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REVIEW

Therapeutic Options for Metallo-β-Lactamase-Producing Enterobacterales

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Xing Tan[1]
Hwan Seung Kim[1]
Kimberly Baugh[2]
Yanqin Huang[1]
Neeraja Kadiyala[1]
Marisol Wences[1]
Nidhi Singh[1]
Eric Wenzler[1]
Zackery P Bulman[1]

[1]Department of Pharmacy Practice, University of Illinois at Chicago College of Pharmacy, Chicago, IL, USA; [2]Franciscan Health Hammond/Dyer, Hammond, IN, USA

Abstract: The spread of metallo-β-lactamase (MBL)-producing Enterobacterales worldwide without the simultaneous increase in active antibiotics makes these organisms an urgent public health threat. This review summarizes recent advancements in diagnostic and treatment strategies for infections caused by MBL-producing Enterobacterales. Adequate treatment of patients infected with MBL-producing Enterobacterales relies on detection of the β-lactamase in the clinic. There are several molecular platforms that are currently available to identify clinically relevant MBLs as well as other important serine-β-lactamases. Once detected, there are several antibiotics that have historically been used for the treatment of MBL-producing Enterobacterales. Antimicrobials such as aminoglycosides, tetracyclines, fosfomycin, and polymyxins often show promising in vitro activity though clinical data are currently lacking to support their widespread use. Ceftazidime-avibactam combined with aztreonam is promising for treatment of infections caused by MBL-producing Enterobacterales and currently has the most clinical data of any available antibiotic to support its use. While cefiderocol has displayed promising activity against MBL-producing Enterobacterales in vitro and in preliminary clinical studies, further clinical studies will better shed light on its place in treatment. Lastly, there are several promising MBL inhibitors in the pipeline, which may further improve the treatment of MBL-producing Enterobacterales.

Keywords: metallo-β-lactamase, Enterobacterales, carbapenemase, ceftazidime-avibactam, aztreonam, rapid diagnostics

Introduction

β-Lactams have been widely used in the treatment of bacterial infections since the 1940s, accounting for more than half of all parenterally administered antibiotic prescriptions in the United States.[1] β-Lactam antibiotics are efficacious and have been shown to be superior to other antibiotic classes for a variety of infections including those caused by carbapenem-resistant Enterobacterales (CRE) and methicillin susceptible *Staphylococcus aureus* (MSSA).[2–4] They also display favorable safety profiles.[2,4] However, the reliance on β-lactams in the clinical setting has driven bacteria to develop resistance. From the first identification of penicillin resistance in 1940, bacteria in the clinical setting have continued to acquire mechanisms to overcome the wide range of β-lactam antibiotics.[5] β-Lactam resistance can be caused by expression of efflux pumps, mutations in the PBP enzymes, alterations to membrane permeability, or through the production of β-lactamase enzymes, which is the most prevalent mechanism of β-lactam resistance in Enterobacterales. Bacteria can either intrinsically harbor a gene on the chromosome that encodes a β-lactamase or they can gain the ability to produce β-lactamases

Correspondence: Zackery P Bulman
Department of Pharmacy Practice, College of Pharmacy, University of Illinois at Chicago, 833 South Wood Street, Room 164 (M/C 886), Chicago, IL 60612, USA
Tel +1 312-996-1415
Fax +1 312-413-1797
Email bulman@uic.edu

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through the acquisition of genes on plasmids. The β-lactamases that are produced from these genes are most commonly categorized into Ambler class A, B, C, and D, based on amino acid sequence similarity.[6]

An especially troubling group of β-lactamases are carbapenemases, which confer resistance to nearly all of the β-lactams, including the penicillins, cephalosporins, and carbapenems.[7] Carbapenems are a critically important class of β-lactams often reserved as a last-line treatment option for infections that are resistant to more narrow spectrum β-lactams. Carbapenemases are categorized as either a metallo-β-lactamase (MBL) in Ambler class B or a serine β-lactamase in one of the functional subgroups of classes A or D.[6] Class A and D β-lactamases each utilize serine whereas Class B MBL enzymes utilize a Zn^{2+} metal cofactor in their active site to catalyze the inactivation of β-lactams. β-lactamase enzyme classification has been thoroughly discussed previously.[8] Class B β-lactamases are metallo-β-lactamases (MBLs), which have spread globally within Enterobacterales, and can inactivate virtually all clinically used bicyclic β-lactams and serine β-lactamase-inhibiting drugs such as sulbactam, tazobactam, clavulanic acid, and avibactam.[2] These class B β-lactamases are further divided into Ambler subclasses with the most clinically important in Enterobacterales being subclass B1. Subclass B1 falls under the functional β-lactamase group 3a since these enzymes can be inhibited in vitro by EDTA and produce broad spectrum hydrolysis against penicillins, cephalosporins, and carbapenems but not monobactams.[8] Class B1 enzymes include Verona integron-encoded MBLs (VIM), imipenemases (IMP), and New Delhi MBLs (NDM).

Detection of bacterial isolates that harbor MBL genes is increasing globally at an alarming speed, in part due to an increased use of carbapenems clinically.[9] Continued spread of MBLs may have dire consequences to patients since the clinically relevant variants of MBLs possess a broad β-lactam substrate profile and the isolates often simultaneously harbor other antibiotic resistance genes.[10,11] There is substantial geographic variability in the prevalence of MBL enzymes among CRE. For example, in some portions of Southeast Asia, MBLs are the most common carbapenemase detected whereas in other regions of the world where serine carbapenemases are more common, MBLs are only a minor cause of carbapenem resistance.[12,13] In the United States, MBL enzymes account for <5% of detected carbapenemases.[14] IMP enzymes, originally identified in Japan in 1990, were the first MBL identified and remain an important cause of carbapenem resistance in Enterobacterales across Japan and Southeast Asia.[15,16] VIM MBL enzymes were first detected in *P. aeruginosa* isolates in Europe in the mid 1990s and have remained predominant in southern Europe.[17,18] NDM enzymes were the most recently discovered of the B1 MBLs and were first identified in a *K. pneumoniae* isolate from India in 2006.[10,19] Although NDM enzymes were initially confined to the Indian subcontinent, they have since disseminated globally in fewer than 5 years and become a prevalent MBL.[10,20] The rapid spread of bla_{NDM} may in part be due to the limited fitness cost conferred by this enzyme to its bacterial hosts.[21,22] Among MBL enzymes NDM is the most common in Enterobacterales; a study conducted using isolates from 40 countries between 2012 and 2014 revealed that 44.2% of all MBL-producing Enterobacterales possessed bla_{NDM}, 39.3% harbored bla_{VIM}, and 16.5% contained bla_{IMP}.[11] *K.* pneumoniae, followed by *E. coli*, are the most common hosts of bla_{NDM} across global surveillance studies.[23] All three B1 β-lactamases, IMP, VIM, and NDM, have now spread worldwide with multitudes of clinical variants and represent an urgent health threat.

Factors that put patients at risk for becoming infected with MBL-producing Enterobacterales are largely the same as the risk factors for infections caused by other carbapenem-resistant Gram-negative bacteria. These risk factors often include prior antibiotic use, presence of indwelling catheters, healthcare exposure, or comorbidities.[13,24] One study comparing patients infected with MBL-producing Enterobacterales versus those infected with other multidrug-resistant isolates found that prior carbapenem use and central venous catheterization were strongest predictors of MBL infections.[25] Once infected, these patients are at considerable risk of mortality. Two studies conducted in patients with bloodstream infections in Athens, Greece found that 23.9–32.1% of patients died within 14 days following infection with VIM-producing *K. pneumoniae*.[26,27] Another study conducted in a hospital in Southern India looked at 101 patients with bloodstream infections caused by NDM-producing Enterobacterales and found a mortality rate of 33.7%.[25] de Jager et al examined just hospital-associated infections (detected >48 hours after admission) caused by NDM-producers in an ICU in South Africa and observed mortality rates of 55.3%.[28] More recently, a study conducted in Italy and Greece included 102 patients with

bloodstream infections caused by NDM- or VIM-producing Enterobacterales and found an overall mortality rate of 31.4%.[29] Importantly though, the authors found that there was a significant difference in mortality rates based on the antimicrobial regimen administered suggesting that optimizing antimicrobial therapy is a top priority for infections caused by MBL-producing Enterobacterales.

Detection of MBLs Using Rapid Diagnostic Tests

Rapid diagnostics involving organism identification and genotypic resistance mechanism detection have been shown to decrease mortality among Gram-negative blood stream infections with the coordinated efforts of an antimicrobial stewardship team.[30] Since antibiotic recommendations vary substantially based on the cause of carbapenem resistance in Enterobacterales (ie, serine carbapenemases vs MBLs) and traditional phenotypic susceptibility testing cannot determine the underlying mechanism, it is critical to rapidly detect MBL-producing Enterobacterales as the pathogen causing infection. Fortunately, there are several FDA-approved molecular and biochemical rapid diagnostic methods in the market that can detect MBL-producing organisms (Table 1). Of the molecular assays, there are several platforms that identify multiple bacterial species and their resistance mechanisms including Nanosphere Verigene BC-GN, Biofire BCID2 Panel, GenMark Diagnostics ePlex BCID-GN, Biofire FilmArray Pneumonia Panel, and Unyvero Lower Respiratory Tract (LRT) Application.[31–36] These allow for direct sampling from a positive blood culture bottle or respiratory sample, detection of polymicrobial infections, and resistance marker detection. Conversely, there are several molecular assays approved for the detection of various carbapenemase enzymes from rectal swab samples or from a pure colony that are only intended for infection control purposes rather than for guidance of treatment (Cepheid Xpert Carba-R, BD MAX Check-Points CPO, GenePOC Carba).[37–39] There are also biochemical assays that detect the presence of carbapenemases including the NG-Test CARBA 5 and Rapidec Carba NP tests.[40,41] However, these are only intended for infection control purposes. The NG-Test CARBA 5 test is able to distinguish between the type of carbapenemase enzyme while the Rapidec Carba NP test qualitatively indicates hydrolysis of imipenem but the type of resistance mechanism is not characterized. Similar to the Rapidec Carba NP assay, the MBT STAR-Carba IVD Kit is a MALDI-TOF-MS-based assay that detects carbapenem hydrolysis products but cannot distinguish between the type of carbapenemase enzyme.[42] Lastly, the Accelerate PhenoTest BC Kit allows for rapid susceptibility testing through morphokinetic cellular analysis; however, no resistant determinant identification is performed.[43]

Despite the strengths of available technologies, results from these rapid diagnostic tests come with several caveats. Each test has specific organisms or target resistance genes it is testing for, and therefore a negative result does not rule out the presence of bacteria or definitively indicate carbapenem susceptibility. Further, a positive result indicating presence of a resistance gene such as an MBL does not always indicate carbapenem resistance, as the level of conferred resistance will depend on the expression level of the gene and other non-carbapenemase related factors such as the function of the outer membrane porin channels. However, in the case a rapid diagnostic test detects the presence of an MBL it is prudent to assume carbapenem resistance and select therapy accordingly. Rapidly identifying MBL-producing Enterobacterales as the cause of infection will guide selection of appropriate antibiotic therapy and may improve patient outcomes.

Treatment

MBL-producing Enterobacterales is becoming a more prevalent cause of infection globally over the last decade; however, limited treatment options exist. Herein we review the current and pipeline treatment options and available supporting data.

Aztreonam/Avibactam

MBLs can hydrolyze all beta-lactams, except for the monobactam aztreonam (ATM). However, due to the frequent co-production of serine β-lactamases within MBL-producing Enterobacterales, which can hydrolyze aztreonam, aztreonam only remains active against about 30% of these isolates.[44] Thus, a combination between ATM and a β-lactam/β-lactamase inhibitor such as ceftazidime-avibactam (CAZ-AVI) has become an attractive combination with synergistic in vitro activity, even against pathogens co-producing metallo- and serine β-lactamases.[45–50] This in vitro synergy has also been observed against NDM producing *K. pneumoniae* in the murine neutropenic thigh infection model.[46] Avibactam's spectrum of activity includes Class A, C, and some D β-lactamases, including clinically important

Table 1 Rapid Diagnostic Tests Relevant to MBL-Producing Enterobacterales

Test	Technology	Enterobacterales Detected?	Resistance Determinant Genes Detected[a]	Specimen Type	FDA Approved	Ref.
Molecular Assays						
Verigene BC-GN	Multiplex PCR and Hybridization	Yes[b]	***bla*$_{NDM}$, *bla*$_{VIM}$, *bla*$_{IMP}$** *bla*$_{CTX-M}$, *bla*$_{KPC}$, *bla*$_{OXA-48}$, *bla*$_{OXA-23}$, *bla*$_{OXA-40}$, *bla*$_{OXA-58}$	Positive blood culture	Yes	31
Biofire BCID2 Panel	Multiplex PCR	Yes[c]	***bla*$_{NDM}$, *bla*$_{VIM}$, *bla*$_{IMP}$** *bla*$_{KPC}$, *bla*$_{OXA-48-like}$	Positive blood culture	Yes	32
GenMark Diagnostics ePlex BCID-GN	Multiplex PCR	Yes[d]	***bla*$_{NDM}$, *bla*$_{VIM}$, *bla*$_{IMP}$** *bla*$_{CTX-M}$, *bla*$_{KPC}$, *bla*$_{OXA-23}$, *bla*$_{OXA-48}$	Positive blood culture	Yes	36
Biofire FilmArray Pneumonia Panel	Multiplex PCR	Yes[e]	***bla*$_{NDM}$, *bla*$_{VIM}$, *bla*$_{IMP}$** *bla*$_{KPC}$, *bla*$_{OXA-48-like}$	BAL, sputum	Yes	33
Unyvero LRT Application[f]	Multiplex PCR	Yes[g]	***bla*$_{NDM}$, *bla*$_{VIM}$, *bla*$_{IMP}$** *bla*$_{CTX-M}$, *bla*$_{KPC}$, *bla*$_{TEM}$, *bla*$_{OXA-48}$, *bla*$_{OXA-23}$, *bla*$_{OXA-24}$, *bla*$_{OXA-58}$	Endotracheal aspirate, BAL	Yes	34,35
Cepheid Xpert Carba-R	Qualitative PCR	No	***bla*$_{NDM}$, *bla*$_{VIM}$, *bla*$_{IMP}$** *bla*$_{KPC}$, *bla*$_{OXA-48}$	Rectal swabs[h], pure colony	Yes	37
BD MAX Check-Points CPO	Qualitative PCR	No	***bla*$_{NDM}$, *bla*$_{VIM}$/*bla*$_{IMP}$** *bla*$_{KPC}$, *bla*$_{OXA-48}$	Rectal swabs[h]	Yes	38
GenePOC Carba	Qualitative PCR	No	***bla*$_{NDM}$, *bla*$_{VIM}$, *bla*$_{IMP}$** *bla*$_{KPC}$, *bla*$_{OXA-48-like}$	Pure colony	Yes	39
Biochemical Assays						
NG-Test CARBA 5	Qualitative multiplex immunochromatographic assay	No	***bla*$_{NDM}$, *bla*$_{VIM}$, *bla*$_{IMP}$** *bla*$_{KPC}$, *bla*$_{OXA-48-like}$	Pure colony[h]	Yes	40
Rapidec Carba NP	Colorimetric test	No	None, detects hydrolysis of imipenem	Pure colony[h]	Yes	41
Other						
MBT STAR-Carba IVD Kit	MALDI-TOF MS	No	None, detects carbapenem hydrolysis product	Pure colony	No	42
Accelerate PhenoTest BC Kit	Morphokinetic cellular analysis	Yes[i]	None, tests susceptibilities to meropenem (among other antibiotics)	Positive blood culture	Yes	43

Notes: [a]MBL genes bolded. [b]*Enterobacter* spp., *Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Citrobacter* spp., *Proteus* spp. [c]*Enterobacter cloacae* complex, *Escherichia coli, Klebsiella aerogenes, Klebsiella oxytoca, Klebsiella pneumoniae* group, *Proteus spp., Salmonella, Serratia marcescens*. [d]*Citrobacter, Cronobacter sakazakii, Enterobacter cloacae complex, Enterobacter (noncloacae complex), Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae group, Morganella morganii, Proteus, Proteus mirabilis, Salmonella, Serratia, Serratia marcescens*.[e]*Enterobacter cloacae* complex, *Escherichia coli, Klebsiella aerogenes, Klebsiella oxytoca, Klebsiella pneumoniae* group, *Proteus spp., Serratia marcescens*. [f]Other panels in development that allow direct sample testing from urine (Urinary Tract Infection [UTI] Cartridge), blood culture (Blood culture [BCU] Cartridge), sputum, bronchoalveolar lavage, tracheal aspirates (Hospitalized Pneumonia [HPN] cartridge), sonication fluids, swabs, tissue, pus, aspirate/exudate, bone fragments (Implant & Tissue Infection [ITI] cartridge), ascites and peritoneal fluid, pancreatic juice, bile, tissue, puncture fluid, swabs, catheter/drainage tips, and samples from positive blood culture bottles that have been inoculated with ascites/puncture fluid (Intra-Abdominal Infection [IAI] cartridge). [g]*Enterobacter cloacae* complex, *Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Klebsiella variicola, Citrobacter freundii, Morganella morganii, Proteus spp., Serratia marcescens*. [h]Intended for infection control use. [i]*Enterobacter* spp. (ie, *Enterobacter cloacae, Enterobacter aerogenes*, not differentiated), *Klebsiella* spp. (ie, *Klebsiella pneumoniae, Klebsiella oxytoca*, not differentiated), *Escherichia coli, Proteus* spp. (ie, *Proteus mirabilis, Proteus vulgaris*, not differentiated), Citrobacter spp. (ie, *Citrobacter freundii, Citrobacter koseri*, not differentiated), *Serratia marcescens*.

Abbreviations: PCR, polymerase chain reaction; BAL, bronchoalveolar lavage; MALDI-TOF MS, matrix-assisted laser desorption ionization-time of flight mass spectrometry.

enzymes CTX-M, KPC-2, AmpC, and OXA-48.[51] Ceftazidime cannot be hydrolyzed by OXA-48-like carbapenemases.[52] Other β-lactamase inhibitors such as vaborbactam and relebactam could also be useful in combination with aztreonam given their increased activity against class A serine β-lactamases (ie, KPC-3) compared to avibactam.[53,54] However, avibactam offers broader spectrum of activity inhibiting class D serine β-lactamases (eg, OXA-48) while vaborbactam and relebactam do not.[53,55,56] Further, clinical data against MBL-producing Enterobacterales are only available for ATM and CAZ-AVI, thus this combination will be the focus of this review.

The promising synergy of CAZ-AVI plus ATM against MBL-producing pathogens demonstrated in numerous studies has led to the clinical use of this combination regimen. The current available clinical data are limited to observational studies including various case reports and one prospective study to support its efficacy.[29,49,57–61] In the lone prospective observational study, Falcone et al compared outcomes for 102 patients with bloodstream infections caused by MBL-producing Enterobacterales receiving either CAZ-AVI plus ATM or another active antibiotic. The most common causative organism was *K. pneumoniae* (91.2%) and only NDM (80.4%) and VIM (19.6%) were detected among all patients enrolled in the study. The study found that the 30-day mortality rate was lower in the CAZ-AVI plus ATM group compared to the other active antibiotics group (19.2% [n=52] vs 44% [n=50]; p=0.007). A majority of patients in the best available therapy group received a colistin-containing regimen (n=27). Although the study was nonrandomized and observational, there was little difference in severity of illness between groups and a matched propensity score analysis confirmed that treatment with CAZ-AVI plus ATM was associated with lower mortality. Therefore, this study supports CAZ-AVI plus ATM as a promising treatment option for MBL-producing Enterobacterales. However, additional clinical studies evaluating this combination, especially for other types of infection are warranted.

Although the preliminary clinical data are promising, there remain some questions about the use of CAZ-AVI and ATM for the treatment of Enterobacterales. For example, the optimal dosing strategy for the combination of CAZ-AVI and ATM has not yet been fully defined. A recent hollow-fiber infection model study found that human-simulated dosing of CAZ-AVI 2–0.5 g every 8 h plus ATM 2 g every 6 h over 2 h, or both agents administered as continuous infusions yielded the greatest bacterial killing without emergence of resistance over 7 days.[62] This in vitro study may provide guidance for use clinically while awaiting further studies. Furthermore, the pharmacokinetic/pharmacodynamic (PK/PD) target parameters of this combination against MBL-producing Enterobacterales has yet to be fully elucidated. As these agents are two separate FDA-approved agents, automated susceptibility testing for this combination is not available and testing for synergy poses a challenge for many institutional microbiology labs.[63]

To streamline the CAZ-AVI plus ATM combination, a single product formulation of ATM-AVI is currently under development in Phase III studies for the treatment of serious infections (ie, complicated intra-abdominal infections, nosocomial pneumonia including hospital-acquired pneumonia and ventilator-associated pneumonia, complicated urinary tract infections, or bloodstream infections) caused by MBL-producing gram-negative bacteria.[64] Given similar spectrum of microbiologic activity profiles between CAZ-AVI plus ATM and ATM-AVI, the single product ATM-AVI will address many issues encountered with CAZ-AVI plus ATM use, including epidemiological surveillance data (Table 2), susceptibility testing and identifying target exposures predictive of bacterial killing.[63,65] Against MBL-producing Enterobacterales, the addition of avibactam at 4 mg/L

Table 2 Aztreonam and Aztreonam-Avibactam Susceptibilities Among MBL-Producing Enterobacterales

MBL Enzyme	No. of Isolates	$MIC_{50/90}$ [mg/L]		Ref.
		ATM	ATM/AVI[a]	
MBL	267[b] 70[c] 161[d]	64/>128 64/>64 ≥64/≥64	0.12/1 0.5/2 ≤0.125/1	44 67 153
NDM	25[e]	>64/>64	0.25/1	66
VIM	26[e]	16/>64	0.12/1	66
IMP	17[e]	16/>64	0.12/1	66

Notes: Susceptible criteria: ATM ≤4 mg/L based on CLSI; there are currently no interpretive criteria for ATM-AVI. [a]Avibactam 4 mg/L was used in combination with ATM. [b]Clinical Enterobacterales isolates collected from 40 countries worldwide during 2012–2015 harboring MBLs (ie IMP, VIM, NDM, GIM, and SPM). [c]Phenotypically carbapenem-resistant, dual-carbapenemase producing Enterobacterales obtained from reference National Public Health Laboratory in Singapore. [d]Clinical isolates collected from 6 tertiary care hospitals in China between 2016–2017. [e]Collected from multicenter surveillance study (time period or location not specified).

Abbreviations: %S, percent susceptible; ATM, aztreonam; ATM-AVI, aztreonam-avibactam; N/A, not available.

yielded significant reductions in ATM MICs to 1–2 mg/L across several surveillance studies.[44,66,67] The addition of AVI to ATM yielded significant bacterial density reductions in a neutropenic-mouse thigh infection model against 14 MBL-producing Enterobacterales isolates (ATM-AVI MIC ≤16 mg/L) compared to ATM alone, which caused bacterial reductions against only 2 isolates (ATM MIC ≤32 mg/L).[65] Unfortunately, decreased susceptibility to ATM-AVI among MBL-producing *Escherichia coli* has already been observed and determined to be at least in part attributed to a small insertion into PBP3 that impacts binding of aztreonam, ceftazidime, among other β-lactams.[68,69] MBL-producing Enterobacterales that co-harbor an AmpC, such as bla_{CMY}, may be particularly prone to developing ATM-AVI resistance as mutations in the gene encoding for this enzyme have also been shown to cause ATM-AVI resistance.[70,71] The insertion is not associated with MBL β-lactamases and appears limited to *E. coli* isolates.

Recently published PK data for ATM-AVI (REJUVENATE study) suggests that a maintenance dose of 1500–500 mg every 6 hours (3-hour infusion) with a -500–167 mg loading dose (30-minute infusion) displays >90% probability of target attainment at an MIC of 8 mg/L with a target of 60% *f*T>MIC.[72] With MIC_{90} values ≤2 mg/L for most clinical isolates, ATM-AVI appears promising (Table 2). Importantly, the ATM-AVI adverse events were comparable to those reported for ATM monotherapy.

Despite the limitations of using CAZ-AVI plus ATM, this combination still has the most supporting clinical data of any treatment available for MBL-producing Enterobacterales and therefore remains a preferred option while awaiting market availability of ATM-AVI. Optimal dosing can be extrapolated from ATM-AVI PK study as well as available in vitro data. The combination of CAZ-AVI plus ATM was also considered a preferred regimen for MBL-producing Enterobacterales by a recent IDSA guidance document.[73]

Cefiderocol

Cefiderocol is a novel siderophore cephalosporin that enters the bacterial cell through iron transporters, circumventing the need for porin channels thereby evading resistance caused by porin channel mutations and efflux pump overproduction. Additionally, cefiderocol has other chemical structure attributes that confer increased activity against difficult to treat Gram-negative pathogens and stability to hydrolysis by various beta-lactamases in vitro, including MBLs.[74] The chemical modifications include a: pyrrolidinium group on the C-3 side chain that confers stability against β-lactamases (similar to cefepime), a carboxypropanoxyimino group on the C-7 side chain to improve permeability across the outer membrane (similar to ceftazidime), as well as a chlorocatechol group on the C-3 side chain that facilitates the siderophore activity. These modifications translate to a lower catalytic efficiency of cefiderocol by MBL enzymes compared to meropenem (260-fold lower against IMP-1 and VIM-2 among *P. aeruginosa* isolates, and 3-fold lower against NDM-1 among Enterobacterales isolates).[75] The percentage of Enterobacterales exhibiting a cefiderocol MIC ≤ 2mg/L (FDA susceptible breakpoint) was 41% (n=61) to 85.7% (n=49) among NDM-positive isolates, 80.9% (n=47) to 91.7% (n=12) among VIM-positive isolates, and 87.5% (n=8) to 93.3% (n=15) among IMP-positive isolates.[76,77] The percentage of Enterobacterales exhibiting a cefiderocol MIC ≤ 4 mg/L (CLSI susceptible breakpoint) was 72.1% (n=61) to 89.8% (n=49) among NDM-positive isolates, 91.7% (n=12) to 95.7% (n=47) among VIM-positive isolates, and 87.5% (n=8) to 100% (n=15) among IMP-positive isolates (Table 3).[76,77] In a multinational surveillance study (SIDERO-WT-2014 study), mechanisms of resistance were categorized for cefiderocol non-susceptible isolates and among 5 NDM-producing Enterobacterales isolates, it was found that elevated MICs were most likely due to a co-production of metallo- and serine-beta-lactamases and not impacted by porin protein truncation or loss.[76,78] The PK/PD index of cefiderocol for Enterobacterales was determined to be 73.3% and 64.4% *f*T>MIC in the thigh and lung murine infection models, respectively, including isolates producing MBLs.[79] This target appears attainable for organisms up to MIC 4 mg/L.[80] However, considering a target *f*T>MIC of 75%, the probability of target attainment falls quickly to <70% when the cefiderocol MIC is 8 mg/L and is 0% for MICs ≥16 mg/L.[81] Thus, there is a relatively narrow window between high probability of target attainment and predicted treatment failure. This narrow window is particularly concerning for MBL-producing Enterobacterales since they often have MICs closer to the susceptibility breakpoint (Table 3) and are also vulnerable to MIC discrepancies due to variations between testing modalities.[77,82–84]

There is limited clinical data evaluating the use of cefiderocol against MBL-producing Enterobacterales.[85–87]

Table 3 Cefiderocol Susceptibilities Among MBL-Producing Enterobacterales

MBL Enzyme	No. of Isolates	%S ($MIC_{50/90}$ [mg/L] or Range MIC [mg/L])	Ref.
		CFDC	
MBL	64[a]	70 (N/A)	124
NDM	49[b] 12[c] 61[d]	89.8 (1/4) N/A (4/8) 72.1 (4/8)	154 155 77
VIM	12[b] 27[c] 47[d]	91.7 (≤0.12/0.25) 100 (1/4) 95.7 (0.5/4)	154 155 77
IMP	8[b] 15[d]	87.5 (≤0.125–16)[e] 100 (0.25/2)	154 77

Notes: Susceptible criteria: CFDC ≤4 mg/L based on CLSI interpretive criteria. [a]*E. coli* isolates obtained from the US, Asia-West Pacific, Europe, and Latin America. MBL category includes: NDM (n=53), VIM (n=3), IMP (n=8). [b]Clinical isolates collected from the International Health Management Associates (IMHA) (Schaumburg, IL) between 2009 and 2011. [c]Meropenem-resistant (MIC ≥ 4 mg/L) Enterobacterales collected from 99 hospitals in North America and Europe as part of the SIDERO-WT-2014 surveillance study. [d]Representative carbapenemase producing Enterobacterales from Public Health England's Antimicrobial Resistance and Healthcare-Associated Infections (AMRHAI) Reference Unit between 2008–2018. [e] MIC_{90} not available for <10 isolates.

Abbreviations: %S, percent susceptible; CFDC, cefiderocol; N/A, not available.

In cefiderocol's Phase II study for the treatment of complicated urinary tract infections (APEKS-cUTI study) and phase III study for the treatment of nosocomial pneumonia (APEKS-NP), carbapenem-resistant organisms were excluded as the comparator agent was imipenem-cilastatin.[86,88] However, a separate pathogen-focused study (CREDIBLE-CR) was also conducted.[87] CREDIBLE-CR was a phase III, open-label study comparing cefiderocol with the best available therapy against carbapenem-resistant Gram-negative bacteria causing pneumonia, bloodstream infections/sepsis, or complicated urinary tract infections. Overall, there was a numerically higher all-cause mortality rate observed in the cefiderocol group compared to a best available therapy arm (34% vs 18%), which primarily comprised of colistin-containing regimens (61%). No definitive conclusions have been drawn regarding the cause of increased mortality seen in the cefiderocol group, though it appears to have been driven by higher treatment failure rates among patients infected with carbapenem-resistant *A. baumannii*. Yet, this finding is still concerning and led to a warning in the cefiderocol prescribing information.[89] Within the CREDIBLE-CR study, 23 patients had MBL-producing pathogens of which 16 received cefiderocol and 7 received best available therapy. The most common MBL enzyme was NDM (n=15) followed by IMP (n=5) and VIM (n=4); some isolates contained >1 MBL enzyme. Clinical cure rates were 75% in the cefiderocol group at the test of cure compared to 29% in the best available therapy groups, though none of the patients in the best available therapy group received CAZ-AVI plus ATM.

Despite these promising preliminary findings, there remain some concerns for cefiderocol's use against MBL-producing Enterobacterales, including the increased mortality rate in the CREDIBLE-CR study, logistical issues with susceptibility testing and interpretation (discordance between FDA [MIC ≤2 mg/L] vs CLSI [MIC ≤4 mg/L] susceptible breakpoints), and PK/PD concerns for isolates with higher MICs.[83,84,90–92] The recent IDSA guidance update considers cefiderocol as another preferred antibiotic for the treatment of MBL-producing Enterobacterales with CAZ-AVI plus ATM.[73] Although there are some promising data to support the use of cefiderocol against MBL-producing Enterobacterales, there is still less clinical evidence to support its use than there is for the combination of CAZ-AVI plus ATM. Thus, based on the currently available data, we would suggest considering cefiderocol an alternative for when CAZ-AVI plus ATM is not an option.

Carbapenems

MBL enzymes can readily hydrolyze carbapenems in vitro, yet some data suggests that their ability to cause carbapenem resistance is an artifact of the current testing modalities that utilize media with supraphysiologic zinc concentrations.[93] Since zinc is required at the active site of the enzyme, the quantity of zinc at the site of infection could impact the function of the enzyme and also the rate of antibiotic hydrolysis. However, the data are inconclusive. Asempa et al found that meropenem against a panel of NDM-, VIM-, and IMP-producing Enterobacterales appeared resistant in vitro but generated >1 log bacterial killing in murine infection models.[93] They showed that the meropenem in vivo activity better correlated with MICs performed in zinc-depleted media, where the isolates appeared susceptible to carbapenems, than in traditional cation adjusted Mueller Hinton broth.

Roujansky et al also report in vivo efficacy of ertapenem and imipenem against a carbapenem-resistant NDM-1 producing *E. coli* isolate.[94] However, they proposed an alternative hypothesis to this paradoxical activity, suggesting that subinhibitory antibiotic concentrations are

affecting bacterial fitness and the host's immune response. Another recent study did not find the same discordance between in vitro and in vivo meropenem activity in all MBL-producing isolates, though they did suggest that enzyme variations may be driving the inter-isolate variability observed for in vivo meropenem response.[95] MBL-enzymes may also be evolving to retain their catalytic activity under low zinc concentrations.[96] Zinc chelators have also been proposed as adjuvants to carbapenems for MBL-producing Enterobacterales as they may reduce the zinc available to the MBL active site, thereby impairing the enzyme's ability to hydrolyze carbapenems.[97] One in vivo study showed that a zinc chelator (DMSA) used in combination with a carbapenem significantly reduced bacterial counts in an MBL-producing *E. coli* murine peritonitis model compared to carbapenems alone.[98]

The clinical implications of these findings remain uncertain. While some case reports have shown mostly positive outcomes with carbapenem-based regimens for infections caused by MBL-producing Enterobacterales,[99] Falcone et al noted that among 6 patients who received meropenem-containing combinations, 3 of them died, though none of them were receiving carbapenem monotherapy.[29] Given the conflicting preclinical data and the very limited clinical data, the risks of using a carbapenem to treat an MBL-producing Enterobacterales isolate seem to outweigh the potential benefit given that alternative treatment strategies are available.[100] Of note, the newer carbapenem-β-lactamase inhibitor combinations (meropenem-vaborbactam and imipenem-relebactam) do not display additional activity against MBL-producing Enterobacterales compared to their carbapenem counterparts alone. This is due to the inability of both vaborbactam and relebactam to inhibit MBLs, as has been discussed previously.[53,101]

Aminoglycosides

Aminoglycosides are rapidly bactericidal and exert antibacterial activity through protein synthesis inhibition by binding to the 30S ribosome. However, aminoglycoside-modifying enzymes (AMEs) can confer resistance to some of the aminoglycosides and are common among MBL-producing Enterobacterales.[102–106] Plazomicin is the newest semi-synthetic aminoglycoside and is able to evade the most common AMEs in Enterobacterales.[107–109] Though, plazomicin is still liable to the aminoglycoside resistance conferred by the 16S rRNA methyltransferases (16S-RMTases) that prevent all clinically available aminoglycosides from binding to the ribosome.[108,110] 16S-RMTases are commonly co-harbored by MBL-producing Enterobacterales. Across several surveillance studies, plazomicin was the most active aminoglycoside compared to amikacin, tobramycin, and gentamicin (Table 4).[108,111–113] Although amikacin susceptibility rates were similar to those of plazomicin in several studies, this should be interpreted with caution due to the high amikacin MIC breakpoint set by CLSI relative to other organizations such as EUCAST or USCAST.[114] A surveillance study in 26 European countries revealed that among 37 MBL-producing Enterobacterales isolates (bla_{VIM} and bla_{NDM-1}), only 40.5% were susceptible to plazomicin and 16S rRNA methyltransferases (primarily *rmtB* and *armA*) were detected in 60% of isolates.[108] In isolates only harboring an AME, plazomicin retained susceptibility

Table 4 Aminoglycoside Susceptibilities Among MBL-Producing Enterobacterales

MBL Enzyme	No. of Isolates	%S ($MIC_{50/90}$ [mg/L])				Ref.
		PLZ	AMK	TOB	GENT	
MBL	37[a,b]	42.1 (128/>128)	13.5 (>32/>32)	NR (>8/>8)	21.6 (>8/>8)	108
	552[c]	N/A	32.6 (N/A)	N/A	27.7 (N/A)	156
NDM	282[d]	22.7 (N/A)	N/A	N/A	N/A	115
	42[e]	35.7 (>128/>128)	38.1 (>128/>128)	9.5 (>128/>128)	14.3 (>128/>128)	111
	277[f]	52.7 (2/>128)	52.7 (2/>64)	20 (>16/>16)	32 (>16/>16)	112
VIM	182[d]	89.6 (N/A)	N/A	N/A	N/A	115
	20[g]	95 (0.5/0.5)	90 (16/16)	0 (16/64)	15 (16/128)	113
IMP	24[d]	100 (N/A)	N/A	N/A	N/A	115

Notes: Susceptible criteria: PLZ ≤2 mg/L, AMK ≤16 mg/L, TOB ≤4 mg/L, GENT ≤4 mg/L based on CLSI (AMK, TOB, GENT) and FDA interpretive criteria (PLZ). [a]Enterobacterales isolates carrying bla_{VIM} and bla_{NDM-1} collected from European and adjacent countries during 2014–2015. [b]Based on EUCAST breakpoints (AMK ≤8 mg/L, TOB ≤2 mg/L, GENT ≤2 mg/L). [c]Collected from 33 hospitals of 5 countries of the Arabian Peninsula between 2009–2017. [d]Collected from global surveillance program between 2014–2017. [e]Collected from US, Canada, Singapore. [f]Collected from AR Lab Networks in the US between 2017–2018. [g]Clinical isolates collected from single academic medical center during routine care.

Abbreviations: %S, percent susceptible; PLZ, plazomicin; AMK, amikacin; TOB, tobramycin; GENT, gentamicin; N/A, not available.

in 99%. In the largest reported study of MBL-producing Enterobacterales (n=488), plazomicin was active against >75% of all isolates however the difference in activities between NDM, VIM, and IMP are noted, with all aminoglycosides being the least active against NDM-producers.[115] Similar susceptibilities were noted in other studies (Table 4).[111–113] Taken together, plazomicin susceptibility rates were low for NDM-producing isolates (22.7% to 52.7%) but were much higher for VIM- and IMP-producing isolates (89.6% to 95% for VIM, and 100% for IMP). This suggests that 16S-RMTases may be more commonly co-harbored in NDM-producing isolates, though future studies are warranted. Apramycin, which is in Phase I clinical trials, has been shown to be active against Enterobacterales that produce 16S-RMTases, which confer resistance to all other currently available aminoglycosides.[116,117] Although limited data about apramycin against MBL-producing Enterobacterales is currently available, it holds potential to become a therapeutic option for MBL-producing Enterobacterales based on its spectrum of activity.

Beyond susceptibility studies, very limited data exists that evaluates plazomicin against MBL-producing Enterobacterales. One in vitro time-kill study found synergy with plazomicin plus meropenem, colistin, or fosfomycin against two *K. pneumoniae* isolates with bla_{VIM}.[118] A phase III, randomized, open-label, pathogen-directed study was performed assessing plazomicin plus meropenem or tigecycline compared with colistin plus meropenem or tigecycline for bloodstream infection or hospital-acquired or ventilator-associated bacterial pneumonia caused by a carbapenem-resistant Enterobacterales (CARE trial).[119] The most common carbapenemase gene detected was bla_{KPC} but it is not reported if any patients were infected with MBL-producing isolates. The study was stopped early due to slow enrollment; however, 24% (4/17) in the plazomicin group versus 50% (10/20) of patients in the colistin group had a composite of death from any cause at 28 days or significant disease-related complications. In summary, the high resistance rates preclude the use of aminoglycosides as empiric therapy for NDM-type MBLs. If the isolate is susceptible an aminoglycoside, such as plazomicin, may be a possible adjuvant to other active agents for MBL-producing Enterobacterales, though additional data is required in order to make a reliable recommendation.

Tetracyclines

The tetracyclines exert antibacterial activity by binding to the 30S ribosomal subunit and preventing the docking of amino-acyl-transfer RNA (tRNA).[120] Resistance to tetracyclines emerge by efflux, ribosomal protection, and enzymatic inactivation of drug. With two recent additions (eravacycline and omadacycline) to join tigecycline and minocycline among the crucial tetracyclines to combat MDR Enterobacterales, their activity against MBL-producers is an important question. Investigations into tetracycline resistance among MBL-producing Enterobacterales are scarce. One study reports tigecycline resistance among 5 NDM-positive *E. coli* isolates to be attributed to a single nucleotide substitution in the 30S ribosome.[121] Another study showed high transferability and stability of plasmids carrying *tet*(X4) in NDM-positive *E. coli* isolates conferring resistance to tigecycline and eravacycline.[122] In a large surveillance study of MBL-producing Enterobacterales isolates collected in the US between 2017 and 2018, tetracycline susceptibilities are illustrated.[112] Among 275 Enterobacterales isolates harboring bla_{NDM} tigecycline was the most active tetracycline agent followed by eravacycline (Table 5). In another

Table 5 Tetracycline Susceptibilities Among MBL-Producing Enterobacterales

MBL Enzyme	No. of Isolates	%S ($MIC_{50/90}$ [mg/L])				Ref.
		TGC	MIN	ERV	OMD	
MBL	64[a]	98 (N/A)	N/A	95 (N/A)	N/A	124
	552[b]	57.2 (N/A)	N/A	N/A	N/A	156
NDM	275[c]	86.5 (≤0.5/4)	48.4 (8/>16)	66.2 (0.5/2)	59.6 (4/32)	112
	42[d]	97.6 (0.5/2)	40.48 (8/32)	71.4 (0.25/1)	N/A	123
VIM	44[d]	97.3 (0.5/2)	52.3 (4/16)	77.3 (0.5/1)	N/A	123
IMP	15[d]	66.7 (0.5/4)	53.3 (4/32)	60 (0.5/2)	N/A	123

Notes: Susceptible criteria: TGC ≤2 mg/L, MIN ≤4 mg/L, ERV ≤0.5 mg/L, OMD ≤4 mg/L based on CLSI and FDA interpretive criteria. [a]*E. coli* isolates obtained from the US, Asia-West Pacific, Europe, and Latin America. MBL category includes: NDM (n=53), VIM (n=3), IMP (n=8). [b]Collected from 33 hospitals of 5 countries of the Arabian Peninsula between 2009–2017. [c]Collected from AR Lab Networks in the US between 2017–2018. [d]Collected from clinical laboratories from the United Kingdom.

Abbreviations: %S, percent susceptible; TGC, tigecycline; MIN, minocycline; ERV, eravacycline; OMD, omadacycline; N/A, not available.

susceptibility study, tigecycline, eravacycline, and minocycline susceptibilities were evaluated against NDM (n=42), VIM (n=44), and IMP-producing (n=15) Enterobacterales isolates.[91,123] Similarly, tigecycline was the most active agent followed by eravacycline and susceptibilities between the different types of MBL enzymes were similar. Tigecycline and eravacycline were also highly active (>95% rates of susceptibility) against another collection of MBL-producing *E. coli* isolates from around the world.[124] In a murine lung infection model, tigecycline was evaluated as monotherapy and in combination with ceftazidime-avibactam and aztreonam.[125] Two humanized doses simulating tigecycline 50 mg every 12 h and 100 mg every 12 h were used. As monotherapy, both tigecycline groups resulted in bacterial regrowth while all combinations resulted in ≥2 $\log_{10}$ reduction in CFU, supporting tigecycline's potential role in combination therapy against MBL-producing Enterobacterales.

Clinical data evaluating any of the tetracycline analogues against MBL-producing Enterobacterales is limited to one observational study in which tigecycline monotherapy or combination therapy was used in 15 septic patients with various infection types caused by VIM-1 producing *K. pneumoniae*.[126] The overall 30-day mortality rate was 25% and mortality was associated with underlying severity of disease. Although, due to the small sample size and variability of infection types, general conclusions are difficult to draw from this study. Based on the available data, tigecycline followed by eravacycline are the most active tetracycline analogues in vitro. There are important pharmacokinetic properties to note for minocycline, tigecycline, eravacycline, and omadacycline. Generally, all four tetracyclines have higher tissue concentrations than serum, concentration-dependent plasma protein binding ranging from 70% to 90% (except eravacycline is 21%), and exhibit minimal renal clearance. Although incompletely understood, the higher tissue concentrations relative to serum of the tetracyclines make them an important class of antibiotics for infections located in various tissues. The organism's MIC along with the pharmacokinetics of these agents considering the infection site should be taken into consideration when selecting therapy. More in vitro, in vivo, and clinical studies are needed to determine the tetracyclines' place in therapy.

Fosfomycin

Fosfomycin inhibits the MurA enzyme that disrupts peptidoglycan synthesis in bacteria.[127] The major mechanisms of resistance are conferred through chromosomal mutations leading to decreased uptake, decreased binding to target MurA, and enzymatic inactivation (FosA). There are only a few studies that have evaluated the activity of fosfomycin against MBL-producing Enterobacterales (Table 6) with limited data on the mechanisms of fosfomycin resistance among MBL-producing Enterobacterales.[128] One study found that 76.2% (n=48/63) of VIM-1-producing *K. pneumoniae* isolates were susceptible (MIC ≤64 mg/L) to fosfomycin; however, this data is only applicable to urinary isolates.[91,129] In a neutropenic murine thigh infection model, the fosfomycin AUC/MIC ratio to achieve stasis and 1-log kill was 11 and 22, respectively, against *a K. pneumoniae* isolate harboring NDM-1 (fosfomycin MIC 4 mg/L).[130]

Table 6 Fosfomycin Susceptibilities Among MBL-Producing Enterobacterales

MBL Enzyme	No. of Isolates	FOS $MIC_{50/90}$ (mg/L) or Range MIC (mg/L)[a]	Ref.
NDM	17[b]	4/≥256	157
VIM	5[b]	8-≥256[c]	157
IMP	13[b]	4/≥256	157

Notes: [a]Percent susceptibility is not reported since CLSI breakpoints are only applicable to urinary isolates. [b]Isolates from United Kingdom hospitals. [c]$MIC_{50/90}$ not available for <10 isolates.
Abbreviation: FOS, fosfomycin.

There are no clinical studies examining the use of fosfomycin against MBL-producing Enterobacterales directly; thus, the discussion here focuses on available pharmacokinetic studies for Enterobacterales generally. A phase III study for intravenous fosfomycin utilized a dose of 6 g IV every 8 h in the treatment of complicated urinary tract infections or acute pyelonephritis and met its primary end point for non-inferiority compared with piperacillin-tazobactam.[131] Based on the pharmacokinetic study of intravenous fosfomycin, a 6 g IV every 8 h dose would yield an exposure ~715 μg·h/mL, suggesting that AUC/MIC ratios required for 1-log kill can be achieved with fosfomycin MIC 8 mg/L among Enterobacterales, irrespective of strain and β-lactamase.[130–132] The high exposures achieved also suggest its potential use in systemic infections, such as has been done in countries who have had access to intravenous fosfomycin.[133] However, in vitro pharmacodynamic studies also need to be taken into

consideration as they suggest that monotherapy fosfomycin may not be useful due to baseline heteroresistant subpopulations and rapid regrowth, despite fosfomycin MICs of 0.5–8 mg/L.[134–136] Susceptibility testing issues also remain a challenge and are another limitation to the widespread clinical use of fosfomycin.[137] Larger surveillance and clinical studies are needed to determine fosfomycin's place in therapy against contemporary MBL-producing Enterobacterales and in various infection types.[138,139]

Polymyxins

The polymyxin antibiotics (colistin and polymyxin B) were originally discovered in the 1940s and retain high rates of in vitro activity against many carbapenem-resistant Gram-negative bacteria. The polymyxins bind to the lipid A portion of the lipopolysaccharide (LPS) molecule, thereby destabilizing the bacterial outer membrane which causes increased permeability and cell death. Resistance to polymyxins mostly involves the addition of 4-amino-4-deoxy-1-arabinose or phosphoethanolamine to the LPS, which decreases binding of polymyxins to lipid A. These chemical modifications are caused by chromosomal mutations in two-component regulatory systems or acquired phosphoethanolamine transferase genes harboured by plasmids (eg, *mcr-1*).[140] Several studies have investigated prevalence of polymyxin resistance among MBL-producing Enterobacterales isolates (Table 7). In a global surveillance program that aimed to determine polymyxin activity in β-lactamase producing isolates, it was found that among Enterobacterales that harbored an MBL (n=81), 92.6% of isolates were susceptible to colistin, which was higher than in KPC-positive (87.9%) or OXA-48-positive isolates (84.2%) using EUCAST breakpoints (MIC ≤2 mg/L).[141] The prevalence of MBL-producing Enterobacterales among colistin-resistant isolates (1.6%, 309/19,719) was also low (6 isolates). Despite high susceptibility among MBL-producing Enterobacterales, colistin-containing regimens were associated with higher mortality rates than CAZ-AVI plus ATM (59.3% vs 19.2%, respectively) for MBL-producing CRE in the study by Falcone et al.[29] Extrapolating from previous studies that assessed polymyxins against other carbapenem-resistant organisms (non-MBL) further suggests that polymyxins are no longer a preferred agent for MBL-producing Enterobacterales. Furthermore, dose-limiting nephrotoxicity is common with polymyxin use.[142] Thus, the data suggests that polymyxins should be considered a backup to β-lactam-based regimens, such as CAZ-AVI plus ATM or cefiderocol, when they are available.[2,143] If polymyxins are used, combination therapy is recommended for treatment of CRE.[144] Some in vitro data shows promise for combinations between polymyxin and aztreonam against Enterobacterales harboring bla_{NDM} or bla_{VIM}, which represents a potential area for future research and may revitalize the utility of the polymyxins for MBL-producing Enterobacterales.[145,146]

Table 7 Polymyxin Susceptibilities Among MBL-Producing Enterobacterales

MBL Enzyme	No. of Isolates	Polymyxin B or Colistin $MIC_{50/90}$ (mg/L)	Ref.
MBL	81[a]	≤0.12/1	141
NDM	275[b]	0.5/1	112
VIM	N/A	N/A	
IMP	N/A	N/A	

Notes: [a]Isolates collected from global surveillance program between 2012–2013. [b]Collected from AR Lab Networks in the US between 2017–2018.
Abbreviation: N/A, not available

Pipeline Agents

All of the recently approved β-lactamase inhibitors are only active against serine β-lactamases in class A or D; MBL inhibitors are urgently needed. There are several MBL inhibitors in the pipeline that may address the growing global threat of MBL-producing bacteria (Table 8).[147] Taniborbactam (formerly VNRX-5133) is a cyclic boronate β-lactamase inhibitor in phase III clinical trials and the first to display activity against class A-D β-lactamases (including MBLs with the exception of IMP) and is currently being co-developed with cefepime.[148,149] LYS228 is

Table 8 MICs for Pipeline Agents Against MBL-Producing CRE

MBL Inhibitors	Current Clinical Development Stage	No. of Isolates	$MIC_{50/90}$ (Range) (mg/L)	Ref.
Taniborbactam (VNRX-5133)	Phase III	87[a]	16/64 (N/A)	148
LYS228	Phase II	33[b]	0.5/4 (≤0.06–16)	150
QPX7728	Phase I	N/A	N/A	–
Meropenem/ ANT2681	Pre-clinical	>1000[c]	8 (N/A)	95

Notes: [a]NDM-producing Enterobacterales; [b]Clinical isolates from Novartis collection obtained between 2000–2016; [c]Clinical NDM-positive Enterobacterales isolates, unpublished data.
Abbreviation: N/A, not available.

a novel monobactam currently in phase II development as a stand-alone agent with stability against MBLs and a broad spectrum of serine β-lactamases while retaining antibacterial activity through inhibition of penicillin-binding protein 3.[150,151] LYS228 has been shown to be less stable to PER and VEB β-lactamases, as well as other non-β-lactamase-mediated resistance mechanisms. QPX7728 is another cyclic boronate β-lactamase inhibitor with an expanded spectrum of inhibition compared to taniborbactam, including against class A (CTX-M, SHV, TEM, VEB, PER and carbapenemases KPC, SME, NMC-A, BKC-1), B (NDM, VIM, CcrA, IMP, and GIM), C (CMY, FOX, MIR, DHA, P99, PDC, ADC), and D (OXA-48, OXA-23/24/72/58).[152] QPX7728 is currently undergoing a Phase I study. Thiazole carboxylate derivative, ANT2681, inhibits MBLs through interaction with the dinuclear zinc ion cluster and is being co-developed with meropenem.[95] It is currently ready to enter phase I clinical development with positive in vitro and in vivo results where it potentiated meropenem activity (decreasing meropenem MIC from >32 mg/L to 8 mg/L). The MBL inhibitor pipeline holds much potential to address a global unmet need.

Conclusions

MBL-producing Enterobacterales are an urgent global public health threat that have rapidly disseminated worldwide and cause infections that are associated with mortality rates of ~30-50%. Rapid diagnostic tests are important to detect MBLs and guide early treatment since the mechanism of carbapenem resistance in CRE dictates the preferred treatment option. Fortunately, there are many available FDA-approved instruments that can detect MBLs and are able to help meet the challenges associated with increasing MBL prevalence. Although many antibiotics display in vitro activity, there is little clinical data to clearly define their place in treatment. However, newer data generally support the use of ceftazidime-avibactam in combination with aztreonam as a primary treatment option for MBL-producing Enterobacterales. Cefiderocol may be a reasonable alternative if isolates are found to be susceptible, though additional clinical studies are necessary. Various agents in the pipeline are active against MBL-producing Enterobacterales and may eventually add to our treatment armamentarium. Future studies are warranted and can be used to refine the treatment approach for treating MBL-producing Enterobacterales infections and improve patient outcomes.

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