European Journal of Clinical Microbiology & Infectious Diseases
https://doi.org/10.1007/s10096-025-05080-1

REVIEW

In vitro activity and resistance mechanisms of novel antimicrobial agents against metallo-β-lactamase producers

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Received: 15 November 2024 / Accepted: 18 February 2025

Abstract

The carbapenemase-producing Gram-negative organisms represent an urgent clinical and public health concern, as they have been associated with increased mortality and high dissemination in healthcare settings. Although overall incidence rates of infections sustained by metallo-β-lactamase (MβL)-producers have remained lower than those sustained by other carbapenemase-producers, albeit with substantial geographic differences, a significant increase in the prevalence of MβL-producers has been observed over the last decade. The recent development of new antimicrobials expanded the armamentarium to counter the challenge of metallo-β-lactamase (MβL)-producers. Cefiderocol and aztreonam/avibactam are already clinically available and recommended by international guidelines. In addition, two new classes of β-lactam/ β-lactamase combinations are under clinical evaluation: (*i*) combination of β-lactam with novel boronic-derived inhibitors (e.g. taniborbactam and xeruborbactam), (*ii*) combination of β-lactam with last generation diazabicyclooctane β-lactamase inhibitors (e.g. zidebactam and nacubactam), active on most of serine-β-lactamases but also showing strong intrinsic activity on PBP-2. This review aims to provide up-to-date data on the characteristics, activity and emerging resistance mechanisms of the armamentarium of clinically available or soon-to-be introduced drugs for the treatment of MβL-producing Gram-negative organisms.

Keywords Metallo-β-lactamase · NDM · Avibactam · Taniborbactam · Zidebactam · Xeruborbactam · Cefiderocol · Durlobactam

Introduction

The development and use of antibiotics since the second half of the twentieth century revolutionized the approach to the treatment and prevention of infectious diseases, enabling the evolution of modern medicine.

However, the huge increase in antimicrobial resistance (AMR) affecting all countries and healthcare sectors leads us to imagine a surreal scenario with a lack of access to effective antibiotic drugs in the near future. Bacterial AMR is estimated to have been directly responsible for 1.27 million global deaths and contributed to 4.95 million deaths in 2019, and the picture is expected to rise to 10 million per year by 2050 in the absence of effective interventions [1, 2]. The COVID-19 pandemic then exacerbated the concerns by accelerating the transmission and emergence of AMR [3–5]. Among the threats of AMR, carbapenems resistance is the most pressing, given the important role of this class of β-lactams in the clinical armamentarium [2]. The increase in the rate of carbapenem resistance, resulting in

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Published online: 10 March 2025

the global spread of carbapenem resistant organisms (CRO) (Fig. 1), was matched by an increase in associated deaths, from 619000 in 1990 to 1,03 million in 2021 [6]. Among CROs, Enterobacterales, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* are among the top three multi-drug-resistant pathogens on WHO's priority list, being worthy of urgent study to develop new antibiotics (Fig. 1). The carbapenemase-producing subgroup of CROs is of great clinical and public health interest, as it has been associated with increased mortality and high dissemination in healthcare settings [7–9]. Several carbapenemases enzymes belonging to β-lactamases Ambler class A (e.g. *Klebsiella pneumoniae* carbapenemase, KPC), Ambler class B [metallo-β-lactamases, (MβLs)] and Ambler class D (oxacillinase, OXA-like) are largely reported to be associated with the global spread of CROs [7].

Although the overall incidence rates of infections sustained by MβL-producers have remained almost constant and lower than those sustained by other carbapenemase-producers (KPC- and OXA-like- producers), albeit with substantial geographic differences, a significant increase in the prevalence of MβL-producing CROs has been observed in recent years [1–7]. The recent introduction into clinical practice of new β-lactamase inhibitor combinations (e.g. ceftazidime/avibactam, meropenem/vaborbactam and imipenem/relebactam) may have contributed to this phenomenon, exerting strong selective pressure for the spread of MβLs, as the latter are not inhibited by the β-lactamase inhibitors approved to date [8].

Recently, cefiderocol and aztreonam/avibactam have been approved for the treatment of infections sustained by CRO, including MβL producers (Table 1). Moreover, new combinations of β-lactam/β-lactam inhibitors are under clinical evaluation and represent promising additional therapeutic options (Table 1).

Herein, we reviewed current literature providing up-to-date data on *(i)* the epidemiological landscape of MβL-producing pathogens, *(ii)* the characteristics, activity and emerging resistance mechanisms of the latest clinically available or soon-to-be introduced drugs for treatment of MβL-producing Gram-negative infections.

Metallo-β-lactamases

MβLs belong to Ambler class B, whereas class A, C and D include serine β-lactamases [10]. Serine β-lactamases essentially consist of two structural domains (an all α domain and an α/β domain) and the serine active-site is located in the groove between the two domains [11]. In MβLs (class B enzymes), the situation is more complex because the nucleophile is not one active-site serine, but an activated water/

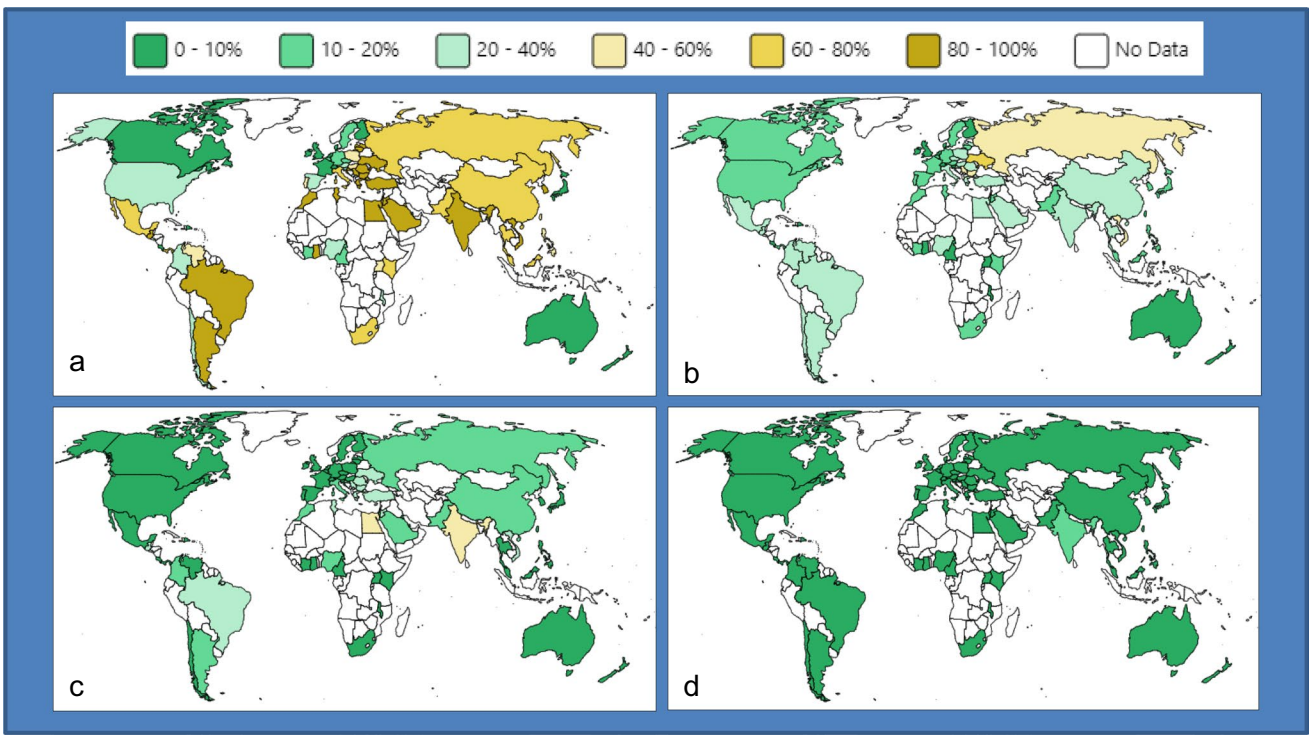

Fig. 1 Global prevalence of carbapenem resistance (2013–2022) among clinical isolates of a. *Acinetobacter baumannii*, b. *Pseudomonas aeruginosa*, c. *Klebsiella pneumoniae*, d. *Escherichia coli*, according to the Antimicrobial Testing Leadership and Surveillance (ATLAS) database (available at: https://atlas-surveillance.com)

Table 1 New antimicrobial agents, approved or under clinical investigation, with activity against metallo-β-lactamase producing Gram-negative bacilli

Antimicrobial agent	Characteristics	Year of FDA approval	Clinical trial	Inhibition profile				Direct activity of the β-lactamase inhibitor on PBPs	Targeted species	Resistance mechanisms
				SβLs			MβLs			
				A	C	D				
Cefiderocol	siderophore-cephalosporin	2019		NA	NA	NA	NA	NA	Enterobacterales, *P. aeruginosa*, *A. calcoaceticus-baumannii* complex, *S. maltophilia*	Mutations in genes related to iron transfer systems; alterations in PBP-3; expression of β-lactamases (mostly NDM-type) combined with other mechanism
Aztreonam/avibactam	monobactam + DBO inhibitor	-	Phase 3, NCT03580044	yes	yes	yes	no	no	Enterobacterales, *S. maltophilia, P. aeruginosa*	Mutation in PBP-3 encoding gene and concomitant expression of class C β-lactamases (e.g. CMY-45 and CMY-59)
Cefepime/taniborbactam	fourth-generation cephalosporin + cyclic boronate	-	Phase 3, NCT03840148; Phase 3, NCT06168734 (ongoing)	yes	yes	yes	yes	no	Enterobacterales, *P. aeruginosa*	IMP-like expression, NDM-9 or NDM-30 expression, alterations in PBP-3, loss of porins, upregulation of efflux pumps
Cefepime/zidebactam	fourth-generation cephalosporin + DBO inhibitor	-	Phase 3, NCT04979806	yes	yes	yes	no	Yes (PBP-2)	Enterobacterales, *P. aeruginosa*	Multiple mutations in genes encoding MexAB-OprM and its regulators, as well as PBP-2 and PBP-3; bla_{PER-1} overespression (*P. aeruginosa*)
β-lactam/xeruborbactam	β-lactam + cyclic boronate (ceftibuten/cefiderocol)	-	Ceftibuten/xeruborbactam: Phase 1, NCT06079775, NCT06157242 (ongoing) Cefiderocol/xeruborbactam: Phase 1, NCT06547554 (ongoing)	yes	yes	yes	yes	no	Enterobacterales, *P. aeruginosa, A. calcoaceticus-baumannii* complex	MexAB-OprM efflux pump overexpression (*P. aeruginosa*)

Table 1 (continued)

Antimicrobial agent	Characteristics	Year of FDA approval	Clinical trial	Inhibition profile				Direct activity of the β-lactamase inhibitor on PBPs	Targeted species	Resistance mechanisms
				SβLs			MβLs			
				A	C	D				
β-lactam/nacubactam	β-lactam (cefepime/aztreonam) + DBO inhibitor	-	Phase 3, NCT05887908 (completed) and NCT05905055 (ongoing)	yes	yes	yes	no	Yes (PBP-2)	Enterobacterales, *P. aeruginosa*	Mutations in PBP-2 encoding gene (*pbpA*); MexAB-OprM efflux pump overexpression, increased expression of PDC β-lactamase (*P. aeruginosa*)
Sulbactam/durlobactam	β-lactam derived by penicillin with β-lactamase inhibition activity (first generation) + DBO inhibitor	2023[a]		yes	yes	yes	no	Yes (PBP-2)	*A. baumannii*, Enterobacterales	MβL expression, alterations in PBP-3 and/or PBP-2 (*A. baumannii*)

[a] Approved for treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia caused by susceptible strains of *Acinetobacter baumannii-calcoaceticus* complex

Abbreviations: FDA, food Drug Administration; PBP, penicillin binding protein; SβL, serine β-lactamase; MβL, metallo-β-lactamase; DBO, diazabicyclooctane; NA, not applicable

hydroxide coordinated to one or two Zn(II) ions, which in turn are coordinated by a set of amino acid ligands. The identity of these ligands falls into three patterns, which define the three subclasses of B-class enzymes, named B1, B2 and B3 [12].

Most of the MβLs identified so far belong to subclass B1, including the imipenemase (IMP), Verona imipenemase (VIM), and New Delhi MβL (NDM) families [13]. A limited number of enzymes belongs to subclass B2, including CphA and Sfh-I, produced by *Aeromonas* species (e.g. *A. hydrophila* and *A. veronii*) and *Serratia fonticola*, respectively. Subclass B3 includes around 50 distinct MβL enzymes, of which L1 MβL is clinically relevant being constitutively expressed by *Stenotrophomonas maltophilia*, an emerging multidrug-resistant Gram-negative organism causing healthcare acquired infections [14]. While the β-lactamase genes encoding class B2 and B3 enzymes have chromosomal localization, those of class B1 are largely plasmids borne and can readily spread by horizontal gene transfer both intra- and inter-species. Among more than 50 enzymes belonging to class B1, NDM, VIM and IMP MβLs are the most relevant from an epidemiological and clinical point of view. Their ability to hydrolyze all β-lactams except aztreonam, the lack of clinically usable inhibitors, their spread in several Gram-negative organisms such as Enterobacterales and non-fermenting species, as well as in nosocomial and environmental reservoirs make them one of the main and growing public health concerns [15]. In addition, new variants with higher affinity for zinc or requiring less of it are emerging, favoring their hydrolytic activity on β-lactam drugs in contexts of relative zinc scarcity, such as human infection sites [16, 17].

IMP-type β-lactamases

The first MβL of the IMP group was identified in an imipenem-resistant *P. aeruginosa* clinical strain collected in 1988 in Japan [18]. The localization of the bla_{IMP} in a 47.7 kbp conjugative plasmid, pMS350, contributed to its spread to other bacterial species as it was subsequently found in the chromosome and as part of an integron in transferable plasmids of several clinical isolates of *P. aeruginosa*, *Pseudomonas putida*, *Pseudomonas stutzeri*, *Serratia marcescens* and *Citrobacter freundii* [19–23]. The first report of an IMP-type enzyme in Europe occurred in a MDR *A. baumannii* strain isolated from respiratory secretions of a critically ill patient in Italy [24]. Further analysis showed that the gene coded for IMP-2 and was carried in a gene cassette as part of a class I integron located on the chromosome. The $bla_{\text{IMP-2}}$ gene cassette was located downstream of intI1 and the variable region also included aac(60)-Ib and ant(300)-Ia [24, 25]. The second identification of an IMP-type enzyme in Europe was carried out in Portugal in an *A. baumannii* strain isolated from urine [26]. Further analysis of that gene concluded that it was a new member, named $bla_{\text{IMP-5,}}$ which followed the two new variants $bla_{\text{IMP-3}}$ and $bla_{\text{IMP-4}}$ previously identified in Asia [27, 28]. IMP-4 was subsequently found within a class 1 integron in isolates of *A. baumannii* and in similar integrons in strains of *A. pitti*, *K. pneumoniae*, *E. coli* and *Enterobacter cloacae*. [29, 30]. To date, the sequences of 102 variants of IMP MβLs, mostly identified in *P. aeruginosa*, *Enterobacter* spp., *K. pneumoniae* and *A. baumannii* clinical isolates are deposited in Genbank. IMP are still the predominant MβLs in Southeast Asia, where they are mostly detected in *P. aeruginosa, A. baumannii*, and Enterobacterales species. Considering bla_{IMP} variants in countries with high prevalence in Asia, $bla_{\text{IMP-1}}$ was the most frequently reported in Japan (23%) and Singapore (50%). $bla_{\text{IMP-4}}$ and $bla_{\text{IMP-14}}$ were the most frequently reported in China (27%) and Thailand (27%), respectively [31]. However, recent regional or sporadic outbreaks have also been reported in the United States, Latin America (Brazil and Argentina), Australia, Lebanon, Egypt and some European countries such as Greece, France, United Kingdom, and Turkey [32–35].

VIM-type β-lactamases

Among MβLs, VIM enzymes have cephalosporins as their preferred substrate and achieve a lower hydrolysis of carbapenem than that produced by enzymes of the IMP and NDM families [36].

The first two VIM variants, named VIM-1 and VIM-2, were identified in Italy and France in 1997 and 1996, respectively. They were both detetcted in *P. aeruginosa* isolates containing bla_{VIM} gene cassettes inserted into a class 1 integron [37, 38]. Despite the high amino acid sequence identity, the two genes had a different location: $bla_{\text{VIM-1}}$ was located within the chromosome and included a second aac(60)-Ib-containing gene cassette, whereas $bla_{\text{VIM-2}}$ was included in a unique gene cassette, located in an integron within a ~ 45-kbp non-conjugative plasmid. Furthermore, the enzymes were not closely related to other MβL, with only 28–31% sequence identity between VIM-1/VIM-2 and IMP-1 [37, 38]. After the first identification, VIM enzymes spread rapidly throughout Southern Europe, with outbreaks in Italy and Greece in 2006, first in isolates of *P. aeruginosa* and then of *K. pneumoniae* [33, 39–41]. Until 2017, VIM-type was the predominant MβLs in Europe, especially in Mediterranean countries.

The rapid global spread of VIM MβLs, especially in *Enterobacteriacea*e and *Pseudomonas*, has led to the identification of a large number of new variants in the recent years (87 uploaded on Genbank, last accessed on September 2024). Currently, VIM MβLs are found globally, mainly in *K. pneumoniae*, *E. cloacae* complex and *P. aeruginosa* [33]. VIM-2-like MβLs are mostly reported in *P. aeruginosa*, whereas VIM-1-like MβLs (e.g. VIM-4) are frequently

reported in *Enterobacteriaceae* species. Furthermore, the presence of VIM variants (VIM-1, VIM.2, VIM-3, VIM-6, VIM-11, VIM-25) in *A. baumannii* isolates has been reported in Korea, Greece, Saudi Arabia and Iran since the early 2000s [42].

NDM-type β-lactamases

The NDM MβL was first described in 2009 in a *K. pneumoniae* isolate from a urine sample of a Swedish patient, previously admitted to two Indian hospitals [43]. The $bla_{\text{NDM-1}}$ was located in a 180 kbp plasmid including multiple antibiotic resistance genes. BLAST analysis showed that NDM-1 shared very little sequence homology with other MβLs, and the closest relative was VIM-1, with only 32.4% of amino acid identity [44]. The detection of a MDR *E. coli* strain harboring the same $bla_{\text{NDM-1}}$-carrying plasmid suggested that plasmid transfer by conjugation occurred with high frequency, and this was then demonstrated by in vitro conjugation assays [43]. The rapid spread of $bla_{\text{NDM-1}}$-carrying plasmid in many species of enteric bacteria, foodborne pathogens (*Shigella* spp., *Vibrio cholerae*), and non-fermenting Gram-negative species (*A. baumannii*, *P. aeruginosa*) led to its worldwide dissemination [33, 41, 45, 46]. According to Genbank data (last accessed on September 2024), 68 different variants of bla_{NDM} were identified to date. In addition to multiple sequences of the gene, several plasmids carrying $bla_{\text{NDM-like}}$ and different sequence typing of the species involved were identified, demonstrating the promiscuity of bla_{NDM}.

Currently, bla_{NDM} is endemic not only in the Indian subcontinent but also in the Asia–Pacific region, Balkan countries, Eastern Europe, North Africa and Arabian Peninsula [33, 46–48]. Furthermore, regional or sporadic health-care dissemination of NDM-producing *Enterobacteriaceae* in Latin America, USA, and many Western European countries such as, Netherlands, Denmark, Spain, and Italy was recently reported [49–55]. A recent surveillance study involving 24,580 carbapenem-resistant Enterobacterales isolates collected in 2020–2022 from 64 medical centers located in Europe, Latin America, and Asia–Pacific region showed that NDM was the second most common carbapenemase (29.9%) after KPC (44.6%). Its occurrence was highest in the Asia–Pacific region (55.4%), followed by Latin America (31.7%), Eastern Europe (27.3%) and Western Europe (15.7%) [56]. Similar finding emerged by a surveillance study involving Enterobacterales isolates (n = 34.623) collected in 86 US hospitals from 2016 to 2020 [57]. Among MBL-positive isolates globally collected during the period 2016–2020, NDM-positive was the most common genotype collected globally (83.3%); NDM-1, NDM-5 and NDM-7 were the most prevalent variants (61.4%, 32.4% and 4.2%, respectively) followed by NDM-4, NDM6, NDM-9, NDM-16, NDM-19, NDM-24 (overall 2%) [58].

Therapeutic options for MβLs

In addition to inactivation by metal chelators, all MβLs share further functional characteristics, including hydrolytic activity on carbapenems, resistance to the clinically available β-lactamase inhibitors (e.g. clavulanate, sulbactam, tazobactam, avibactam, vaborbactam, relebactam) and no activity against monobactams. Moreover, the location of MβL encoding genes in genomic contexts with multiple resistance determinants is often associated to resistance towards more drug classes other than β-lactams. As a result, the optimization of antibiotic therapy of infections sustained by MβL-producers is challenging. Although "old" drugs such colistin, fosfomycin, tetracyclines and aminoglycosides may show in vitro efficacy, they are associated with less bactericidal activity or more toxicity [48]. Recently, cefiderocol and aztreonam/avibactam have been approved by the FDA and/or EMA agencies for treating MβL-producing pathogens infections.

Moreover, recent research has been increasingly focused on broad spectrum β-lactamase inhibitors. Bicyclic boronates have been developed as successful inhibitors of both MBLs and serine β-lactamases. Two bicyclic boronates, taniborbactam and xeruborbactam, were proposed as promising candidates for dual inhibitors of MBLs and serine β-lactamases (Fig. 2 and Table 1). Moreover, the development of new non-β-lactam antibiotics targeting penicillin binding proteins (PBPs) is another option taken in consideration to counter MBL-mediated resistance. For instance, the diazabicyclooctane derivative zidebactam, nacubactam and durlobactam shows activity against PBP-2, as well as inhibition of the main serine β-lactamases (Fig. 2 and Table 1).

Cefiderocol

Cefiderocol (formerly S-649266, GSK2696266) is a new siderophore cephalosporin developed and marketed by Shionogi & Co., Ltd. as a promising drug for the treatment of multidrug-resistant Gram-negative bacilli infections (Fig. 2 and Table 1). It was approved by FDA and EMA on November 2019 and April 2020, respectively.

The unique characteristic of binding to extracellular free iron via a siderophore side chain allows active transport into the periplasmic space of Gram-negative bacteria via active iron transport systems. Therefore, unlike other β-lactams, cefiderocol uses both this active iron transport and the traditional porin-mediated transport system to enter the bacterial cell and target PBPs. This 'Trojan horse' strategy of action allows cefiderocol to overcome the resistance mechanisms

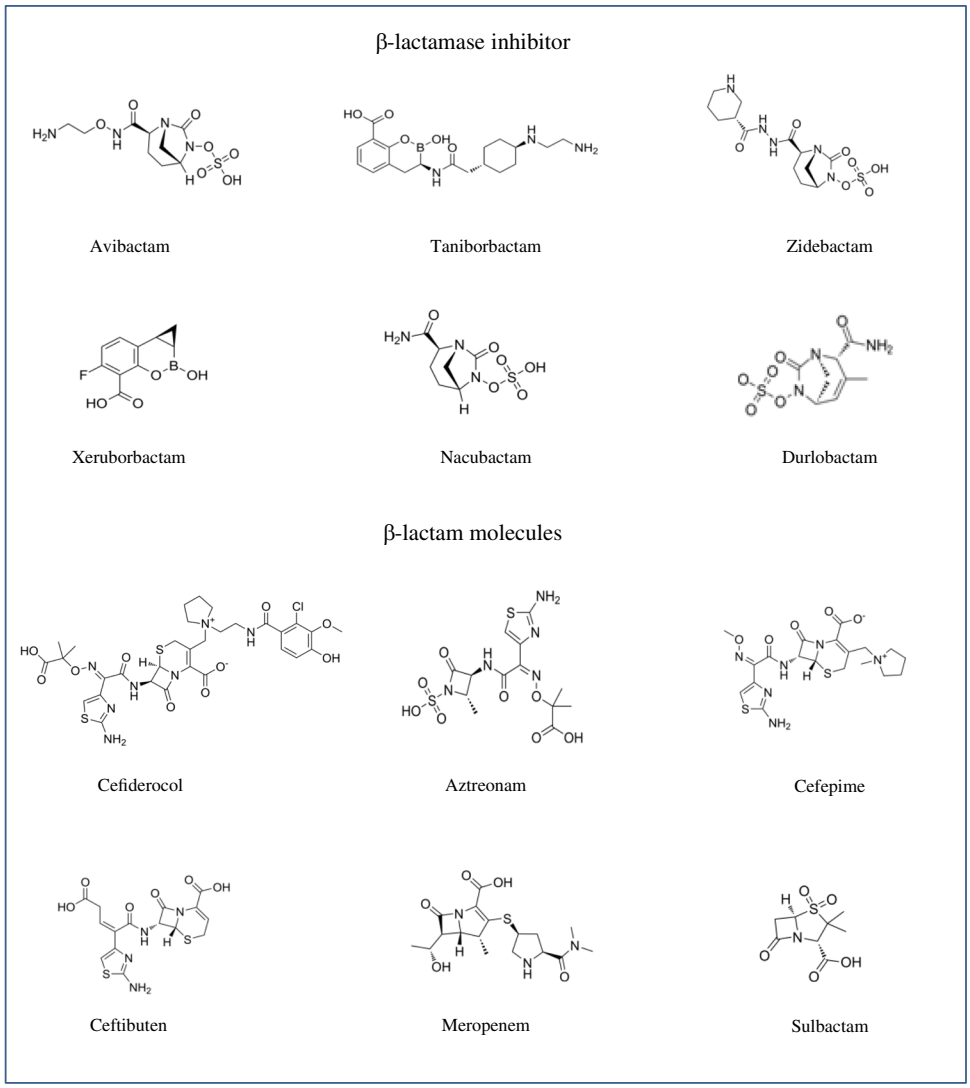

Fig. 2 Chemical structures of β-lactamase inhibitors and β-lactams analyzed in this review

that alter permeability of the outer membrane (e.g. overexpression of efflux pumps, loss of the porin channels) [59]. Moreover, its structure, similar to that of cefepime and ceftazidime but with the addition of different constituent groups, confers an enhanced stability to the action of β-lactamases including MβL [59].

In vitro activity of cefiderocol against carbapenem-non-susceptible and MβL-producing pathogens was investigated in several studies, including surveillance reports and a recent meta-analysis (Table 2) [60–77]. Using the EUCAST/CLSI breakpoint thresholds, cefiderocol susceptibility rates were generally high in carbapenem-non-susceptible pathogens (82.5–92.6%, 94.8–98.5%, 88.6–91.8% in Enterobacterales, *P. aeruginosa* and *A. baumannii* complex isolates, respectively), lower in MβL producers (72.1–86.6%, 94.3–97.5%, 51.4–75.8% in Enterobacterales, *P. aeruginosa* and *A. baumannii* complex isolates, respectively), and even lower in NDM-producing isolates (50.5–75%, 71.2–82.1%, 47.6–71.5%, in Enterobacterales, *P. aeruginosa* and *A. baumannii* complex isolates, respectively) (Table 2). As shown, there were significant differences in cefiderocol susceptibility rates when comparing results between EUCAST and CLSI breakpoints, which was not the case with *S. maltophilia* (97.2–99.2%).

In vivo activity of cefiderocol against MβL-producing pathogens was evaluated in the CREDIBLE-CR and APEKS-NP studies [78–80]. Overall, cefiderocol monotherapy was effective in the treatment of infections sustained by MβL-producing Gram-negative bacteria. The rates of clinical cure (70.8%), microbiological eradication (58.3%) and all-cause mortality at 28 days (12.5%) compared favorably with the best available therapy and high-dose meropenem (40.0%; 30.0%; and 50.0%), respectively. Clinical recovery was lower for NDM-producing infections (56.2%) than for non-NDM-producing infections (100%) [78–80].

In vivo emergence of cefiderocol resistance following therapy with cefiderocol or other β-lactams (e.g. ceftazidime/avibactam and ceftolozane/tazobactam) against *P.*

Table 2 In vitro activity of cefiderocol against MDR Gram-negative clinical isolates collections including metallo-β-lactamase producers

Reference	Country	Period of isolates collection	Breakpoint	Carbapenem non-susceptible			MβL producers				NDM producers		
				Enterobacterales	*P. aeruginosa*	*ACB*	Enterobacterales	*P. aeruginosa*	*ACB*	*S. maltophilia*	Enterobacterales	*P. aeruginosa*	*ACB*
[60]	Worldwide	2006–2023	CLSI	6638/7175; 92.5%	4321/4389; 98.4%	5560/6047; 91.9%	1400/1679; 83.4%	540/562; 96.1%	74/93; 79.5%	2922/3003; 97.3%	1096/1476; 74.2%	33/41; 80.5%	66/85; 77.6%
			EUCAST	4614/5589; 82.5%	3823/4041; 96.4%	4296/4831; 88.9%	1064/1507; 70.6%	495/527; 93.9%	55/93; 59.1%	3019/3030; 99.6%	490/1024; 47.8%	37/51; 72.5%	47/85; 55.3%
[61]	China	2014–2022	CLSI	289/320; 90.3%	-	-	49/57; 86%	-	-	-	49/57; 86%	-	-
[62]	Worldwide	2019–2021	CLSI	-	790/806; 98%	-	-	160/164; 97.5%	-	-	-	11/13; 84.6%	-
			EUCAST	-	766/806; 95%	-	-	147/164; 89.6%	-	-	-	9/13; 69.2%	-
[63]	Swiss	2022–2023	EUCAST	-	31/39; 79.5%		31/39; 79.5%				6/12; 50%		
[64]	Japan	2019–2020	CLSI	300/307; 97.7%	18/18; 100%	49/57; 86%	272/278; 97.8%	16/16; 100%	8/10; 80%	-	20/24; 83.3%	-	1/3; 33.3%
[65]	Italy	2019–2021	EUCAST	108/124; 87.1%	25/26; 96.1%	68/70; 97.1%	8/12; 66.7%	3/4; 75%	5/6; 83.3%	12/12; 100%	0/2; 0%	-	5/6; 83.3%
[66]	Spain	2015–2020	EUCAST	83/90; 92.2%	-	-	28/35; 80%	-	-	-	8/14; 57.1%	-	-
[67]	North America and Europe	2014–2019	CLSI	181/198; 91.4%	227/227; 100%	15/25; 60%	181/198; 91.4%	227/227; 100%	15/25; 60%	-	80/94; 85.1%	2/2; 100%	11/21; 52.4%
			EUCAST	133/198; 67.2%	221/227; 97.3%	11/25; 44%	133/198; 67.2%	221/227; 97.3%	11/25; 44%	-	49/94; 52.1%	1/2; 50%	7/21; 33.3%
[68]	Spain	2015-2020	CLSI	153/160; 95.6%	68/68; 100%	-	153/160; 95.6%	68/68; 100%	-	-	-	-	-
			EUCAST	129/160; 80.6%	68/68; 100%	1/4; 25%	129/160; 80.6%	68/68; 100%	1/4; 25%	-	-	-	-
[69]	Taiwan	2013–2021	CLSI	171/195; 87.7%	-	-	123/143; 86%	-	-	-	58/74; 78.4%	-	-
[70]	Türkiye	2017	EUCAST	-	233/244; 95.5%	-	-	13/14; 92.8%	-	-	-	4/5; 80%	-
[71]	Europe	2020	EUCAST	130/148; 87.8%	-	-	20/35; 57.1%	-	-	-	13/27; 48.1%	-	-
			CLSI	139/148; 93.9%	-	-	26/35; 74.2%	-	-	-	19/27; 70.4%	-	-

Table 2 (continued)

Reference	Country	Period of isolates collection	Breakpoint	Carbapenem non-susceptible			MβL producers				NDM producers		
				Enterobacterales	*P. aeruginosa*	*ACB*	Enterobacterales	*P. aeruginosa*	*ACB*	*S. maltophilia*	Enterobacterales	*P. aeruginosa*	*ACB*
[72]	Poland	2019–2022	EUCAST	60/60; 100%	-	-	60/60; 100%	-	-	-	60/60; 100%	-	-
[73]	Mexico	2012–2022	CLSI	-	-	-	-	-	-	96/101; 95%	-	-	-
[74]	Europe	2020	EUCAST	-	135/139; 97.1%	193/227; 85%	-	29/30; 96.7%	0/12; 0%	-	-	1/2; 50%	0/12; 0%
[75]	Northern Ireland, Spain and the Netherlands	-	EUCAST	-	-	-	-	-	-	88/102; 86.3%	-	-	-
[76]	Taiwan	2019–2021	CLSI	-	110/110; 100%	122/129; 94.6%	-	-	-	46/47; 97.9%	-	-	-
[77]	Italy	2019–2020	EUCAST	31/41; 75.6%	7/8; 87.5%	-	31/41; 75.6%	7/8; 87.5%	-	-	1/9; 11.1%	-	-
Pooled data		2006–2023	CLSI	7871/8503; 92.6%	5534/5618; 98.5%	5746/6258; 91.8%	2006/2315; 86.6%	1011/1037; 97.5%	97/128; 75.8%	3064/3151; 97.2%	1196/1594; 75%	46/56; 82.1%	78/109; 71.5%
			EUCAST	5288/6410; 82.5%	5309/5598; 94.8%	4569/5157; 88.6%	1504/2087; 72.1%	983/1042; 94.3%	72/140; 51.4%	3119/3144; 99.2%	627/1242; 50.5%	52/73; 71.2%	59/124; 47.6%

Susceptibility data were re-interpreted according to:

EUCAST susceptibility breakpoint (v_14.0, 2024): ≤ 2 mg/L;

CLSI susceptibility breakpoints (CLSI M100 ED34:2024): Enterobacterales, *Pseudomonas*, *Acinetobacter*, ≤ 4 mg/L; *S. maltophilia* ≤ 1 mg/L

Abbreviation: *ACB*, *Acinetobacter baumannii-calcoaceticus* complex

aeruginosa, *A. baumannii* complex and Enterobacterales infections was reported [81–86]. Resistance to cefiderocol was shown to be a consequence of combinations of various mechanisms, including mutations in genes related to iron transfer systems (e.g. *piuA*, *pirA, cirA* and *tonB*), expression of β-lactamases (e.g. NDM-type, KPC variants linked to ceftazidime/avibactam resistance, OXA-427, CMY-185, CMY-186 and PER-type), mutations in penicillin binding protein PBP-3, porin loss and efflux pump overexpression [59].

Aztreonam/avibactam

Aztreonam/avibactam (Emblaveo, Pfizer) is a combination including a monobactam that interferes with bacterial cell wall synthesis and a non-β-lactam β-lactamase inhibitor that is active against class A, class C and some class D β-lactamases (Fig. 2 and Table 1). It was approved by the EMA on April 2024 for patients suffering from MDR infections and limited treatment options, including complicated intra-abdominal infections (cIAI), hospital-acquired pneumonia (HAP), and complicated urinary tract infections (cUTI) [87]. Although aztreonam is not hydrolyzed by MβLs, co-expression of MβLs with β-lactamases of the other Ambler classes able to hydrolyze aztreonam is frequent. Therefore, aztreonam monotherapy is often not active against MβL-producing strains. Pending regulatory agencies approval, co-administration of ceftazidime/avibactam and aztreonam has been recommended for the treatment of MβL-producing Enterobacterales infections by both the Infectious Disease Society of America (IDSA) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [88, 89].

Several studies have evaluated the in vitro activity of aztreonam/avibactam against worldwide isolates of Enterobacterales and *P. aeruginosa* exhibiting carbapenem non-susceptibility and/or MβL-production [48, 53, 56, 58, 63, 69, 71, 74, 76, 90–97] (Table 3). According to EUCAST/CLSI 2024 breakpoints, among the 88,592 carbapenem-non-susceptible and/or carbapenemase-producing Enterobacterales isolates tested, the pooled susceptibility rate was 99.5%, and only a small reduction was observed in the MβL- or NDM- producers subgroups (96.9% and 95.6%, respectively). Moreover, a recent report showed excellent in vitro activity of aztreonam/avibactam against Enterobacterales isolates producing dual-carbapenemase (MβL + class A carbapenemase, n = 14; MβL + class D carbapenemase, n = 35), revealing 100% susceptibility and overall MIC_{50} and MIC_{90} of ≤ 0.25 mg/L and 0.5 mg/L, respectively [98].

Conversely, lower rates of aztreonam/avibactam susceptibility were reported among carbapenem-non-susceptible (72.2–83%) and MβL-producing *P. aeruginosa* isolates (55.8–72.5%). These findings were consistent with data on MIC_{50} and MIC_{90} (0.125 mg/L to 0.25 mg/L *vs.* 16 to 32 mg/L, in Enterobacterales and *P. aeruginosa*, respectively) [99]. This difference in susceptibility could be due to the presence of multiple resistance mechanisms commonly detected in *P. aeruginosa*, such as overexpression of efflux systems, production of PDC-like, PER-like and OXA-like β-lactamase variants, and loss of porins. Consequently, these data might suggest the use of aztreonam/avibactam mainly for the treatment of infections sustained by MβL-producing Enterobacterales [99]. Aztreonam-avibactam showed also to be a promising β-lactam/β-lactamase-inhibitor combination against MDR *S. maltophilia* [100, 101]. Sader et al. evaluated the in vitro activity of aztreonam/avibactam against 1.839 *S. maltophilia* isolates collected worldwide and showed high activity, regardless of the geographic region or type of infection (overall $MIC_{50/90}$, 4/4 mg/L; 97.8% inhibited at ≤ 8 mg/L [101].

As far as in vivo studies are concerned, a phase 2a trial showed both relevant attainment of PK/PD targets and favorable benefit–risk ratio for aztreonam/avibactam [102]. The recommended daily dose for aztreonam/avibactam was a 30-min infusion with 500/167 mg aztreonam/avibactam as loading dose and maintenance dose with 3-h infusions of 1500/500 mg aztreonam/avibactam every 6 h. This resulted in a higher daily dose of avibactam as compared to the combination aztreonam plus ceftazidime/avibactam dosing (2-h infusion of ceftazidime/avibactam, 2000/500 mg every 8 h with aztreonam, 2000 mg every 6 h) [102, 103]. The REVISIT phase 3 trial (NCT03329092; registration date: 2017–10-06; https://clinicaltrials.gov/study/NCT03329092) assessed aztreonam/avibactam ± metronidazole compared to meropenem ± colistin in patients suffering from cIAI and HAP/VAP caused or suspected to be caused by Gram-negative bacteria. The cure rate of patients with cIAI and treated with aztreonam/avibactam was higher than that of those treated with meropenem (85.1% *vs.* 79.5%). In cases of patients with HAP, the aztreonam/avibactam cure rate was lower (46.7% *vs.* 54.5%). The 28-day mortality rates were low for both groups (1.9% and 2.9% for the aztreonam/avibactam and the meropenem group, respectively) [103, 104]. The ASSEMBLE phase 3 trial was early terminated due to difficulty in recruiting patients. However, before termination, 5/12 (41.7%) patients with confirmed MβL Gram-negative infections were cured with aztreonam/avibactam and none out three with best-available therapy (NCT03580044; registration date: 2018–06-04; https://clinicaltrials.gov/study/NCT03580044).

In vivo emergence of resistance to aztreonam/avibactam has been unfrequently reported in the real-world experience [105, 106]. Mutations in genes encoding for PBP-3 (*ftsl*) and expression of mutated AmpC β-lactamase CMY were identified as potential resistance mechanisms occurred in NDM-5-producing *E. coli* following aztreonam plus avibactam based-therapies [105, 106]. Resistance to aztreonam/

Table 3 In vitro activity of aztreonam/avibactam against MDR Gram-negative clinical isolates collections including metallo-β-lactamase producers

Reference	Country	Period of isolates collection	Breakpoint	Carbapenem non-susceptible		MβL producers		NDM producers	
				Enterobacterales	*P. aeruginosa*	Enterobacterales	*P. aeruginosa*	Enterobacterales	*P. aeruginosa*
[48]	China	2021	CLSI	298/306; 97.4%	71/138; 51.4%	99/102; 97%	8/15; 53.3%	-	-
			EUCAST	298/306; 97.4%	97/138; 70.3%	99/102; 97%	11/15; 73.3%	-	-
[63]	Swiss	2022–23	EUCAST	-	34/39; 87.2%	-	34/39; 87.2%	-	-
			CLSI	-	16/39; 41%	-	16/39; 41%	-	-
[53]	USA	2019–21	CLSI/ EUCAST	258/261; 98.8%	-	32/33; 97%	-	28/29; 96.5%	-
[56]	Worldwide	2020–22	CLSI/ EUCAST	1011/1016; 99.5%	-	356/356; 100%	-	-	-
[58]	Worldwide	2016–2020	CLSI/ EUCAST	82,642/82.785; 99.8%	-	1681/1707; 98.5%	-	1395/1421; 98.2%	-
[69]	Taiwan	2013–2021	CLSI/ EUCAST	189/195; 96.9%	-	137/143; 95.8%	-	69/74; 93.2%	-
[71]	Europe	2020	EUCAST/ CLSI	140/148; 94.6%	-	35/35; 100%	-	27/27; 100%	-
[74]	Europe	2020	EUCAST	-	58/139; 41.7%	-	22/30; 73.3%	-	1/2, 50%
			CLSI	-	17/139; 12.2%	-	9/30; 30%		1/2, 50%
[76]	Taiwan	2019–2021	CLSI	-	14/110; 12.7%	-	-	-	-
			EUCAST	-	44/110; 40%	-	-	-	-
[90]	Spain	2018	CLSI/ EUCAST	54/55; 98.2%	-	54/55; 98.2%	-	9/10; 90%	-
[91]	China	2019	CLSI/ EUCAST	110/119; 92.4%	-	35/44; 79.5%	-	32/41; 78%	
[92]	UK	2015, 2017, 2019	CLSI/ EUCAST	413/464; 89%	-	413/464; 89%	-	193/243; 79.4%	-
[93]	Europe	2019–2020	CLSI/ EUCAST	421/424; 99.3%	-	109/109; 100%	-	81/81; 100%	-
[94]	Worldwide	2016–2017	CLSI/ EUCAST	582/583; 99.8%	-	114/114; 100%	-	-	-
[95]	China	2016–2017	CLSI/ EUCAST	161/161; 100%	-	161/161; 100%	-	151/151; 100%	-
[96]	Worldwide	2012–2015	EUCAST	1378/1498; 92%	-	249/267; 93.2%	319/452; 70.6%	-	-
			CLSI	1378/1498; 92%	8692/11842; 73.4%	249/267; 93.2%	280/452; 61.9%	-	-
[97]	Worldwide	2012–2013	EUCAST	537/577; 93.1%	3246/3766; 86.2%	91/91; 100%	88/118; 74.6%	-	-
			CLSI	537/577; 93.1%	2772/3766; 73.6%	91/91; 100%	52/118; 44.1%	-	-
Pooled data		2012–2023	EUCAST	88,196/88592; 99.5%	3479/4192; 83%	3566/3681; 96.9%	474/654; 72.5%	1985/2077; 95.6%	1/2; 50%
			CLSI	88,196/88592; 99.5%	11,582/16034; 72.2%	3566/3681; 96.9%	365/654; 55.8%	1985/2077; 95.6%	1/2; 50%

For susceptibility testing purpose, the concentration of taniborbactam was fixed at 4 mg/L

No available clinical breakpoints for aztreonam/avibactam. Susceptibility data were re-interpreted according to aztreonam susceptibility breakpoints as follows:

EUCAST susceptibility breakpoint (v_14.0, 2024): Enterobacterales, ≤ 4 mg/L; *Pseudomonas*, ≤ 16 mg/L

CLSI susceptibility breakpoints (CLSI M100 ED34:2024): Enterobacterales, ≤ 4 mg/L; *Pseudomonas*, ≤ 8 mg/L

avibactam is increasingly reported in *E. coli* in Asia [107, 108] and Europe [109–111] due to co-expression of PBP-3 mutations and NDM. Moreover, since PBP-3 is also a target of other β-lactams, occurrence of co-resistance to cefiderocol was reported [105, 106]. The most commonly reported aztreonam/avibactam non-susceptible clones at high-risk are those carrying mutations in PBP-3, in particular a four amino acid insertion (YRIN/K) at residue 333 or 338 of PBP-3 [105, 106, 112–117]. However, presence of mutated PBP-3 alone may not be sufficient to confer high-level resistance, and concomitant production of class C β-lactamases (e.g. CMY-45 and CMY-59) was often observed [105, 106, 112, 114–117]. Although resistance to aztreonam/avibactam was essentially observed in high-risk clones of *E. coli*, co-resistance to ceftazidime/avibactam and aztreonam/avibactam in *K. pneumoniae* was correlated with expression of mutated KPC enzymes [86, 118].

Cefepime/taniborbactam

Taniborbactam (formerly VNRX-5133, Venatorx Pharmaceuticals) belongs to the cyclic boronate family and exhibits β-lactamase inhibitory activity against KPC, OXA-48 and some MβLs (VIM and NDM but not IMP) (Fig. 2 and Table 1) [119–121]. This compound was the first boronate inhibitor to show direct inhibitory activity against serine β-lactamases and MβL enzymes via different mechanisms. While avibactam is exclusively an inhibitor of serine β-lactamases, the addition of an aromatic group with a carboxylic acid to the boronate ring confers taniborbactam the ability to bind MβL enzymes as well [122]. In steady-state kinetic analysis experiments, taniborbactam was confirmed as a competitive inhibitor of VIM-2 and NDM-1 but not IMP-1 [inhibition constant (Ki) of 0.019, 0.081 µM and 30 µM, respectively] [123]. Moreover, inhibitory activity of taniborbactam was shown against various class A and C enzymes and OXA-48 like class D, with Ki values similar to those of avibactam. Taniborbactam inhibits serine β-lactamases through slow dissociation, while also acting as a reversible competitive inhibitor with a low Ki and rapid dissociation from MβLs [123].

A global surveillance study assessed *in vitro* activity of cefepime/taniborbactam against a 2018–2020 worldwide collection of Enterobacterales ($n = 13{,}731$) and *P. aeruginosa* ($n = 4{,}619$) isolates [124]. Using the fixed concentration 4 mg/L of taniborbactam, the MIC_{50}/MIC_{90} were 0.06/0.25 mg/L, 2/8 mg/L, and rates of inhibition at ≤ 16 µg/mL or ≤ 8 µg/mL were 99.7%/99.5% and 97.4%/94.2% in Enterobacterales and *P. aeruginosa*, respectively [124]. Data on in vitro activity of cefepime/taniborbactam against carbapenem-non-susceptible and/or carbapenemase-producers, and MβL-positive Enterobacterales and *Pseudomonas* spp. was reported in Table 4. According to the proposed provisional susceptibility breakpoint (≤ 16 mg/L) [124], the pooled susceptibility rates were 86.7% and 82% for Enterobacterales and *Pseudomonas* spp, respectively, followed by 72.3% and 77.3% in the respective MβL-positive subgroups. Among MβL-positive isolates, in vitro activity was higher among VIM-positive than NDM-positive isolates (98.7% *vs.* 64.1% in Enterobacterales, and 81.4% *vs.* 0% in *Pseudomonas* spp, respectively). Interpretation of the overall MIC values using the susceptibility breakpoints of cefepime from EUCAST (2024) and CLSI (2024) led to a significant reduction in susceptibility rates with values below 60% in the overall MβL-positive isolates (range 47–58.3%) and below 50% in the NDM-positive Enterobacterales (ramge 36.4–43.4%) (Table 4). Of note, various studies showed a considerable discrepancy in susceptibility rates to cefepime/taniborbactam [63, 71, 74, 124–130]. For instance, among NDM-positive Enterobacterales, susceptibility rates (≤ 16 mg/L) of 90–100% were reported in Spain [128, 129], 96.3% in Europe [71], 86.5% in a worldwide collection [124], 79.9% in the UK [126], 66.7% in China [125] and 28% in India [130]. These differences in data could be due to the different geographical distribution of bacterial clones harboring resistance mechanisms such as the expression of specific β-lactamase variants [131–133]. Genomic characterization of cefepime/taniborbactam-resistant Enterobacterales strains showed that multiple mechanisms may be associated with cefepime/taniborbactam resistance, including production of IMP-like carbapenemases, alterations in PBP-3, loss of porins (OmpA, OmpR, Omp35, OmpK36), upregulation of efflux pumps, often with concomitant expression of NDM variants or class D β-lactamases [124, 129, 131–133]. Terrier et al. showed that that taniborbactam exhibits an overall excellent activity against B1 MβLs including most NDM- and VIM-like as well as SPM-1, GIM-1, and DIM-1 enzymes, but not against NDM-9, NDM-30 (differing from NDM-1 by a single amino acid substitution), and VIM-1 like enzymes (particularly VIM-83) [134, 135]. Furthermore, Drusin et al. revealed that the replacement of Glu149 by a Lys residue in NDM-9 results in a reduction of taniborbactam affinity and activity [136]. Similarly, WGS characterizations have identified multiple resistance mechanisms in *P. aeruginosa* isolates displaying high MICs of cefepime/taniborbactam, such as IMP production, PBP-3 mutations, upregulation of efflux pumps, and overexpression of AmpC beta-lactamase (PDC) [124, 129].

The phase 3 trial CERTAIN-1 (NCT03840148; registration date: 2019–02–06; https://clinicaltrials.gov/study/NCT03840148) compared efficacy and safety of cefepime/taniborbactam with meropenem for the treatment of adults with cUTI not caused by MβL-producing bacteria [137]. Cefepime/taniborbactam showed higher microbiological and clinical success than meropenem (treatment difference, 12.6%; 95% confidence interval, 3.1 to 22.2; $p = 0.009$)

Table 4 In vitro activity of cefepime/taniborbactam against MDR Gram-negative clinical isolates collections including metallo-β-lactamase producers

Reference	Country	Period of isolates collection	Breakpoint	Carbapenem non-susceptible and/or carbapenemase-producers		MβL producers		NDM producers		VIM producers		IMP producers
				Enterobacterales	*P. aeruginosa*	Enterobacterales	*P. aeruginosa*	Enterobacterales	*P. aeruginosa*	Enterobacterales	*P. aeruginosa*	Enterobacterales
[63]	Swiss	2022–23	EUCAST/CLSI	-	20/39; 51.3%	-	20/39; 51.3%	-	-	-	-	-
			Provisional BP	-	21/39	-	21/39	-	-	-	-	-
[71, 74]	Europe	2020	EUCAST	139/145	83/139; 59.7%	24/37; 64.9%	16/30; 53.3%	19/27; 70.4%	0/2; 0%	5/7; 71.4%	15/24; 62.5%	-
			CLSI	124/145; 85.5%	83/139; 59.7%	18/34; 52.9%	16/30; 53.3%	13/27; 48.1%	0/2; 0%	5/7; 71.4%	15/24; 62.5%	-
			Provisional BP	144/145	114/139; 82%	33/34; 97%	18/30; 60%	26/27; 96.3%96.3%	0/2; 0%	7/7; 100%	17/24; 70.8%	-
[123]	-	2005–2018	EUCAST	59/60; 98.3%	38/41; 92.7%	19/20; 95%	5/5; 100%	9/9; 100%	-	8/8; 100%	5/5; 100%	-
			CLSI	57/60; 95%	38/41; 92.7%	17/20; 85%	5/5; 100%	8/9; 88.9%	-	7/8; 87.5%	5/5; 100%	-
			Provisional BP	60/60; 100%	39/41; 95.1%	20/20; 100%	5/5; 100%	9/9; 100%	-	8/8; 100%	5/5; 100%	-
[124]	Worldwide	2018–2020	EUCAST	534/625; 85.4%	151/216; 69.9%	158/229; 69%	120/159; 75.5%	139/207; 67.1%	-	19/22; 86.4%	120/159; 75.5%	-
			CLSI	472/625; 75.5%	151/216; 69.9%	150/229; 65.5%	120/159; 75.5%	132/207; 63.8%	-	18/22; 81.8%	120/159; 75.5%	-
			Provisional BP	595/625	177/216; 81.9%	201/229; 87.8%	139/159; 87.4%	179/207; 86.5%	-	22/22; 100%	139/159; 87.4%	-
[125]	China	2017–2019	EUCAST	132/207; 63.8%	15/21; 71.4%	37/87; 42.5%	-	37/87; 42.5%	-	-	-	-
			CLSI	105/207; 50.7%	15/21; 71.4%	30/87; 34.5%	-	30/87; 34.5%	-	-	-	-
			Provisional BP	163/207;	18/21; 85.7%	58/87; 66.7%	-	58/87; 66.7%	-	-	-	-
[126]	UK	2013–2016	EUCAST	276/342; 80.7%	7/24; 29.2%	144/217; 66.3%	7/24; 29.2%	103/164; 62.8%	0/4; 0%	38/40; 95%	7/20; 35%	3/13; 23%
			CLSI	240/342; 70.2%	7/24; 29.2%	123/217; 56.7%	7/24; 29.2%	76/164; 46.3%	0/4; 0%	37/40; 92.5%	7/20; 35%	0/13; 0%
			Provisional BP	304/342	10/24; 41.7%	180/217; 82.9%	10/24; 41.7%	131/164; 79.9%	0/4; 0%	40/40; 100%	10/20; 50%	9/13; 69.2%
[127]	Greece	2019–2020	EUCAST	78/97	46/100, 46%	78/97; 80.4%	46/100; 46%	-	-	-	-	-

Table 4 (continued)

Reference	Country	Period of isolates collection	Breakpoint	Carbapenem non-susceptible and/or carbapenemase-producers		MβL producers		NDM producers		VIM producers		IMP producers
				Enterobacterales	*P. aeruginosa*	Enterobacterales	*P. aeruginosa*	Enterobacterales	*P. aeruginosa*	Enterobacterales	*P. aeruginosa*	Enterobacterales
			CLSI	61/97; 62.9%	46/100; 46%	61/97; 62.9%	46/100; 46%	-	-	-	-	-
			Provisional BP	89/97	89/100; 89%	89/97	89/100	-	-	-	-	-
[128]	Spain	2018	EUCAST	388/400	-	48/56; 85.7%	-	6/10; 60%	-	40/42; 95.2%	-	2/4; 50%
			CLSI	360/400; 90%	-	42/56; 75%	-	5/10; 50%	-	37/42; 88.1%	-	0/4; 0%
			Provisional BP	398/400	-	54/56; 96.4%	-	9/10; 90%		41/42; 97.6%		4/4; 100%
[129]	Spain	2020	EUCAST	229/247; 92.7%	115/170; 67.6%	38/45; 84.4%	25/53; 47.2%	2/4; 50%	-	36/39; 92.3%	25/45; 55.5%	0/2; 0%
			CLSI	207/247; 83.8%	115/170; 67.6%	34/45; 77.8%	25/53; 47.2%	0/4; 0%	-	34/39; 87.2%	25/45; 55.5%	0/2; 0%
			Provisional BP	245/247	147/170; 86.5%	43/45; 95.5%	35/53; 66%	4/4; 100%	-	38/39; 97.4%	35/45; 77.8%	1/2; 50%
[130]	India	2019–2021	EUCAST	209/570	-	14/250; 5.6%	-	14/250; 5.6%	-	-	-	-
			CLSI	172/570; 30.2%	-	12/250; 4.8%	-	12/250; 4.8%	-	-	-	-
			Provisional BP	338/570	-	70/250; 28%	-	70/250; 28%	-	-	-	-
Pooled data		2005–2023	EUCAST	2044/2693; 75.9%	475/750; 63.3%	560/1038; 53.9%	239/410; 58.3%	329/758; 43.4%	0/6; 0%	146/158; 92.4%	172/253; 68%	5/19; 26.3%
			CLSI	1798/2693; 66.8%	475/750; 63.3%	487/1035; 47%	239/410; 58.3%	276/758; 36.4%	0/6; 0%	138/158; 87.3%	172/253; 68%	0/19; 0%
			Provisional BP	2336/2693; 86.7%	615/750; 82%	748/1035; 72.3%	317/410; 77.3%	486/758; 64.1%	0/6; 0%	156/158; 98.7%	206/253; 81.4%	14/19; 73.7%

For susceptibility testing purpose, the concentration of taniborbactam was fixed at 4 mg/L

Susceptibility data were interpreted according to following breakpoints:

EUCAST cefepime susceptibility breakpoint (v_14.0, 2024): Enterobacterales, ≤ 4 mg/L; *Pseudomonas*, ≤ 8 mg/L

CLSI cefepime susceptibility breakpoints (CLSI M100 ED34:2024): Enterobacterales, ≤ 2 mg/L; *Pseudomonas*, ≤ 8 mg/L

Provisional cefepime/taniborbactam susceptibility breakpoint: ≤ 16 mg/L [124]

Abbreviation: BP, breakpoint

[137]. Another phase 3 clinical trial on efficacy and safety of cefepime/taniborbactam is ongoing (NCT06168734; registration date: 2023–12-04; https://clinicaltrials.gov/study/NCT06168734).

β-lactam/xeruborbactam

Xeruborbactam (formerly QPX7728, Qpex Biopharma) is a bicyclic boronate-based β-lactamase inhibitor that shows ultrabroad-spectrum activity against all classes of β-lactamases (Fig. 2 and Table 1) [120, 138]. It was recently discovered in a project involving modification of boric acid pharmacophore to expand β-lactamase inhibition spectrum and achieve oral bioavailability [139]. Although its binding mode resembles that of taniborbactam, the introduction of a cyclopropyl group into the xeruborbactam structure enhances the hydrophobic interaction in the active site and the inhibitory activity. Xeruborbactam showed a potent inhibitory activity against class A extended-spectrum β-lactamases (CTX-M, SHV, TEM, VEB, PER) and carbapenemases (KPC, SME, NMC-A, BKC-1), plasmid-determined (CMY, FOX, MIR, DHA) and chromosomally encoded (P99, PDC, ADC) class C β-lactamases, class D enzymes, including OXA-48-like and OXA enzymes from *A. baumannii* (OXA-23/24/72/58), as well as various class B1 MβLs (NDM, VIM, CcrA, IMP, and GIM but not SPM or L1) [139, 140]. Despite xeruborbactam has similar relative inhibitory concentrations to taniborbactam against NDM and VIM enzymes, it showed being effective against taniborbactam resistant enzymes, such as NDM-9, NDM-30, VIM-83 and most of IMP enzymes [141].

Data on in vitro activity of xeruborbactam in combination with β-lactams are limited, and mainly involving meropenem/xeruborbactam combination [142–147]. Data on in vitro activity of meropenem/xeruborbactam against surveillance Gram-negative isolates, including MβL-producers, were reported in Table 5. Overall, potent in vitro activity was shown for carbapenem-resistant and/or carbapenemase-producing Enterobacterales (n = 1625) (> 94% of susceptibility), MβL-producing Enterobacterales (n = 534), and carbapenem-resistant and/or carbapenemase-producing *A. baumannii complex* isolates (n = 275) (> 95% of susceptibility). Lower susceptibility rates and higher MIC_{50}/MIC_{90} values were observed in *P. aeruginosa*, especially among isolates resistant to carbapenems and/or ceftazidime/avibactam and/or ceftolozane/tazobactam (n = 290) (MIC_{50}/MIC_{90} 8/64, 60.3% of susceptibility), and among MβL-producing isolates (n = 61) (MIC_{50}/MIC_{90} 32/ > 64, 31.1% of susceptibility). Le Terrier et al. showed that xeruborbactam was less active than taniborbactam to reduce MIC values of β-lactams in MβL-producing *P. aeruginosa* recombinant strains, and this was caused by the activity of MexAB-OprM efflux pump [141].

Data on in vivo efficacy of β-lactam/xeruborbactam combinations are lacking. Currently, phase 1 clinical studies on xeruborbactam in combination with ceftibuten are ongoing to evaluate the safety and pharmacokinetics of orally administered treatments (NCT06079775; registration date: 2023–10-06; https://clinicaltrials.gov/study/NCT06079775; and NCT06157242; registration date: 2023–11–27; https://clinicaltrials.gov/study/NCT06157242). In addition, a recently registered phase 1 clinical study (NCT06547554; registration date: 2024–08-02; https://clinicaltrials.gov/study/NCT06547554) aims at evaluating the combination cefiderocol/xeruborbactam in healthy adults.

Cefepime/zidebactam

Zidebactam (formerly WCK 5107; Wockhardt, Aurangabad, India) is a diazabicyclooctane β-lactamase inhibitor, with PBP-2 binding activity (Fig. 2) [148]. Combination of zidebactam with cefepime (formerly WCK 5222) represents the first β-lactam/β-lactamase inhibitor combination that elicits rapid bactericidal activity at the sub-MIC level through the simultaneous inactivation of PBP-2 (zidebactam) and PBP-3 (cefepime) (Table 1). The enhancement of cefepime activity by high-affinity binding of PBP-2 by zidebactam occurs independently of β-lactamase expression. Therefore, this combination is different from the previous ones that merely preserve the activity of β-lactam antibiotic partners. Moreover, zidebactam is reported to inhibit several class A and class C β-lactamases and some class D enzymes [148]. Thus, the cefepime plus zidebactam offers a potential treatment for the infections caused by cefepime-resistant Gram-negative bacilli isolates, carbapenem-resistant isolates (KPC or MBL-producing), and for many other MDR isolates [63, 128, 130, 149–156]. Data on in vitro activity of cefepime/zidebactam (tested at ratio 1:1) were reported in Table 6. Cefepime/zidebactam showed high activity towards carbapenem-resistant and/or carbapenemase-producing Enterobacterales (90.6–98%) and *P. aeruginosa* (89.4–99.1%). Moreover, high in vitro activity was shown towards MβL-producers [83.4–95.3% and 83.9–96.4%, in Enterobacterales (n = 1326) and *P. aeruginosa* (n = 338), respectively]. Conversely, significant discrepancy in susceptibility rates (95.7% *vs.* 24.9%) was observed in carbapenem-resistant and/or carbapenemase-producing *A. baumannii* using the provisional PK/PD susceptibility breakpoint (≤ 64 mg/L) and the CLSI susceptibility breakpoint of cefepime (≤ 8 mg/L), respectively.

Excellent in vitro activity of cefepime/zidebactam was shown against ceftazidime/avibactam and ceftolozane/tazobactam resistant *P. aeruginosa* [157]. Moreover, high activity with both MIC_{50} and MIC_{90} at 0.25 mg/L was observed in aztreonam/avibactam and cefepime/taniborbactam resistant *E.coli* strains harboring NDM-variants (NDM-1, NDM-4, NDM-5), CMY-42 and mutated PBP-3 [158].

Table 5 In vitro activity of meropenem/xeruborbactam against MDR Gram-negative clinical isolates collections including metallo-β-lactamase producers

References	Origin of isolates	Period of isolates collection	Fixed concentration of xeruborbactam	Bacterial species	MIC_{50}/MIC_{90} (mg/L), susceptibility % (n° of isolates tested)				
				Enterobacterales					
					Carbapenem non-susceptible and/or carbapenemase-producers	MBL-producers	NDM-producers	VIM-producers	IMP-producers
[142]	Worldwide	2001–2017	4 mg/L		≤0.06/4, 96.5% (n = 598)	≤0.06/4, 95.5% (n = 224)	≤0.06/4, 94.7% (n = 151)	≤0.06/2, 98.1% (n = 53)	≤0.06/4, 95% (n = 20)
			8 mg/L		≤0.06/0.5, 99.3% (n = 598)	≤0.06/1; 98.2% (n = 224)	≤0.06/2, 98% (n = 151)	≤0.06/0.5, 100% (n = 53)	≤0.06/2, 95% (n = 20)
[143]	Worldwide	2018–2020	4 mg/L		0.06/0.5, 98.3% (n = 1027)	0.06/4, 95.8% (n = 310)	0.06/4, 95.8% (n = 287)	≤0.03/0.5, 100% (n = 20)	
			8 mg/L		≤0.03/0.25, 99.6% (n = 1027)	≤0.03/1, 98.7% (n = 310)	≤0.03/1, 99% (n = 287)	≤0.03/0.06, 100% (n = 20)	
				A. baumannii-calcoaceticus complex					
					Carbapenem-resistant	NDM-producers			
[144]	Worldwide	1998–2018	4 mg/L		2/8 mg/L, 94.5% (n = 275)	60% (n = 5)			
			8 mg/L		1/4 mg/L, 98.5% (n = 275)	100% (n = 5)			
				P. aeruginosa					
					Overall isolates	DTT *isolates*	MβL-producers		
[145]	Worldwide	2016–2018	8 mg/L		0.25/8, 91.6% (n = 500)	8/64, 60.3% (n = 290)	32/ > 64, 31.1% (n = 61)		

For susceptibility testing purpose, the concentration of xeruborbactam was fixed at 4 mg/L or 8 mg/L

No available clinical breakpoints for meropenem/xeruborbactam. Susceptibility data were interpreted according to EUCAST/CLSI (2024) meropenem susceptibility breakpoints: ≤ 8 mg/L

MIC_{50}/MIC_{90} values were not reported for isolates number ≤ 10

Abbreviations: DTT, difficult to treat

Inactivation of serine-β-lactamases combined with the direct antibacterial effect of zidebactam results in modest impact of β-lactamases, including double carbapenemase production [141, 147]. Moreover, no impact on resistance was observed in Omp-deficient *E. coli* and *K. pneumoniae,* suggesting synergistic activity of cefepime and zidebactam overcomes mechanisms affecting cell permeability [147, 159–162]. On the other hand, resistance to cefepime/zidebactam required multiple mutations in genes encoding MexAB-OprM and its regulators, as well as PBP-2

Table 6 In vitro activity of cefepime/zidebactam against MDR Gram-negative clinical isolates collections including metallo-β-lactamase producers

References	Country	Period of isolates collection	Breakpoint	Carbapenem non-susceptible and/or carbapenemase-producers			MβL producers			NDM producers
				Enterobacterales	*P. aeruginosa*	ACB	Enterobacterales	*P. aeruginosa*	ACB	Enterobacterales
[63]	Swiss	2022–23	EUCAST/CLSI	-	21/39; 53.8%	-	-	21/39; 53.8%	-	-
			Provisional BP	-	28/39; 71.8%	-	-	28/39; 71.8%	-	-
[128]	Spain	2018	EUCAST	398/400; 99.5%	-	-	52/56; 92.8%	-	-	10/10; 100%
			CLSI	384/400; 99.5%	-	-	46/56; 82.1%	-	-	10/10; 100%
			Provisional BP	400/400; 100%	-	-	54/56; 96.4%	-	-	10/10; 100%
[130]	India	2019–2021	EUCAST	553/569; 97.2%	-	-	402/418; 96.2%	-	-	-
			CLSI	529/569; 93%	-		379/418; 90.7%	-	-	-
			Provisional BP	569/569; 100%	-		418/418; 100%	-	-	-
[150]	Worldwide	-	EUCAST	984/1018; 96.7%	157/262; 59.9%	-	-	-	-	-
			CLSI	896/1018; 88%	157/262; 59.9%	-	-	-	-	-
			Provisional BP/PKPD	1003/1018; 98.5%	261/262; 99.6%	-	203/214; 94.8%	94/94; 100%	-	-
[151]	Taiwan	2012–2018	EUCAST	-	74/81; 91.3%	-	-	3/4; 75%	-	-
			CLSI	-	74/81; 91.3%	11/135; 8.1%	-	3/4; 75%	-	-
			Provisional BP	179/180; 99.4%	-	-	92/92; 100%	-	-	-
[152]	UK	2015–2016	EUCAST	568/619; 91.8%	91/96; 94.8%	-	183/234; 78.2%	76/81; 93.8%	-	-
			CLSI	536/619; 86.6%	91/96; 94.8%	98/202; 48.5%	155/234; 66.2%	76/81; 93.8%	0/19; 0%	-
			Provisional BP/PKPD	586/619; 86.6%	96/96; 100%	188/202; 93.1%	201/234; 85.6%	81/81; 100%	6/19; 31.6%	-
[153]	Greek	2014–2018	EUCAST	406/422; 96.2%	154/172; 89.5%	-	176/186; 94.6%	93/106; 87.7%	-	-
			CLSI	391/422; 92.6%	154/172; 89.5%	20/181; 11%	166/186; 89.2%	93/106; 87.7%	-	-
			Provisional BP	415/422; 98.3%	171/172; 99.4%	174/181: 96.1%	182/186; 97.8%	105/106; 99%	-	-
[154]	China	2019	Provisional BP	364/379; 96%	224/228; 98.2%	455/471; 96.6%	114/126; 90.5%	-	-	105/117; 89.7%
[155]	Worldwide	2018–2019	EUCAST	656/681; 96.3%	1108/1147; 96.6%	-	-	-	-	-
			CLSI	626/681; 91.9%	1108/1147; 96.6%	-	-	-	-	-
			Provisional BP	666/681; 97.8%	1146/1147; 99.9%	-	-	-	-	-
[156]	USA	-	EUCAST/CLSI	-	98/108; 90.7%	-	-	15/18; 83.3%	-	-
			Provisional BP	-	108/108; 100%	-	-	18/18; 100%	-	-
Pooled data		2012–2023	EUCAST	3565/3709; 96.1%	1703/1905; 89.4%	-	813/894; 90.9%	208/248; 83.9%	-	10/10; 100%
			CLSI	3362/3709; 90.6%	1703/1905; 89.4%	129/518; 24.9%	746/894; 83.4%	208/248; 83.9%	0/19; 0%	10/10; 100%
			Provisional BP	4182/4268; 98%	2034/2052; 99.1%	817/854; 95.7%	1264/1326; 95.3%	326/338; 96.4%	6/19; 31.6%	115/127; 90.5%

Cefepime and zidebactam were tested at a ratio of 1:1

Susceptibility data were interpreted using EUCAST (2024), CLSI (2024) and provisional breakpoints [150] as follows:

EUCAST cefepime susceptibility breakpoint (v_14.0, 2024): Enterobacterales, ≤ 4 mg/L; *Pseudomonas*, ≤ 8 mg/L

CLSI cefepime susceptibility breakpoints (CLSI M100 ED34:2024): Enterobacterales, ≤ 2 mg/L; *Pseudomonas*, ≤ 8 mg/L; *Acinetobacter*, ≤ 8 mg/L;

Provisional cefepime/zidebactam susceptibility breakpoints: Enterobacterales, ≤ 8 mg/L; *Pseudomonas* (PK/PD breakpoint) ≤ 32 mg/L; *Acinetobacter* (PK/PD breakpoint) ≤ 64 mg/L

Abbreviation: ACB, *Acinetobacter baumannii-calcoaceticus* complex; BP, breakpoint

and PBP-3 [159–163]. PBP-2 is a transpeptidase that is involved in peptidoglycan cross-linking and cell wall elongation. Inhibition of PBP-2 by zidebactam leads to round cell formation [164, 165]. Resistance to zidebactam was shown to be due to missense mutations in the transpeptidase domain of *pbpA* gene (from D351 to V598) and the I450 position involved in direct interaction with zidebactam [159, 160]. Insertion of IS*Pa1635* in IS*CR1* upstream of bla_{PER-1} resulted in elevated transcription of bla_{PER-1} and increased resistance to ceftazidime/avibactam, ceftolozane/tazobactam and cefepime/zidebactam in a *P. aeruginosa* clinical strain [166].

Translational in vivo studies in neutropenic mice lung or thigh models showed efficacy of cefepime/zidebactam against MβL-expressing *P. aeruginosa* and carbapenemase-producing *K. pneumoniae* at mimicking human exposures [167–169]. Cefepime/zidebactam is currently under evaluation in a global phase 3 trial in adult patients with cUTI or acute pyelonephritis (NCT04979806; registration date: 2021–07-05; https://www.clinicaltrials.gov/study/NCT04979806). Successful compassionate use in treating NDM-producing *P. aeruginosa* infections was already reported [170–172].

β-lactam/nacubactam

Nacubactam (formerly RG6080/OP0595; Roche, Fedora, Meiji) is a new diazabicyclooctane β-lactamase inhibitor that inhibits various types of β-lactamases, including Ambler class A, class C, and class D (OXA-48) β-lactamases (Fig. 2 and Table 1). Similarly to zidebactam, nacubactam has significant affinity for PBP-2 of many Gram-negative species, allowing it to exert both a direct antibacterial effect and enhancing partner β-lactams that bind to PBP-3 [173, 174].

IC_{50} values of nacubactam for representative class A and C β-lactamases were similar to those of avibactam or slightly higher. Conversely, class D β-lactamases, and particularly OXA-23, appeared more resistant to inhibition [173]. These characteristics allowed to consider nacubactam in combination with various β-lactam agents (meropenem, cefepime, aztreonam) as a potential drug against MDR Gram-negative bacteria, including MβL-producers. Data on in vitro activity of β-lactam/nacubactam combinations are very limited [173–175].

Meropenem/nacubactam and cefepime/nacubactam showed high activity against MβL producing Enterobacterales (NDM, n = 158; VIM, n = 52; IMP, n = 99), regardless both MβL type and aztreonam-resistance status [174]. In detail, meropenem/nacubactam at 8 + 4 mg/L and cefepime/nacubactam at 8 + 4 mg/L were active against 87.1% and 93.3% of isolates tested [174]. Terrier et al. also evaluated in vitro activity of aztreonam in combination with novel β-lactamase inhibitors (at fixed concentration 4 mg/L) and cefiderocol against Enterobacterales (n = 64) and *P. aeruginosa* (n = 39) clinical isolates producing representative MβLs [NDM (n = 64), VIM (n = 32), IMP (n = 8) and SPM (n = 2)]. Among Enterobacterales isolates, aztreonam/zidebactam showed the highest activity (98.4%), followed by aztreonam/nacubactam (84.4%), aztreonam/taniborbactam (75%), aztreonam/avibactam (70.3%) and cefiderocol (39.1%). Lower activity was observed against MβL-producing *P. aeruginosa* isolates, with susceptibility rates of 66.7% for aztreonam/nacubactam and aztreonam/taniborbactam, and 69.2% with aztreonam/avibactam, aztreonam/zidebactam and cefiderocol [175]. These findings could be due to low intrinsic activity of nacubactam against *P. aeruginosa*, owing to the higher intrinsic resistance of this pathogen (MICs of 32 mg/L when tested alone) [173]. Moreover, common resistance mechanisms in *P. aeruginosa* such as *mexAB-oprM* overexpression and OprD deficiency, or increased expression of bla_{PDC} have been associated to resistance to meropenem-based combinations, including meropenem/nacubactam [161].

Moreover, since nacubactam as well as zidebactam targets PBP-2, mutations in *pbpA* gene are expected to be involved in resistance in both Enterobacterales and *Pseudomonas* species [159, 160].

Nacubactam combined with β-lactams (meropenem, cefepime, aztreonam) showed high in vivo antimicrobial activity in murine model against carbapenem-resistant and carbapenemase (including MβL)-producing *E. coli* and *K. pneumoniae* [176–178]. Safety profile of meropenem/nacubactam and favorable pharmacokinetic parameters were reported in healthy adults [179]. Two phase 3 trials evaluating safety and efficacy of nacubactam combined with cefepime and aztreonam for the treatment of cUTI or acute uncomplicated pyelonephritis caused by carbapenem-resistant Enterobacterales have been registred (NCT05887908; registration date: 2023–04–25; https://clinicaltrials.gov/study/NCT05887908; and NCT05905055 registration date: 2023–03-02; https://clinicaltrials.gov/study/NCT05905055).

Sulbactam/durlobactam

Sulbactam/durlobactam (XACDURO®, Entasis Therapeutics), was approved in May 2023 by the U.S. Food and Drug Administration for the treatment of adult patients with HAP/VAP caused by susceptible isolates of *A. baumannii* complex (Table 1) [180, 181].

Sulbactam (a penicillin derivative) is a β-lactam antibacterial and Ambler class A serine β-lactamase inhibitor that also has bactericidal activity due to its inhibition of PBP-1 and PBP-3 [182]. Durlobactam (formerly ETX2514, Entasis Therapeutics) is a next generation diazabicyclooctane β-lactamase inhibitor with potent activity against class A, C, and D serine β-lactamases and intrinsic antibacterial activity on PBP-2 (Fig. 2 and Table 1) [183]. However, PBP-2

inhibition by durlobactam resulted in intrinsic antibacterial activity against *E. coli* and several other Enterobacterales species, but it has little to no effect on the growth of *A. baumannii* or *P. aeruginosa* when administered alone [184]. The key feature as compared to zidebactam and nacubactam is its activity against class D carbapenemases of the OXA family, which are prevalent in *A. baumannii* [184]. Hence, combination of durlobactam to sulbactam was reported to lower MIC_{90} by 32-fold (from 64 mg/L to 2 mg/L) compared to sulbactam alone in *A. baumannii* [185], resulting in high susceptibility rates (> 97%) in global collections of MDR *A. baumannii* clinical isolates [185, 186]. Furthermore, clinical efficacy was shown in the phase 3 ATTACK clinical trial, in which sulbactam/durlobactam was observed to be non-inferior to colistin for the treatment of patients with severe infections caused by *A. baumannii* complex [181].

Resistance to sulbactam/durlobactam in *A. baumannii* was associated with both expression of MβLs towards which durlobactam has no inhibitory activity and alteration in PBP-3 and/or PBP-2 [185, 186]. Potent intrinsic activity of durlobactam on PBP-2 of Enterobacterales and its stability to the hydrolytic action of β-lactamases represent an interesting therapeutic potential towards MDR strains including those producing MBLs [187]. A recent report showed high activity of sulbactam/durlobactam against NDM-producing *E. coli*, including several MβL variants (e.g. NDM-5, NDM-1, NDM-7) and strains harboring PBP-3 modifications leading to resistance to aztreonam/avibactam and/or cefiderocol [188]. These findings could legitimize future investigations on sulbactam/durlobactam role in the clinical management of infections sustained by MβL-producing Enterobacterales.

Conclusions

The recent development of new antimicrobials expanded the armamentarium to counter the challenge of MβL-producers. Cefiderocol and aztreonam/avibactam are already available. In addition, two new classes of β-lactam/β-lactamase combinations are under clinical evaluation: (*i*) combination of β-lactam with novel MβL inhibitors (taniborbactam and xeruborbactam), (*ii*) combination of β-lactam with new diazabicyclooctane β-lactamase inhibitors, active on most of serine-β-lactamase but also showing strong intrinsic activity on PBP-2.

In vitro activity of aztreonam/avibactam against MβL-producing Enterobacterales is higher than that of cefiderocol, providing supporting evidence on its key role in the treatment of infections sustained by these strains. On the other hand, aztreonam/avibactam does not show satisfactory activity against MβL-producing *P. aeruginosa* and MDR *A. baumannii* given their ability to display multiple resistance mechanisms. Therefore, in these contexts, cefiderocol may represent a more appropriate therapeutic option, given the excellent activity observed with the exception of some NDM-producing clones. Both cefiderocol and aztreonam/avibactam showed high in vitro activity against *S. maltophilia*, an emerging nosocomial MDR pathogen expressing the L1 chromosomal MβL.

In the group of β-lactam/new MβL inhibitor combinations, cefepime/taniborbactam showed potent activity against MβL-producing Enterobacterales, especially VIM-producing strains. The main limitation is the poor activity of taniborbactam towards IMP-carbapenemases, VIM-83 and some NDM-variants (NDM-9, NDM-30). This limitation is overcome by the xeruborbactam, which has a wide inhibition spectrum, including OXA-23-like carbapenemases commonly expressed by *A. baumannii* isolates. Despite these features, taniborbactam- and xeruborbactam-based combinations, offer a more limited therapeutic opportunity against *P. aeruginosa* given thecommon mechanisms of upregulation of efflux pumps, permeability loss and AmpC beta-lactamase overespression found in this species. Activity of these new combinations, as well as those of cefiderocol and aztreonam/avibactam, are affected by mutations in PBP-3, which is the target of the β-lactam molecule but this could be bypassed by the combinations of β-lactam with new diazabicyclooctane β-lactamase inhibitors nacubactam and zidebactam. This effective strategy has feedback on in vitro activity, especially for cefepime/zidebactam, against MDR Enterobacterales, *P. aeruginosa*, and *A. baumannii* complex isolates, including MβL-producing ones.

Future studies should evaluate the possibility of combining cefiderocol with the new β-lactamase inhibitors (xeruborbactam and zidebactam) investigating the feasibility of new synergistic strategies. Given the presence of resistance mechanisms and the possibility of selection of mutant strains during therapy, the appropriate use of these new drugs should require the availability of commercial assays for in vitro susceptibility testing, which would allow the implementation of surveillance programmes appropriate to the complexity of the phenomenon.

Acknowledgements None

Author contributions Gabriele Bianco and Matteo Boattini contributed to the study conception and design. Literature review, data collection and analysis were performed by Gabriele Bianco, Matteo Boattini, Paolo Gaibani, Sara Comini, Rossana Cavallo, Cristina Costa and Francesco Broccolo. The first draft of the manuscript was written by Gabriele Bianco and Matteo Boattini, and all authors commented on previous versions of the manuscript. All authors read and approved the final version of the manuscript.

Funding Open access funding provided by Università del Salento within the CRUI-CARE Agreement. This work was supported by internal funding.

Data availability No datasets were generated or analysed during the current study.

Declarations

Informed consent Not applicable.

Conflicts of interest The authors declare no competing interests.

Institutional review board Not applicable.

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