, VIM and IMP, popularly termed as metallo-beta-lactamase (MBL), are Ambler class B carbapenemases which typically contain zinc ion at their active site.[15] In our study, among third generation cephalosporin resistant Gram-negative bacteria, 29.5% (n=41) isolates were ESBL producer and 12.2% (n=17) were CRO. Amongst the ESBL-positive strains, 97.6% (n=40) were *E. coli* and 2.4% (n=1) were *K. pneumoniae*, whereas *E. coli*, *K. pneumoniae* and *Citrobacter spp.* accounted for 64.7% (n=11), 29.4% (n=5) and 5.9% (n=1) of CRO isolates respectively. Prevalence of ESBL and CRO have been reported in various studies from India and abroad.[16,17] Gajamer et al documented *E. coli* and *K. pneumoniae* comprised 51.2% and 19.7% of ESBL-producing gram negative isolates respectively and 97% of these isolates also harboured carbapenemase genes like NDM, OXA, IMP and VIM.[17] Among the 81 non-ESBL, non-CRO isolates, *E. coli* (n=43) and *K. pneumoniae* (n=18) accounted for 53.1% and 22.2%, whereas, *P. aeruginosa, Citrobacter spp, P. mirabilis, Enterobacter spp.* and *P. vulgaris* were 9.9%, 7.4%, 3.7%, 2.5% and 1.2% respectively **(Table 1)**.

This resistance landscape emphasizes the importance of evaluating newer and potent therapeutic options for UTI. While carbapenems are the last therapeutic option among beta-lactam drugs for treatment of ESBL-producers, rampant use of carbapenems over last two decades have resulted in widespread dissemination of KPC, OXA and MBL resistant strains.[3] Hence, there is a growing emphasis on developing carbapenem-sparing alternatives.[4,5] Although, piperacillin-tazobactam and cefoperazone-sulbactam have already been in use as carbapenem-sparing BL/BLI agent, both have certain limitations. Some studies found piperacillin-tazobactam and cefoperazone-sulbactam to have comparable antibacterial susceptibility profile, clinical efficacy and safety,[18,19] others found cefoperazone-sulbactam superior.[20] Piperacillin-tazobactam not only gave contradictory findings on outcomes in observational studies, it also displayed unfavourable outcome in a Randomized Clinical Trial.[4,21] Likewise, the antibacterial activity of cefoperazone-sulbactam was found limited in case of ESBL producing organisms in presence of high MIC, multiple comorbidities and severe infections.[22]

Cefepime-enmetazobactam is a recent novel addition to the list of carbapenem-sparing beta-lactam agents. Cefepime is a fourth-generation oxyimino-cephalosporin which resists degradation by AmpC as well as OXA-48 like enzymes, however, it can still be hydrolyzed by certain ESBLs.[9] Enmetazobactam is a new BLI, specifically active against ESBLs and to some extent against AmpC and OXA.[8,23] It is a penicillanic acid sulfone derivative and structurally analogous to tazobactam.[9] However, unlike tazobactam, the zwitterionic effect due to the -CH_3 group present on enmetazobactam's triazole moiety enhances its permeation into bacterial cell. Cefepime and enmetazobactam display similar half-life and tissue distribution and enmetazobactam effectively protects cefepime from ESBLs, making this BL/BLI an optimum combination.[9]

Among the agents tested in our study, meropenem showed 87.8% (n=122) susceptibility and 12.2% (n=17) isolates were meropenem resistant and were considered CRO. Cefepime-enmetazobactam demonstrated a high susceptibility, with 120 isolates (86.3%) being susceptible and only 19 isolates (13.7%) being resistant in disc diffusion method **(Figure 1).** This performance was superior to cefoperazone-sulbactam and piperacillin-tazobactam. While cefoperazone-sulbactam displayed 79.9% (n=111) susceptible, 7.9% (n=11) intermediate and 12.2% (n=17) resistant isolates, piperacillin-tazobactam showed 82% (n=114) susceptible, 1.4% (n=2) intermediate and 16.5% (n=23) resistant isolates. Cefepime, in contrast, showed reduced activity with a high resistance rate of 46.0% (n=64). Cefepime-enmetazobactam displayed remarkable susceptibility (97.6%, n=40) among ESBL producing isolates. Among the 64 isolates that were resistant to cefepime, 45 (70.3%) isolates (including 28 ESBL producers) were susceptible to cefepime-enmetazobactam, indicating a substantial restoration of cefepime susceptibility. Susceptibility of this large fraction of ESBL producing cefepime resistant isolates to cefepime-enmetazobactam highlights the significant contribution of enmetazobactam in restoring the antibacterial efficacy of cefepime. The remaining 19 isolates (29.7%) of which 15 were carbapenem-resistant showed no change in susceptibility, remaining resistant even with the addition of enmetazobactam. It represents the inability of enmetazobactam to counteract carbapenem-resistant pathogens, especially those associated with MBL production, porin mutations and overexpression of efflux pump. We limited the fosfomycin susceptibility testing for 94 *E. coli* isolates as per the CLSI guidelines and the isolates demonstrated 90.4% (n=85) susceptibility. Our findings indicate that cefepime-enmetazobactam has superior in-vitro antimicrobial susceptibility than piperacillin-tazobactam and cefoperazone-sulbactam against ESBL producing gram-negative uropathogens and supports its potential as a carbapenem-sparing antibiotic in UTI and these are in accordance with recent studies. Belley et al reported substantially greater susceptibility to cefepime-enmetazobactam (98.8%) than cefepime (87%), amoxicillin-clavulanate (50%), piperacillin-tazobactam (87.4%) and ceftolozane-tazobactam (92.7%) among Enterobacterales.[24] It was also found that unlike other BL/BLI combinations, cefepime-enmetazobactam retained its potency despite the presence of multiple third-generation cephalosporin resistance genes.[24] Furthermore, Morrissey et al found enhanced susceptibility to cefepime-enmetazobactam despite substantial lack of potency of cefepime among ESBL as well as AmpC producing Enterobacterales in Europe.[23] In another study, cefepime-enmetazobactam had high susceptibility among OXA-48 producers in addition to ESBLs.[8] These findings supports the use of cefepime-enmetazobactam as a potent carbapenem-sparing BL/BLI combination which can be used as empirical as well as definitive therapy. However, the limitations of in vitro studies should always be considered. The in-vitro susceptibility to cefepime-enmetazobactam may not reflect its true clinical efficacy. The therapeutic effectiveness of any antimicrobial agent is governed by its pharmacokinetic and pharmacodynamic (PK/PD) properties, host's physiological state, organ function and immune response as well as microbial factors such as inoculum size, interaction with gut microbiota, biofilm production, rate of mutation and gene transfer.[25] Therefore, clinical studies associating therapeutic outcome, PK/PD and MIC data are essential for determining the clinical breakpoints to predict clinical efficacy of cefepime-enmetazobactam. Another critical consideration is the cost-effectiveness of cefepime-enmetazobactam and its implications in antibiotic stewardship. Chennai-based Orchid Pharma Limited launched this novel drug in June 2024.[26] The cost of cefepime (2g) -enmetazobactam (500 mg) is about Rs. 1,250 per vial.[27] Whereas, meropenem (1g) and piperacillin (4g) -tazobactam (500 mg) cost are Rs. 450 and Rs. 185 per vial from the same manufacturer respectively.[28,29] Considering the comparable thrice daily dosage of these antibiotics, cefepime-enmetazobactam is more costly and may not be affordable for most patients in developing countries like India. Its role in antibiotic stewardship is yet to be validated. Owing to the higher treatment cost it may have a limited impact in antibiotic stewardship in India. However, it needs to be considered in healthcare setups where the potential to develop carbapenem resistance is high.

5. Limitations

The main limitations of the study were small sample size because of which statistical testing may not be reliable. We have not analysed patient risk factors among community and hospital-acquired infections. Due to limitation of resources and cost constraints, Modified Hodge Test (MHT), Carba NP test, PCR for detection of specific carbapenemase, AmpC and detection of cefepime-enmetazobactam minimum inhibitory concentration (MIC) using broth microdilution or E-test were not done. Furthermore, current CLSI guideline does not provide breakpoints for cefepime-enmetazobactam. Hence, we have utilized FDA criteria in this study. However, these criteria are based on clinical and microbiological data from western countries, which may not truly represent Indian scenario. It underscores need for multi-centric studies with large sample size from India to validate these criteria for Indian isolates.

6. Conclusion

We found cefepime-enmetazobactam as a potentially useful option in the management of ESBL-producing uropathogens in our hospital. It showed susceptibility rates greater than piperacillin-tazobactam and cefoperazone-sulbactam and closely matching meropenem. It also had the added benefit of preserving carbapenem utility which is particularly relevant in antimicrobial stewardship by diminishing the emergence and spread of organisms resistant to last-resort beta-lactam agents like carbapenems.

7. Conflict of interest

None.

8. Source of Funding

None.

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None.

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