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REVIEW

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Overview of novel cefepime-based β-lactam/β-lactamase inhibitor combinations

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ABSTRACT

Introduction: The global rise of multidrug-resistant (MDR) Gram-negative pathogens challenges therapy, driving development of novel β-lactam/β-lactamase inhibitor (BL/BLI) combinations. Cefepime-based combinations offer mechanistically diverse options against a broad range of resistance phenotypes.

Areas covered: This review summarizes approved and investigational cefepime-based BL/BLI combinations, including cefepime/enmetazobactam (FEP/EMT), cefepime/taniborbactam (FTB), cefepime/zidebactam (FPZ), and cefepime/nacubactam (FEP/NAC). We discuss microbiological activity, resistance mechanisms, pharmacokinetics/pharmacodynamics, and available clinical evidence. In vitro data show differential activity against ESBL-, AmpC-, and carbapenemase-producing Enterobacterales, as well as difficult-to-treat Pseudomonas aeruginosa, with emerging but limited clinical outcomes. Challenges include incomplete resistance coverage, geographic variability, and limited clinical trials.

Expert opinion: Cefepime-based BL/BLI therapy should be pathogen- and mechanism-driven. FEP/EMT is suited for ESBL- and AmpC-producing Enterobacterales, potentially sparing carbapenems and covering OXA producers if susceptible. FTB may target severe carbapenem-resistant Enterobacterales infections resistant to existing BL/BLI agents, considering coverage for metallo-β-lactamases (MBL). FPZ combines β-lactamase inhibition and β-lactam–enhancer activity, retaining activity against XDR Enterobacterales and P. aeruginosa, including cefiderocol- or aztreonam/avibactam (ATM/AVI)-resistant strains. FEP/NAC shows promise against carbapenem- and MBL-producing strains, though clinical data remain limited. Optimal use relies on rapid molecular diagnostics, susceptibility testing, and antimicrobial stewardship to maximize efficacy and limit the emergence of resistance.

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1. Introduction

Multidrug-resistant (MDR) Gram-negative bacteria represent a major and evolving global public health threat. Therapeutic options remain limited for infections caused by carbapenem-resistant Enterobacterales, difficult-to-treat *Pseudomonas aeruginosa*, and other extensively drug-resistant (XDR) pathogens [1,2]. β-lactamases are the most common mechanism of resistance to β-lactam antibiotics among Gram-negative bacteria. These enzymes are typically grouped into four major classes (A–D) according to the Ambler molecular classification, based on amino acid sequence homology and catalytic mechanisms. Classes A, C, and D include serine β-lactamases (SBLs), whereas class B enzymes correspond to metallo-β-lactamases (MBLs) that require zinc ions for catalytic activity [3]. The diversity of these enzymes, together with the frequent coexistence of multiple resistance mechanisms, has driven the development of novel β-lactamase inhibitors (BLIs) with expanded activity spectra. The introduction of novel β-lactam/β-lactamase inhibitor (BL/BLI) combinations has partially addressed this challenge. However, the emergence of resistance to currently available agents, together with the increasing heterogeneity of resistance mechanisms, continues to complicate treatment decisions [4].

Cefepime (FEP), a fourth-generation cephalosporin with favorable pharmacokinetic properties and broad Gram-negative activity, has emerged as a backbone for innovative BL/BLI combinations [5]. Unlike earlier BL/BLI agents, cefepime-based combinations employ distinct mechanistic strategies. These include classical β-lactamase inhibition, pan-β-lactamase inhibition, and β-lactam–enhancer activity mediated by high-affinity interactions with penicillin-binding proteins (PBPs). These differences result in heterogeneous activity profiles across MDR pathogens and underscore the need for careful clinical positioning.

In this review, we provide a comprehensive overview of currently available and investigational FEP-based BL/BLI combinations. We focus on their microbiological spectrum, resistance mechanisms, pharmacokinetic/pharmacodynamic (PK/PD) characteristics, and the currently available clinical evidence. This choice reflects the recent clinical introduction of FEP/enmetazobactam (FEP/EMT) and the completion of phase 3 clinical trials evaluating FEP/taniborbactam (FTB), FEP/zidebactam (FPZ), and FEP/nacubactam (FEP/NAC). Given the expected near-term availability of these agents in clinical practice, our aim is to provide a clinically oriented overview to guide physicians in their appropriate and rational use for the management of infections caused by MDR Gram-negative pathogens. Furthermore, ZID and NAC exhibit mechanisms of action that extend beyond β-lactamase inhibition, including

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Article highlights

- Cefepime-based β-lactam/β-lactamase inhibitor combinations expand the therapeutic utility of an established cephalosporin against contemporary multidrug-resistant Gram-negative pathogens.
- Cefepime/enmetazobactam is currently the only approved cefepime-based combination and provides a carbapenem-sparing option for ESBL- and AmpC-producing Enterobacterales, with heterogeneous activity against carbapenemase-producing strains.
- Investigational combinations such as cefepime/taniborbactam and cefepime/zidebactam show potent in vitro activity against carbapenem-resistant Enterobacterales and difficult-to-treat *Pseudomonas aeruginosa*, including isolates resistant to existing β-lactam/β-lactamase inhibitor agents.
- β-lactam enhancer activity, mediated by high-affinity penicillin-binding protein targeting (zidebactam and nacubactam), represents a paradigm shift that partially circumvents classical β-lactamase–driven resistance.

intrinsic β-lactam–enhancer activity. This feature provides a rationale for further investigation, as it may represent a promising strategy to overcome resistance conferred by β-lactamase variants that reduce susceptibility to currently available inhibitors.

2. Overview of novel cefepime-based β-lactam/β-lactamase inhibitor combinations

Several novel FEP-based BL/BLI combinations have been developed to expand its activity against MDR Gram-negative pathogens. These include combinations of FEP with EMT, TAN, ZID, and NAC. Currently, the FEP/EMT combination is the only one approved for clinical use. The main characteristics of FEP combinations are summarized in Table 1.

2.1. Cefepime/enmetazobactam: mechanism of action

EMT (formerly AAI101) is a penicillanic acid sulfone with potent inhibitory activity against extended-spectrum β-lactamases (ESBLs), including CTX-M (cefotaxime-Munich), SHV (sulfhydryl reagent variable), and TEM (temoniera). It also inhibits some plasmid-mediated Ambler class C (AmpC) enzymes, such as CMY (cephalomycinase-type) and DHA (Dhahran) [6]. Although EMT lacks significant activity against most AmpC β-lactamases, its combination with FEP provides complementary coverage. This is due to the intrinsic stability of FEP against AmpC, allowing activity against both ESBL- and AmpC-producing Enterobacterales [6]. Structurally, EMT differs from tazobactam by the presence of a methyl group on the triazole ring. This confers zwitterionic properties that enhance penetration into the periplasmic space, similar to FEP [6]. These features support the role of FEP/EMT as a carbapenem-sparing option for infections caused by ESBL- and AmpC-producing organisms.

2.2. Cefepime/taniborbactam: mechanism of action

TAN (formerly VNRX-5133) is a novel broad-spectrum bicyclic boronate BLI with inhibitory activity across all four Ambler classes, although some limitations have been reported [7–9]. Unlike currently available BLIs, TAN inhibits both SBLs and MBLs through distinct mechanisms. It acts as a reversible covalent inhibitor of SBLs with slow dissociation kinetics, while functioning as a competitive inhibitor of MBLs with a very low inhibition constant. In both cases, inhibition is mediated by transition-state mimicry and interactions with conserved catalytic residues [7]. However, it lacks activity against most IMP (imipenemase)-type enzymes (except for IMP-59), selected NDM (New Delhi MBL) variants (e.g. NDM-9, NDM-30, NDM-60), and some VIM (Verona Integron-encoded) variants, often due to single amino acid substitutions [10,11].

TAN lacks intrinsic antibacterial activity and is under clinical development exclusively in fixed combination with FEP (2g/0.5g, FTB). TAN is currently the only BLI demonstrating in vitro activity against MBLs.

2.3. Cefepime/zidebactam and cefepime/nacubactam: mechanism of action

ZID (formerly WCK 5222) and NAC (formerly OP0595) are diazabicyclooctane (DBO) BLIs characterized by a distinctive multimodal mechanism of action. In addition to inhibiting class A, class C, and selected class D β-lactamases, both

Table 1. Overview of novel cefepime-based β-lactam/β-lactamase inhibitor combinations. The table summarizes the inhibitors, distinctive mechanisms of action, primary target pathogens, and key features or potential roles in the treatment of multidrug-resistant and extensively drug-resistant Gram-negative infections. Each combination exhibits unique properties, including the β-lactamase inhibition spectrum, intrinsic antibacterial activity, and β-lactam-enhancing effects.

Combination	Distinct mechanism	Primary target pathogens	Key features
FEP/EMT	ESBL inhibition (CTX-M, SHV, TEM) Limited AmpC inhibition (CMY, DHA); complements FEP AmpC stability	Enterobacterales	Zwitterionic structure and enhanced periplasmic penetration; carbapenem-sparing option.
FTB	Broad-spectrum BLI: Ambler classes A, B (except IMP), C, D; SBL reversible covalent inhibition; MBL competitive inhibition	Enterobacterales and *P. aeruginosa*	No intrinsic antibacterial activity; only BLI with in vitro MBL activity; promising for XDR pathogens with metallo-enzymes.
FPZ	Triple mechanism: class A/C/selected class D β-lactamase inhibition, intrinsic PBP2 activity, enhancer effect on PBP3-targeting β-lactams	Enterobacterales, *P. aeruginosa*	Synergistic multi-PBP targeting (PBP2 by ZID + PBP1a/PBP3 by FEP); preserves activity against MBLs and porin/PBP3 mutant strains; strong potential for XDR infections by Enterobacterales and *P. aeruginosa*.
FEP/NAC	Triple mechanism: class A/C/selected class D β-lactamase inhibition, intrinsic PBP2 activity, enhancer effect on PBP3-targeting β-lactams	Enterobacterales	Synergistic multi-PBP targeting (PBP2 by NAC + PBP1a/PBP3 by FEP); the enhancer effect preserves activity against MBLs and PBP3-mutant Enterobacterales.

Abbreviations: FEP: cefepime; EMT: enmetazobactam; FTB: cefepime/taniborbactam; FPZ: cefepime/zidebactam; NAC: nacubactam; BLI: β-lactamase inhibitor; XDR: extensively drug-resistant.

compounds exhibit intrinsic antibacterial activity through high-affinity binding to PBP2. They also act as β-lactam 'enhancers,' potentiating partner β-lactams via complementary binding to different PBPs [8,12–15]. ZID demonstrated higher PBP2 affinity compared with NAC [16], and kinetic studies indicate that ZID is the strongest inhibitor of AmpC β-lactamases, with very low inhibition constants [17]. Notably, NAC has shown particular activity against oxacillinase (OXA)-48–producing strains. In some cases, this activity exceeds that of ZID when tested alone, highlighting its potential relevance in this challenging resistance setting [15,16,18].

In combination with FEP, ZID and NAC exert synergistic activity through reciprocal PBP targeting. The DBO inhibits PBP2, while FEP targets PBP1a and PBP3. This results in enhanced antibacterial efficacy beyond β-lactamase inhibition alone [8,13–15,19,20]. This mechanism underlies activity against pathogens expressing class B MBLs and certain non-enzymatic resistance mechanisms, despite the lack of direct MBL inhibition.

3. *In vitro* microbiological activity

Several in vitro studies demonstrate that FEP/EMT, FTB, FPZ, and FEP/NAC exhibit potent and broad-spectrum activity against MDR Gram-negative pathogens. Their activity profiles are complementary and reflect the properties of their respective inhibitors.

3.1. Cefepime/enmetazobactam in vitro activity

FEP/EMT showed near-universal susceptibility among ESBL- and AmpC-producing Enterobacterales in European and United States (U.S.) collections. Large in vitro studies demonstrated susceptibility rates approaching 100% against ESBL- and AmpC-producing Enterobacterales. MIC90 values were significantly lower than those of FEP alone for all tested pathogens, except *Serratia marcescens* [21,22]. Comparable results have been reported worldwide, including under high inoculum conditions, with susceptibility rates reaching 100% among ESBL-producing Enterobacterales [23,24]. Furthermore, EMT was more potent than tazobactam against ESBL-producing *K. pneumoniae* [4].

In vitro activity of EMT has also been demonstrated against PenA-like β-lactamases, which are implicated in β-lactam resistance in the *Burkholderia cepacia* complex [25]. In contrast, EMT does not enhance FEP activity against *P. aeruginosa* [22,26].

Activity against carbapenemase-producing Enterobacterales was variable [21,26–29]. Castellano-Sánchez and colleagues reported no in vitro susceptibility to FEP/EMT among *Klebsiella pneumoniae* carbapenemase (KPC)-producing isolates collected in Southern Spain [27]. By contrast, another study reported susceptibility in 15 out of 17 isolates harboring mutated bla_{kpc} genes associated with resistance to ceftazidime/avibactam (CAZ/AVI), whereas isolates carrying wild-type bla_{kpc-2} or bla_{kpc-3} were resistant in nearly all cases [28]. It has been hypothesized that co-production of ESBLs may downregulate blaKPC expression, resulting in an ESBL phenotype and partially explaining the observed susceptibility in some isolates [9].

In carbapenem-resistant but non-carbapenemase-producing Enterobacterales, a French study including 151 isolates (often producing ESBLs and/or AmpC) reported an overall FEP/EMT susceptibility rate of 68.9%, highlighting the importance of in vitro susceptibility testing in this setting [29]. Similar findings were reported by Bonnin et al. [26]. Mutations affecting outer membrane porins, such as OmpK35 and/or OmpK36, were associated with reduced FEP/EMT minimum inhibitory concentrations (MICs) in isolates carrying either wild-type or mutated bla_{kpc} genes [28]. Other porin alterations or efflux pump overexpression have been linked to resistance to FEP and, consequently, to FEP/EMT [6,29].

Good in vitro activity has been observed against OXA-48-producing Enterobacterales [21,26–28,30,31]. Although EMT does not inhibit Ambler class D β-lactamases (with the exception of partial inhibition of OXA-1), activity against these isolates is attributed to the intrinsic stability of FEP toward OXA enzymes and to EMT-mediated inhibition of co-produced ESBLs, similarly to avibactam [6,26,28]. However, variable resistance rates (3.4%–13.2%) have been reported among OXA-48-like-producing *K. pneumoniae*, reinforcing the need for routine susceptibility testing in these cases [32].

3.2. Cefepime/taniborbactam in vitro activity

FTB exhibited broad-spectrum activity in global Enterobacterales isolates (GEARS study), with overall susceptibility exceeding 99%. High activity was observed against KPC-, VIM-, and AmpC-producing strains, as well as ESBL- and OXA-48–like producers. Activity against NDM-producing isolates was substantial but reduced in strains expressing multiple carbapenemases [33]. Non-fermenters such as *P. aeruginosa* were generally susceptible, though MBL producers and permeability-defective strains showed variable responses [34–42].

Among 18,350 Enterobacterales and *P. aeruginosa* isolates, FTB inhibited a higher proportion of resistant phenotypes and genotypes than CAZ/AVI, meropenem vaborbactam (MEV), and ceftolozane/tazobactam (TOL/TAZ) at concentrations ≤16 mg/L [34]. Overall, 99.7% of Enterobacterales isolates were inhibited, including 100% of VIM-, AmpC-, and KPC-producing strains. High activity was also observed against ESBL-producing (98.7%) and OXA-48-like– producing isolates (98.8%), with notable activity against NDM-producing strains (84.6%). Susceptibility rates of 90.2% and 80.6% were reported for isolates resistant to MEV and CAZ/AVI, respectively [34]. Against *P. aeruginosa*, FTB inhibited 97.4% of isolates, including those resistant to meropenem and classified as difficult-to-treat resistant (DTR). Activity was retained against isolates resistant to CAZ/AVI or TOL/TAZ (>75%) and against 87.4% of VIM-positive isolates [34]. However, overall susceptibility among MBL-producing *P. aeruginosa* was lower (66.5%), highlighting greater variability compared with Enterobacterales, likely related to permeability defects and non-enzymatic resistance mechanisms [34].

In a multicenter Spanish study, FTB showed microbiological superiority over CAZ/AVI, MEV, and imipenem/relebactam (IMI/REL) for Enterobacterales and carbapenemase-producing

P. aeruginosa; however, activity was reduced against carbapenem-resistant *P. aeruginosa* lacking detectable carbapenemases (susceptibility 46.5%), where it was comparable to TOL/TAZ and IMI/REL and inferior to CAZ/AVI [41]. Furthermore, FTB may represent an alternative therapeutic option in selected *P. aeruginosa* infections by inhibiting Pseudomonas-derived cephalosporinases (PDCs), including variants that confer resistance to CAZ/AVI and TOL/TAZ, provided that major permeability defects are absent [34,43].

FTB showed antimicrobial activity against ceftazidime-resistant *Burkholderia pseudomallei*, *B. cepacia* complex, *Burkholderia gladioli*, and *Stenotrophomonas maltophilia*. TAN demonstrated the ability to inhibit the PenA1 β-lactamase [44,45].

Finally, the role of FTB against cefiderocol-resistant isolates remains controversial. While some studies reported restoration of cefiderocol susceptibility in NDM-producing *P. aeruginosa* when combined with TAN [11,46] others demonstrated limited activity of novel BLIs, including TAN, in this setting [47,48]. FTB shows limited activity against carbapenem-resistant *Acinetobacter baumannii* (CRAB), including cefiderocol-resistant strains [48]. However, TAN may partially restore cefiderocol activity by inhibiting PER (Pseudomonas Extended Resistance)-like enzymes, potentially offering a future option in highly selected CRAB infections [48]. In addition, in Enterobacterales, reduced cefiderocol susceptibility has sometimes been associated with co-production of CMY- or SHV-type β-lactamases alongside NDM-like enzymes, for which combination with TAN can confer an additional advantage [42].

3.3. Cefepime/zidebactam: in vitro activity

FPZ demonstrates exceptional potency, with high in vitro activity against MBL-producing Enterobacterales (NDM, VIM, IMP), as well as KPC- and OXA-48–like producers. Activity is retained against isolates resistant to FTB or aztreonam/avibactam (ATM/AVI), as well as strains with combined enzymatic and non-enzymatic resistance mechanisms [16,49–63]. Synergistic PBP2 inhibition by ZID and PBP3 targeting by FEP underlies activity even in the presence of permeability defects, while intrinsic antibacterial activity of ZID contributes to potent inhibition of Enterobacterales and *P. aeruginosa*, including MBL producers and strains resistant to CAZ/AVI, TOL/TAZ, and colistin [58,64,65].

FPZ maintained activity against *K. pneumoniae* expressing combined enzymatic (KPC, OXA, NDM) and non-enzymatic resistance mechanisms, including porin loss (OmpK35/OmpK36 defects) [58]. ZID retained effective periplasmic penetration and PBP2 binding, inducing membrane perturbations that partially overcome permeability-associated resistance. Combined PBP2 and PBP3 inhibition resulted in synergistic activity and markedly reduced FPZ MICs compared with either agent alone [58]. Activity was also preserved in *Escherichia coli* harboring MBLs and PBP3 mutations [59]. In a study, among ATM/AVI-resistant *E. coli*, all isolates remained susceptible to FPZ ($MIC_{50}/_{90}$ 0.25 mg/L), whereas resistance to FTB was observed due to PBP3 mutations [62]. ZID also demonstrated superior activity if compared with NAC against *E. coli*, largely attributable to its higher PBP2 affinity, while retaining activity against high-risk clones (ST167, ST410, ST131) carrying diverse resistance determinants [16]. However, genomic analyses identified multiple mutations in PBPs 1–3, with variations in PBP2 most closely associated with differences in ZID and NAC susceptibility [16].

Early CHINET surveillance (2018–2019) showed high activity against Enterobacterales, including bla_{KPC-2}- and bla_{NDM}-positive isolates [54,55]. Large worldwide surveillance collections confirmed high susceptibility rates (80 ~ 100%), depending on species and resistance phenotype [49,50]. A multicenter Greek study including more than 800 Gram-negative isolates from 15 hospitals reported high FPZ susceptibility among carbapenem-resistant Enterobacterales, including MBL-, OXA-48–, and dual-carbapenemase–producing strains [56]. Similarly, a Taiwanese collection (2012–2018) of imipenem-non-susceptible *E. coli* and *K. pneumoniae* reported 100% susceptibility to FPZ, including OXA-48- and MBL-positive isolates [57].

Additional studies have confirmed excellent in vitro activity of FPZ against isolates producing multiple carbapenemases, including MBLs and an Indian study showed that FPZ had potent activity regardless of carbapenemase type or bacterial species, with more than 99% of isolates inhibited at concentrations ≤8 mg/L, including strain with colistin resistance [33,54,63,66–68].

Reduced FPZ susceptibility has been reported in a Chinese study among NDM-producing Enterobacterales, particularly *K. pneumoniae* with deleterious OmpK35 alterations, although resistance rates remained species-dependent [69].

FPZ retained activity against KPC variants conferring resistance to CAZ-AVI through omega-loop mutations [70]; however, resistance has been described for selected KPC variants, particularly those involving the 270-loop [64]. Overexpression of bla_{NDM-5} and alterations in PBP2 have been proposed as additional resistance mechanisms, and rare pan-resistant *K. pneumoniae* isolates, including FPZ resistance, have been reported [71,72].

In non-fermenting Gram-negative pathogens, the activity of FPZ is largely attributable to the intrinsic antibacterial activity of the β-lactam–enhancing effect of ZID when combined with FEP, which is conserved among clinically relevant species [56,61,73]. FPZ exhibited excellent in vitro activity against *P. aeruginosa*. Nearly all isolates, including MBL producers and strains resistant to CAZ/AVI, TOL/TAZ, and colistin, were susceptible at a breakpoint of 32 µg/mL [53,55,60,61,63]. Activity against *S. maltophilia* and *Burkholderia* spp. has also been reported [63]. However, the behavior of non-fermenters besides *P. aeruginosa* was species-specific [61].

Against CRAB, FPZ activity is variable with elevated MICs reported in several studies, but reduced MICs were observed, especially in OXA-producing isolates [52,54–56,61,66,70,73,74]. Notably, ZID restored sulbactam susceptibility in 91% of sulbactam-resistant CRAB isolates, including bla_{NDM-1}/bla_{OXA-23} producers [75].

ZID may retain activity against cefiderocol-resistant microorganisms primarily through intrinsic PBP2 binding rather than β-lactamase inhibition alone. In Indian multicenter studies, FPZ demonstrated markedly superior in vitro activity compared with cefiderocol against NDM-producing *E. coli*, *K. pneumoniae*, and *P. aeruginosa*, achieving 100% susceptibility among Enterobacterales and ≥90% among *P. aeruginosa* at FEP breakpoints ≤8 mg/L [65]. In some cases, ZID may restore

susceptibility when combined with cefiderocol in cefiderocol-resistant strains. Reduced susceptibility to cefiderocol has been associated with multiple mechanisms, including the presence of MBLs, mutations in PBP3, and alterations in siderophore-mediated iron transport systems. ZID may overcome these resistance mechanisms through its intrinsic antimicrobial activity and β-lactam enhancer activity previously discussed. Furthermore, inhibition of SBLs may also help restore activity against isolates exhibiting reduced susceptibility to cefiderocol [42,48,72,76]. In addition, Xu et al. by transcriptome analysis, hypothesized that a synergistic activity of ZID and cefiderocol may be related to the inhibition of key respiratory enzymes [72].

Finally, resistance to FPZ was associated with the accumulation of multiple mutations in genes encoding the MexAB-OprM efflux system and its regulatory elements, leading to efflux pump overexpression, the presence of certain VIM- or IMP-type MBL, production of the PDC-382 β-lactamase, as well as alterations in PBP2 and PBP3, although FPZ susceptibility generally exceeded that of comparator BL/BLI combinations [7,61,77-80].

3.4. Cefepime/nacubactam: in vitro microbiological activity

Compared with other combinations, limited data are available for FEP/NAC.

NAC markedly reduces FEP MICs against carbapenemase-producing Enterobacterales, including wild-type and mutant KPC- and OXA-48-producers, although single amino acid substitutions may reduce susceptibility through structural rearrangements that interfere with NAC binding and acylation [81]. In vitro studies have shown intrinsic antibacterial activity of NAC alone in most Enterobacterales, with elevated MICs (>4 mg/L) observed in approximately 20% of *K. pneumoniae* and *Enterobacter* spp., 100% of *Morganella morganii*, and 80% of *Serratia* spp. isolates. However, when combined with FEP, NAC markedly reduced MICs, particularly against carbapenemase-producing *K. pneumoniae*, including both KPC- and OXA-48-producing strains [15]. Despite in vitro kinetic properties that appear less favorable than those of AVI, NAC's intrinsic antibacterial and enhancer activities targeting PBP2 and PBP3, respectively, support its potential efficacy in combination therapies active against isolates resistant to CAZ/AVI [14,81].

Furthermore, like ZID, restores FEP susceptibility in many MBL-producing isolates, but with limited activity against Proteeae [15,20,33,81–83]. Notably, activity was observed against isolates producing dual carbapenemases and strains resistant to other last-line agents, such as FTB (e.g. *E. coli* NDM-9) [15,20,33,82,83]. Furthermore, FEP/NAC shows limited effects on non-fermenters except for notable inhibition of *Stenotrophomonas maltophilia* [15,84,85].

4. *In vivo* pharmacokinetics and pharmacodynamics and clinical development

In vivo and clinical studies of novel FEP-based BL/BLI combinations demonstrate favorable PK and PD profiles. These agents are predominantly eliminated via the renal route and show effective penetration into epithelial lining fluid (ELF), supporting their use in complicated urinary tract infections (cUTIs) and hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP). PK data and Phase 3 clinical trials are summarized in Tables 2 and 3, respectively.

4.1. Cefepime/enmetazobactam in vivo studies

In vivo murine models demonstrated favorable PK and PD properties of FEP/EMT for the treatment of HAP, with ELF/plasma ratios of 0.61 for FEP and 0.53 for EMT [94]. Pulmonary surfactant did not impair EMT activity [95]. Efficacy was confirmed in murine pneumonia models caused by OXA-48-producing *K. pneumoniae* [96]. Both FEP and EMT are predominantly eliminated via the renal route, supporting their clinical use in cUTIs [6].

Early clinical development of FEP/EMT included two Phase I studies (NCT03680352 and NCT03775668) evaluating PK, metabolism, mass balance, and safety following intravenous administration in healthy adults, including subjects with renal impairment [97,98]. These studies demonstrated predictable exposure, primary renal elimination, and good tolerability, supporting dose selection for subsequent trials. A Phase II study in adults with cUTI and acute pyelonephritis (NCT03680612) confirmed preliminary efficacy, microbiological response, and safety against Gram-negative pathogens [99]. On this basis, a Phase II pediatric trial in cUTI (NCT05826990) is currently ongoing across several European countries to assess PK, safety, and tolerability in children and adolescents [100].

Table 2. Comparative pharmacokinetic parameters of new β-lactamases inhibitors in humans.

Parameter	FEP	EMT	TAN	ZID	NAC
Dosing	2 g	0.5 g	0.5 g	1 g	1 g
Elimination Half-life (t1/2)	2.7 h	2.6 h [86]	2–5.8 h [87]	1.8–2 h [88]	No data
Volume of Distribution	~16.9–20 L	~20.6–25.3 L [86]	Similar to FEP [88]	Similar to FEP [88]	No data
Renal Clearance	~85% unchanged	~90% unchanged [86]	Similar to FEP [89]	Similar to FEP	Similar to FEP [90]
Protein Binding	~20%	Minimal (0%) [86]	Minimal (0%) [89]	<10% [90]	~5% [90]
Dose Proportionality	Yes (linear)	Yes (linear)	Yes (linear)	Yes (linear)	Yes (linear)
ELF/Plasma Ratio	20–73%	53–62% [91]	15–25% [92]	~40% [93]	No human data

Abbreviations: FEP: cefepime; ELF: epithelial lining fluid; EMT: enmetazobactam; NAC: nacubactam; TAN: taniborbactam; ZID: zidebactam.

Table 3. Summary of phase 3 trials of new cefepime and new β-lactamases inhibitor combinations.

Trials	Agent	Design	Target pathogens	Status	Efficacy vs. control
ALLIUM (NCT03687255)	FEP/EMT	Multicenter, randomized double-blind, non-inferiority study comparing FEP/EMT to TZP in hospitalized adults with cUTI, including AP	Enterobacterales, including ESBL-producing (~20%)	Completed, results published	Clinical cure plus microbiological eradication at day 14: FEP/EMT 79.1% vs. TZP 58.9%.
CERTAIN-1 (NCT03840148)	FTB	Multicenter, randomized, double-blind, active-controlled noninferiority study evaluating the efficacy, safety, and tolerability of FTB compared with MEM for the treatment of cUTIs and AP	Enterobacterales and *P. aeruginosa* susceptible to MEM	Completed, results published	Clinical cure plus microbiological eradication: FTB 70.6% vs. MEM 58.0%
CERTAIN-2 (NCT06168734)	FTB	Multicenter, randomized, double-blind, active-controlled noninferiority study evaluating the efficacy and safety of FTB vs. MEM for the treatment of VAP and vHAP	Bacterial pathogen susceptible to MEM	Suspended	Not available
NCT04979806	FPZ	Multicenter, randomized, double-blind, active-controlled noninferiority study evaluating the efficacy, safety, and tolerability of FPZ vs. MEM for cUTIs and AP	Unspecified	Completed, results unpublished	Clinical cure plus microbiological eradication: At EOT, FPZ showed non-inferiority to MEM (96.1% vs. 97.1%) in the mMITT (89.0% vs. 68.4%), while showing superiority at TOC (89.0% vs. 68.4%)
INTEGRAL-1 (NCT05887908)	FEP/ NAC	Multicenter, randomized, double-blind, active-controlled study evaluating the efficacy and safety of FEP/NAC and ATM/NAC vs. IMI/c in adults with cUTIs or acute uncomplicated pyelonephritis	Bacterial pathogen susceptible to IMI and MEM except for *A. baumannii*	Completed, results published	Clinical cure plus microbiological eradication in the intention-to-treat population at the end of treatment: FEP/NAC 93.0% vs. IMI/c 89.5%
INTEGRAL-2 (NCT05905055)	FEP/ NAC	Multicenter, randomized controlled study comparing safety of FEP/NAC and ATM/NAC vs. BAT in cUTIs, AP, HAP, VAP, and cIAI	Carbapenem-Resistant Enterobacterales	Completed, results unpublished	Not available

Abbreviations: AP: acute pyelonephritis; ATM: aztreonam; BAT: best available therapy; cUTI: complicated urinary tract infection; cIAI: complicated intrabdominal infection; EMT: enmetazobactam; EOT: end of therapy; FEP: cefepime; FTB: cefepime/taniborbactam; FPZ: cefepime/zidebactam; IMI/c: imipenem/cilastatin; MEM: meropenem; mMITT: microbiological modified intention to treat population; NAC: nacubactam; HAP: hospital acquired pneumoniae; TOC: test of cure; TZP: piperacillin/tazobactam; VAP: ventilator associated bacterial pneumonia; vHAP: ventilated hospital acquired bacterial pneumoni.

The ALLIUM trial (NCT03687255) was a Phase III, multicenter, randomized controlled study comparing FEP/EMT (2 g FEP +0.5 g EMT q8h) with piperacillin/tazobactam (4.5 g IV q8h) in hospitalized adults with cUTI [101]. Concurrent bacteremia was observed in 11.0% (38/345) of patients receiving FEP/EMT. The primary composite endpoint, clinical cure plus microbiological eradication at day 14, was achieved more frequently with FEP/EMT than with piperacillin/tazobactam (79.1% vs 58.9%). Although clinical cure rates alone were similar, FEP/EMT demonstrated significantly higher microbiological eradication rates overall and in infections caused by ESBL-producing Enterobacterales. These findings were confirmed in a post-hoc analysis excluding isolates resistant to piperacillin/tazobactam according to updated CLSI and EUCAST breakpoints. Notably, approximately 80% of enrolled patients did not harbor ESBL-producing pathogens, suggesting that standard β-lactams remain appropriate in many cases. Adverse event rates were comparable between treatment arms, while microbiological recurrence was lower in the FEP/EMT group [102,103]. A subsequent meta-analysis identified FEP/EMT as the most effective treatment option for ESBL-related cUTIs [104].

Although the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Medicines and Healthcare products Regulatory Agency (MHRA) have all authorized the drug, their approved indications differ. The FDA approved FEP/EMT only for adults with cUTI, including pyelonephritis. In contrast, the EMA and MHRA approved it for a broader range of infections, including cUTI, HAP (including VAP), and associated bacteremia [105].

4.2. *Cefepime/Taniborbactam* in vivo *studies*

The approved investigational dosing regimen for FTB consists of FEP 2 g plus TAN 0.5 g administered every 8 hours. Both agents exhibit predictable, complementary PKs, with a predominantly extracellular distribution and primary renal elimination, enabling synchronized dosing. TAN has a plasma half-life comparable to FEP and achieves adequate plasma and ELF concentrations. From a PD standpoint, FEP efficacy is driven by the percentage of free drug time above the MIC (%fT >MIC), whereas TAN activity correlates with the area under the concentration– time curve to MIC ratio (AUC/MIC), ensuring sustained β-lactamase inhibition. Preclinical PK/PD studies support the use of FTB for the treatment of infections caused by Enterobacterales [106,107]. TAN demonstrates dose-proportional pharmacokinetics with low interindividual variability, and in vitro infection models have shown a correlation between AUC and reduction in bacterial burden [106,108]. Dose adjustment is required in patients with renal impairment, including those undergoing hemodialysis, due to reduced clearance [108]. Data on continuous renal replacement therapy remain limited [109]. ELF penetration studies in healthy volunteers support a potential role for FTB in the treatment of pneumonia, with a regimen of 2.5 g every 8 hours administered as a 4-hour infusion [92,107].

FTB has advanced to Phase 3 clinical development. In the CERTAIN-1 double-blind randomized controlled trial, FTB was compared with meropenem for the treatment of cUTIs and acute pyelonephritis caused by Enterobacterales and *P. aeruginosa*. Among 436 randomized patients, composite clinical and microbiological success at test of cure was achieved in 70% of patients receiving FTB versus 58% of patients receiving meropenem, demonstrating both non-inferiority and superiority. Only 10 cases in the extended intention-to-treat population had carbapenem-resistant isolates, of which 8/10 were successfully treated with FTB. Among these, two were *P. aeruginosa*: one was successfully treated, and one was not. Outcomes were also favorable in patients with bacteremia (81.6%), supporting its potential use for the treatment of bacteremia. FTB was well tolerated, with serious adverse events occurring in approximately 2% of patients [39]. The CERTAIN-2 trial (NCT06168734), evaluating FTB for VAP and HAP, has been suspended; no public safety concerns have been reported to date [110].

4.3. *Cefepime/zidebactam* in vivo *studies*

In vivo studies in neutropenic murine lung and thigh infection models demonstrated the efficacy of FPZ against KPC- and OXA-48–producing *K. pneumoniae*, MBL-expressing *P. aeruginosa*, and strains with PBP mutations and non-enzymatic resistance mechanisms [13,111,112]. PK studies in murine models and healthy volunteers have shown that FPZ concentrations in plasma and ELF are sufficient to treat pulmonary infections [93,111]. The combination has been evaluated in Phase 1 and Phase 2 clinical studies, showing favorable PK/PD properties and an acceptable safety profile.

FPZ has undergone extensive Phase 1 clinical evaluation, demonstrating favorable PK/PD properties and an acceptable safety profile. Phase 1 studies (NCT02674347, NCT02707107, NCT03554304, NCT03630094) showed linear pharmacokinetics, predictable exposure, and no clinically relevant QT prolongation or major cardiovascular adverse events [113–116]. A dedicated renal impairment study (NCT02942810) confirmed the need for dose adjustment in moderate-to-severe renal dysfunction, while maintaining good tolerability across all cohorts [117]. FPZ has progressed to late-phase clinical development. A global, randomized, double-blind, multicenter Phase 3 non-inferiority trial (NCT04979806) comparing FPZ (2 g FEP +1 g ZID q8h) with meropenem (1 g q8h) for cUTIs and acute pyelonephritis has completed enrollment, with results submitted in January 2026 [118]. In India, FPZ is currently being evaluated in a Phase 2 observational study (CTRI/2024/04/065043) for HAP/VAP pneumonia, complicated intra-abdominal infections (cIAIs), and cUTIs caused by meropenem-resistant Gram-negative pathogens [119].

Compassionate use of FPZ has been reported in five cases of extensively drug-resistant *P. aeruginosa* infections (four osteoarticular and one endovascular graft infection) between 2023 and 2024. All isolates were susceptible to FPZ despite resistance to IMI/REL and CAZ/AVI, and all patients achieved clinical and radiological improvement without drug-related adverse events [120]. Resistance mechanisms included class D β-lactamases, cephalosporin-hydrolyzing enzymes, the NDM-1 metallo-β-lactamase, upregulation of efflux pumps (MexAB-OprM), and mutations in PBP3 [120]. Additional successful cases include IAI sepsis due to NDM-producing XDR *P. aeruginosa* [121], ecthyma gangrenosum with disseminated infection in an immunocompromised host [122], complex IAI caused by cefiderocol-resistant MBL-producing *K. pneumoniae* and *P. aeruginosa* [123], and a pediatric empyema

due to *P. aeruginosa* [124]. Conversely, treatment failure with emergent FPZ resistance has been described in a case of *P. aeruginosa* pneumonia associated with progressive resistance to multiple BL/BLI combinations, including FPZ, driven by cumulative mutations affecting efflux regulation, OprD, and PBP targets [125].

4.4. *Cefepime/nacubactm* in vivo *studies*

Preclinical studies have demonstrated robust in vitro and in vivo activity of FEP/NAC against carbapenem-resistant and carbapenemase-producing Enterobacterales. Murine models of pneumonia and cUTI showed that clinically relevant lung and urinary concentrations of NAC, in combination with FEP or meropenem, were sufficient to significantly reduce bacterial burden, including strains resistant to carbapenems, CAZ/AVI, and MBL producers [126–130].

Phase I studies in healthy volunteers demonstrated a favorable safety profile for NAC following single ascending doses (NCT02134834) and multiple ascending doses up to 7 days (NCT02972255), with mostly mild, non–dose-related adverse events, primarily headache [131,132]. A Chinese Phase I study further confirmed the safety of 1 g or 2 g NAC in healthy participants [133]. PK analyses showed linear, dose-proportional exposure, rapid attainment of peak plasma concentrations after infusion, a short elimination half-life, and predominant renal excretion of unchanged drug (87–91%) [107,132]. A study investigating the intrapulmonary penetration of NAC in healthy participants (NCT03182504) has been completed, but results have not yet been published [134].

The Phase III INTEGRAL-1 trial (NCT05887908) was a randomized, double-blind, active-controlled study evaluating FEP/NAC and ATM/NAC versus imipenem/cilastatin in adults with cUTIs or acute uncomplicated pyelonephritis [135]. FEP/NAC demonstrated superior efficacy compared with imipenem/cilastatin for the composite endpoint of clinical cure and microbiological eradication, achieving a composite outcome in 93.0% of patients in the microbiological modified intention-to-treat population at the end of treatment, compared with 89.5% in the control group. Approximately 600 patients were enrolled, all infected with Gram-negative pathogens susceptible to carbapenems at baseline [135].

The Phase III INTEGRAL-2 trial (NCT05905055), evaluating NAC-based regimens in pyelonephritis, pneumonia (including HAP/VAP), and IAIs, has been completed, but results are not yet available [136].

5. Limitations

Despite encouraging microbiological and PD data, several limitations currently restrict the clinical positioning of novel cefepime-based combinations.

For FEP/EMT, activity against carbapenem-resistant Enterobacterales remains heterogeneous and highly dependent on the underlying resistance mechanisms. Although robust activity has been consistently demonstrated against ESBL- and AmpC-producing isolates, susceptibility among carbapenemase-producing Enterobacterales, particularly KPC- and OXA-48-like producers, is variable and largely supported by in vitro studies. Observed activity in selected KPC-producing isolates appears to be influenced by factors such as ESBL co-production, altered KPC expression, and porin mutations, rather than direct inhibition of carbapenemases by EMT. Consequently, routine susceptibility testing is essential, and empirical use for infections caused by carbapenem-resistant Enterobacterales is not recommended. Moreover, clinical evidence for FEP/EMT is primarily derived from cUTI studies, while its potential role in severe infections such as HAP/VAP is supported mainly by pharmacokinetic/pharmacodynamic modeling and preclinical data. In addition, the ALLIUM trial enrolled a substantial proportion of patients infected with non-ESBL-producing pathogens, limiting extrapolation to high-MDR epidemiological settings.

For FTB, important limitations relate to incomplete MBL coverage and the emergence of resistance. Although TAN is the only BLI combined with cefepime that exhibits activity against MBLs, coverage is incomplete, with no activity against most IMP-type enzymes (except IMP-59), selected NDM variants (e.g. NDM-9, NDM-30, NDM-60), some VIM variants, and B2/B3 MBLs. These represent enzyme-spectrum limitations, where resistance results from incomplete inhibition of specific carbapenemase variants. In contrast, other therapeutic strategies rely on distinct mechanisms. For example, ATM/AVI exploits the intrinsic stability of ATM to promote MBL hydrolysis, while inhibiting co-produced SBLs. Cefiderocol, on the other hand, depends on siderophore-mediated uptake and may be affected by alterations in iron transport systems or permeability pathways. Finally, β-lactam enhancers such as ZID and NAC act primarily by high-affinity binding to PBP2 and by complementary multitarget engagement of PBPs when combined with FEP, and therefore do not directly inhibit MBL enzymes.

In addition, FTB activity is further compromised by non-enzymatic resistance mechanisms, including porin loss, PBP3 alterations, efflux overexpression, and AmpC deregulation, particularly in *P. aeruginosa*, resulting in greater variability compared with Enterobacterales. Reduced susceptibility has been reported in isolates co-producing multiple carbapenemases, in the presence of heteroresistance, and in strains harboring PBP3 insertions, where cross-resistance with cefiderocol has also been described. Finally, clinical data remain limited for infections caused by carbapenem-resistant and MBL-producing pathogens, which were underrepresented in pivotal trials, and evidence in severe infections, such as HAP/VAP, is currently lacking.

Considering FPZ, a large proportion of available in vitro susceptibility data originates from Southeast Asia, a region characterized by a high prevalence of PBP3 alterations and distinct resistance epidemiology, which may limit generalizability to Europe and North America. Moreover, translational interpretation is complicated by differences between experimental settings: most preclinical in vivo studies employed a 2:1 FPZ ratio, whereas in vitro susceptibility testing is frequently performed at a 1:1 ratio. Despite highly promising microbiological data, clinical evidence remains scarce, with no randomized controlled trial results available and only limited compassionate-use experience reported to date.

For FEP/NAC, several additional limitations should be acknowledged. Reduced outer membrane permeability, particularly due to porin loss, may impair intracellular NAC accumulation and compromise its activity. Furthermore, systematic evaluations of FEP/

NAC susceptibility with respect to specific carbapenemase variants, PBP mutations, and non-enzymatic resistance mechanisms are lacking, thereby limiting the mechanistic interpretation of in vitro findings. NAC also lacks intrinsic antibacterial activity against non-fermenting Gram-negative pathogens, and its activity against P. aeruginosa appears to be limited to selected isolates and primarily depends on β-lactamase inhibition rather than on enhancer activity. From a clinical perspective, evidence is currently limited to the INTEGRAL-1 trial, which compared FEP/NAC with a carbapenem in infections caused by carbapenem-susceptible organisms. Consequently, the efficacy of FEP/NAC against carbapenemase-producing Enterobacterales, including MBL producers, remains unproven in vivo.

In summary, while FEP-based combinations represent important additions to the antimicrobial armamentarium, their use is constrained by heterogeneous activity profiles, incomplete coverage of resistance mechanisms, geographic variability in susceptibility patterns, and, most critically, a lack of robust clinical data in MDR and XDR infections. Well-designed randomized clinical trials targeting carbapenem-resistant pathogens are needed to define their definitive therapeutic role.

6. Conclusion

FEP-based BL/BLI combinations represent a mechanistically diverse and expanding class of agents against MDR Gram-negative pathogens. FEP/EMT demonstrates consistent in vitro activity and clinical efficacy against ESBL- and AmpC-producing Enterobacterales, with heterogeneous activity against carbapenem-resistant Enterobacterales. Investigational combinations, including FTB, FPZ, and FEP/NAC, show potent in vitro activity against carbapenem-resistant Enterobacterales, MBL-producing isolates, and selected XDR P. aeruginosa. Their distinct mechanisms, including broad β-lactamase inhibition and β-lactam–enhancer effects via high-affinity PBP targeting, underlie complementary and synergistic antibacterial activity. PK/PD data support their use in cUTI and HAP, including VAP, although clinical outcome data remain limited for several combinations, particularly against carbapenem-resistant and non-fermenting Gram-negative pathogens. These findings underscore the potential of FEP-based BL/BLI combinations to expand the therapeutic arsenal against MDR Gram-negative infections while highlighting the need for mechanism-driven application guided by susceptibility testing and antimicrobial stewardship.

7. Expert opinion

The increasing availability of FEP-based BL/BLI combinations introduces new therapeutic options for the management of MDR Gram-negative infections. However, their optimal clinical use requires careful positioning based on microbiological phenotype, resistance mechanisms, infection severity, and site of infection, within the framework of antimicrobial stewardship. The spectrum of activity of the main FEP-based combinations against key MDR pathogens, and their potential use according to bacterial species and underlying resistance mechanisms, are summarized in Table 4 and Figure 1, based on a review of the currently available literature.

Table 4. Spectrum of in vitro activity of currently available β-lactam/β-lactamase inhibitor combinations and cefepime-based combinations under clinical development against major multidrug-resistant Gram-negative pathogens. Activity is primarily derived from *in vitro* susceptibility data; clinical evidence remains limited or unavailable for several combinations and pathogen groups. The table summarizes the relative activity of each combination against the indicated pathogens. Color coding indicates: green, high *in vitro* activity; yellow, intermediate or variable activity; red, low or absent activity; orange, marked variability across studies, with potential activity only in selected microbiological or clinical settings, or when used in combination with other agents.

Antibiotic	ESBL+/ampC+ Enterobacterales	CRE KPC+	CRE OXA-48/like +	CRE MBL+	XDR *P. aeruginosa*	PBP3 mutations	CRAB
CAZ/AVI							
MEV							
IMI/REL							
FDC							
ATM/AVI							
FEP/EMT		*[a]					
FTB				*[b]	*[d]		
FPZ					*[e]		*[f]
FEP/NAC				*[c]			

Abbreviations: CRE: carbapenem-resistant Enterobacterales; XDR: extensively drug-resistant; PBP: penicillin-binding protein; CRAB: carbapenem-resistant *A. baumannii*; CAZ/AVI: ceftazidime/avibactam; MEV: meropenem/vaborbactam; IMI/REL: imipenem/relebactam; ATM/AVI: aztreonam/avibactam; FDC: cefiderocol; FEP: cefepime; EMT: enmetazobactam; FTB: cefepime/taniborbactam; FPZ: cefepime/zidebactam; NAC: nacubactam.

*[a]Limited activity against KPC-producing isolates; in vitro activity reported against selected KPC-2 and KPC-3 variants, including occasional CAZ/AVI-resistant strains.

*[b]FTB lacks activity against IMP-type MBLs (except IMP-59) and selected NDM (e.g. NDM-9, NDM-30, NDM-60) and VIM variants.

*[c]NAC intrinsic activity and β-lactam–enhancer effect contribute to activity against MBL-producing Enterobacterales when combined with FEP; clinical and microbiological data remain limited.

*[d]Greater susceptibility variability compared with Enterobacterales, likely driven by permeability defects and non-enzymatic resistance mechanisms.

*[e]In non-fermenting Gram-negative pathogens, FPZ activity is largely driven by ZID intrinsic antibacterial activity via high-affinity PBP2 binding and β-lactam–enhancer effects.

*[f] In vitro studies show MIC reductions when FEP was associated with ZID against CRAB and restoration of sulbactam or cefiderocol susceptibility in selected isolates.

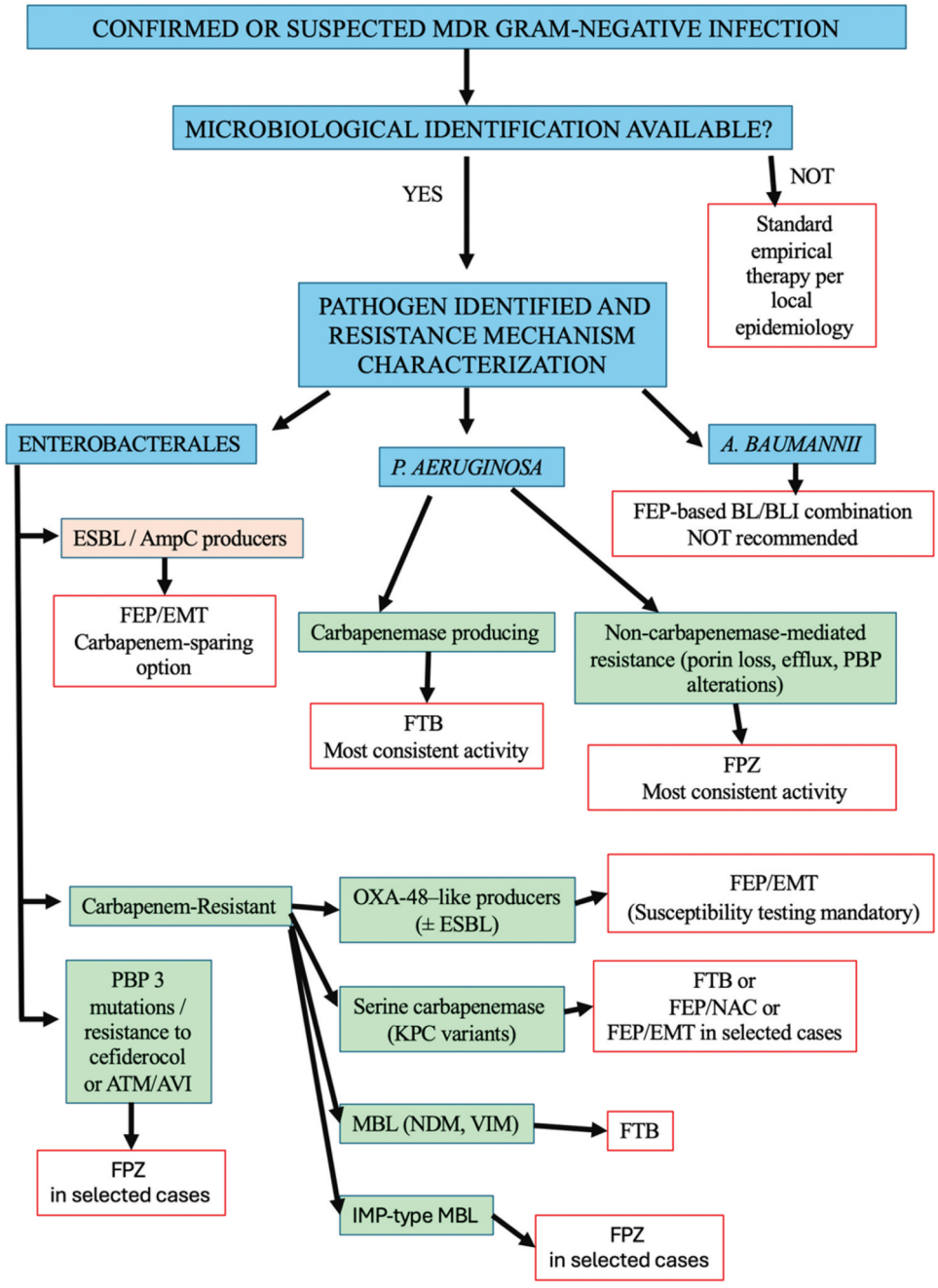

Figure 1. Schematic representation of potential therapeutic strategies using new cefepime (FEP)-based combinations, guided by the underlying resistance mechanisms. Molecules with broader activity, such as cefepime/taniborbactam (FTB) and cefepime/zidebactam (FPZ), are reserved for infections caused by highly resistant pathogens, while other combinations may be considered for less resistant isolates. The figure illustrates a stepwise approach that integrates in vitro activity, β-lactamase profiles, and non-enzymatic resistance determinants to support rational selection of cefepime-based regimens. Importantly, this scheme is intended as a within-class selection framework among cefepime-based combinations rather than a general therapeutic algorithm for the management of multidrug-resistant Gram-negative microorganisms.
Abbreviations: FEP: cefepime; EMT: enmetazobactam; FTB: cefepime/taniborbactam; FPZ: cefepime/zidebactam; NAC: nacubactam.

FEP/EMT currently represents the most established FEP-based combination, supported by phase III clinical data and regulatory approval by the FDA and EMA.

Its primary role is in treating cUTIs, but PK and PD data also support its use for other severe infections, including HAP, VAP, IAIs, and BSIs, caused by ESBL- and AmpC-producing Enterobacterales, offering a carbapenem-sparing alternative to established therapies. According to in vitro data, FEP/EMT may be considered for infections caused by OXA-48–producing and other OXA-producing Enterobacterales when susceptibility is documented, potentially allowing sparing of CAZ/AVI, owing to the intrinsic stability of FEP against OXA enzymes and the inhibitory activity of EMT against co-produced ESBLs, offering an alternative to CAZ/AVI, which can be instead persevered for KPC-producing microorganisms and *P. aeruginosa*.

In vitro data indicate variable susceptibility among carbapenem-resistant Enterobacterales, particularly those harboring KPC-2 and KPC-3 mutated variants, highlighting the need for further in vivo evaluation, especially against CAZ/AVI–resistant

strains. It does not provide additional benefit over FEP alone against *P. aeruginosa*, where TOL/TAZ continues to represent a key therapeutic choice for difficult-to-treat strains.

Accordingly, routine susceptibility testing is mandatory before use of FEP/EMT outside well-defined Enterobacterales ESBL settings.

FTB is a promising option for treating carbapenem-resistant Enterobacterales, particularly when resistance to currently available BL/BLI combinations such as CAZ/AVI or MEV is present. Its unique ability to inhibit both SBLs and MBLs (except for most IMP and some NDM and VIM variants) supports its potential role in infections caused by organisms producing KPC variants and MBLs, representing a promising alternative to ATM/AVI and cefiderocol.

In particular, FTB may also be considered as a cefiderocol-sparing option in infections caused by Enterobacterales co-producing KPC variants that confer resistance to currently available BLI such as avibactam, vaborbactam, and relebactam, and MBLs. Furthermore, FTB should be considered in Enterobacterales with reduced cefiderocol susceptibility, as these organisms may co-produce CMY- or SHV-type β-lactamases alongside NDM-like enzymes.

However, current evidence is limited to in vitro data, and clinical trial data have not specifically included carbapenem-resistant pathogens.

Nevertheless, accurate identification of the specific MBL type remains crucial given the known limitations of TAN against certain MBLs. In *P. aeruginosa*, FTB in vitro activity is more variable and strongly influenced by non-enzymatic resistance mechanisms, including porin loss, efflux overexpression, and PBP alterations. Similarly, in the setting of MBL-producing *P. aeruginosa*, FTB may represent a potential carbapenem- and cefiderocol-sparing option.

FPZ introduces a distinct therapeutic paradigm by combining β-lactamase inhibition with β-lactam –enhancer activity, achieved through high-affinity binding to PBP2 and multitargeting PBPs. This triple mechanism enables FPZ to retain activity against a broad spectrum of MDR Gram-negative pathogens, including MBL-producing Enterobacterales, isolates harboring PBP3 alterations, and XDR *P. aeruginosa*, often independently of the specific β-lactamase class expressed. Based on consistent in vitro activity, preclinical in vivo data, and emerging compassionate-use experience, FPZ may represent a valuable option for selected infections caused by XDR Enterobacterales and *P. aeruginosa*, particularly in settings where resistance to cefiderocol, ATM/AVI, or other novel BL/BLI combinations limits therapeutic choices due to its unique triple mechanism of action, which allows activity against MBL-producing isolates even in the absence of direct MBL inhibition.

In addition, both FZP and FTB may retain in vitro activity in cases of cefiderocol resistance associated with mutations or downregulation of siderophore-mediated iron uptake pathways. This is because FEP enters Gram-negative bacteria primarily through porin channels rather than via siderophore-mediated uptake and is therefore not dependent on iron transport systems for intracellular accumulation. However, this remains a theoretical consideration and requires confirmation in clinical settings.

Similarly, FEP/NAC combines β-lactamase inhibition with intrinsic antibacterial and β-lactam– enhancer activity, primarily targeting Enterobacterales, although in vitro data showed limited efficacy outside of Enterobacterales.

Overall, FEP-based BL/BLI combinations should be positioned as pathogen- and mechanism-driven therapies, rather than empirical replacements for existing agents. Their use should be guided by rapid molecular diagnostics, comprehensive susceptibility testing, and careful consideration of infection site and severity. As clinical data continue to emerge, these agents may progressively expand the therapeutic armamentarium against MDR Gram-negative infections, provided their deployment remains aligned with antimicrobial stewardship principles.

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