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REVIEW

# Navigating the Current Treatment Landscape of Metallo-β-Lactamase-Producing Gram-Negative Infections: What are the Limitations?

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## ABSTRACT

The spread of carbapenemase-producing gram-negative pathogens, especially those producing metallo-β-lactamases (MBLs), has become a major health concern. MBLs are molecularly the most diverse carbapenemases, produced by a wide spectrum of gram-negative organisms, including the Enterobacterales, *Pseudomonas* spp., *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*, and can hydrolyze most β-lactams using metal ion cofactors in their active sites. Over the years, the prevalence of MBL-carrying isolates has increased globally, particularly in Asia. MBL infections are associated with adverse clinical outcomes including longer length of hospital stay, ICU admission, and increased mortality across the globe. The optimal treatment for MBL infections not only depends on the pathogen but also on the underlying resistance mechanisms. Currently, there are only few drugs or drug combinations that can efficiently offset MBL-mediated resistance, which makes the treatment of MBL infections challenging. The rising concern of MBLs along with the limited treatment options has led to the need and development of drugs that are specifically targeted towards MBLs. This review discusses the prevalence of MBLs, their clinical impact, and the current treatment options for MBL infections and their limitations. Furthermore, this review will discuss agents currently in the pipeline for treatment of MBL infections.

**Keywords:** Metallo-β-lactamase; Carbapenem resistant; Cefiderocol; Aztreonam; Avibactam

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**Key Summary Points**

The emergence and spread of infections caused by metallo-β-lactamase (MBL)-producing pathogens are emerging as a global public health threat with increase in prevalence and spread in all the regions, including non-endemic areas.

Infections caused by MBL-producing pathogens have a severe clinical impact with more ICU admissions, increased length of hospital stay, and increased mortality.

Current treatment options such as the co-administration of aztreonam with ceftazidime-avibactam and cefiderocol show activity against some MBL-producing species, but are limited by resistant genotypes within some species, lack of standardized dosing and difficulties in testing susceptibilities, lack of clinical trials in MBLs, and emergence of additional resistance mechanisms.

There are some promising drugs, including aztreonam-avibactam, now approved, and cefepime-taniborbactam in development, which demonstrate high in vitro activity against MBL-producing Enterobacterales.

The optimal management of MBL infections requires constant monitoring along with stewardship measures driven by rapid diagnostics, and knowledge of local epidemiology.

## INTRODUCTION

The spread of carbapenem resistance in gram-negative pathogens through acquisition of carbapenemases has become a major health concern [1]. These carbapenemases include Ambler class A and class D serine-β-lactamases (SBLs), and class B metallo-β-lactamases (MBLs) [2–4]. Among these, MBLs are the most diverse carbapenemases, molecularly, and are capable of hydrolyzing most β-lactams using metal ion cofactors in their active sites [4, 5]. MBLs can be found across a wide spectrum of clinically important gram-negative pathogens, including the Enterobacterales, *Pseudomonas* spp., *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*, and other non-fermenting gram-negative bacilli [6]. MBLs are divided into three subclasses—B1, B2, and B3, mainly dependent on the differences in the amino acid sequence and zinc ion dependence. The subclass B1 has emerged as the most clinically relevant, and includes KHM (Kyorin Hospital MBL), GIM (German imipenemase), SIM (Seoul imipenemase), DIM (Dutch imipenemase), SPM (Sao Paulo MBL), TMB (Tripoli MBL), VIM (Verona integron-encoded MBL), IMP (imipenemase), and NDM (New Delhi MBL) MBLs among others [7, 8]. Among these, the most prevalent MBLs are NDM, IMP, and VIM [9, 10].

Analysis of the genetic background of the IMP and VIM MBL genes has revealed that these genes mostly occur as cassettes along with other resistance genes within integrons and are integrated on chromosomes or plasmids [6–8]. The NDM genes are associated with mobile genetic elements such as plasmids belonging to different replicon or Inc types (IncFII, IncHI2, IncN, and IncX3), insertion sequences (ISAba125, ISCR1), and transposons (Tn*125*) [11]. The B2 and B3 MBLs are usually chromosomally encoded and generally not transmissible, though ubiquitously present in their host species [6]. For example, the chromosomal MBL $bla_{\text{BlaB}}$ and $bla_{\text{GOB}}$ found in *Elizabethkingia* spp., and the L1 (class B3) MBL in *S. maltophilia* confer resistance to the majority of the available β-lactams [6, 12].

The MBLs have a broad-spectrum substrate profile and can hydrolyze and inactivate most β-lactam antimicrobials. Monobactams (e.g., aztreonam) are refractory to hydrolysis by MBLs [13, 14]. However, aztreonam is inactive against Enterobacterales co-producing other β-lactamases such as extended spectrum β-lactamases and AmpC [14, 15]. Only few drugs, including those used to treat infections caused by SBL-producing organisms, are able to also treat MBL infections [13, 14]. The current review will discuss the prevalence of MBLs, their clinical impact, and current and future treatment options for MBL infections and their limitations.

This article is based on previously conducted studies and does not contain any new studies

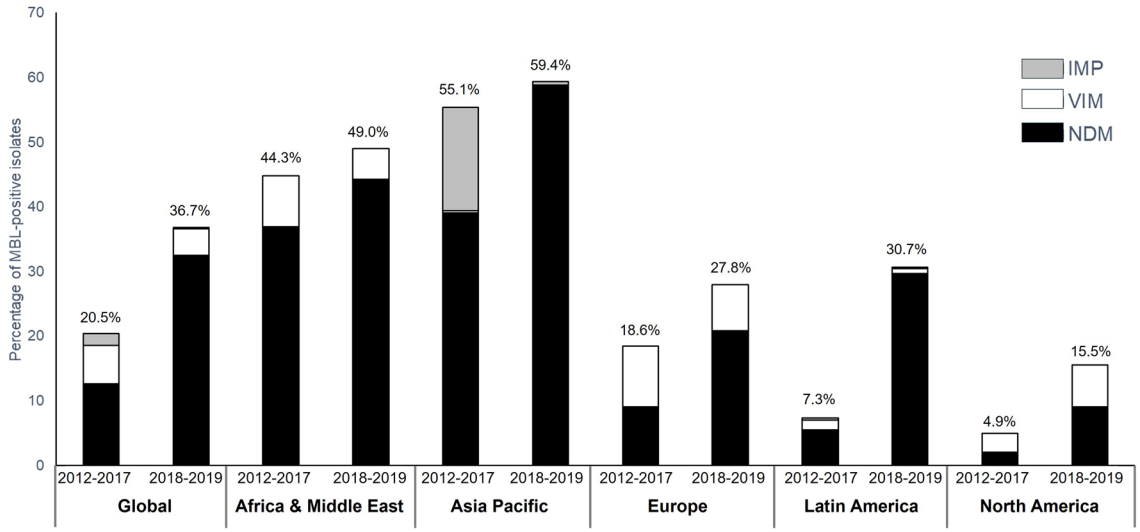


**Fig. 1** Distribution of MBL-positive Enterobacterales isolates among the carbapenem-nonsusceptible isolates collected globally and in each region between 2012 and 2017 compared to those collected between 2018 and 2019 [21, 22]. *APAC* Asia–Pacific, *AfME* Africa/Middle East, *LATAM* Latin America, *MBL* metallo-β-lactamases. The number of carbapenem-nonsusceptible (C-NS) and MBL-positive isolates collected in each region were Global, MBL/C-NS, 2012–2017, 547/2666 and 2018–2019, 818/2228; AfME, 2012–2017, 62/140 and 2018–2019, 94/192; APAC, 2012–2017, 162/294 and 2018–2019, 300/505; Europe, 2012–2017, 268/1441 and 2018–2019, 284/1020; LATAM, 2012–2017, 50/689 and 2018–2019, 123/401; North America, 2012–2017, 5/102 and 2018–2019, 17/110

with human participants or animals performed by any of the authors.

## PREVALENCE OF MBLS

The MBLs that are widespread geographically include IMP, VIM, and NDM [4]. IMPs were identified as the first transferable MBL from clinical isolates of *P. aeruginosa* in Japan in 1988 [16], and have become the predominant MBLs in southeast Asia [17]. The VIM MBLs were first reported from carbapenem-resistant *P. aeruginosa* in Italy in 1999 [18] and, until 2017, were the predominant MBLs in European and Mediterranean countries [7]. The NDM MBLs were first identified from *K. pneumoniae*, and *Escherichia coli* strains isolated from a patient returning to Sweden from India in 2008 [19]. Since then, among the MBLs, NDMs have spread the fastest and widest, geographically [1, 20]. Over the years, the prevalence of MBL-carrying isolates has increased globally and regionally. Based on the studies from the Antimicrobial Testing Leadership and Surveillance (ATLAS) program, the proportion of MBL-positive isolates among the carbapenem-nonsusceptible Enterobacterales were consistently higher between 2018–2019 than between 2012–2017, globally and in each of the regions, namely Asia–Pacific (APAC), Africa/Middle East (AfME), Europe, Latin America (LATAM), and North America (Fig. 1) [21, 22]. The ATLAS study from 2018–2019 further reported that the proportion of MBLs among those that are carbapenem-nonsusceptible varies across regions, with MBLs predominantly observed in isolates collected from APAC (59.4%, 300/505) and AfME (49.0%, 94/192). The study also reported that globally, 7.8% (173/2228) of meropenem-nonsusceptible Enterobacterales carried two carbapenemases, where the most prevalent combination was NDM and OXA-48-like carbapenemases (84.4%, 146/173) [21]. A global ATLAS surveillance study between 2017

and 2019 revealed that MBLs, namely VIMs (14.7%, 615/4187), were the predominant carbapenemases among carbapenem-resistant *P. aeruginosa* isolates ($n=4187$). Moreover, the study reported that VIM MBLs were predominant in LATAM (23.9%, 182/2811) whereas the NDM (8.5%, 60/706) and IMP (4.3%, 30/706) MBLs were predominant in APAC [23]. Overall, these studies highlight the heterogeneity in MBL predominance across regions.

### Asia–Pacific

A considerable burden of MBL-producing isolates has been observed in Asia. The global ATLAS surveillance study, 2018–2019, highlighted that MBLs were the predominant resistance mechanism among the meropenem-nonsusceptible Enterobacterales in APAC (59.4%, 300/505) [21]. An ATLAS surveillance study from APAC (2015–2019) among carbapenem-resistant *P. aeruginosa* isolates reported that VIM (29.0%, 71/245) and NDM (24.95, 61/245) MBLs were the most commonly observed β-lactamase genes. The study further reported that the geographic distribution of β-lactamase genes including MBLs varied across countries in the APAC region [24]. A study conducted in India (2014–2016) demonstrated that among carbapenemase-producing gram-negative bacteria ($n=282$), NDM (63.0%, 178/282) was the predominant carbapenemases followed by VIM (18.4%, 52/282) [25]. A study from Guangzhou, China (2015–2018) reported that among the carbapenem-resistant Enterobacterales isolates ($n=146$), 19.2% (28/146) were MBL-positive [26]. A multicenter study in China (2016–2017) among MBL-producing Enterobacterales ($n=161$) showed that NDM (93.7%, 151/161) was the most frequently reported MBL followed by IMP (8.1%, 13/161) and VIM (1.2%, 2/161) [27]. Another study in China (2017–2019) among patients infected with *P. aeruginosa* isolates reported that 55.2% (149/270) of isolates were MBL-positive with significantly higher IMP-1 (27.5%, 41/149; $P=0.023$), followed by VIM-2 (18.8%, 28/149), VIM-1 (16.1%, 24/149), and NDM-1 (9.4%, 14/149) [28].

### Africa/Middle East

MBLs have become prevalent carbapenemases across AfME in recent years. A global surveillance study based on the ATLAS program (2012–2017) revealed that 44.0% of meropenem-nonsusceptible Enterobacterales isolates collected in AfME were MBL-positive [22]. Another ATLAS surveillance study from AfME (2018–2020) among carbapenemase-producing Enterobacterales and *P. aeruginosa* isolates reported that 49.6% (167/337) of Enterobacterales isolates and 92.0% (81/88) of *P. aeruginosa* isolates were MBL-positive. NDM-1 (59.9%, 100/167) among Enterobacterales and VIM-2 (65.4%, 53/81) among *P. aeruginosa* were the most common MBLs identified [29]. In South Africa, NDM-1 was first documented among Enterobacterales in 2011 [30], and case reports from South Africa have demonstrated the occurrence of both local and imported cases of NDM-producing Enterobacterales [31]. Another study from Morocco (2018–2019) reported that among imipenem-resistant *A. baumannii* isolates, 82% (47/58) were MBL-positive [32].

### Europe

The percentage of MBL-positive isolates varies across countries in Europe. A recent multinational SIDERO-WT study (2014–2019) reported that MBL-producing Enterobacterales strains were predominantly identified in Greece (3.6%, 52/1428) followed by Russia (2.2%, 38/1719), Turkey (2.0%, 26/1334), and Italy (1.9%, 35/1883). NDMs and VIMs were the predominant MBLs identified in Greece, Turkey, and Italy. However, all MBL-producing Enterobacterales isolates in Russia were NDM-producing strains. Among *P. aeruginosa* isolates, the highest proportion of MBL-producing strains were isolated in Russia (20.4%, 106/520) followed by Greece (9.9%, 30/304), Czech Republic (6.3%, 21/334), and Spain (4.4%, 21/482), with VIMs identified as the predominant MBLs in these countries. For *A. baumannii* isolates, the percentage of MBL-producing strains was highest in the UK (2.7%, 3/109) followed by Russia

(1.6%, 7/437), Germany (1.5%, 4/265), and Italy (0.8%, 4/505). NDM-producing strains were isolated in multiple countries including Russia, Italy, and UK [33]. Multiple outbreaks of NDM-producing carbapenem-resistant Enterobacterales (CRE) across the European Union (EU)/European Economic Area (EEA) have been reported [34]. A nationwide survey in Greek hospitals (2013–2022) among *K. pneumoniae* isolates ($n=310$; carbapenem-resistant/susceptible with increased exposure) reported that 35.2% of isolates carried an MBL gene alone or in combination with other carbapenemase genes [35]. The Italian surveillance system reported a large outbreak of NDM-producing CRE in Tuscany with 350 cases observed between 2018 and 2019 [34]. Per the English Surveillance Programme for Antimicrobial Use and Resistance (ESPAUR) report, overall, NDMs (25.1%) were the second most frequently acquired carbapenemases in England after OXA-48 (41.8%) in 2021. However, frequency of MBLs varied by region across England [36]. The surveillance systems in Germany reported increasing numbers of NDM-1-producing *K. pneumoniae* since March 2022, with an average of 44 cases per month in March to September 2022 compared to an average of 28 cases (95% prediction interval 18–38) during 2017–2020. The study also showed a high prevalence of ST147 and ST307 epidemic clones which most likely led to clonal dissemination and onward transmission in Germany [37].

### Latin America

MBLs have been observed in several Latin American countries [10]. An ATLAS surveillance study between 2017 and 2019 from LATAM among clinical isolates of meropenem-nonsusceptible Enterobacterales and *P. aeruginosa* isolates reported that 24.4% (139/570) of Enterobacterales isolates and 25.6% (81/835) of *P. aeruginosa* isolates tested for presence of β-lactamases were positive for MBLs. The proportion of MBL-positive isolates among overall Enterobacterales from LATAM was low (1.7%, 146/8416). However, the frequency of MBL-positive isolates was higher compared to previous years, with 0.2% of isolates collected in 2012–2015 and 0.6% of isolates collected in 2015–2017 reported to be MBL-positive. The percentage of MBL-positive *P. aeruginosa* isolates also increased over the years, with 25.6% of meropenem-nonsusceptible *P. aeruginosa* isolates carrying MBLs during 2017–2019 compared to 14.7% of MBL-positive *P. aeruginosa* isolates nonsusceptible to meropenem, doripenem, or imipenem during 2012–2015 [38]. NDMs were the most common MBLs and the second most common carabepenemases among Enterobacterales, whereas VIMs were the predominant carbapenemases among *P. aeruginosa* isolates [38]. A retrospective observational study in Brazil (January 2017–April 2021) identified 42 NDM-producing Enterobacterales in 39 patients. The frequency of NDM cases increased significantly from 2017 (5%) to 2021 (46%; $P<0.0001$) [39].

### North America

The frequency of MBLs in the USA has increased over recent years. A surveillance study in the USA as part of International Network for Optimal Resistance Monitoring (INFORM, 2016–2020) reported that 2.7% of carbapenem-nonsusceptible Enterobacterales were positive for MBLs [40]. A recent INFORM surveillance study (2019–2021) in the USA reported that MBLs (12.6%, 33/261) were the second most common carbapenemases after KPC (65.5%, 171/261) among CRE isolates [41]. Over time, NDMs have become prevalent in Canada—a population-based surveillance data from Toronto, Canada (2007–2015) demonstrated that NDMs (51.0%) were the predominant carbapenemases observed among the carbapenemase-producing Enterobacterales-positive ($n=291$) patients [42].

## CLINICAL IMPACT OF MBL INFECTIONS

The worldwide continued spread of MBL, specifically the clinically relevant IMP, VIM, and NDM MBL, represents a global health threat [13, 43]. MBL infections are associated with adverse clinical outcomes including longer length of hospital

stay, ICU admission, and increased mortality across the globe.

### Length of Hospital Stay

Three prospective observational studies conducted by Falcone et al., one in Italy and Greece in 2018–2019 and two others in Italy in 2018–2020 and 2019–2022 that included hospitalized patients with infections caused by MBL-Enterobacterales, reported significantly higher ICU hospitalizations among patients infected with MBL-CRE as compared to those infected with carbapenem-susceptible (CS) gram-negative bacteria (GNB) (49.4% vs. 19.8%; $P<0.001$) [44]; overall length of stay of 16.5 days (median interquartile range [IQR] 10–31.5 days) due to BSI caused by MBL-Enterobacterales [45]; and overall hospitalization rates of 46.2% (157/340) and ICU stay rates of 42% (144/343) due to MBL infections [46]. A retrospective case–control study conducted by Rodríguez-Noriega et al. in Mexico between 2012 and 2018 also assessed the risk factors associated with nosocomial infections caused by NDM-1-producing *K. pneumoniae* among 139 patients and compared them to 486 control cases. They reported that the length of hospital stay was significantly higher in the NDM-1 group compared to the controls (43.05 ± 31.3 vs. 15.58 ± 14.4 days; $P<0.001$) [47].

### Mortality

In the studies conducted by Falcone et al., the overall 30-day mortality was 31.4% (2018–2019) [45] and 29.7% (2019–2022) [46], and the attributable mortality was 35% (2018–2020) [44] in patients with MBL-Enterobacterales. The study conducted in 2018–2020 in Italy reported that infection with MBL-producing CRE was significantly associated with 30-day mortality as compared to infection with carbapenem-susceptible gram-negative bacilli (CS-GNB) (adjusted OR [aOR] 5.86, 95% CI 2.72–12.76); and the 30-day mortality was significantly higher among those infected with MBL-producing CRE as compared to those infected with CS-GNB (36.4% vs. 13.7%; 95% CI 2.16–5.9; $P<0.001$) [44]. In the study conducted by de Jager et al. in 2011–2012, a significantly higher mortality rate among ICU patients infected with NDM-1-positive Enterobacterales (cases) compared to controls (55.3% vs. 14.7%; adjusted OR 11.29; $P<0.001$) was reported [48]. A retrospective study conducted by Persoon et al. in a tertiary care hospital in the Netherlands between 2004 and 2016 demonstrated significantly higher 28-day in-hospital all-cause crude mortality in patients with VIM-positive *P. aeruginosa* bacteremia compared to patients with CS *P. aeruginosa* bacteremia (42.5% vs. 19.6%, difference = 22.9%, $P=0.001$) [49].

### Antimicrobial Use

Both Rodríguez-Noriega et al. and Snyder et al. reported that prior carbapenem use was associated with significantly higher risk of NDM-1 *K. pneumoniae* infection as compared to controls (Rodríguez-Noriega et al., odds ratio [OR] 17.066, 95% CI 10.821–26.915, $P<0.001$; Snyder et al., OR 8.4, 95% CI 1.0–68.1, $P<0.05$) [47, 50]. Furthermore, prior antimicrobial use (any antimicrobial) was also associated with significantly higher risk of NDM-1 *K. pneumoniae* infection (OR 12.25, 95% CI 5.296–28.346; $P<0.001$) [47]. This highlights the importance of optimization of antimicrobial therapy; however, such optimization is challenging in cases of infections caused by MBL-producing bacteria [14]. Many antimicrobials such as fosfomycin, tetracyclines, and aminoglycosides display in vitro activity, but little clinical data are available to accurately define their place in treatment of MBL infections. Colistin, though effective in vitro against MBL-producing bacteria, shows low bactericidal activity and high toxicity [14, 43].

## TREATMENT RECOMMENDATIONS FOR MBL INFECTIONS

Treatment of MBL infections is challenging because of the availability of only few drugs or

drug combinations that can efficiently offset MBL-mediated resistance; this makes the treatment of MBL infections highly difficult [6, 13, 43].

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) has published guidelines in 2022 and the Infectious Disease Society of America (IDSA) published a guidance document in 2021, updated in 2023, for treatment of infections caused by various MBL-producing gram-negative bacteria [51, 52]. While the recommendations are specific for infections caused by MBL-producing CRE and difficult-to-treat *P. aeruginosa* (DTR-PA), those for carbapenem-resistant *A. baumannii* and *S. maltophilia* are not specific for MBL-producing pathogens. Treatment recommendations as per both guidelines are listed in Table 1.

## CURRENT TREATMENT OPTIONS FOR MBL INFECTIONS

Infections caused by MBL-producing pathogens are severe with increased mortality, length of hospital stay, and their treatment requires hospital-based IV therapy. Furthermore, only limited treatment options exist currently. The available treatment options along with their molecule class, date of approval, and mechanism of action are listed in Table 2. We further discuss each of the drugs along with their limitations.

### Aminoglycosides

Amikacin and plazomicin (approved in the USA only) are the aminoglycoside drugs used for treatment of MBL infections [51–54]. Both the IDSA and ESCMID recommend aminoglycoside monotherapy for treatment of urinary tract infections caused by CRE (IDSA—single dose for uncomplicated cystitis; ESCMID—cUTI) [51, 52]. Among the aminoglycosides, plazomicin has been shown to be most active in vitro against MBL-carrying Enterobacterales isolates, including those producing aminoglycoside-modifying enzymes (AME) [55–57].

Plazomicin does not protect against resistance mechanisms of changes in membrane permeability, increased expression of efflux pumps, or in the presence of ribosomal methyltransferase and hence has limited activity against *Pseudomonas* spp. and *Acinetobacter* spp. [58]. It is also not active against Enterobacterales that co-carry 16S ribosomal RNA methyltransferases and NDM [59]. Furthermore, high resistance among isolates carrying NDM-type MBLs to all aminoglycosides has been reported [60]. Aminoglycoside monotherapy is not recommended for systemic infections due to suboptimal attainment of PK/PD resulting in worse outcomes [61]. Treatment with aminoglycosides is associated with increased mortality and nephrotoxicity [62, 63]. On the basis of the evidence for increasing resistance and adverse events with aminoglycosides, treatment with plazomicin remains a concern.

### Co-administration of Aztreonam and Ceftazidime-Avibactam

The co-administration of aztreonam (ATM) with ceftazidime-avibactam (CAZ-AVI) was first suggested by Marshall et al. in 2017 as a potential treatment for MBL Enterobacterales [64]. ATM is a monobactam that is not hydrolyzed by MBLs. However, there is frequent co-production of MBLs with class A β-lactamases or AmpC-type determinants which are able to inactivate ATM. Avibactam is a non-β-lactam β-lactamase inhibitor that is active against class A β-lactamases, and some class D and class C β-lactamases. It is available in combination with ceftazidime. CAZ-AVI and ATM were used because of a lack of availability of a combination of ATM and AVI [15]. Interestingly, this co-administration is suggested as a preferred treatment option against MBL Enterobacterales by both IDSA and ESCMID [51, 52]. The combination of ATM + CAZ-AVI showed high in vitro activity against MBL Enterobacterales [15], and potential effectiveness for the treatment of infections by MBL Enterobacterales [45, 46, 65].

This co-administration of ATM + CAZ-AVI is not active against the majority of the MBL *P. aeruginosa* isolates [15]. The majority of the clinical evidence supporting this co-administration belongs to case reports and there are no

**Table 1** Treatment recommendations for MBL-producing pathogens as per IDSA and ESCMID guidelines

| | IDSA [52] | ESCMID [51] |
|---|---|---|
| CRE | ATM + CAZ-AVI or cefiderocol | ATM + CAZ-AVI or cefiderocol |
| | ATM + MEM-VAB or imipenem-cilastatin-relebactam[b] | |
| | Tigecycline or eravacycline[c] | Combination therapy with two of the following agents: polymyxin, aminoglycosides, or fosfomycin[e] |
| DTR-PA | Cefiderocol | Combination therapy with two of the following agents: polymyxin, aminoglycosides, or fosfomycin[f] |
| CRAB[a] | Combination therapy of high dose ampicillin-sulbactam with either tetracycline derivatives (minocycline or tigecycline) or polymyxin B or cefiderocol | Ampicillin-sulbactam |
| | | Polymyxin or high dose tigecycline[g] |
| | | Combination therapy with two of the following agents: polymyxin, aminoglycoside, tigecycline, sulbactam |
| *S. maltophilia*[a] | Combination therapy with two of the following agents: TMP-SMX, minocycline/tigecycline, cefiderocol, levofloxacin | NR |
| | ATM + CAZ-AVI[d] | |

*ATM* aztreonam, *CAZ-AVI* ceftazidime-avibactam, *CRE* carbapenem-resistant Enterobacterales, *CRAB* carbapenem-resistant *Acinetobacter baumaanii*, *DTR-PA* difficult-to-treat *Pseudomonas aeruginosa*, *MEM-VAB* meropenem-vaborbactam, *NR* no recommendation, *TMP-SMX* trimethoprim/sulfamethoxazole

[a]No specific recommendations for MBL-producing pathogens

[b]In cases where treatment with ATM + CAZ-AVI or cefiderocol is not possible and OXA-type carbapenemases are not present

[c]Not for infections of the bloodstream or urinary tract

[d]In cases of critical illness or intolerance or inactivity of other agents

[e]In case of severe infections that show in vitro susceptibility only to polymyxins, aminoglycosides, tigecycline, or fosfomycin or in case of non-availability of β-lactamase/β-lactamase inhibitors

[f]Clinical evidence on the management of infections caused by DTR-PA

[g]For infections caused by sulbactam-resistant CRAB

available clinical trial results for this co-administration [15]. There is also a lack of standardized approach for in vitro testing of this combination [52]. There is also a lack of ready-to-use commercially available tests for this ad hoc combination making in vitro testing time consuming and costly [66, 67]. Furthermore, there is no optimized dosing regimen determined for this co-administration [15, 65].

**Table 2** Current treatment options for MBL infections

| Molecules | Molecule class | Year of approval | Indication | Mechanism of action |
|---|---|---|---|---|
| Co-administration of ATM and CAZ-AVI | Co-administration β-lactam (ATM) and of cephalosporin + non-β-lactam β-lactamase inhibitor (CAZ-AVI) | No approval | NA | Aztreonam is not hydrolyzed by MBLs and avibactam (of CAZ-AVI) is a non-β-lactam β-lactamase inhibitor with activity against class A, class C, and some class D enzymes [15] |
| Cefiderocol | Combination of cephalosporin and siderophore | FDA: 14 November, 2019<br>EMA: 23 April, 2020 | FDA: Treatment of cUTI including pyelonephritis and HABP and VABP [154]<br>EMA: Treatment of infections due to aerobic gram-negative organisms in adults with limited treatment options [155] | Has a chlorocatechol group that utilizes the siderophore–iron complex pathway for outer membrane penetration of gram-negative bacteria and the cephalosporin inhibits cell wall synthesis [156] |
| Colistin | Polymyxin | 1950s<br>Updated dosage recommendation<br>FDA: 2015<br>EMA: 2014 | FDA: Treatment of acute or chronic infections due to sensitive strains of certain gram-negative bacilli [77]<br>EMA: Treatment of treatment of serious infections due to susceptible bacteria, in patients whose other treatment options are limited [77] | Acts on bacterial cell membrane by destabilizing the lipopolysaccharide component of the membrane [157] |
| Eravacycline | Fluorocycline | FDA: 28 August, 2018<br>EMA: 20 September, 2018 | Treatment of cIAI<br>Not to be used for treatment of cUTI [158, 159] | Acts by binding to bacterial ribosome and inhibiting protein synthesis [160] |

**Table 2** continued

| Molecules | Molecule class | Year of approval | Indication | Mechanism of action |
|---|---|---|---|---|
| Fosfomycin | Phosphonic acid | 1969 | FDA and EMA: treatment of uncomplicated UTI (cystitis) in susceptible strains of *Escherichia coli* and *Enterobacter faecalis* [161]<br>EMA: IV fosfomycin-approved for treatment of difficult-to-treat infections of abdomen, urinary tract, blood, respiratory, and skin and soft tissue infections [162] | Acts by inhibiting bacterial cell cycle [162] |
| Plazomicin | Aminoglycosides | FDA: 25 June, 2018<br>EMA: Authorization withdrawn [53] | Treatment of complicated urinary tract infections including pyelonephritis [54] | Acts by binding to 30S ribosome and inhibiting bacterial protein synthesis [163] |
| Tigecycline | Semi-synthetic glycylcycline derived from minocycline | FDA: 15 June, 2005<br>EMA: 24 April, 2006 | FDA: treatment of cSSTI, excluding diabetic foot infections, cIAI, and CAP, but not HABP [164]<br>EMA: for treatment of cSSTI and cIAI, excluding diabetic foot infections [165] | Acts by inhibiting the bacterial protein translation [166] |

**Table 2** continued

| Molecules | Molecule class | Year of approval | Indication | Mechanism of action |
|---|---|---|---|---|
| Aztreonam/avibactam | Fixed combination of aztreonam and avibactam | EC approval: 22 April, 2024 | EMA: for the treatment of adult patients with cIAI, HAP, including VAP, and cUTI, including pyelonephritis. It is also indicated for the treatment of infections due to aerobic gram-negative organisms in adult patients with limited treatment options | Aztreonam acts by inhibiting penicillin-binding proteins [64]. Aztreonam is not hydrolyzed by MBLs and avibactam is a non-β-lactam β-lactamase inhibitor with activity against class A, class C, and some class D enzymes [15] |

*ATM* aztreonam, *CAP* community-acquired pneumonia, *CAZ-AVI* ceftazidime-avibactam, *cUTI* complicated urinary tract infections, *cSSTI* complicated skin and skin structure infections, *cIAI* complicated intra-abdominal infections, *EMA* European medicines agency, *FDA* Food and Drug Administration, *HABP* hospital-acquired bacterial pneumonia, *VABP* ventilator-associated bacterial pneumonia, *EC* European Commission

### Cefiderocol

Cefiderocol is recommended as an alternative option for the treatment of MBL-Enterobacterales by both IDSA and ESCMID and against MBL *P. aeruginosa* as per IDSA guidelines [51, 52]. Cefiderocol has been shown to have in vitro activity against carbapenemase-producing *P. aeruginosa*, and *S. maltophilia* [33, 68]. In the pivotal clinical trials, APEKS-NP6 (non-inferiority trial for the treatment of nosocomial pneumonia caused by GNB) and CREDIBLE-CR (assessing safety and efficacy of cefiderocol against best available therapy against CR-GNB), cefiderocol was shown to have a numerically higher clinical cure rate (cefiderocol vs. comparators, 17/24 vs. 4/10), microbiological eradication (14/24 vs. 3/10), and a lower 28-day all-cause mortality (3/24 vs. 5/10) against MBL-producing GNB [69–71].

However, in the CREDIBLE-CR trial, there were higher numbers of deaths reported in the cefiderocol group for *Acinetobacter* spp. infections [70]. There have been multiple reports of NDM-mediated resistance to cefiderocol among *A. baumannii* and Enterobacterales [33, 72, 73]. A meta-analysis by Karakonstantis et al. reported that among NDM-producers, the cefiderocol nonsusceptible rates for Enterobacterales and *A. baumannii* were 38.8% (95% CI 22.6–58.0%, EUCAST) and 44.7% (95% CI 34.5–55.4%, EUCAST), respectively [74]. There are issues with accuracy, reproducibility, and susceptibility interpretation of isolates under area of uncertainty by EUCAST [75], as well as cefiderocol testing by disk diffusion and broth microdilution per CLSI [76]. Cefiderocol could be considered as a good treatment option against MBL *P. aeruginosa*.

### Colistin

Colistin has been available for clinical use since the 1950s. Later, its use was stopped because of adverse events, especially nephrotoxicity [77]. However, it came back into clinical use in the 1990s and has been widely used as a salvage therapy for treating infections, particularly

those caused by multidrug-resistant (MDR) and extensively drug-resistant (XDR) GNB [78]. Furthermore, the EMA in 2014 and the FDA in 2015 updated the dosage and administration of colistin based on a review of its safety and effectiveness [77]. Colistin shows high in vitro activity against MBL-carrying isolates [79, 80]. The ESCMID guidelines recommend colistin for treatment of CRE or carbapenem-resistant *A. baumannii* (CRAB) in case the infection-causing isolates show in vitro susceptibility only to colistin. Furthermore, the guidelines recommend colistin-based combination therapies only for treatment of CR *P. aeruginosa* [51]. Combination therapies of colistin with aminoglycosides, carbapenems, CAZ-AVI, and tigecycline have shown clinical efficacy in the treatment of carbapenem-resistant *A. baumannii* and *P. aeruginosa* [81, 82]. While there is clinical evidence to suggest that combination therapy with colistin is better than monotherapy, there are other reports that suggest that there is no difference in outcomes [83, 84].

Interestingly, the IDSA guidance does not recommend colistin for treatment of infections caused by CRE [52]. Colistin has a narrow therapeutic margin, and higher amounts are associated with increased mortality and nephrotoxicity [51, 52, 85]. Furthermore, there are concerns about the accuracy of colistin susceptibility testing and hence there are no susceptible breakpoints for colistin by CLSI [52]. While colistin is overall active against MBL infections, it is the last choice for treatment because of associated toxicity and adverse events.

### Tigecycline

Tigecycline shows high in vitro activity against MBL-carrying isolates, especially Enterobacterales [86–88]. The IDSA guidance recommends tigecycline as an alternative for treatment of CRE infections caused by MBL-producing pathogens, except in BSI and cUTI, and the ESCMID guidelines recommend high dose tigecycline for treatment of CR-*A. baumannii* resistant to sulbactam [51, 52]. High dose tigecycline and combination therapies of tigecycline with colistin, sulbactam, and carbapenems are effective in treatment of a variety of infections including HAP, BSI, and those caused by CRE [81, 89–92].

Some studies have suggested that treatment with tigecycline is associated with increased clinical and microbiological failure, septic shock, and increased risk of mortality compared to other regimens [93, 94]. Although tigecycline is active against MBLs, and is a potential treatment option, lack of clinical evidence against MBL infections, the associated adverse events, and risk of mortality make it a last resort antibiotic.

### Eravacycline

Eravacycline shows potent in vitro activity against MBL-carrying isolates, especially NDM-positive Enterobacterales [88, 95]. The ESCMID guidelines recommend eravacycline as one of the treatment options for infections caused by MBL Enterobacterales, while the IDSA recommends eravacycline as an alternative option for treatment of CRE infections other than bloodstream and urinary tract [51, 52].

The pivotal clinical trials evaluating the efficacy of eravacycline had limited numbers of patients with CRE, and no patients with MBL infections were included [96, 97]. Furthermore, eravacycline is not recommended for treatment of bloodstream infections or cUTI caused by NDM Enterobacterales because of its limited concentration in serum and urine following administration. Moreover, it is recommended for treatment of CRAB only when other tetracycline drugs are not active or well tolerated [52]. Eravacycline has limited clinical evidence against MBL infections, and more studies are needed to assess its clinical efficacy.

### Fosfomycin

Fosfomycin has been shown to be active in vitro against MBL isolates [98, 99]. Furthermore, in vitro, fosfomycin shows synergy with a variety of antimicrobial classes [100] against Enterobacterales [101–105], *P. aeruginosa* [104, 106, 107], and *Acinetobacter* spp. [101, 108]. Interestingly, both IDSA and ESCMID guidelines recommend fosfomycin-based combination therapies

for treatment of CRE infections [51, 52]. Combination therapies of fosfomycin with carbapenems (doripenem, meropenem, imipenem) and cefiderocol have shown improved cure and survival rate against CR-and MBL-*P. aeruginosa*, CR-*A. baumannii*, and CR-*K. pneumoniae* infections [109–112].

Fosfomycin shows low-to-very low activity against MDR *P. aeruginosa* and MDR *A. baumannii* [113]. The frequency of acquired mutations conferring resistance to fosfomycin is high among *P. aeruginosa* and *Klebsiella* spp. [113]. Furthermore, fosfomycin resistance has been increasing with increase in β-lactam resistance [113]. Additionally, the *fos*A gene which produces the FosA enzyme that inactivates fosfomycin is widely distributed among gram-negative bacteria especially among *Klebsiella* spp., *P. aeruginosa*, and *Enterobacter* spp. [114]. Fosfomycin is effective for treatment of MBL infections in combination therapy. However, its use is restricted by lack of standardized combination regimens and emergence of resistance.

### Aztreonam-Avibactam

Aztreonam-avibactam (ATM-AVI) has been recently approved in Europe for the treatment of adult patients with complicated intra-abdominal infections (cIAI), hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP), and complicated urinary tract infections (cUTI), including pyelonephritis and also for the treatment of infections due to aerobic gram-negative organisms in adult patients with limited treatment options [115, 116]. ATM-AVI shows high in vitro activity against MBL-producing Entrobacterales and *S. maltophilia* [15, 80]. An in vitro study assessing the activity of ATM-AVI against CRE isolates from Asia, Europe, and Latin America collected in 2019–21 reported that ATM-AVI inhibited 99.6% ($MIC_{90}$ 0.5 mg/L) of the CRE isolates and 100% ($MIC_{90}$ 0.5 mg/L) of the MBL-producing ones [80]. However, reduced susceptibility of *E. coli* to ATM-AVI due to a combination PBP3 modification by insertion of amino acid sequences, and presence of CMY β-lactamases has been reported [117]. Clinically, the pharmacokinetics and safety profile of ATM-AVI was characterized in a phase 2a study which leveraged existing data on the two molecules from a phase 1 study and supported the clinical development of the phase 3 program by optimizing the dosing regimen for the phase 3 study [118, 119]. The study showed attainment of PK/PD targets and a favorable benefit–risk ratio for ATM-AVI [118]. The recommended daily dose for ATM-AVI was a 30-min infusion with 500/167 mg (ATM/AVI) as loading dose and maintenance dose with 3-h infusions of 1500/500 mg (ATM/AVI) every 6 h. The ATM-AVI dosing had advantages of more frequent dosing and longer infusion times leading to a higher daily dose of AVI as compared to the ATM + CAZ-AVI dosing (2-h infusion of CAZ/AVI, 2000/500 mg every 8 h with ATM, 2000 mg every 6 h) [118, 120]. Results of a phase 3 trial, the REVISIT study, assessing ATM-AVI ± metronidazole in comparison to meropenem ± colistin in patients with cIAI and HAP/VAP caused or suspected to be caused by Gram-negative bacteria showed that ATM-AVI ± metronidazole was effective in treating patients and displayed similar efficacy to meropenem ± colistin (ATM-AVI ± metronidazole vs. meropenem ± colistin; clinical response at test of cure in the intention-to-treat analysis set, 68.4% vs. 65.7%) [121–123]. Another phase 3 trial, the ASSEMBLE study, showed that the clinical cure at test of cure in patients with MBL-producing gram-negative bacteria was 41.7% (5/12) in those receiving ATM-AVI vs. 0% (0/3) in those receiving best available therapy [121]. The in vitro evidence, and the initial results of the clinical trials along with the established safety profiles of ATM alone, and AVI in combination with CAZ suggest that ATM-AVI has the potential to respond to the important unmet treatment need in MDR gram-negative organisms including MBL-producing Enterobacterales.

## AGENTS IN THE PIPELINE

The current treatment options for MBL infections are limited and no MBL-specific β-lactamase inhibitors are currently available. On the basis of the increasing prevalence

and clinical need for effective and targeted treatment options for MBL infections, newer agents are under development. The agents currently under development are combinations of β-lactam antibiotics with β-lactamase inhibitors having direct activity against MBLs such as boronate derivatives (xeruborbactam) and those that do not have direct activity against MBLs such as zidebactam and nacubactam. The completed and ongoing phase 2 and phase 3 clinical trials of the agents under development are listed in Table 3.

### Cefepime-Taniborbactam

Cefepime is broad-spectrum fourth-generation cephalosporin and taniborbactam is a pan-spectrum β-lactamase inhibitor with activity against all Ambler classes of β-lactamase enzymes [124, 125]. Cefepime-taniborbactam shows potent in vitro activity against MBL-carrying Enterobacterales and *P. aeruginosa* isolates, especially those carrying VIM [126–129]. A global evaluation of antimicrobial resistance via surveillance study assessing the in vitro activity of cefepime-taniborbactam against Enterobacterales and *P. aeruginosa* isolates reported a susceptibility of 86.4% for MBL-positive Enterobacterales, 84.6% for NDM-positive Enterobacterals with an $MIC_{90}$ > 16 µg/mL, and 100% for VIM-positive Enterobacterales with an $MIC_{90}$ 8 µg/mL. The VIM-positive *P. aeruginosa* had a susceptibility of 87.4% ($MIC_{90}$ 32 µg/mL) to cefepime-taniborbactam [127]. However, cefepime-taniborbactam is not active against isolates carrying NDM-9, NDM-30, NDM-*A. baumannii* isolates, VIM-83, and isolates carrying IMP-type MBLs [127, 129–131]. Furthermore, cefipime-taniborbactam also has limited activity against NDM-producing Enterobacterales, and *P. aeruginosa*, especially those from India because of the presence of mutations in PBP3 or efflux-related genes [127, 132]. The safety of the drug has been demonstrated in a phase 1 study [133]. A phase 3 trial assessing efficacy and safety of cefepime-taniborbactam compared to meropenem for the treatment of adults with cUTI with cefepime-taniborbactam showed superiority to meropenem in microbiological and clinical success (treatment difference, 12.6 percentage points; 95% confidence interval, 3.1 to 22.2; $P = 0.009$) [134].

Cefepime-taniborbactam could be a potential drug with activities against VIM-producing Enterobacterales and *P. aeruginosa* and some NDM-producing Enterobacterales.

### Meropenem-Xeruborbactam

Xeruborbactam is a cyclic boronate β-lactamase inhibitor which is active against serine β-lactamases and MBLs and mediates its activity by binding to PBP and inducing changes in cellular morphology [135]. Meropenem-xeruborbactam has been shown to be active in vitro against MBL-producing *A. baumannii*, Enterobacterales, and *P. aeruginosa* [136–138].

The in vitro activity of meropenem-xeruborbactam against MBL-producing pathogens suggests it could be a potential treatment option. However, further in vitro and clinical studies are needed.

### Cefepime-Zidebactam

Cefepime-zidebactam is a β-lactam/β-lactam "enhancer" combination that is currently under phase 3 trials for treatment of cUTI infections [139, 140]. Several studies have reported that cefepime-zidebactam is active in vitro against MBL Enterobacterales and *P. aeruginosa* [139, 141–144]. Clinically, the safety and tolerability of cefepime-zidebactam have been demonstrated in healthy subjects [145]. A case report described the successful treatment of intra-abdominal infection in an adult caused by NDM-producing *P. aeruginosa* after unsuccessful treatment with polymyxin B and tigecycline [146].

### Nacubactam

Nacubactam is a β-lactamase inhibitor that acts by inhibiting serine β-lactamases and also penicillin binding protein 2 [147]. It acts synergistically when combined other β-lactams to

**Table 3** Completed and ongoing clinical trials for agents in the pipeline against MBLs

| Molecule | Class | Study type | Phase | Population | Indication | Comparator | Clinical trial identifier | Status |
|---|---|---|---|---|---|---|---|---|
| Cefepime-taniborbactam | β-lactam + β-lactamase inhibitor | Safety and efficacy | 3 | Adult | Complicated urinary tract infections | Meropenem | NCT03840148 | Completed |
| Cefepime-zidebactam | β-lactam + β-lactam "enhancer" | Non-inferiority study to evaluate the efficacy, safety, and tolerability | 3 | Adult | Complicated urinary tract infection or acute pyelonephritis | Meropenem | NCT04979806 | Ongoing |
| Cefepime-nacubactam/aztreonam-nacubactam | β-lactam + β-lactamase inhibitor | Safety and efficacy | 3 | Adult | Infection due to carbapenem-resistant Enterobacterales | Best available therapy | NCT05905055 | Ongoing |
| | | Safety and efficacy | 3 | Adult | Complicated urinary tract infection or uncomplicated pyelonephritis | Imipenem/cilastatin | NCT05887908 | Ongoing |

enhance their activity and thus has the ability to target multiple penicillin binding proteins [148]. Nacubactam combinations with aztreonam, cefepime, and meropenem have been shown to be active in vitro against MBL Enterobacterales and *P. aeruginosa* [149, 150]. The safety profile of meropenem-naucbactam has been demonstrated in healthy adults [147].

Nacubactam combinations are promising, with activities against MBL Enterobacterales and *P. aeruginosa*. Two phase 3 trials evaluating the safety and efficacy of cefepime and aztreonam combinations with nacubactam for treatment of CRE and cUTI or acute uncomplicated pyelonephritis are ongoing [151, 152].

## DISCUSSION AND CONCLUSION

MBL infections are emerging as a global public health threat with increase in prevalence and spread in all the regions, including non-endemic areas. Infections caused by MBL-producing pathogens have a severe clinical impact with more ICU admissions, increased length of hospital stay, and increased mortality [44, 45, 47–50]. Treatment of MBL infections is challenging with no single drug that works against all MBL infections, and the appropriate treatment durations not well established [153]. Furthermore, the optimal treatment for MBL infections not only depends on the pathogen but also on the underlying resistance mechanisms. Current treatment options such as ATM + CAZ-AVI and cefiderocol show activity against some MBL-producing species. However, they are limited by resistant genotypes within some species, lack of standardized dosing and difficulties in testing susceptibilities, lack of clinical trials in MBLs, and development of additional resistance mechanisms. The rising concern of MBLs along with limited treatment options has led to the need and development of drugs that are specifically targeted towards MBLs. There are some promising drugs, including ATM-AVI, now approved, and cefepime-taniborbactam in development, which demonstrate high in vitro activity against MBL isolates. However, more in vivo studies and clinical efficacy and safety data are needed to establish their place in the treatment of MBL infections. The increasing spread and constantly evolving resistance patterns of MBLs requires constant monitoring and careful use of drugs because of the increase in risk of MBLs with overuse of drugs [47, 50]. Stewardship measures driven by rapid diagnostics along with appropriate assessment of clinical signs and symptoms, history of antibiotic use, and knowledge of local epidemiology should be used for optimal management of MBL infections.

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### *Declarations*

***Conflict of Interest.*** Nathalie Baillon-Plot is an employee of Pfizer and holds stock/stock options. Francis F Arhin is a former employee of Pfizer and holds stock/stock options. Beatrice Grabein has consulted for or received speaker fees from Advanz Pharma, Gilead, Infectopharm,

MSD, Mundipharma, Pfizer and Shionogi. Luke S P Moore has consulted for or received speaker fees from bioMerieux, Eumedica, Pfizer, Sumitovant, Shionogi, Qiagen, and Gilead, and receives academic support from the National Institute of Health Research (NIHR) CW+Charity, North West London Pathology, LifeArc, Shionogi, and the Healthcare Infection Society. George L Daikos and V Balaji have no conflicts of interest to declare.

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