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CASE REPORT

Ventilator-Associated Pneumonia Due to ESBL-Producing *Escherichia coli* Successfully Treated with Cefepime/Enmetazobactam: A European Case Report

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ABSTRACT

Extended-spectrum β-lactamase (ESBL)-producing Enterobacterales represent a growing cause of ventilator- associated pneumonia (VAP) in critically ill patients. Although carbapenems remain the standard treatment, carbapenem-sparing strategies are increasingly needed to limit the emergence of carbapenem resistance. Cefepime/enmetazobactam (FEP/META) is a novel β-lactam/β-lactamase inhibitor combination with demonstrated activity against ESBL-producing organisms and favorable intrapulmonary pharmacokinetic properties. We present one of the first reported European cases of VAP due to CTX-M-producing *Escherichia coli* successfully treated with cefepime/enmetazobactam in a 72-year-old patient admitted to the intensive care unit for traumatic spinal cord injury. The isolate was resistant to third-generation cephalosporins and cefepime but remained susceptible to carbapenems and FEP/META (minimum inhibitory concentration [MIC] 0.06 mg/L). Targeted treatment with FEP/META (2.5 g every 8 h intravenously) was administered for 7 days. Rapid clinical and microbiological improvement was observed, with resolution of fever, decline in inflammatory biomarkers, and improvement in oxygenation parameters. No relapse or adverse events occurred. This case supports the potential role of FEP/META as a carbapenem-sparing option for ESBL-related VAP and highlights the importance of pharmacokinetic/

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pharmacodynamic considerations in optimizing antimicrobial stewardship strategies.

PLAIN LANGUAGE SUMMARY

Ventilator-associated pneumonia (VAP) is a serious lung infection that occurs in patients receiving mechanical ventilation in the intensive care unit. Some bacteria causing ventilator-associated pneumonia produce enzymes called extended-spectrum β-lactamases (ESBLs), which make them resistant to many commonly used antibiotics. Carbapenems are often used to treat these infections, but their widespread use may promote the development of further resistance. Cefepime/enmetazobactam is a new antibiotic combination designed to treat infections caused by ESBL-producing bacteria. We describe the case of a 72-year-old critically ill patient who developed ventilator-associated pneumonia caused by ESBL-producing *Escherichia coli*. The infection was successfully treated with cefepime/enmetazobactam without the need for carbapenem therapy. The patient improved rapidly and experienced no recurrence of infection. This report suggests that cefepime/enmetazobactam may represent an effective carbapenem-sparing treatment option for certain severe lung infections, although further clinical studies are needed.

Keywords: Ventilator-associated pneumonia; ESBL; Cefepime/enmetazobactam; Carbapenem-sparing therapy; Antimicrobial stewardship

Key Summary Points

Ventilator-associated pneumonia (VAP) caused by ESBL-producing Enterobacterales is increasingly encountered in critically ill patients and is typically treated with carbapenems.

Carbapenem-sparing treatment strategies are needed to limit the emergence and spread of carbapenem-resistant organisms.

Cefepime/enmetazobactam is a novel β-lactam/β-lactamase inhibitor combination with strong activity against ESBL-producing pathogens and favorable intrapulmonary pharmacokinetics.

We present one of the first reported European cases of ventilator-associated pneumonia caused by CTX-M-producing *Escherichia coli* successfully treated with cefepime/enmetazobactam.

Rapid clinical and microbiological response without relapse suggests cefepime/enmetazobactam may represent a promising carbapenem-sparing option for ESBL-related VAP.

INTRODUCTION

Ventilator-associated pneumonia (VAP) caused by extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales represents a therapeutic challenge in critically ill patients.

Carbapenems are currently considered the standard treatment for severe infections caused by ESBL-producing Enterobacterales [1, 2]. However, increasing global dissemination of carbapenem-resistant organisms underscores the necessity of carbapenem-sparing strategies [3].

Cefepime/enmetazobactam (FEP/META) combines a fourth-generation cephalosporin with a novel penicillanic acid sulfone-based β-lactamase inhibitor. Enmetazobactam differs from tazobactam by the presence of a methyl group on the triazole ring, which enhances its potency by conferring a zwitterionic structure and improved penetration. This combination exhibits activity against class A serine β-lactamases, including CTX-M, TEM, SHV, and VEB enzymes, but lacks activity against carbapenemases such as KPC, metallo-β-lactamases, and most OXA-type enzymes. Its spectrum does not include *Stenotrophomonas maltophilia*, difficult-to-treat *Pseudomonas aeruginosa*, carbapenems-resistant *Acinetobacter baumannii*,

Enterococcus spp., methicillin-resistant *Staphylococcus aureus*, or anaerobes [4–6].

Although clinical trials primarily evaluated FEP/META in complicated urinary tract infections (cUTI), intrapulmonary pharmacokinetic (PK) studies in healthy volunteers demonstrated substantial epithelial lining fluid (ELF) penetration [7], supporting biological plausibility for pulmonary use. However, no clinical experiences in pneumonia are currently reported.

Here we report a case of VAP caused by ESBL-producing *Escherichia coli* successfully treated with FEP/META. The treatment was administered as an Early Access Program and approved by a local ethics committee. Written informed consent for treatment and publication was obtained from the patient's legal representatives, in accordance with the Declaration of Helsinki.

CASE PRESENTATION

A 72-year-old male with a history of left hip prosthesis and benign prostatic hyperplasia was admitted to the Neuro-Intensive Care Unit (ICU) at Careggi University Hospital of Florence, Italy, following severe craniofacial trauma. Upon admission, neurological examination revealed signs consistent with cervical spinal cord injury, characterized by motor impairment at the C6 level and sensory level at T3–T4, resulting in incomplete tetraplegia classified as American Spinal Injury Association (ASIA) Impairment Scale grade B. Computed tomography (CT) imaging demonstrated cervical canal stenosis at the C4–C5 level, aggravated by posterior disc protrusion with clear evidence of spinal cord compression. Owing to neurological deterioration and respiratory muscle weakness secondary to high cervical involvement, the patient required endotracheal intubation and invasive mechanical ventilation (IMV). During the initial days of intensive care management, he remained hemodynamically stable but dependent on IMV.

On day 10 of ICU stay, the patient developed new-onset fever (38.7 °C), purulent tracheal secretions, worsening oxygenation with a reduction in the ratio of arterial oxygen partial pressure to fraction of inspired oxygen (PaO_2/FiO_2 190), and new bilateral pulmonary infiltrates on chest CT imaging (Fig. 1).

Laboratory investigations revealed leukocytosis (white blood cells [WBC] 15,400/µL) and elevated inflammatory biomarkers (mid-regional proadrenomedullin [proADM] 1.5 nmol/L and procalcitonin [PCT] 2.4 ng/mL). Serum creatinine was 0.42 mg/dL, with an estimated glomerular filtration rate (eGFR) of 111.5 mL/min × 1.73 m^2.

The clinical and radiological findings fulfilled criteria for VAP, and sequential organ failure assessment score (SOFA) score at the time of diagnosis was 6, indicating moderate severity.

A bronchoalveolar lavage (BAL) was obtained for microbiological evaluation, and rapid molecular testing using a molecular syndromic panel (Filmarray Pneumonia plus) detected *Escherichia coli* (10^6 DNA copies/mL) and the presence of CTX-M ESBL gene. Antimicrobial susceptibility testing was performed using broth microdilution according to EUCAST methodology. The culture confirmed the presence of *Escherichia coli* exceeding 10^7 colony-forming units per milliliter, supporting a diagnosis of true lower respiratory tract infection. Antimicrobial susceptibility testing of the isolate revealed resistance to amoxicillin–clavulanate, ceftriaxone, ceftazidime, cefepime, and ciprofloxacin. The isolate remained susceptible to carbapenems, including imipenem and meropenem, and to recently

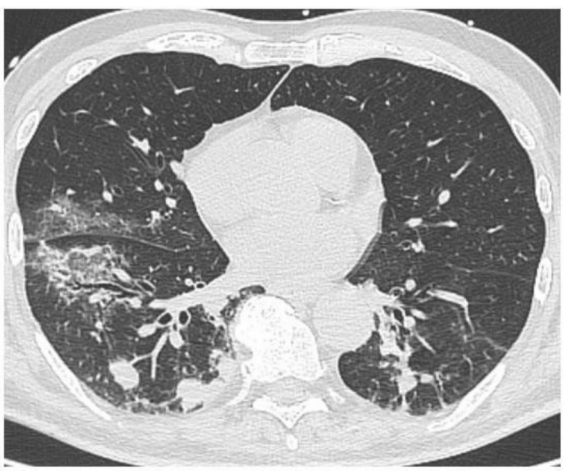

Fig. 1 New bilateral pulmonary infiltrates on chest CT imaging

approved non-carbapenem-based β-lactam/β-lactamase inhibitor combinations such as ceftolozane–tazobactam, ceftazidime–avibactam, and FEP/META. Notably, the minimum inhibitory concentration (MIC) of FEP/META was 0.06 mg/L (Table 1). EUCAST clinical breakpoints for *Escherichia coli* were applied for interpretation.

Despite preserved carbapenem activity, a carbapenem-sparing therapeutic strategy was pursued in the context of antimicrobial stewardship (AMS) considerations and favorable microbiological profile. Targeted therapy with FEP/META was initiated at a dose of 2.5 g every 8 h administered intravenously. No empiric antibiotic therapy was administered prior.

Clinical response was rapid and sustained. Defervescence occurred within 48 h of treatment initiation, and inflammatory markers progressively declined, with marked reduction in leukocyte count and procalcitonin levels. Moreover, oxygenation parameters improved steadily, and no drug-related adverse events were observed. After 7 days of therapy, FEP/META was discontinued. The patient remained clinically stable with no evidence of microbiological or clinical relapse: PaO_2/FiO_2 290, WBC 8700/µL, PCT 0.27 ng/mL, and proADM 0.5 nmol/L (Fig. 2).

Table 1 Antimicrobial susceptibility testing of *Escherichia coli*

Antibiotic	MIC (mg/L)	Interpretation
Amoxicillin–clavulanate	32	R
Ceftriaxone	32	R
Ceftazidime	32	R
Cefepime	> 16	R
Ciprofloxacin	> 2	R
Piperacillin/tazobactam	> 8	R
Imipenem	≤ 0.25	S
Meropenem	≤ 0.25	S
Ceftazidime–avibactam	≤ 0.12	S
Ceftolozane–tazobactam	≤ 0.25	S
Cefepime–enmetazobactam	0.06	S

S sensible; *R* resistant

DISCUSSION

To the best of our knowledge, this is one of the first reported cases in Europe of FEP/META use for the treatment of VAP caused by ESBL-producing *Escherichia coli*. The clinical course illustrates the potential role of this new agent as a carbapenem-sparing option in severe ESBL-related pulmonary infection.

ESBL-producing Enterobacterales have become a frequent cause of hospital-acquired and ventilator-associated pneumonia, historically requiring carbapenems for treatment. This approach is supported by randomized clinical trial data demonstrating inferior outcomes with piperacillin–tazobactam compared with meropenem in bloodstream infections due to ceftriaxone-resistant *Escherichia coli* or *Klebsiella pneumoniae*, the majority of which were ESBL producers [8].

However, the increasing global dissemination of carbapenem-resistant organisms underscores the ecological consequences of widespread carbapenem use. AMS strategies therefore emphasize carbapenem-sparing approaches whenever microbiologically and pharmacodynamically justified [9, 10].

Large in vitro surveillance programs conducted in North America and Europe have consistently shown that the addition of enmetazobactam restores susceptibility in the vast majority of ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* isolates, with activity levels approaching those of carbapenems. The marked reduction in MIC observed in our isolate after combination testing mirrors these surveillance data and provided a strong microbiological rationale for its clinical use [4, 11].

Clinical efficacy of FEP/META has been demonstrated in randomized trials for complicated urinary tract infections, where it showed noninferiority to piperacillin–tazobactam and favorable outcomes in infections due to ESBL-producing pathogens [12]. Although

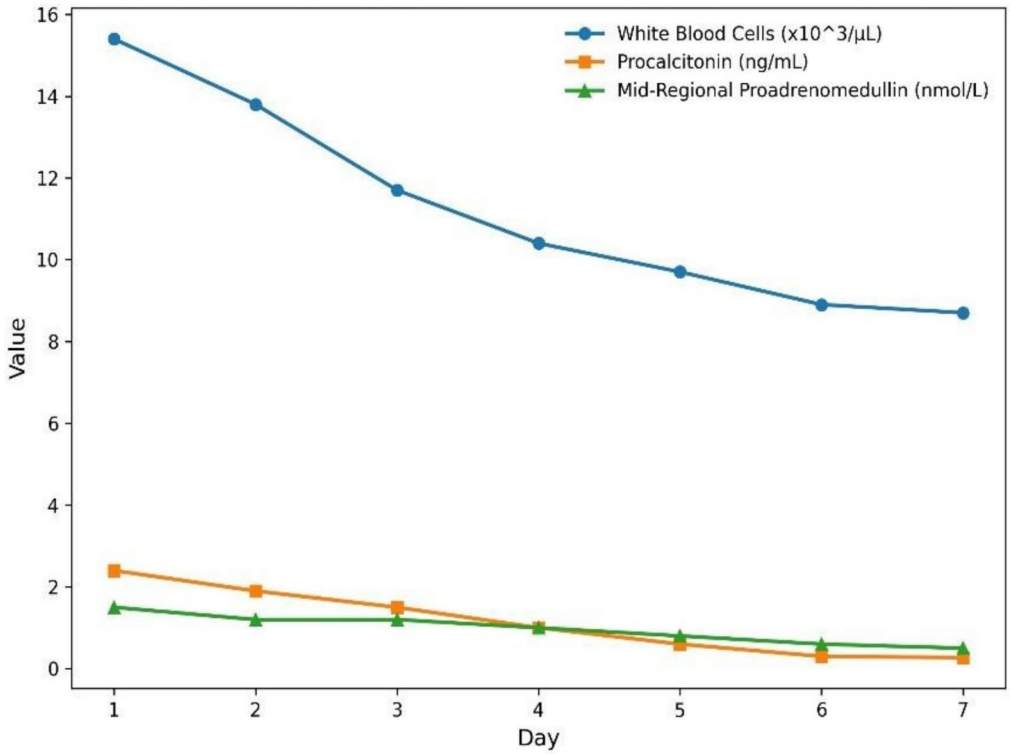

Fig. 2 Temporal evolution of inflammatory markers and oxygenation following initiation of cefepime/enmetazobactam therapy

pneumonia was not the primary focus of these trials, the PK and pharmacodynamic (PD) properties of FEP/META provide biological plausibility for pulmonary use [6]. In fact, intrapulmonary PK studies in healthy volunteers have shown that both cefepime and enmetazobactam achieve substantial penetration into epithelial lining fluid (ELF), with mean plasma-to-ELF partitioning of approximately 60% for cefepime and 53% for enmetazobactam. Importantly, joint probability of target attainment (PTA) modeling demonstrated near-complete target attainment in ELF for isolates with MIC values up to 4 mg/L and high probability even at 8 mg/L [7]. Moreover, murine pneumonia models have demonstrated robust efficacy of FEP/META against ESBL-producing Enterobacterales. In neutropenic mice with pneumonia caused by ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae*, FEP/META achieved ≥ 2-log kill in lung tissue when plasma cefepime time > MIC and enmetazobactam time > 2 mg/L were maintained for ≥ 20% of the dosing interval [13].

Given the extremely low MIC of 0.06 mg/L observed in our isolate, PD target attainment in the pulmonary compartment would be expected to be robust.

When compared with other recently introduced β-lactam/β-lactamase inhibitor combinations, FEP/META occupies a distinct ecological niche. Ceftazidime–avibactam is primarily positioned for the treatment of carbapenem-resistant Enterobacterales [14], and ceftolozane–tazobactam has strong activity against *Pseudomonas aeruginosa*, while retaining activity against some ESBL producers [1]. In addition, FEP/META is specifically optimized for ESBL and AmpC-producing Enterobacterales and avoids the carbapenem backbone [15]. In clinical scenarios where carbapenemase production is absent and susceptibility is confirmed, FEP/META use may allow preservation of carbapenem efficacy. However, it does not reliably inhibit class D β-lactamases,

including OXA-type enzymes, and shows reduced activity compared with avibactam and relebactam in this context.

An interesting and emerging consideration is also FEP/META's potential role against Enterobacterales coproducing ESBLs and OXA-48-like carbapenemases. In fact, recent murine pneumonia studies demonstrated that FEP/META achieved bacteriostatic to bactericidal activity against OXA-48-producing *Klebsiella pneumoniae*, with MICs up to 8 mg/L, while meropenem showed limited efficacy despite in vitro susceptibility [16].

Finally, FEP/META demonstrates sustained antimicrobial activity at elevated bacterial inocula relative to other β-lactam/β-lactamase inhibitor combinations [17].

This preservation of efficacy under high-inoculum conditions further supports its use in clinical settings characterized by substantial bacterial burden, such as VAP.

In Italy, we experience a high-prevalence of carbapenem-resistant Gram-negative infections, and therefore, as infectious diseases specialists, we constantly feel the pressure to limit their use when possible. Interestingly, in the present case, carbapenems remained fully active, but we opted for a carbapenem-sparing strategy based on FEP/META in consideration of the known intrapulmonary PK profile of FEP/META and of the low FEP/META MIC versus known PD profile of FEP/META. The rapid clinical and microbiological response supported the adequacy of this approach.

This report represents a single case without a comparator, and therefore, conclusions regarding efficacy should be interpreted with caution. Moreover, no therapeutic drug monitoring was performed in this case, representing a limitation, particularly in critically ill patients with altered pharmacokinetics. However, it provides real-world clinical evidence complementing existing in vitro and PK data and supports further investigation of FEP/META as a carbapenem-sparing option for ESBL-related VAP.

Finally, we also want to underline how the use of novel agents such as FEP/META must also consider cost, availability, and ecological impact, and should be reserved for cases where microbiological and PK/PD rationale supports their use.

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Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of Interest. Bruno Viaggi has the following conflicts of interest: Abbott, Accelerate Diagnostics, Ada, Advanz Pharma, Alifax, Angelini, Becton Dickinson, Bellco, Biomerieux, Biotest, Cepheid, Correvio, Dasit, Diasorin, Emmegi Diagnostica, Gilead, InfectoPharm, Menarini, MercK Sharp & Dohme, Mundipharma, Nordic Pharma, Pfizer, Roche Diagnostics, Shionogi, Thermofischer Scientific, and Viatris. Gianmaria Rossolini reports grants or contracts to the laboratory from Ada, Alifax, Angelini, Arrow Diagnostics, Biomedical Service, bioMérieux, Cepheid, Copan, Menarini , MSD, Qlinea, Qvella, SD Biosensor, Seegene, and Shionogi; consulting fees from Advanz Pharma, bioMérieux, Deepull, MSD, and Viatris; honoraria for lectures, presentations, manuscript writing, or educational events from bioMérieux, Menarini, MSD, Pfizer, Shionogi, and Relab. Tommaso Giani reports grants or contracts to the laboratory from Alifax, Angelini, Arrow Diagnostics, bioMérieux, Menarini, and MSD, and consulting fees from Advanz Pharma, and bioMérieux. Emanuele Palomba, Andrea Gori, Alberto Farese, and Marta Colaneri declare that they have no competing interests.

Ethical Approval. The treatment was administered as an Early Access Program and

approved by a local ethics committee. Written informed consent for treatment and publication was obtained from the patient's legal representatives, in accordance with the Declaration of Helsinki.

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