Drugs
https://doi.org/10.1007/s40265-024-02102-8

REVIEW ARTICLE

The Challenge of Treating Infections Caused by Metallo-β-Lactamase–Producing Gram-Negative Bacteria: A Narrative Review

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Accepted: 19 September 2024

Abstract

Gram-negative multidrug-resistant (MDR) bacteria, including Enterobacterales, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*, pose a significant challenge in clinical practice. Infections caused by metallo-β-lactamase (MBL)–producing Gram-negative organisms, in particular, require careful consideration due to their complexity and varied prevalence, given that the microbiological diagnosis of these pathogens is intricate and compounded by challenges in assessing the efficacy of anti-MBL antimicrobials. We discuss both established and new approaches in the treatment of MBL–producing Gram-negative infections, focusing on 3 strategies: colistin; the recently approved combination of aztreonam with avibactam (or with ceftazidime/avibactam); and cefiderocol. Despite its significant activity against various Gram-negative pathogens, the efficacy of colistin is limited by resistance mechanisms, while nephrotoxicity and acute renal injury call for careful dosing and monitoring in clinical practice. Aztreonam combined with avibactam (or with avibactam/ceftazidime if aztreonam plus avibactam is not available) exhibits potent activity against MBL–producing Gram-negative pathogens. Cefiderocol in monotherapy is effective against a wide range of multidrug-resistant organisms, including MBL producers, and favorable clinical outcomes have been observed in various clinical trials and case series. After examining scientific evidence in the management of infections caused by MBL–producing Gram-negative bacteria, we have developed a comprehensive clinical algorithm to guide therapeutic decision making. We recommend reserving colistin as a last-resort option for MDR Gram-negative infections. Cefiderocol and aztreonam/avibactam represent favorable options against MBL–producing pathogens. In the case of *P. aeruginosa* with MBL–producing enzymes and with difficult-to-treat resistance, cefiderocol is the preferred option. Further research is needed to optimize treatment strategies and minimize resistance.

1 Introduction

Antimicrobial resistance (AMR) is recognized as one of the major global health challenges of the 21st century. The global burden associated with drug-resistant infections assessed in 2019 was an estimated 4.95 million deaths, of which 25.6% were directly attributable to drug resistance. Actions for reducing AMR burden include therapeutic approaches, the reduction of antimicrobial selective pressure, the reduction of transmission, and the restoration of populations of antibiotic-susceptible bacteria [1]. The management of infections caused by multidrug-resistant microorganisms should be approached from a global institutional perspective and requires the collaboration of an expert multidisciplinary team to design a strategy for prevention, diagnosis and treatment [2]. The target patient is usually a complex case involving multiple comorbidities, prolonged hospitalization, and bacterial colonization [3, 4]. Mortality is influenced by host factors, infection-related factors, and therapeutic factors, such as delay in initiating antibiotic therapy [5]. Holistic treatment includes supportive therapy, when necessary, control of the infectious focus whenever possible, and timely and appropriate antimicrobial administration [6]. Local epidemiology and microorganism susceptibility must also be considered [7].

In 2017, the World Health Organization published a list of antibiotic-resistant "priority pathogens" [8], recognizing carbapenem-resistant Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter* spp. as bacteria of critical importance [8]. The list was updated in 2024 [9] and in this new version, carbapenem-resistant *P. aeruginosa* is not included

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Published online: 28 October 2024

Key Points

Metallo-β-lactamase (MBL)-producing Gram-negative organisms, such as Enterobacterales, *Acinetobacter baumannii,* and *Pseudomonas aeruginosa*, present a complex and varied prevalence in clinical practice, with intricate microbiological diagnosis and challenges in assessing the efficacy of anti-MBL antimicrobials.

Cefiderocol and the recent combination of aztreonam with avibactam (or with ceftazidime/avibactam if aztreonam/avibactam are not available) are identified as favorable treatment options for MBL–producing Gram-negative infections, while colistin, despite its in vitro activity, is limited by difficulties for in vitro testing, the selection of resistance mechanisms and nephrotoxicity, making it a last-resort option.

A comprehensive clinical algorithm recommends cefiderocol as the preferred option for *P. aeruginosa* with difficult-to-treat resistance. Cefiderocol and aztreonam/avibactam are highlighted as a favorable options for MBL–producing Enterobacterales. Continuous research is emphasized to optimize treatment strategies and minimize resistance development.

in the "critical" group, but is included in the "high priority" group. In most regions, carbapenem resistance in these organisms is frequently due to production of carbapenem-hydrolyzing β-lactamases (carbapenemases), which include enzymes belonging to molecular classes A (i.e., *Klebsiella pneumoniae* carbapenemase [KPC] enzymes), B (metallo-β-lactamases [MBLs]), C (only a few examples known, such as CMY-10) or D (OXA-like enzymes), that fall into functional groups 2df, 2f, or 3 (Table 1). In some countries and for some organisms (i.e., *P. aeruginosa* or *Enterobacter cloacae* complex in Spain), carbapenem resistance is more commonly associated with a combination of the production of β-lactamases that have poor anti-carbapenem activity, porin loss, and upregulated efflux pumps.

Bush et al provide a comprehensive overview of carbapenemases and other important β-lactamases [10]. The most important discoveries on β-lactamases, and MBL in particular, are presented in Table 2.

This paper will review the most relevant epidemiologic and microbiological aspects and the main therapeutic options for infections caused by MBL–producing microorganisms.

2 Mechanism and Type of Metallo-β-Lactamases (MBLs)

The biochemical mechanism of β-lactam hydrolysis by MBLs proposes that the active site orients and focuses the β-lactam bond to make a more straightforward nucleophilic attack by zinc. The most frequent zinc-binding motif is histidine-X-histidine-X-aspartic acid (HXHXD).

Metallo-β-lactamases are encoded by chromosomal or plasmid genes. Most bacteria producing chromosomal MBLs are environmental organisms or opportunistic pathogens that usually do not cause severe infections, the most clinically relevant being *Stenotrophomonas maltophilia* (producing the L1 enzyme) and *Bacillus anthracis* (producing Bla2). Regarding plasmid-mediated MBLs, the most frequent families include imipenemase (IMP; active on imipenem), VIM (Verona integron-encoded MBL), and NDM (New Delhi MBL), but many other less common enzymes are also known [11–13]. On most occasions, MBL plasmid genes are located within a variety of integrons (mainly class 1 integrons).

Metallo-β-lactamases are divided into three subclasses (B1, B2, and B3) based on their amino acid sequence at the active site, zinc ligands and stoichiometry, loop architecture and substrate profiles [11–13]. In the B1 group, key zinc is coordinating residues of three histidines and one cysteine. This group include VIM, IMP, NDM plasmid-mediated enzymes and most of the chromosomally encoded MBLs. Class B2 includes enzymes that harbor an asparagine instead of the histidine at the first position of the principal zinc-binding motif, NXHXD. They accommodate a single zinc ion (despite that most MBLs accommodate two zinc ions) and include the CphA enzyme from *Aeromonas* spp. Finally, the class B3, which is functionally represented as a tetramer, includes the already-mentioned L1 enzyme.

3 Testing MBL-Producing Bacteria: Challenges and Limitations

Because MBL–producing bacteria usually express other resistance mechanisms, their susceptibility is not predictable and, in practice, an antibiogram is needed for informing optimally directed treatment.

Metallo-β-lactamase–producing organisms are susceptible to aztreonam (ATM) when no additional enzymes hydrolyzing this compound are also expressed. A high proportion of isolates expressing MBL are also susceptible to cefiderocol [14, 15]. When an MBL enzyme is poorly expressed in Enterobacterales, the organism can present some level of susceptibility to carbapenems.

Table 1 Classification of β-lactamases of major clinical relevance (Bush and Jacoby 2010 [164], Bush and Bradford 2020 [10])

Molecular class	Type	Functional group	Relevant/distinctive substrates	Inhibition by clavulanic acid	Inhibition by avibactam	Inhibition by EDTA	Examples (families or representatives)
A	SBL	2a	P	+	+	−	PC1
		2b	P, Cp	+	+	−	TEM-1, SHV-1
		2be	P, Cp, E, M	+	+	−	TEM-ESBL, SHV-ESBL, CTX-M
		2br	P	−	+	−	Inhibitor-resistant TEM, SHV-10
		2c	P	±	+	−	CARB-1
		2e	P, Cp, E	+	+	−	CepA
		2f	P, Cp, E, M, Cp	±	+	−	KPC, SME
B	MBL	3a (B1) 3a (B3)	P, Cp, E, Cb	−	−	+	IMP, VIM, NMD L1
		3b (B2)	Cb	−	−	+	CphA
C	SBL	1	Cp	−	+	−	Chromosomal AmpC Plasmid-mediated AmpC
		1e	Cp, E	−	+	−	GC1
D	SBL	2d	P	±	+	−	OXA-1
		2de	P, E, M	±	+	−	OXA-11
		2df	P, Cb	−	+	−	OXA-48, OXA-23

Cb carbapenems, *Cp* cephalosporins, *E* expanded-spectrum β-lactamases, *ESBL* extended-spectrum β-lactamases, *M* monobactams, *MBLs* metallo-β-lactamases, *P* penicillins, *SBL* serine β-lactamases

Table 2 Milestones in β-lactamase discovery with emphasis on metallo-β-lactamases (MBLs)

Year	Milestone	Comments	Refs.
1966	Essential role of zinc on the activity of the *Bacillus cereus* "cephalosporinase"	The enzyme was inhibited by ethylenediaminetetraacetic acid (EDTA)	[154]
1980	Definition of structural (molecular) classes of β-lactamases	Class A (serine β-lactamases, or SBL); Class B: MBLs	[155]
1985	Introduction of terms MBLs and metalloenzymes	MBLs hydrolyze carbapenems (carbapenemases)	[156]
1981 1988	Class C and class D SBL defined		[157, 158]
1988	First functional classification of β-lactamases	Classification based on substrate and inhibitor (clavulanic acid vs EDTA) profiles	[159]
1991	The first acquired MBL (IMP-1) identified (in *Pseudomonas aeruginosa,* in Japan)		[160]
1995	Updated functional classification of β-lactamases	Functional groups 1, 2 and 3 defined	[161]
1999	VIM-1 discovered (in *P. aeruginosa*, in Italy)		[162]
2008	NDM-1 discovered (in *Klebsiella pneumoniae* and *Escherichia coli*, in a traveler from India to Sweden)		[163]
2010	Updated functional classification of β-lactamases	Additional β-lactamase subgroups defined	[164]

Phenotypic tests for MBL detection are based on the hydrolytic activity of these enzymes against carbapenems (and other β-lactams). For MBL producers, minimum inhibitory concentrations (MICs) of carbapenems will be reduced in the presence of an efficient MBL inhibitor (i.e., Ethylenediaminetetraacetic acid [EDTA], dipicolinic acid, sodium mercaptoacetate, 1,10-O-phenanthroline), but this approach is not commonly used in the clinical laboratory. In the carbapenem inactivation method (CIM), a disk of (usually) meropenem is incubated into a bacterial suspension; the disk is then placed on the surface of a plate, which has been previously streaked with a carbapenem-susceptible *E. coli* marker strain; after incubation, a reduction in the size of the inhibition zone indicates that the investigated bacteria produce a carbapenemase. When considering *P. aeruginosa* and *Acinetobacter baumannii*, both sensitivity and specificity improve when bacterial cells are extracted with 0.5 M TrisHCl (CIMTris). Another variant,

EDTA-mCIM (eCIM), can differentiate MBLs and SBL among carbapenemase producers [16–19].

The Carba NP assay is a rapid (less than 3 h) turnaround test. It detects acidification of a solution containing a carbapenem after the compound has been degraded by a carbapenemase [20, 21].

Peaks of hydrolyzed carbapenems can be detected by matrix-assisted laser desorption/ionization time-of-flight (MALDI-Tof) [22, 23] (and by liquid chromatography-coupled tandem mass spectrometry (LC-MS/MS) [24].

Metallo-β-lactamases and other common carbapenemases can be detected by multiplex lateral flow immunoassays, which are technically simple, provide results within 15 min, and have good sensitivity and specificity. Unfortunately, these tests show negative results for some carbapenemase alleles [25].

Molecular tests are faster than methods based on bacterial growth. They can detect one or more genes coding for MBLs but require the genes to be previously known. There are multiple commercial molecular assays based on PCR, loop-mediated isothermal amplification (LAMP) and DNA microarrays that detect several MBLs with high sensitivity and specificity and can be applied directly to clinical samples or positive blood culture bottles [26–29]. More recently, whole-genome sequencing (WGS) has been increasingly used for the detection of resistance-related genes, including those coding for MBLs [30–33].

In addition, various testing methods are available for drugs targeting microorganisms producing MBLs, including colistin, aztreonam plus avibactam (ATM/AVI) (or ATM plus ceftazidime [CAZ]/AVI) and cefiderocol.

For colistin, the reference method is broth microdilution. Agar dilution, disk diffusion or gradient test, are not recommended, and semi-automated methods can produce false susceptibility results. Aztreonam plus avibactam may be tested by standard methods in clinical laboratories. For ATM combined with CAZ/AVI, in vitro synergy tests are not standardized and the results from different methods for synergism may offer variable results [34–39].

For testing cefiderocol, MICs of cefiderocol in cation-adjusted Mueller-Hinton broth are not reproducible and do not represent the actual in vivo activity of this compound, which is highly influenced by iron content. Minimum inhibitory concentrations of cefiderocol should be determined in an iron-depleted medium (≤ 0.03 mg/L of iron), which is not usually available in routine clinical laboratories and is not currently used by commercial panels of semi-automated methods [40]. Several commercial tests based on broth microdilution are available as an easy approach to determining cefiderocol MICs in clinical laboratories; the European Committee on Antimicrobial Susceptibility Testing (EUCAST) evaluation of these assays is ongoing, but results are not yet available. In vitro activity of cefiderocol can be alternatively determined by disk diffusion; EUCAST has defined areas of technical uncertainty for this assay (ATU, available at EUCAST [36]) for both Enterobacterales and *P. aeruginosa*, and when they occur, EUCAST has suggested several possible solutions (available at EUCAST [41]).

Results from susceptibility testing assays for MBL–producing organisms should be presented as clinical categories alone or with detailed MIC values (of great value from a clinical perspective when pharmacokinetics/pharmacodynamics [PK/PD] issues are considered in concrete patients), as defined by committees such as EUCAST or Clinical and Laboratory Standards Institute (CLSI). Breakpoints for colistin, ATM/AVI and cefiderocol are presented in Tables 3 (MIC values) and 4 (inhibition zones).

4 Epidemiology

The global prevalence and geographic distribution of MBLs are not comprehensively known due to scant data and limited updated information, particularly in certain regions such as Africa.

Verona integron-encoded MBL enzymes have been reported worldwide from multiple species, particularly *P. aeruginosa* and Enterobacterales (mainly *K. pneumoniae*, *E coli* and *E. cloacae* complex). These enzymes are widely distributed in Europe, and several outbreaks have been reported in Greece, Italy, Spain, and other countries [42].

New Delhi MBL variants are widespread in the Indian subcontinent. India, Pakistan and Bangladesh are considered reservoirs for these enzymes, as is the Balkan region in Europe. New Delhi MBL enzymes are the second most frequent enzymes (after OXA-48) in the Middle East [43, 44] and predominate in some regions of Russia [45]. Outbreaks with NDM–producing organisms have been reported in several European countries including Italy, Greece, Romania, Poland, and Denmark [46]. An increasing number of NDM-1- and NDM-1/OXA-48–producing *Klebsiella pneumoniae* were detected in Germany in 2022, associated with patients with a documented history of previous presence in Ukraine [47].

The IMPs are currently endemic in Japan and are more common in Asian countries [48, 49], with IMP-4 being particularly important in China and Australia [50]. A large number of acquired minor MBLs limited to specific geographical areas are also known; for a review, see reference [10].

The EuSCAPE project analyzed carbapenemase production in Enterobacteriaceae isolated from 38 European countries in 2015. The most common enzymes were KPC and OXA-48 enzymes, but VIM was most common in

Table 3 The MIC (mg/L) breakpoints for colistin, aztreonam/avibactam and cefiderocol against different microorganisms.

	Colistin				Aztreonam/avibactam		Cefiderocol			
	Susceptible		Resistant		Susceptible	Resistant	Susceptible		Intermediate	Resistant
	EUCAST	CLSI	EUCAST	CLSI	EUCAST	EUCAST	EUCAST	CLSI	CLSI	EUCAST	CLSI
Enterobacterales[a]	≤ (2)[b]	≤2	>(2)[b]	≥4	≤4	>4	≤2	≤4	8	>2	≥16
Pseudomonas aeruginosa	≤ (4)[b]	≤2	>(4)[b]	≥4			≤2	≤4	8	>2	≥16
Acinetobacter spp.	≤ (2)[b]	≤2	>(2)[b]	≥4			IE	≤4	8	IE	≥16
Stenotrophomonas maltophilia							IE	≤4	8	IE	≥16

Empty cells when breakpoints have not been defined

ATU area of technical uncertainty, *CLSI* Clinical and Laboratory Standards Institute, *EUCAST* European Committee for Antimicrobial Susceptibility Testing, *IE* insufficient evidence, *MIC* minimum inhibitory concentration

[a]CLSI breakpoints for Enterobacterales do not apply to *Salmonella* and *Shigella* spp.

[b]Breakpoints in brackets (details in: https://eucast.org/eucastguidancedocuments)

Hungary and NDM in Serbia and Montenegro. The IMPs were rare in most countries [51].

Among Enterobacterales non-susceptible to meropenem evaluated in the ATLAS global surveillance program isolated in 2018–2019, MBLs were more frequent (36.7% of isolates) than KPCs (25.5%) or OXA-48-like (24.1%) enzymes, and were particularly more frequent in Africa, Middle East and the Asia/Pacific (APAC) region. *Klebsiella pneumoniae* represented 71.5% of the isolates. New Delhi MBL enzymes represented the large majority of the identified MBLs (88.4% in total, with NDM-1 in 68.7% of NDM–producing isolates). Verona integron-encoded MBL and IMP enzymes were detected in 11.1% (VIM-1 in 76.1% of the VIM-producing isolates) and 0.5%, respectively [52, 53].

In another recent study on Enterobacterales from 64 medical centers in Europe, Latin-America and the Asia-Pacific (APAC region resistant to the new beta-lactamase inhibitor combinations, MBL genes were detected in 35.0% of carbapenem-resistant Enterobacterales (CRE), and the most frequent MBL was NDM (29.9%). The highest rates of MBL–producing organisms occurred in APAC (59.5%), followed by Latin-America (34.0%) and Europe (23.6% and 28.9%, in Western and Eastern countries, respectively [54]. In the SMART study, MBLs were detected in 4.3% of *P. aeruginosa* from the APAC region (2017–2020), although rates as high as 32.3% and 10.7% were observed in isolates from Vietnam and Thailand, respectively [55]. Also, in the SMART study considering *P. aeruginosa* isolates from Latin America in the period 2018–2020, MBLs were identified in 7.6% of isolates, with rates of 25.3%, 10.6%, and 8.6% in isolates from Chile, Colombia, and Mexico, respectively [56].

The CARBA-ES-19 study, conducted in 71 hospitals, found that the most frequent carbapenemases in *K. pneumoniae* and *E. coli* were OXA-48 and KPC [57]. In the retrospective CARBA-MAP study (2014 to 2018, 30 hospitals), which focussed on carbapenemase-producing Enterobacterales and *P. aeruginosa*, VIM, NDM and OXA-48-like+NDM MBLs were found in 6.9%, 1.8% and 1.3% *K. pneumoniae*, respectively. In the *E. cloacae* complex (n = 334), class B enzymes were the most frequent carbapenemases (VIM, 37.4%; NDM, 19.2% and IMP 3.3%). *E. coli* (n = 114) and *K. aerogenes* (n = 11) produced VIM enzymes in 14.9% and 36.3%, while NDM was expressed by 6.1% and 9.1% of these species, respectively [58].

Most carbapenem-resistant *P. aeruginosa* strains in Spain do not produce carbapenemases. However, when they are expressed, the most commonplace enzymes are of the VIM type. In a multicenter study with isolates from 2022, a slight decrease in VIM enzymes was observed in comparison to a previous similar study in 2017, although carbapenemases

Table 4 Inhibition zone (mm) breakpoints for colistin, aztreonam-avibactam (30–20 µg disc) and cefiderocol (30 µg disc) against different groups of microorganisms

	Aztreonam/avibactam			Cefiderocol					
	Susceptible	ATU	Resistant	Susceptible		ATU	Intermediate	Resistant	
	EUCAST		EUCAST	EUCAST	CLSI	EUCAST	CLSI	EUCAST	CLSI
Enterobacterales	≥25	22–24	<25	≥23	≥16	21–23	9–15	<23	≤8
Pseudomonas aeruginosa				≥22	≥18	21–22	13–17	<22	≤12
Acinetobacter spp.				*Note*[a]	≥15[b]				
Stenotrophomonas maltophilia				*Note*[c]	≥15				

Breakpoints not defined by EUCAST or CLSI for colistin

ATU area of technical uncertainty, *CLSI* Clinical and Laboratory Standards Institute, *EUCAST* European Committee for Antimicrobial Susceptibility Testing, *MIC* minimum inhibitory concentration

[a]Zone diameters of ≥17 mm correspond to MIC values ≤2 mg/L

[b]Zone diameters ≤ 14 mm should not be interpreted or reported because zone diameters ≤ 14 mm occur with resistant, intermediate, and susceptible isolates. A MIC test should be done in this situation

[c]Zone diameters of ≥20 mm corresponds to MIC values ≤2 mg/L

significantly increased in extensively drug-resistant or meropenem-resistant isolates [59].

5 Drugs for Treating Infections Caused by MBL–Producing Organisms

From a clinical perspective, it is standard practice for clinicians to directly receive microbiological laboratory results in a report. These reports are interpreted by microbiologists based on in vitro findings.

Furthermore, the selection of treatment must carefully consider various additional factors. These include the severity of the infection, the patient's comorbidities, the antibiotic penetration into the site of infection, and any potential adverse effects. Each of these factors is critical in determining the appropriateness and efficacy of the treatment regimen.

5.1 Colistin

Colistin (polymyxin E) shows significant activity against most Enterobacterales, *A. baumannii, P. aeruginosa* and *S. maltophilia*. However, some Gram-negative species are naturally resistant to colistin, including *Proteus* spp., *Providencia* spp., *Morganella morganii*, or *S. marcescens*.

The most common colistin resistance mechanism is the modification of lipopolysaccharides (LPS) via the addition of cationic molecules, such as L-aminoarabinose and phosphoethanolamine [60]. This is frequently linked to mutations in 2-component regulatory systems [61, 62]. Mutations in *mgrB*, coding for a negative PhoPQ regulator, are frequently associated with colistin resistance in *K. pneumoniae* [63]. Colistin resistance in *A. baumannii* may emerge by mutations in lipid A biosynthesis genes *lpxA*, *lpxC*, or *lpxD*, leading to complete loss of LPS production [64]. Several mobile colistin resistance (*mcr*) genes carried by transferable plasmids have been reported, after they were discovered (2016) in an *E. coli* strain isolated in China [65].

An extensive global surveillance program from 39 countries has noted an association between the presence of a carbapenemase and increased resistance to colistin among surveillance isolates of Enterobacteriaceae. Colistin susceptibility was established at 98.4% overall, while it decreased to 88% among carbapenemase producers. Colistin susceptibility was 92.6% among MBL-positive isolates [66]. In a large surveillance study (SIDERO-CR), which included 457 isolated carbapenem-resistant Enterobacteriaceae, colistin susceptibility was 93.5% for VIM producers and 78.4% for NDM producers [67]. In an observational prospective study performed in two Italian hospitals, which focused on MBL, NMD-producing strains had a colistin susceptibility rate of 90.2%, while VIM-producing strains had a rate of 80% [68].

Although colistin and polymyxin B were initially abandoned due to toxicity, they regained relevance given the lack of effective antimicrobials against MDR Gram-negative pathogens [69, 70].

There are other issues that clearly limit their use in clinical practice. First, PK/PD is critical for optimizing dosing. Colistin administration as an inactive prodrug affects the time needed to achieve desirable plasma concentrations [71]. A target plasma colistin concentration of 2 mg/L seems appropriate, but the risk of nephrotoxicity increases above 2.5 mg/L. Achieving target concentrations in plasma may not be sufficient for adequately treating lower respiratory tract infections due to reduced lung penetration [71–74].

Preclinical lung infection models suggest poor in vivo response to the polymyxins when administered parenterally

[74]. The PK and concentration of colistin in bronchoalveolar lavage (BAL) were evaluated in 13 adult patients who developed ventilator-associated pneumonia (VAP) caused by *A. baumannii* and *P. aeruginosa* during their ICU stay. The administration of 2 million International Units (IU) of colistin every 8 h results in apparently suboptimal plasma concentrations of colistin, which was undetectable in BAL [75]. Epithelial lining fluid penetration ratios appear reduced in critically ill patients; nebulized administration of antibiotics has been advocated to achieve target concentrations at the infection site with minimal systemic toxicity [76]. The data indicate that higher doses of nebulized colistin may achieve adequate concentrations in lung compartments; however, in order to optimize drug delivery both the nebulizers and nebulization technique are also important [77]. In a recent metanalysis, nebulized colistin was associated with better microbiological outcomes but did not result in any remarkable changes in the prognosis of patients with VAP [78].

Second, acute kidney injury (AKI) is a concern. This typically occurs 5–7 days after exposure, often as a result of acute tubular necrosis [79]. Lodise et al found an AKI incidence of 25.1% (RIFLE criteria). Acute kidney injury was associated with a higher incidence of mortality and increased costs [80].

Clinical experience for colistin efficacy against infections caused by MBLs is limited. A multicenter study analyzed 102 cases of bacteremia, 82 of which were caused by NDM-producing *K. pneumoniae* or *E. coli*, and 20 by MIV-producing strains (70% of which were *K. pneumoniae*). The overall mortality rate in the group treated with the combination ATM plus CAZ/AVI was 19%, while the mortality rate in the group treated with colistin was 59.3% [68].

In fact, in a recent report on 343 patients with MBL–producing Enterobacterales infections, the 30-day mortality rate was 29.7%. Sensitivity analysis showed that ATM plus CAZ/AVI, compared with colistin, was independently associated with a reduced 30-day mortality rate [81].

5.2 Aztreonam/Avibactam (ATM/AVI)

Aztreonam/avibactam, recently approved in April 2024 by European Medicines Agency (EMA), combines the inherent stability of ATM against MBLs with classes A, C and some D (OXA-48-like) β-lactamase inhibition offered by AVI. Many carbapenem-resistant Enterobacterales (CRE) strains co-produce MBL and serine enzymes that can inactivate ATM. In fact, β-lactamase inhibitors, such as AVI, zidebactam or nacubactam, protect ATM from hydrolysis and enhance its anti-MBL activity against Enterobacterales and, to a lesser extent, *P. aeruginosa* [82, 83]. Furthermore, a large in vitro broth microdilution study recently confirmed the potent activity of ATM/AVI against Enterobacterales isolates. In particular, all carbapenemase-producing Enterobacterales tested were inhibited at a concentration threshold of 8 mg/L [84].

Resistance to ATM/AVI in MBL producing Enterobacterales has been reported to be lower than 1% globally [85]. However, resistance to ATM/AVI in 15% NDM producing *E. coli* has been specifically linked to the production of CMY-42 and/or PBP3 modifications [86]. Production of double carbapenemases may also compromise the activity of ATM/AVI in Enterobacterales [87]. The picture is different for *P. aeruginosa*. First, the co-production of MBLs and ESBL or other carbapenemases is infrequent in this species. Second, while the overexpression of AmpC may compromise the activity of ATM to some extent, the main chromosomal resistance mechanism to ATM is related to the expression of the efflux pump MexAB-OprM [88]. Thus, the added value of AVI in *P. aeruginosa* is lower than for Enterobacterales, and synergy between ATM and AVI cannot be taken for granted. Likewise, the activity of ATM/AVI activity is much lower in MBL producing *P. aeruginosa* as compared with MBL producing Enterobacterales. For example, in one study, the susceptibility rate of ATM against MBL–producing *P. aeruginosa* strains (53.8%) was only slightly increased with the addition of AVI (69.2%). On the other hand, ATM, alone or combined with AVI, shows no significant activity against *A. baumannii* [89].

In vitro study data found that the addition of AVI could reduce or close the mutant selection window (MSW) of ATM in Enterobacterales harboring MBLs. For ATM/AVI dosing regimens evaluated in clinical trials, the free drug concentration was above the mutant prevention concentration values of >90% and >80%, whereas the fraction of time within the 24 h that the free drug concentration was within the mutant selection window measures were <10% and <20% in plasma and epithelial lining fluid, respectively [90].

An open-label, multicenter Phase 2 trial of ATM/AVI in complicated intra-abdominal infections (cIAI) compared 3 dosing regimens for PK/PD target achievement. The regimen that prevailed, with no safety concerns, was the 500-mg/167-mg loading dose followed by 1500-mg/500-mg four times daily in a 3-h infusion [91].

The results of the ASSEMBLE (NCT03580044) study showed that 5/12 (41.7%) patients with confirmed MBL–producing Enterobacterales infections, who received ATM/AVI ± metronidazole (MTZ), were cured at test of cure (TOC) versus 0/3 (0%) of those on best available therapy [92].

Aztreonam plus avibactam is indicated for the treatment of adult patients for cIAI, hospital-acquired pneumonia, including ventilator-associated pneumonia, and complicated urinary tract infection (cUTI), including pyelonephritis. Aztreonam plus avibactam is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options [93]. This resolution also highlights the microbiology data that indicate

that ATM in combination with AVI may also be of particular utility in infections caused by MBL–producing Enterobacterales and that this combination could therefore address an unmet medical need. The most common side effects are serum transaminase elevation, and diarrhea [91]. Dose selection for ATM/AVI, including adjustments for renal impairment based on a series of iterative population PK modeling and probability of target attainment (PTA) analyses, has recently suggested optimized dosing regimens [94]. Given the microbiologically active molecules now approved, the use of this combination would be reasonable and could replace ATM plus CAZ/AVI.

5.3 Aztreonam plus Ceftazidime/Avibactam

Aztreonam plus CAZ/AVI has been used as an alternative to ATM/AVI in the past due to lack of other therapeutic options. In the absence of ATM/AVI in clinical practice, the combination of CAZ/AVI plus ATM can be considered. However, it is essential that the microbiology laboratory verifies the synergy between AVI (from the CAZ/AVI combination) and ATM, since such synergy does not always occur, and in its absence, the use of this bi-therapy would not be feasible. Aztreonam plus CAZ/AVI has been used as an alternative to ATM/AVI due to limited options, although clinical experience is mainly from case reports [95–98]. Falcone et al. [99] noted better outcomes with ATM plus CAZ/AVI for NDM- or VIM-producing Enterobacterales bacteremia compared to colistin. A retrospective study showed clinical cure rates of 91.6%, 66.7%, and 85.7% for ATM plus CAZ/AVI alone, with polymyxin, and with fosfomycin, respectively, in NDM and OXA-48 infections [100]. Timsit et al reported clinical cure in 5 of 7 NDM-producing Enterobacterales cases with this combination [101].

A systematic review by Mauri et al found a 19% 30-day mortality rate for ATM plus CAZ/AVI, lower than the 44 % in the control group (odds ratio 0.33; 95% CI 0.13–0.66) [82] although effectiveness was low against MBL–producing *P. aeruginosa*. A meta-analysis showed ATM plus CAZ/AVI had a lower 30-day mortality risk compared to polymyxins (risk ratio 0.51; 95% CI, 0.34–0.76) [102].

5.4 Cefiderocol

Cefiderocol is a novel siderophore cephalosporin with activity against a large range of multi-resistant organisms, including MBL producers.

Resistance to cefiderocol has been documented in several bacterial species and is generally mediated by the interplay of the expression of β-lactamases with potent cephalosporinase activity, such as several extended spectrum beta lactamases (ESBLs) or carbapenemases, with mutations in iron uptake systems [103–105]. Coppi et al. [106] have recently reported a nosocomial outbreak by cefiderocol-resistant NDM-1–producing *Klebsiella pneumoniae* occurring in a large tertiary care hospital in Florence. Retrospective analysis of cases observed in January 2021–June 2022 revealed that 21/52 were cefiderocol resistant due to the inactivation of the cirA siderophore receptor gene. Cefiderocol resistance in *K. pneumoniae* has also been associated with the production of NDM-5 [107]. In another recent report by Lasarte-Rubio et al. [108], cefiderocol resistance in an epidemic *E. cloacae* complex strain was associated with the production of the MBL VIM-1, the ESBL SHV-12 and the inactivation of a FcuA-like siderophore receptor. Likewise, high-level cefiderocol resistance in a ST167 *E. coli* strain was associated with the production of NDM-35, showing an approximate 10-fold increase in hydrolytic activity toward cefiderocol compared to NDM-1 [109]. Additionally, the isolate co-produced a CMY-type β-lactamase, exhibited a four amino-acid insertion in PBP3, and possessed a truncated *CirA*. Moreover, the acquisition of a transferable extrachromosomal *fec* operon has been associated with a cefiderocol MIC increase in Enterobacterales [110]. The number of reports of cefiderocol resistance in *P. aeruginosa* is lower than for Enterobacterales. Iron transport systems are also typically involved, but in addition to the expression of ESBLs or carbapenemases, a major source of resistance development, are the mutations within the catalytic center of AmpC [111, 112]. Recent in vitro evolution experiments in *P. aeruginosa*, including XDR high-risk clones, revealed that the most frequent mutations associated with cefiderocol resistance were those on *piuC*, *fptA* and *pirR*, related to iron uptake [113]. Additionally, an L320P AmpC mutation was selected in multiple lineages, and cloning confirmed its major impact on cefiderocol (but not ceftolazane/tazobactam or CAZ/AVI) resistance [113]. Mutations in CpxS and PBP3 were also documented. Cefiderocol resistance in *A. baumannii* has been shown to be multifactorial and dependent on the interplay of the expression of β-lactamases, siderophore receptors and PBP3 mutations [114].

Hypotheses suggest that undetected hetero-resistance of *Acinetobacter* to cefiderocol – defined as the presence of resistant subpopulations within a majority population susceptible to this agent – might explain the higher all-cause mortality rates observed in the CREDIBLE-CR study among patients with infections caused by this organism [115, 116]. However, a subsequent study focused exclusively on carbapenem-resistant isolates of the *Acinetobacter calcoaceticus-baumannii* complex, which were cultured from patients treated with cefiderocol in the CREDIBLE-CR study. This study employed the methodology Population Analysis Profiling (PAP) and surprisingly, for infections caused by PAP-hetero-resistant isolates, the clinical cure rate was higher and mortality lower than for infections due to PAP-susceptible or PAP-resistant isolates [117]. The underlying causes of

cefiderocol hetero-resistant phenotypes remain poorly understood. In other studies involving *K. pneumoniae,* hetero-resistance has been linked to mutations in cirA (which codes for a siderophore receptor) [118] and to blaSHV-12 amplification [119]. Cefiderocol hetero-resistance has also been hypothesized to be related to bacterial recurrence in a patient with bacteremia caused by caused NDM-5–producing *K. pneumoniae* [120]. Importantly, the standard methodology for defining hetero-resistance (population analysis profiling) lacks clinical validation as a predictor of patient outcomes, both clinically and microbiologically. At present, correlating hetero-resistance to cefiderocol with clinical outcomes in patients treated with this cephalosporin remains challenging.

Specific tissue penetration data are available for the respiratory system: in healthy volunteers after a single 2-g intravenous (IV) dose, the drug penetrates into epithelial lining fluid (ELF) with geometric mean concentration ratios, over 6 h, ranging from 0.0927 to 0.116 mg/L for ELF and total plasma. In patients with VAP, the geometric mean ELF concentration of cefiderocol was 7.63 mg/L at the end of infusion, and 10.40 mg/L 2 h later. The ELF/unbound plasma concentration ratio was 0.212 (21.2 %) at the end of infusion and 0.547 after 2 h, suggesting delayed lung distribution, with concentrations sufficient to treat Gram-negative bacteria [121, 122].

Although few reports have evaluated the efficiency of newly developed antibiotics in relation to the inoculum effect, this phenomenon could be responsible for clinical failure and the selection of resistant bacteria. A recent study investigated the impact of inoculum size on the MICs of cefiderocol and new β-lactams/β-lactamase inhibitors. When the inoculum increased to 10^7 colony-forming units (CFU)/mL, all molecules were affected, particularly cefiderocol and imipenem-relebactam. In contrast, CAZ/AVI remained only mildly affected [123]. Another recent paper demonstrated that NDM producers exhibited lower susceptibility to cefiderocol and ATM/AVI compared to VIM or IMP producers. Inoculum effects on cefiderocol and ATM/AVI were observed in over 90% of susceptible carbapenemase-producing Enterobacteriaceae isolates [124].

Pivotal clinical trials [125, 126] demonstrated the efficacy of cefiderocol monotherapy against infections caused by MBL–producing Gram-negative bacteria. Overall, the rates of clinical cure (70.8% [17/24]), microbiological eradication (58.3% [14/24]), and all-cause mortality at 28 days (12.5% [3/24]) were favorable compared to the comparator arms in the trials. These included the option of prescriber-judged best available therapy and high-dose meropenem, with rates of 40.0% (4/10), 30.0% (3/10), and 50% (5/10), respectively [127].

A higher mortality rate was observed in patients with *Acinetobacter* infections, which was 50% compared to 18% in those who received the best available therapy [125]. These differences were likely due to deaths occurring within the first 72 h and after 29 days, as well as the fact that patients in the cefiderocol arm were more severely ill, with higher rates of ICU admission, septic shock, and mechanical ventilation. All these factors are known independent predictors of mortality [128].

The efficacy of combination treatment compared to cefiderocol monotherapy remains unresolved. In carbapenem-resistant *A. baumannii* (CRAB) infections, a meta-analysis by Onorato et al. evaluated cefiderocol monotherapy and the combination therapy among seven studies. They found a significantly lower mortality rate among patients receiving cefiderocol in monotherapy as compared to treated with combination regimens. However, these findings were not confirmed in the sub-analysis including only patients with bloodstream infections nor in the analysis including patients with pneumonia [129]. A recent review also found no significant difference in terms of mortality, microbiological eradication and clinical cure between monotherapy and combination therapy [130, 131].

The most frequently reported treatment-emergent adverse events were diarrhea, pyrexia, and vomiting. Liver enzyme increases or clotting abnormalities occurred more frequently in the cefiderocol group [125]. Treatment-emergent adverse events reported in at least 5% of patients in either treatment group were generally balanced across treatment groups. Four of 148 (3%) patients in the cefiderocol group and four of 150 (3%) patients in the meropenem group developed *Clostridium difficile* infection or colitis [126].

In randomized clinical trials conducted with cefiderocol in patients with nosocomial pneumonia, bacteremia, and sepsis or complicated urinary tract infections (cUTI), cefiderocol demonstrated numerically higher rates of clinical cure and microbiological eradication compared to comparators against MBL–producing pathogens, including enterobacteria and non-fermenters [132]. The benefit in outcomes was observed across different genera or species and cefiderocol MIC levels (up to 4 µg/mL), demonstrating effective eradication of highly carbapenem-resistant bacteria. A similar observation can be made for NDM-type carbapenemases, as the clinical cure rate (56.2% [9/16]) for NDM-producing infections was lower than for non-NDM enzymes (100% [8/8]) [101, 127].

A recent narrative case series by a French group documented the experience with a cefiderocol regimen in treating a cohort of 16 critically ill patients with difficult-to-treat nosocomial infections caused by MDR Gram-negative bacteria [133]. Within this cohort, four patients with five isolates of MBL–producing Gram-negative bacteria (all characterized as VIM) were highlighted. All these patients received cefiderocol treatment, primarily as monotherapy, except 1 patient with *A. baumannii*-induced ventilator-associated pneumonia in whom it was combined with tigecycline.

Importantly, none of these patients treated with cefiderocol for infections caused by MBL–producing Gram-negative bacteria died during their ICU stay. In another case series, among 18 evaluable patients with infections caused by cefiderocol-susceptible MBL–producing CRE (clinical cure was 72.2 % [13, 18], eradication at end of treatment was 77.8 % [14, 18], and 28-day mortality was 22.2 % [4 of 18 patients: 4 of 16 in NDM-producing CRE vs 0 of 2 in VIM-producing CRE]) [134].

6 Guideline Recommendations

Clinical practice guidelines from various scientific societies have addressed this issue. In 2022, the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) recommended the use of cefiderocol for the treatment of severe infections caused by MBL–producing CRE or those resistant to all other antibiotics, including CAZ/AVI and meropenem/vaborbactam (low-level evidence) [135]. According to ESCMID, for patients with non-severe CRE infections, it is recommended to use an antibiotic that has been shown to be effective in vitro, and the choice of antibiotic should be based on the individual case and the source of the infection. In case of urinary tract infections, aminoglycosides, such as plazomicin, are recommended over tigecycline (conditional recommendation and low evidence). Tigecycline is not recommended for bacteremia or nosocomial or ventilator-associated pneumonia. Finally, guidelines suggested that if tigecycline was deemed necessary for treating pneumonia, it should be administered at high doses (low certainty of evidence) [135].

According to IDSA guidelines, the preferred antibiotics for infections outside the urinary tract caused by NDM-producing CRE are CAZ/AVI in combination with ATM, or cefiderocol as monotherapy. In cases of *P. aeruginosa*-difficult to treat resistance (PA-DTR) isolates producing MBL, the recommended treatment is cefiderocol monotherapy. Cefiderocol should be reserved for CRAB infections unresponsive to other antibiotics or when other agents cannot be used due to intolerance or resistance. When used for CRAB infections, cefiderocol should be included in a combination regimen (https://www.idsociety.org/practiceguideline/amr-guidance/) [131].

Given this situation, hospital antimicrobial stewardship programs play a fundamental role in the recommendation and appropriateness of empirical or targeted antibiotic treatment with cefiderocol in patients with suspected or confirmed infection with MBL–producing Gram-negative bacilli. Recommendations take into account the following premises: patients' clinical situation (febrile, septic or in shock) and epidemiological characteristics (i.e., age, immunosuppression, recent admissions, living in a nursing home, and administration of antibiotics in the last 3 months); local epidemiology considering susceptibility rates and resistance mechanisms of the main microorganisms isolated from the hospital center; and the type and source of the infection (high inoculum, such as pneumonia, CNS, and bacteremia; or low inoculum, such as urinary tract infection or skin and soft tissue infection) [136].

7 New Approaches

Several new β-lactamase inhibitors combined with different β-lactams have recently been introduced in clinical practice. The already commented successful combination of AVI with ATM for treating MBL–producing organisms is not similar to the situation with other inhibitors such as vaborbactam (combined with meropenem) or relebactam (combined with imipenem), as they are not active against class B β-lactamases, but only class A and C enzymes.

7.1 Cefepime/Zidebactam (WCK 5222)

Cefepime/Zidebactam (WCK 5222) is a singular combination of cefepime with a bicyclo-acylhydrazide zidebactam that acts as a β-lactam enhancer mediating multiple penicillin-binding proteins (PBP) binding. Zidebactam not only protects cefepime from hydrolysis by certain serine β-lactamases but also has stand-alone antibacterial activity due to its potent PBP2 binding in all Gram-negative bacteria (Enterobacterales and *P. aeruginosa*) [137, 138]. Several studies have demonstrated the potent activity of cefepime/zidebactam against a range of carbapenem-resistant pathogens, including VIM/NDM-expressing *P. aeruginosa* isolates, which co-amplify efflux and impermeability [139, 140].

7.2 Taniborbactam

Taniborbactam (formerly VNRX-5133) is a cyclic boronate with a broad spectrum of activity, including KPC, OXA-48 and MBLs (VIM and most NDM, but not IMP) and is the first inhibitor against all classes of β-lactamases. It uses a different mechanism to inhibit both SBLs and MBLs. For MBLs, it acts as a reversible competitive inhibitor with low inhibition constants (Ki) and rapid dissociation. Taniborbactam is being developed in combination with cefepime or meropenem to treat severe infections caused by MDR pathogens (CRE and carbapenem-resistant *P. aeruginosa*) [141].

7.3 Xeruborbactam

Xeruborbactam (formerly QPX7728) is an ultra-broad-spectrum cyclic boronic acid beta-lactamase inhibitor (BLI) with activity against SBLs and MBLs. Preliminary data have shown that the meropenem/QPX7728 combination appears to CRAB, producing carbapenem-hydrolyzing class D β-lactamases (CHDLs), NDM and KPC. Overall, it seems to have excellent affinity for important carbapenemases such as KPC-2, IMP-1, VIM-1, NDM-1, OXA-23 and OXA-48 [142].

8 Expert Opinion

Delivering a timely and appropriate empirical or targeted treatment against Gram-negative MDR bacteria, such as Enterobacterales, *A. baumannii*, and *P. aeruginosa* is critical. A comprehensive clinical algorithm for the choice of treatment of infections caused by MBL–producing Gram-negative bacteria is shown in Fig. 1.

From a microbiological perspective, the choice of treatment for infections caused by MBL–producing Gram-negative bacteria is crucial. The prevalence of carbapenemase-producing microorganisms, particularly of the MBL type, varies geographically and depends on the microbial species involved. In *P. aeruginosa*, MBLs are the most prevalent enzyme types when the organism produces carbapenemases, but in some regions this is not the main mechanism of carbapenem resistance in this organism. The wide spectrum of activity and associated co-resistances mean that an early and accurate diagnosis is essential to ensure appropriate antimicrobial therapy. However, assessing the in vitro activity of anti-MBL antimicrobials remains challenging, especially when evaluating synergism between ATM and CAZ/AVI (not routinely performed) or AVI/ATM (without a breakpoint according to EUCAST, with the exception of Enterobacterales, for which the EUCAST breakpoints define susceptible as ≤4 mg/L and resistant as >4 mg/L) [37] and cefiderocol for susceptibility testing. A standardized method for studying the in vitro combination of antimicrobial agents is imperative because the results of the various assays currently in use are not always equivalent. Moreover, enhancing technical capabilities for studying synergy in vitro will lead to a better understanding of the correlation between microbiological data and clinical outcomes. As for testing cefiderocol, the main limitation in practice derives from the need to use an iron-depleted medium, which is not routinely available in clinical laboratories; this has also prevented manufacturers of semi-automated susceptibility testing systems from preparing panels with cefiderocol as one of the test drugs. For both reasons, other standardized approaches (basically, the disk diffusion assay) or specific commercial assays (gradient strips, commercial broth microdilution) are commonly used when testing cefiderocol. It also important to consider that the activities of cefiderocol and ATM/AVI against MBL–producing Gram-negative bacteria is highly dependent on the species and the concrete enzyme involved, so treatment algorithms should be individualized (see Fig. 1). There are also growing reports on emerging resistance to these novel beta-lactam combinations, so clinical microbiology laboratories must have reliable susceptibility testing procedures for these novel agents at their disposal. While the choice of cefiderocol versus ATM/AVI or ATM plus CAZ/AVI will depend on several of the above variables, either of these options are preferable to colistin, unless resistance is proved for both options (see Fig. 1).

From a clinical perspective, understanding the efficacy and safety of different treatment options is essential for managing infections caused by MBL–producing Gram-negative bacteria. Stewardship teams have to promote the prudent use of antimicrobials in an effort to achieve a balance between effectiveness, in terms of clinical response and outcomes, and adverse events. Given its PK/PD characteristics, reported toxicities and poor clinical outcomes, colistin may be an option only when new-generation antimicrobials are not available or are inactive, or when cross-reactivity in patients with β-lactam allergy is likely.

Aztreonam plus avibactam could be an acceptable option in infections caused by MBL–producing Enterobacterales, for which efficacy and safety results from Phase 3 trials showed a percentage (95% CI) of patients with clinical cure of 41.7 (18.0–68.8) and the effectiveness of the combination in clinical practice must be tested in observational studies. In view of the recent approval of these new molecules, it would be advisable to utilize this new combination instead of ATM plus CAZ/AVI. In case of infections due to PA-DTR, this antibiotic does not work because AVI does not contribute to restoring ATM activity. Cefiderocol has a key role in treating infections caused by MBL–producing *P. aeruginosa* and MBL–producing CRE in complex or critically ill patients, given its novel mechanism of action that promotes activity in the presence of these enzymes, active efflux pumps, or porin loss.

The use of all antimicrobials should be personalized for each patient or episode. In the case of cefiderocol, monitoring involves the strict adaptation of the dosing regimen to the different ranges of renal function to achieve a 90% probability of target attainment of 75% fT>MIC [143–146]. This should avoid or at least predict the development and selection of resistance in vivo [147], usually generated by the combined expression of various mechanisms [103].

Some clinical guidelines [131, 135, 148] propose AVI/ATM as the first choice against MBL producers [149, 150]. However, in certain clinical situations cefiderocol is considered the first choice, due to its lower MIC values with

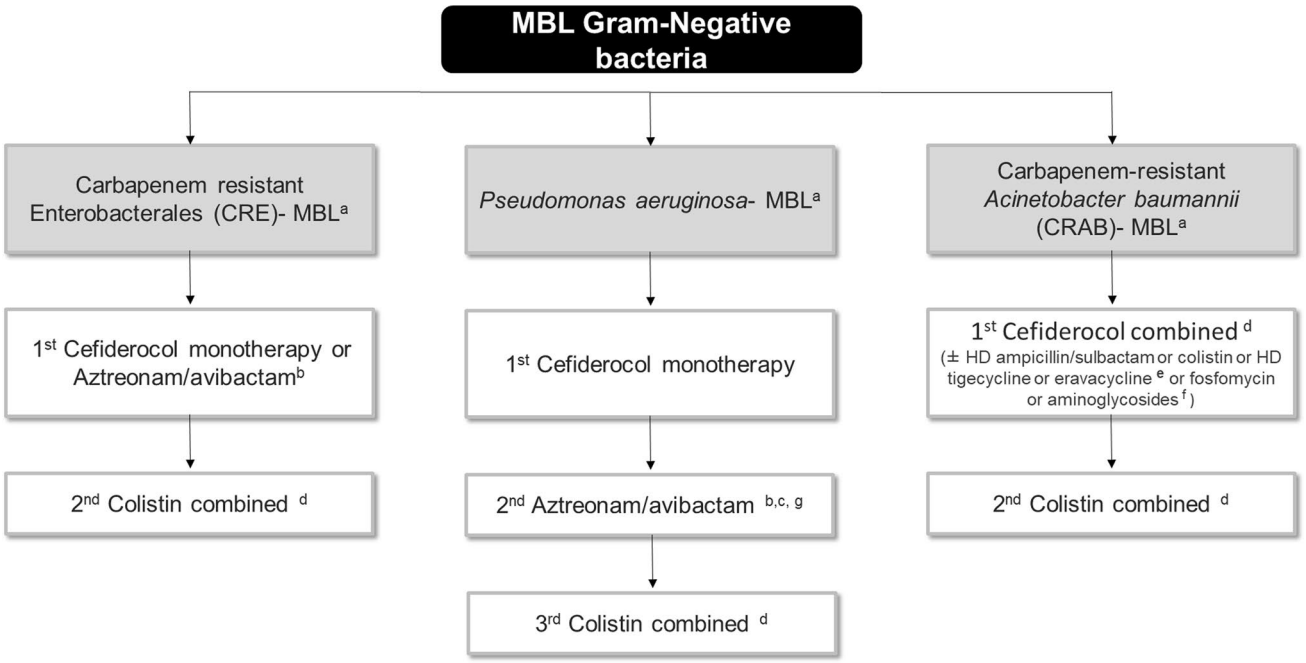

Fig. 1 Flowchart of treatment options for infections caused by metallo-β-lactamase-producing Gram-negative bacteria. CRAB: carbapenem-resistant *Acinetobacter baumannii*; CRE: carbapenem-resistant Enterobacterales; HD: high doses; refers to the need to use loading doses of certain drugs and/or doses higher than those usually recommended by the technical sheet; MBL: metallo-β-lactamases. **a** Ideally the choice of treatment should be guided by appropriate susceptibility testing results. According to current trends of resistance to the novel β-lactams, this is particularly relevant in the case of ATM/AVI for NDM-producing Gram-negative bacilli and for all MBL–producing *P. aeruginosa*. **b** Aztreonam/avibactam, approved in April 2024, is not yet available for clinical use. Ceftazidime/avibactam plus aztreonam could be used as an alternative, although some limiting factors should be considered: (i) there is no evidence of clinical equivalence with aztreonam-avibactam, (ii) there is a risk of emergence of resistant mutants if dosing is not optimal, and (iii) there is a lack of standardized synergy testing methods. **c** Avibactam does not significantly contribute to increased aztreonam activity in aztreonam-resistant *P. aeruginosa* and is not usually an adequate option for PA-DTR. The CHMP positive opinion, highlights its utility in infections caused by MBL–producing Enterobacterales. **d** Combined: The combination could depend on the source of infection; recommended in hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP), bloodstream infections, cIAI and cUTI. The combined treatment option for colistin includes the possibility of its inhalation route through aerosol therapy in pneumonia, along with other systemic antibiotics. Combinations that increase nephrotoxicity or other adverse effects should be avoided." **e** Eravacycline is not yet (April 2024) available. **f** Combined with aminoglycosides in cUTI. **g** ATM/AVI is approved for the treatment of MBL–producing Enterobacterales and for the treatment of infections caused by aerobic Gram-negative organisms in adult patients with limited treatment options.

higher activity and reported efficacy against MBL–producing *P. aeruginosa* [151, 152] compared to Enterobacterales (see Fig. 1). In short, when an infection is identified as being caused by MBL–producing Gram-negative bacteria (e.g., NDM, VIM or IMP), which typically cause cross-resistance phenomena between β-lactams and co-resistance to other antibiotic families, the therapeutic options currently include cefiderocol monotherapy or AZT/AVI. Actually, in the absence of comparative studies between cefiderocol and AVI/ATM in infections caused by MBL–producing Enterobacterales, it is difficult to establish the order of priority in the choice between the two drugs, so the decision will depend on local epidemiology, microorganism type, and the MBL expressed. Considering the in vitro and clinical data discussed above, cefiderocol could be a first option for MBL–producing *P. aeruginosa* and in combination with a second agent for *A. baumannii* (see Fig. 1). All decisions must be comprehensive and taken under the guidance of the stewardship team.

Combining antibiotics might be a useful strategy to improve the success rate and efficacy of these drugs and may prevent the emergence of resistance to new agents, although some authors believe that it may lead to increased tolerance to antibiotics and favor the development of resistance [153]. Cefiderocol could also be an option as an empirical choice for early active treatment of well selected patients with severe infections and resistance risk factors in areas endemic for more than one MBL–producing Gram-negative organism (Enterobacterales, *P. aeruginosa* or *A. baumannii*). In such a situation, rapid de-escalation to another agent is crucial whenever possible, based on rapid and detailed microbiological characterization of the causative pathogen,

and following recommendations by stewardship team. Finally, therapeutic alternatives to antibiotics are emerging, such as bacteriophage therapy. Nevertheless, the clinical use of phages (usually as personalized treatment) is still limited by their excessive specificity and by technical preparation issues. In summary, cefiderocol in monotherapy or combination, and AZT/AVI are a suitable option for MBL–producing Gram-negative infection. Further innovation and research with new antimicrobial molecules in monotherapy or combination therapy will be decisive in addressing this controversial matter.

9 Conclusion

Infections caused by MBL–producing Gram-negative bacteria present a significant clinical challenge due to their resistance mechanisms and the limited therapeutic options available. Our review highlights the critical roles of new therapeutic agents, specifically cefiderocol and the combination of ATM with AVI, in treating these infections. Cefiderocol has shown efficacy against a wide range of multidrug-resistant organisms, including MBL producers Enterobacterales and *P. aeruginosa*, and is particularly recommended for *P. aeruginosa* and for complex or critically ill patients. The ATM/AVI combination also offers potent activity against MBL–producing pathogens, especially Enterobacterales. However, colistin should be reserved as a last-resort option due to its nephrotoxicity and the emergence of resistance. Further research is necessary to optimize treatment strategies and minimize the development of resistance. Comprehensive antimicrobial stewardship and individualized patient care are essential in managing these infections effectively.

Acknowledgments The authors thank Laura Vilorio Marqués, PhD and Blanca Piedrafita, PhD, from Medical Statistics Consulting (MSC), Valencia, Spain, for medical writing and editorial assistance based on the authors' input and direction. The concept for this publication arose independently from the authors during an advisory board meeting sponsored by Shionogi S.L.U. The sponsor had no role in the decision to publish or in the preparation of the manuscript but reviewed the final manuscript to ensure technical accuracy and regulatory compliance. Support for third-party writing assistance for this article was funded by Shionogi SLU in accordance with Good Publication Practice (GPP2022) guidelines (https://www.ismpp.org/gpp-2022).

Declarations

Funding The publication of this article was supported by Shionogi, Spain.

Conflict of Interests CH-T has conducted consulting work for Shionogi, Angellini, Advanz, ViiV, Gilead Sciences, Janssen, and Merck Sharp & Dohme. CH-T has received research grants from Gilead Sciences and ViiV, as well as financial compensation for presentations from Shionogi, Gilead Sciences, Janssen, Merck Sharp & Dohme, and ViiV Healthcare. LM-M has been a consultant for MSD, Shionogi and Advanz, has served as a speaker for MSD, Pfizer and Shionogi and has received research grants from Pfizer, MSD and Shionogi. MR-A has conducted consulting work for Shionogi and Viatris. MR-A has served as a speaker for Pfizer, Gilead Sciences and Shionogi. AO has received research grants and speakers fees from Shionogi, Pfizer and MSD. GB has been a consultant for Pfizer, Astellas, Roche, MSD, Shionogi and Advanz, has served as a speaker for MSD, Pfizer, Roche, Advanz and Shionogi and has received research grants from Pfizer, Advanz and MSD. MSL has received remuneration for lectures and advisory boards (Advanz Pharma, Angelini Pharma, Janssen, Menarini, MSD, Pfizer, Shionogi, Viatris) and educational grants (Gilead, Tedec-Meiji).

Author Contributions All authors have contributed to the conception of the work. All authors wrote the original draft and performed substantial contributions to the final manuscript. All authors reviewed and approved the final manuscript for submission. All authors agreed to be accountable for all aspects of the work.

Ethics Approval, Informed Consent, and Data Availability Not applicable for this review.

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