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Cefepime Enmetazobactam: A Carbapenem Sparing Strategy Against ESBL Producing Enterobacterales

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ABSTRACT

Background & Objectives: The rise of antimicrobial resistance, particularly among Gram-negative pathogens producing extended-spectrum β-lactamases (ESBLs), is a major global concern. Carbapenems remain the mainstay of therapy but their overuse has led to the emergence of carbapenemases, emphasizing the need for carbapenem-sparing alternatives. Cefepime combined with Enmetazobactam, a novel β-lactam/β-lactamase inhibitor combination, has shown promising activity against ESBL-producing Enterobacterales. The present study aimed to evaluate in-vitro susceptibility profile of Cefepime-Enmetazobactam compared to other commonly used antimicrobials.
Methods: This prospective study was carried out in the Department of Microbiology over a six-month period (April–September 2025). A total of 192 ESBL-producing Enterobacterales isolates obtained from blood, urine and respiratory samples of patients aged ≥18 years were included. Susceptibility testing of Cefepime–enmetazobactam and other antibiotics were assessed by Kirby Bauer disk diffusion, and results were interpreted using EUCAST 2024 guidelines.
Results: Among the 192 ESBL-producing Enterobacterales isolates, *E.coli* (48%) was the most common pathogen, followed by *Klebsiella* spp.(45%) and *Enterobacter* spp.(6%).Cefepime–enmetazobactam showed an overall susceptibility rate of 91.7%,with higher activity against *E. coli* (94.6%),*Klebsiella* spp.(88.5%) and *Enterobacter* spp.(91.7%).When compared with other antibiotics, Cefepime–enmetazobactam demonstrated superior efficacy over Meropenem(47.9%),Imipenem(43.2%)and Piperacillin–tazobactam(20.8%).Higher susceptibility to Cefepime–enmetazobactam was observed in urinary tract infections(95.5%) and bloodstream infections(95%) compared to lower respiratory tract infections(77.5%).
Conclusion: Cefepime-Enmetazobactam exhibited superior in-vitro activity against ESBL-producing Enterobacterales compared to most β-lactams and fluoroquinolones, and demonstrated comparable efficacy to carbapenems. These findings support its potential role as a carbapenem-sparing therapeutic option, especially in urinary tract infections. Continuous surveillance and clinical outcome studies are warranted to establish its role in antimicrobial stewardship programs.

Keywords: ESBL-producing Enterobacterales, Cefepime–Enmetazobactam, β-lactamase inhibitors, Carbapenem-sparing therapy, antimicrobial susceptibility testing, Kirby–Bauer disk diffusion, EUCAST breakpoints

INTRODUCTION

The burden of antimicrobial resistance (AMR) among Gram-negative bacteria has become a critical global health concern. Recent global estimates indicate that AMR is associated with millions of deaths annually, with projections suggesting a substantial increase in mortality by 2050 if current trends persist.[1] Among Gram-negative pathogens, Enterobacterales producing extended-spectrum β-lactamases (ESBLs) represent a particularly serious challenge, as these enzymes confer resistance to penicillins, first, second, third- and fourth-generation cephalosporins, and monobactams, thereby significantly narrowing available treatment options.[2,3] Carbapenems have traditionally been considered the drugs of choice for severe infections caused by ESBL-producing Enterobacterales due to their stability against ESBL-mediated hydrolysis. However, the unrestricted use of these agents over the past two decades has driven the emergence of diverse carbapenemases, thereby making carbapenem-sparing therapeutic strategies a critical priority.[4]

β -Lactamase inhibitors (BLI) were developed to counter β-lactamases and are combined with β-lactam antibiotics since BLIs do not normally possess direct penicillin binding protein (PBP) inhibitory activity. Although β-lactamase inhibitors were initially effective, the emergence and widespread dissemination of novel β-lactamases have progressively declined their efficacy, thereby necessitating the development of more potent agents. Enmetazobactam (formerly AAI101) is a penicillanic acid sulfone β-lactamase inhibitor structurally related to tazobactam, differing only by the presence of an additional methyl group on the triazole ring.[5] This modification imparts zwitterionic characteristics that enhance penetration into the bacterial periplasm, a property shared with cefepime.[6] Cefepime, a fourth-generation cephalosporin, exhibits broad-spectrum antibacterial activity and favourable pharmacokinetic properties, including enhanced penetration into Gram-negative bacteria.[2,6] Since Cefepime is intrinsically stable against hydrolysis by most AmpC and OXA β-lactamases, it represents an optimal partner for enmetazobactam.[5]Like other β-lactamase inhibitors, enmetazobactam possesses minimal intrinsic antibacterial activity; however, its combination with cefepime markedly restores cefepime efficacy against ESBL-producing organisms, achieving substantially reduced MIC values(MIC_{50} values -0.06mg/l and MIC_{90} values- 0.5 mg/L, respectively).[7] The combination of Enmetazobactam with cefepime represents a potent carbapenem-sparing treatment regimen for infections caused by Enterobacterales producing ESBLs. Therefore, this study aims to assess the susceptibility of the drug Cefepime Enmetazobactam against ESBL producing Enterobacterales.

MATERIALS & METHODS

The study was conducted in the Department of microbiology, for a period of 6 months (From April 2025 to September 2025). 192 ESBL isolates were isolated from blood, urine and respiratory specimens from inpatients of all Intensive Care units and clinical departments at Mysore Medical College Hospital and Research Institute. Patients above 18 years of age were included in the study. The Kirby-Bauer disk diffusion method was used to test antimicrobial susceptibility and interpreted following (European Committee on Antimicrobial Susceptibility Testing) EUCAST 2024 guidelines.[8] ESBL screening was done by using both ceftazidime (30 µg) disc alone and in combination with clavulanic acid (30 µg/10 µg).[9] Phenotypic confirmation of

ESBL production was performed using the double-disc synergy test. Drug discs were placed 20 mm apart (center to center) on the agar surface and incubated at 37ºC overnight. An increase of more than 5 mm in the inhibition zone diameter for Ceftazidime clavulanate compared to ceftazidime alone was interpreted as ESBL production.

Cefepime Enmetazobactam was tested against ESBL producers by disk diffusion method and the zone of inhibition measured. The results were interpreted according to the EUCAST guidelines as updated in 2024.Antibiotic susceptibility for cefepime enmetazobactam (30/20 *μg*) was taken susceptible as ≥22 mm as per EUCAST breakpoints released in 2024(EUCAST breakpoint tables v. 15.0).[8]

RESULTS

Among 192 ESBL-producing Enterobacterales isolates analysed, *Escherichia coli* (48%), *Klebsiella* spp. (45%), and *Enterobacter* spp. (6%) were predominant pathogens (Table1). Cefepime /Enmetazobactam demonstrated 91.7% overall susceptibility, with higher activity against E. coli (94.6%), Klebsiella spp. (88.5%) and Enterobacter spp (91.7%). All the susceptible isolates were tested for the susceptibility to other beta lactam antibiotic drugs such as the beta lactam/beta lactam inhibitor Piperacillin tazobactam(100/10µg), Amoxicillin clavulanate(20/10µg), the carbapenems Imipenem(10µg), Meropenem (10µg), Cefepime (30µg, the aminoglycoside Gentamicin(10µg) and the fluoroquinolone Ciprofloxacin(5µg). Antibiotic Susceptibility pattern of the ESBL isolates is summarized in Table 1.

Table 1: Antibiotic Susceptibility pattern of the ESBL isolates

Organisms	**E. coli (n=93)**		**Klebsiella spp (n=87)**		**Enterobacter spp (n=12)**		**Total(n=192)**	
Drugs	**Sensitive**	**Resistant**	**Sensitive**	**Resistant**	**Sensitive**	**Resistant**	**Sensitive**	**Resistant**
Cefepime Enmetazobactam (30/20µg)	88 (94.6%)	5 (5.4%)	77 (88.50%)	10 (11.5%)	11 (91.70%)	1 (8.30%)	176 (91.70%)	16 (8.30%)
Cefepime (30µg)	3 (3.20%)	90 (96.8%)	1 (1.1%)	86 (98.9%)	0 (0%)	12 (100%)	4 (2.1%)	188 (97.9%)
Amoxicillin Clavulanate (20/10µg)	6 (6.5%)	87 (93.5%)	8 (9.2%)	79 (90.8%)	0 (0%)	12 (100%)	14 (7.3%)	178 (92.7%)
Piperacillin Tazobactam(100/10µg)	27 (29%)	66 (71%)	12 (13.8%)	75 (86.2%)	1 (8.3%)	11 (91.7%)	40 (20.8%)	152 (79.2%)
Imipenam (10µg)	47 (50.5%)	46 (49.5%)	31 (35.6%)	56 (64.4%)	5 (41.7%)	7 (58.3%)	83 (43.2%)	109 (56.8%)
Meropenam (10µg)	54 (58.1%)	39 (41.9%)	35 (40.2%)	52 (59.8%)	3 (25%)	9 (75%)	92 (47.9%)	100 (52.1%)
Gentamicin (10µg)	49 (52.7%)	44 (47.3%)	41 (47.1%)	46 (52.9%)	5 (41.7%)	7 (58.3%)	95 (49.5%)	97 (50.5%)
Ciprofloxacin (10µg)	10 (10.8%)	83 (89.2%)	9 (10.3%)	78 (89.7%)	3 (25%)	9 (75%)	22 (11.5%)	170 (88.5%)

Cefepime/Enmetazobactam demonstrated higher sensitivity (91.7%) compared to other tested antibiotics, including meropenem (47.9%), imipenem (43.2%), gentamicin (49.5%), and piperacillin-tazobactam (20.8%), highlighting its superior efficacy against ESBL-producing Enterobacterales (Table 1).

Sensitivity to Cefepime/ Enmetazobactam shows higher susceptibility in urinary tract infections (95.5%) compared to bloodstream infections (95%) and lower respiratory tract infections (77.5%) highlighting its potential as a more effective therapeutic option in managing ESBL-associated infections (Table 1).

DISCUSSION

Enterobacterales - most notably *Escherichia coli* and *Klebsiella pneumoniae*, are responsible for a wide spectrum of infections affecting both hospitalized patients and individuals in community care settings.[10] Antimicrobial resistance among Gram-negative bacteria, particularly extended-spectrum β-lactamase (ESBL)–producing Enterobacterales, represents a major and growing clinical challenge worldwide. ESBL-producing Enterobacterales have been classified as a Serious Threat by the CDC and designated as a critical priority pathogen in the WHO Bacterial Priority Pathogens List 2024.[11] In India, the prevalence of ESBL producers reported across multiple studies ranges from 60% to 80%, emphasizing the urgent need for effective therapeutic alternatives.[9,13]Globally, increasing resistance to third- and fourth-generation cephalosporins has resulted in escalating carbapenem use, which in turn has driven the emergence and spread of carbapenem resistance.[12] This concerning trend has intensified efforts to identify carbapenem-sparing strategies, including novel β-lactam/β-lactamase inhibitor (BL/BLI) combinations and effective non-β-lactam agents.

In the present study, 91.7% of ESBL-producing isolates were susceptible to cefepime-enmetazobactam, a rate notably higher than those observed for Imipenem (43.2%), Meropenem (47.9%), and Piperacillin–tazobactam (20.8%). These findings highlight the strong in-vitro activity of Cefepime-enmetazobactam against ESBL producers and its potential role as a Carbapenem-sparing alternative. Our results are broadly consistent with international data. Morrissey et al. (2019), in a study of 1,993 isolates from U.S. and European hospitals, reported that Cefepime–enmetazobactam inhibited more than 98% of Enterobacterales, with particularly strong activity against *Escherichia coli* and *Klebsiella pneumoniae*, comparable to Meropenem.[6] It also demonstrated noninferiority, and in some outcomes superiority, compared with piperacillin–tazobactam for the treatment of complicated urinary tract infections (cUTIs) and acute pyelonephritis which aligns with our study wherein urinary isolates showed the highest susceptibility (95.5%).[7,14,15]

Cefepime-enmetazobactam is approved at a dose of 2 g cefepime plus 0.5 g enmetazobactam every 8 hours, administered by intravenous infusion over 2 hours for complicated UTIs,[11,15] and over 4 hours for hospital-acquired and ventilator-associated pneumonia.[17] For MIC determination, the enmetazobactam concentration is fixed at 8µg/ml.[12]Adverse effects of Cefepime is generally typical of β-lactam antibiotics, including allergic reactions and antibiotic-associated diarrhoea but when administered with enmetazobactam, the regimen has demonstrated good tolerability, with mainly low-grade and reversible elevations in hepatic enzymes reported in clinical studies.[5] Darlow et al. (2025) demonstrated high urinary excretion of the Cefepime enmetazobactam combination and confirmed its efficacy against ESBL-producing Enterobacterales, supporting its role as an effective treatment option for complicated UTIs.[5] Furthermore, Bonnin et al. (2025) reported sustained activity against OXA-48–like carbapenemase producing strains, with susceptibility rates of 96–97%, although activity remained limited against metallo-β-lactamase (MBL) producers such as NDM and VIM.[16]

Consistent with these observations, One limitation of the present study is this study did not include MIC determination for cefepime-enmetazobactam. Although disk diffusion–based susceptibility testing reflects real-world laboratory practice and supports clinical decision-making, the absence of MIC values limits detailed pharmacokinetic/ pharmacodynamic correlation and comparison with international surveillance studies.

Metallo-β-lactamase (MBL)–producing organisms were not evaluated. This exclusion was intentional, as enmetazobactam, like other serine β-lactamase inhibitors, lacks inhibitory activity against class B metallo -β-lactamases, and inclusion of such isolates would not be expected to reflect the intrinsic activity of the cefepime–enmetazobactam combination.[2,16,19] Moreover, focusing on ESBL producing Enterobacterales allowed for a more accurate assessment of the combination's intended clinical and microbiological spectrum, in line with its approved indications and current therapeutic role.[15,18]Overall, our findings, in conjunction with global evidence, support cefepime-enmetazobactam as a promising therapeutic option for ESBL-producing Enterobacterales and reinforce its role in antimicrobial stewardship strategies aimed at preserving carbapenem efficacy.

CONCLUSION

Cefepime/enmetazobactam exhibited superior in-vitro activity against ESBL-producing Enterobacterales compared to most β-lactam- β-lactam inhibitor combinations, carbapenems, aminoglycosides and fluoroquinolones. These findings support its potential role as a carbapenem-sparing therapeutic option, especially in urinary tract infections. Continuous surveillance and clinical outcome studies are warranted to establish its role in antimicrobial stewardship programs.

Declaration by Authors

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