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Review Article

Cefepime-Enmetazobactam: a novel β-Lactam/β-Lactamase inhibitor combination for complicated urinary tract infections

Arunkumar Ramaraj*, Natarajan Thangam Nivasini, Vikram Balaji, Jerin James, Sathyanarayanan Varadarajan

Department of Pharmacology, SRM Medical College Hospital & Research Centre, Kattankulathur, Tamil Nadu, India

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***Correspondence:**
Dr. Arunkumar Ramaraj,
Email: drarun094@gmail.com

ABSTRACT

Complicated urinary tract infections (cUTIs) represent a significant global health challenge, particularly with the rising prevalence of extended-spectrum β-lactamase (ESBL)-producing pathogens. Cefepime-Enmetazobactam, approved in India in June 2024, represents a novel β-lactam/β-lactamase inhibitor combination specifically developed to address multidrug-resistant Gram-negative infections. This review examines the pharmacological properties, clinical efficacy, and therapeutic potential of Cefepime-Enmetazobactam in managing cUTIs. The Phase 3 ALLIUM trial demonstrated superior clinical cure and microbiological eradication rates compared to Piperacillin-Tazobactam, with particularly pronounced efficacy against ESBL-producing Enterobacterales (73.7% vs 51.5%). The combination exhibits a favourable safety profile with transaminase elevation, increased bilirubin, headache, and infusion site reactions being the most common adverse events. As a carbapenem-sparing option, Cefepime-Enmetazobactam addresses critical antimicrobial stewardship concerns while providing an effective treatment alternative for resistant pathogens. While demonstrating promising results, further research regarding long-term outcomes, resistance development, and cost-effectiveness is warranted to fully establish its role in contemporary antimicrobial therapy.

Keywords: Complicated urinary tract infections, Cefepime-Enmetazobactam, ESBL-producing pathogens, β-lactamase inhibitor, Antimicrobial resistance, Carbapenem-sparing therapy

INTRODUCTION

Urinary tract infections (UTIs) represent one of the most prevalent bacterial infections encountered in both community and healthcare settings.[1] Traditionally, UTIs are classified as either uncomplicated or complicated, a distinction first established by the Infectious Diseases Society of America (IDSA) and the European Society of Clinical Microbiology and Infectious Diseases to standardize clinical research populations. Uncomplicated UTIs (uUTIs) typically occur in otherwise healthy, non-pregnant women with normal urinary tract anatomy and function. These infections generally respond well to standard antimicrobial therapy and rarely result in serious complications. In contrast, complicated UTIs (cUTIs) are associated with factors that increase the risk of treatment failure or serious outcomes. These factors include structural or functional abnormalities of the urinary tract, significant comorbidities (such as diabetes mellitus, renal insufficiency, or immunosuppression), as well as special populations including pregnant women, patients with urinary calculi, and individuals with indwelling urinary devices or obstructive uropathy.

Neurogenic bladder and renal transplantation also classify UTIs as complicated.[2] Pyelonephritis, an infection involving the renal parenchyma, represents a severe manifestation of UTI that requires prompt diagnosis and appropriate management to prevent complications such as renal scarring and systemic sepsis. In India, UTI prevalence demonstrates considerable regional variation, ranging from 21.8% to 31.3%.[3] Culture positivity rates in various studies range from 42.1% among non-pregnant women in Odisha to 52% in hospital-based populations,

with cUTIs predominating in inpatient settings in several reports.[4-6]

A significant challenge in managing cUTIs is the rising prevalence of antimicrobial resistance (AMR), particularly among Gram-negative organisms.[7] Global resistance patterns show alarming trends, with fluoroquinolone resistance ranging from 10% to 80%, third-generation cephalosporin resistance from 10% to 70%, and carbapenem resistance from 5% to 35%. In India, resistance to ciprofloxacin in *Escherichia coli* has exceeded 57%, largely attributed to the widespread use of fluoroquinolones and cephalosporins. The emergence and dissemination of resistant organisms have substantially complicated the management of cUTIs. Current guidelines from the IDSA and the European Association of Urology (EAU) emphasize judicious antibiotic use and antimicrobial stewardship to combat resistance.[8]

Despite this urgent need, the development pipeline for novel antibiotics remains limited. A significant barrier is the insufficient financial incentives for pharmaceutical companies. According to U.S. FDA guidance, the antimicrobial market offers lower financial returns compared to other therapeutic areas such as oncology.[9] Consequently, less than 5% of venture capital investments in pharmaceuticals are directed toward antimicrobial development, resulting in stagnation of new drug discovery efforts.

ESBL-producing gram-negative pathogens

Extended-spectrum β-lactamases (ESBLs) constitute a critical resistance mechanism in Gram-negative bacteria, conferring resistance to a broad spectrum of β-lactam antibiotics, including penicillin, first- through third-generation cephalosporins, and the monobactam aztreonam.[10]

ESBLs typically remain susceptible to inhibition by β-lactamase inhibitors such as clavulanic acid, sulbactam, and tazobactam, and generally do not hydrolyse cephamycin or carbapenem, distinguishing them from other β-lactamases. Their enzymatic activity results from specific amino acid substitutions in the active site, frequently originating from mutations in TEM-1, TEM-2, or SHV-1 β-lactamases, leading to an expanded substrate spectrum.[11] The genes encoding these enzymes are predominantly located on plasmids, mobile genetic elements capable of horizontal transfer, facilitating rapid dissemination of resistance across bacterial populations in both healthcare and community environments. ESBLs primarily belong to ambler class A β-lactamases, encompassing TEM, SHV, and the increasingly prevalent CTX-M families. In contrast, ambler class B enzymes, known as metallo-β-lactamases, utilize zinc ions and possess broader hydrolytic capacity, including carbapenem antibiotics. While distinct from ESBLs, the frequent co-occurrence of carbapenemases with ESBLs further complicates clinical management and underscores the growing threat of multidrug-resistant Gram-negative bacterial infections.

Several risk factors have been consistently associated with an increased likelihood of UTIs caused by ESBL-producing organisms.[10] Other significant risk factors include recent hospitalization, prolonged hospital stays, invasive urological procedures, and the presence of indwelling urinary catheters. Prior antibiotic exposure, particularly to cephalosporins, is a well-established contributor due to the selective pressure it exerts on microbial populations. Demographic factors such as advanced age and male gender have been associated with increased susceptibility, especially among older adults. In paediatric populations, recurrent UTIs and absence of fever at presentation have been linked to increased ESBL risk. Additional factors such as diabetes mellitus and certain environmental exposures, including freshwater swimming, have been reported in community-acquired ESBL-UTIs.

E. coli is the predominant pathogen isolated in both uncomplicated and complicated UTIs, accounting for approximately 75–90% of cases and serving as a major producer of ESBLs.[12] Klebsiella pneumoniae represents the second most common uropathogen, and together with E. coli, belongs to the Enterobacterales order-Gram-negative bacteria commonly inhabiting the gastrointestinal tract.

In healthcare settings, polymicrobial infections are not uncommon, with frequent isolates including *Pseudomonas aeruginosa*, Enterococcus spp., Candida spp., *Staphylococcus aureus*, and Group B Streptococcus, particularly in complicated UTIs. While non-Enterobacteriaceae Gram-negative bacteria such as *P. aeruginosa* and *Haemophilus influenzae* can also produce ESBLs, their role in UTIs is less prominent. The predominance of gastrointestinal flora, particularly Enterobacterales, in ESBL-UTIs underscores the significance of intestinal colonization as a reservoir for resistant organisms and highlights the complexity of selecting appropriate empiric therapy, especially in healthcare-associated and complicated infections.

Cefepime

Cefepime, a fourth-generation cephalosporin antibiotic, is distinguished by its broad-spectrum activity primarily against Gram-negative bacteria, including certain strains producing extended-spectrum β-lactamases (ESBLs).[13] Its bactericidal mechanism of action involves penetration of bacterial cell walls and selective binding to penicillin-binding proteins (PBPs), particularly PBP3, thereby disrupting peptidoglycan synthesis and inducing bacterial cell lysis.

In clinical practice, cefepime is widely utilized for severe infections, including pneumonia, urinary tract infections, and bloodstream infections, often as empiric therapy pending pathogen identification. Despite its extensive

clinical application, the therapeutic efficacy of cefepime can be compromised by specific β-lactamases, notably Ambler class A and C enzymes.[14]

The pharmacokinetic profile of cefepime facilitates convenient intravenous or intramuscular administration; however, its predominant renal elimination necessitates dosage adjustments in patients with impaired renal function to prevent toxicity.

Cefepime, present as cefepime hydrochloride monohydrate, is a white to pale yellow powder. The chemical name for cefepime is (6R,7R, Z) -7-(2-(2-aminothiazol-4-yl)-2-(methoxyimino) acetamido)-3-((1-methylpyrrolidinium-1-yl) methyl)-8-oxo-5-thia-1-aza-bicyclo (4.2.0) oct-2-ene-2-carboxylate. Its chemical structure is shown in Figure 1.

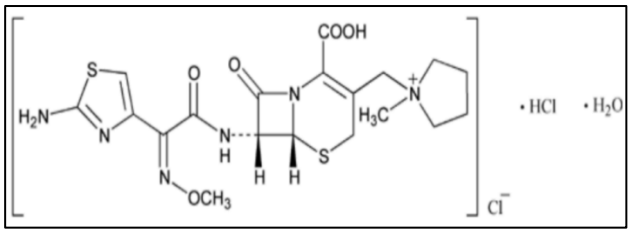

Figure 1: Structure of cefepime.

Enmetazobactam

Enmetazobactam represents a novel β-lactamase inhibitor developed through structure-based drug design, offering potent inhibitory activity against a broad spectrum of β-lactamases, including Ambler class A, C, and select D enzymes. Its mechanism of action involves irreversible binding to β-lactamase enzymes, neutralizing their activity and thereby restoring the efficacy of β-lactam antibiotics against resistant pathogens.[15]

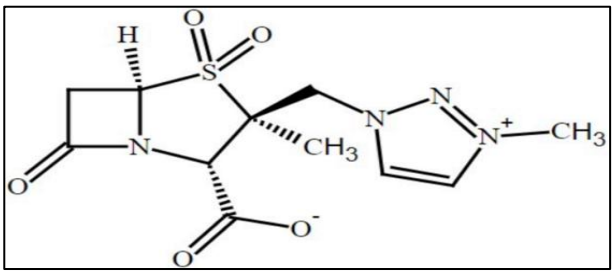

Figure 2: Structure of Enmetazobactam.

The optimized molecular structure of Enmetazobactam facilitates efficient membrane penetration and strong enzyme affinity, distinguishing it from traditional β-lactamase inhibitors such as tazobactam. The development and subsequent global regulatory approval of Enmetazobactam, originating in India, highlights the country's growing contribution to pharmaceutical innovation and antimicrobial resistance management.[16-19] Enmetazobactam is a white to off-white powder, with a molecular weight of 314.38. The chemical name for Enmetazobactam is (2S,3S,5R)-3-methyl-3-((3-methyl-1H-1,2,3-triazol-3-ium-1-yl) methyl)-7-oxo-4-thia-1-azabicyclo (3.2.0) heptane-2-carboxylate 4,4-dioxide, its chemical structure is shown in Figure 2.

Cefepime-Enmetazobactam

The combination of cefepime and enmetazobactam, introduced in India in June 2024 by Orchid Pharma and Cipla, represents an important advancement in treating infections caused by multidrug-resistant Gram-negative bacteria, including ESBL-producing Enterobacterales. Approved by the Drugs Controller General of India (DCGI) for complicated UTIs, hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP), this combination shows superior clinical efficacy compared to traditional therapies like Piperacillin-Tazobactam.[21]

Notably, the phase 3 ALLIUM trial demonstrated enhanced clinical cure and microbiological eradication rates for complicated UTIs and pyelonephritis.[20,22] In vitro studies have shown efficacy comparable to carbapenems, positioning this combination as a valuable carbapenem-sparing option. While generally vulnerable to carbapenemases, preliminary research indicates potential efficacy against specific enzymes such as KPC and OXA-48-like types.

Given its interaction profile, similar to cefepime but with additional considerations from enmetazobactam, careful management of concomitant medications is essential. Cefepime-enmetazobactam aligns well with antibiotic stewardship principles, offering targeted therapy that reduces carbapenem reliance, crucial for managing resistance patterns prevalent in India. Continued research and clinical surveillance will be vital to fully optimize its therapeutic potential within national guidelines.

CLINICAL TRIAL DETAILS

Summary

This clinical trial is designed to evaluate the efficacy of Cefepime-Enmetazobactam in adult patients (18 years and older) with complicated urinary tract infections (cUTI).[23]

Study type

This was an interventional study.

Phase

This was phase 3 study.

Study design

Allocation: The allocation of the study was randomized.

Masking: Double-blind.

Primary purpose: The primary purpose was therapeutic intervention.

Target indications: Complicated urinary tract infections, pyelonephritis.

Interventions

Experimental arm: Cefepime (2 g) and Enmetazobactam (0.5 g), administered intravenously every 8 hours via infusion over 2 hours, for a duration of 7 to 14 days, based on clinical need.

Active comparator arm: Piperacillin/Tazobactam (4.5 g) administered intravenously every 8 hours via infusion over 2 hours, for the same duration.

Eligibility

Sex and gender: Both sexes were eligible.

Ages: 18 years and older (adults and older adults).

PRESCRIBING INFORMATION (FDA APPROVED)

Therapeutic indications

Combining cefepime, a cephalosporin antibacterial, and enmetazobactam, a beta-lactamase inhibitor, is indicated for treating complicated urinary tract infections (cUTI), including pyelonephritis, caused by susceptible microorganisms such as *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, and *Enterobacter cloacae* complex.

Limitations of use

To minimize the development of drug-resistant bacteria and maintain effectiveness, it should be exclusively used for confirmed or highly suspected bacterial infections.

Dosage and application guidelines

Standard dose:

2.5 g (2 g Cefepime and 0.5 g Enmetazobactam) every 8 hours via intravenous infusion over 2 hours for patients with eGFR 60-129 ml/min.

Dose adjustments required for eGFR <60 ml/min or ≥130 ml/min.

Dosage forms and strengths

Supplied as sterile powder in single-dose vials containing 2 grams Cefepime and 0.5 grams Enmetazobactam.

Contraindications

It is contraindicated in patients with a known serious hypersensitivity reaction to any component or other beta-lactam antibacterials.

Warnings and precautions

Hypersensitivity: Serious and potentially fatal allergic reactions (anaphylaxis) may occur. Discontinue immediately if allergic reactions are observed.

Neurotoxicity: Can occur especially in patients with renal impairment without proper dosage adjustments. Monitor closely.

Clostridioides difficile-associated diarrhoea: Consider this diagnosis if diarrhoea occurs during or after treatment.

Adverse drug reactions (≥5% incidence)

Elevated transaminases, increased bilirubin, headache, phlebitis/infusion site reactions.

Drug interactions

Monitor renal function closely when co-administered with aminoglycosides or diuretics. May cause false-positive results for glucose in urine.

Use in specific populations

Pregnancy: Limited human data available; animal studies did not show malformations but did indicate possible maternal toxicity at high doses.

Lactation: Cefepime detected in breast milk in low concentrations; Enmetazobactam presence likely but unknown.

Paediatric: Safety and effectiveness not established for patients younger than 18 years.

Geriatric: Increased risk of neurotoxicity in elderly patients with renal impairment.

Renal impairment

Dose adjustments required based on the degree of renal impairment. Regular monitoring is recommended.

Hepatic impairment

Dose adjustment is unlikely necessary as both components have minimal hepatic metabolism.

Overdosage

May lead to neurological complications such as seizures. Both cefepime and enmetazobactam can be removed by haemodialysis; however, clinical experience is limited.

Table 1: Summary of phase 2 and phase 3 studies of cefepime-enmetazobactam for complicated urinary tract infections.

Study	Study design	N	Treatment arms	Safety outcomes	Efficacy outcomes
Phase 2	Randomized, multicentre, double-blind study in hospitalized adults with cUTI/AP	45	Cohort 1: FEP 1g/EMT 0.5 g (n=15) vs FEP 1g (n=7). Cohort 2: FEP 2g/EMT 0.75 g (n=15) vs FEP 2g (n=8) IV q8h by 2h infusion for 7-10 days with 28-day follow-up	AEs: 43.3% (13/30) FEP-EMT vs 40.0% (6/15) FEP. Serious AEs: 2 patients in FEP 2 g/EMT 0.75 g group. Drug-related TEAEs: 13.3% (4/30) FEP-EMT vs 20.0% (3/15) FEP. Discontinuations: 2 patients due to allergic dermatitis. No deaths	Microbiological eradication: 83.3% (20/24) FEP-EMT vs 73.3% (11/15) FEP. Clinical cure: 95.8% (23/24) FEP-EMT vs 93.3% (14/15) FEP. ESBL isolate eradication: 85.7% (6/7) FEP-EMT vs 75.0% (3/4) FEP. Most common pathogens: *E. coli* (66.7%), *K. pneumoniae* (23.1%); 28.2% ESBL producing
Phase 3 (ALLIUM)	Multinational, double-blind, randomized (1:1) controlled trial in patients with cUTI/AP	1034	FEP 2 g/EMT 0.5 g q8h (n=516) vs PTZ 4 g/0.5 g q8h (n=518) IV infusion over 2h for 7-14 days; up to 14 days for patients with concurrent bacteremia	Discontinuations due to AEs: 3% (13/516) FEP-EMT vs 2% (10/518) PTZ. Deaths: 0.6% (3/516) FEP-EMT vs 0.6% (3/518) PTZ. Most common AEs (≥5%) in FEP-EMT: transaminases increased (20%), bilirubin increased (7%), headache (5%), phlebitis/infusion site reactions (5%)	Overall success (clinical cure+microbiological eradication). mMITT population: 79.1% (273/345) FEP-EMT vs 58.9% (196/333) PTZ; Difference: 21.2% (95% CI: 14.3, 27.9). ESBL subgroup: 73.7% (56/76) FEP-EMT vs 51.5% (34/66) PTZ; Difference: 30.2% (95% CI: 13.4, 45.1). mMITT+R ESBL subgroup: 73.6% (67/91) FEP-EMT vs 50.6% (41/81) PTZ; Difference: 30.0% (95% CI: 14.9, 43.3). Bacteremia patients: 71% (27/38) FEP EMT vs 50% (14/28) PTZ

AEs: adverse events, AP: acute pyelonephritis, cUTI: complicated urinary tract infection, EMT: enmetazobactam, ESBL: extended spectrum β-lactamase, FEP: cefepime, mMITT: microbiological modified intent-to-treat, PTZ: piperacillin-tazobactam, q8h: every 8 hours, TEAEs: treatment-emergent adverse events.

mMITT population definition

All randomized patients who received any study drug and had at least 1 baseline gram-negative pathogen ≥10^5 CFU/ml in urine culture or the same pathogen in blood and urine cultures that is not resistant to study drugs.

mMITT+R definition

Includes patients within the mMITT population with baseline pathogens also resistant to either cefepime-enmetazobactam (≥16 µg/ml) or piperacillin-tazobactam (≥128 µg/ml).

DISCUSSION

Extended-spectrum β-lactamases (ESBLs) and carbapenemases, prevalent among Gram-negative pathogens such as Enterobacterales and *Pseudomonas aeruginosa*, have increasingly limited therapeutic options.[24] Cefepime-Enmetazobactam has emerged as a promising therapeutic strategy to address these resistant infections, demonstrating robust in vitro and clinical efficacy against a broad spectrum of Gram-negative bacteria.

Biochemical studies confirmed that enmetazobactam demonstrates 10-100-fold greater potency against CTX-M-type ESBLs compared to tazobactam, explaining the superior clinical outcomes observed with this combination.[25,26]

The pharmacokinetic and pharmacodynamic profiles of Cefepime-Enmetazobactam are favorable, with effective systemic distribution and renal clearance necessitating precise dose adjustments in patients with impaired renal function. The phase 3 ALLIUM trial assessed the clinical efficacy and safety of this combination in treating complicated urinary tract infections (cUTIs), complicated intra-abdominal infections (cIAIs), and acute pyelonephritis.

The combination demonstrated non-inferiority and, in specific metrics, superiority compared to standard-of-care therapies, including meropenem and Piperacillin-Tazobactam.[27,28]

The safety profile of cefepime-enmetazobactam was rigorously evaluated in both the ALLIUM trial and subsequent post-marketing surveillance studies. Analysis of adverse events found that the combination demonstrated a safety profile consistent with the known profile of cefepime alone, with no evidence of additive toxicity from enmetazobactam.[29]

While the study provided substantial evidence of short-term clinical efficacy, several limitations warrant further investigation. The specific focus on certain infection types could limit generalizability to other clinical settings. Moreover, long-term efficacy, potential resistance development, cost-effectiveness, and accessibility in resource-limited regions require further research. Ongoing surveillance studies will be crucial to monitor resistance patterns and assess the sustained effectiveness of Cefepime-Enmetazobactam in clinical practice.

CONCLUSION

Cefepime–Enmetazobactam emerges as a highly promising therapeutic combination, addressing the escalating global challenge posed by multidrug-resistant Gram-negative bacteria, particularly ESBL-producing Enterobacterales and certain carbapenemase-producing pathogens. Rigorous clinical evidence, notably from the phase 3 ALLIUM trial, demonstrates its superior efficacy compared to conventional therapies such as Piperacillin–Tazobactam, providing a critical alternative for the management of severe infections including complicated urinary tract infections and complicated intra-abdominal infections.

However, ongoing research into long-term outcomes, resistance evolution, economic considerations, and broader clinical applicability remains essential to fully realize the potential of Cefepime-Enmetazobactam. Supported by comprehensive prescribing guidelines and a favourable safety profile, Cefepime–Enmetazobactam represents a significant leap forward in the ongoing battle against multidrug-resistant bacterial infections, offering renewed hope and a robust therapeutic strategy for healthcare providers and patients alike.

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