Drugs (2019) 79:705–714
https://doi.org/10.1007/s40265-019-01112-1

CURRENT OPINION

New Drugs for Multidrug-Resistant Gram-Negative Organisms: Time for Stewardship

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Published online: 10 April 2019

Abstract
A gradual rise in drug-resistant trends among Gram-negative organisms, especially carbapenem-resistant (CR) Enterobacteriaceae (CRE), CR-*Pseudomonas aeruginosa*, and extensively-drug-resistant (XDR) *Acinetobacter baumannii*, poses an enormous threat to healthcare systems worldwide. In the last decade, many pharmaceutical companies have devoted enormous resources to the development of new potent antibiotics against XDR Gram-negative pathogens, particularly CRE. Some of these novel antibiotics against CRE strains are β-lactam/β-lactamase-inhibitor combination agents, while others belong to the non-β-lactam class. Most of these antibiotics display good in vitro activity against the producers of Ambler class A, C, and D β-lactamase, although avibactam and vaborbactam are not active in vitro against metallo-β-lactamase (MβL) enzymes. Nevertheless, in vitro efficacy against the producers of some or all class B enzymes (New Delhi MβL, Verona integron-encoded MβL, etc) has been shown with cefepime-zidebactam, aztreonam-avibactam, VNRX-5133, cefiderocol, plazomicin, and eravacycline. As of Feburary 2019, drugs approved for treatment of some CRE-related infections by the US Food and Drug Administration included ceftazidime-avibactam, meropenem-vaborbactam, plazomicin, and eravacycline. Although active against extended-spectrum and AmpC β-lactamase-producing Enterobacteriaceae, delafloxacin does not show in vitro activity against CRE. Murepavadin is shown to be specifically active against CR- and colistin-resistant *P. aeruginosa* strains. Despite successful development of novel antibiotics, strict implementation of an antibiotic stewardship policy in combination with the use of well-established phenotypic tests and novel multiplex PCR methods for detection of the most commonly encountered β-lactamases/carbapenemases in hospitals is important for prescribing effective antibiotics against CRE and decreasing the resistance burden due to CRE.

1 Introduction

For the last two decades, the spread of drug-resistant Gram-negative bacteria (GNB), especially third-generation cephalosporin- and carbapenem-resistant (CR) Enterobacteriaceae (CRE), CR-*Pseudomonas aeruginosa* and CR-*Acinetobacter baumannii,* has substantially increased morbidity and mortality rates worldwide [1–5]. The global spread of CRE (particularly the producers of *Klebsiella pneumoniae* carbapenemase (KPC), New Delhi metallo-β-lactamase (MβL) (NDM), and oxacillinase (OXA)-48-like enzymes among *K. pneumoniae* and other Enterobacteriaceae isolates) is an important issue because CRE infections are usually associated with delayed administration of appropriate antibiotics and high case-fatality rates, while CRE colonization is a risk associated with high clinical severity [1, 6–10]. In 2018, the World Health Organization ranked the three above-mentioned resistant organisms as top critical-priority with Gram-negative bacteria (GNB) far outweighing methicillin-resistant *Staphylococcus aureus* (MRSA) [11, 12].

Clinical trials of antibiotics against difficult-to-treat multidrug-resistant (MDR)-GNB are now underway. These novel agents are quite distinct from conventional β-lactamase inhibitor-(sulbactam, clavulanate, and tazobactam) containing antibiotics. Those showing potent in vitro activity against MDR pathogens are classified into two structurally different categories, β-lactam/β-lactamase inhibitor antibiotics and non-β-lactam antibiotics [13]. The former group includes ceftolozane-tazobactam, ceftazidime-avibactam, ceftaroline-avibactam, aztreonam-avibactam, imipenem/cilastatin-relebactam, meropenem-vaborbactam, meropenem-nacubactam, cefepime-zidebactam, and cefiderocol, whereas the latter group includes murepavadin, plazomicin, eravacycline, omadacycline, finafloxacin, and delafloxacin

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Key Points

Because of the rise of multidrug-resistance over the last decade, an antibiotic pipeline for Gram-negative bacteria (GNB) has emerged, especially for carbapenem-resistant Enterobacteriaceae (CRE) and *Acinetobacter baumannii* complex isolates.

Novel antibiotics against extensively drug-resistant GNB are grossly categorized into β-lactam combination agents and non-β-lactam agents according to their structural differences. The US Food and Drug Administration has approved the β-lactam combination agents ceftazidime-avibactam and meropenem-vaborbactam and the non-β-lactam agents eravacycline and plazomicin for clinical treatment. Many novel antibiotics are under clinical investigation.

In order to reduce unnecessary antibiotic consumption and the clinical CRE burden, strict implementation of an antibiotic stewardship policy in combination with use of well-established phenotypic tests and novel multiplex polymerase chain reaction methods for the detection of the most commonly encountered β-lactamases/carbapenemases in hospitals is important for prescribing effective antibiotics against CRE and decreasing the resistance burden caused by CRE.

[13]. In addition, the development of arylomycin derivative and antibiotic hybrids has demonstrated new directions in the design of antimicrobials against the clinical extensively drug resistant (XDR) pathogens [14, 15]. A few of these novel antibiotics (including ceftazidime-avibactam, delafloxacin, eravacycline, omadacycline, and meropenem-vaborbactam) have been approved by the US Food and Drug Administration (FDA). Most are presently being evaluated for efficacy and safety in treating CR-GNB infections. As more novel antibiotics become available for prescription in clinical settings, overdependence on tigecycline and colistin against XDR-GNB could be alleviated. Ceftolozane-tazobactam has demonstrated in vitro potency against most CR-*P. aeruginosa* strains, and has been approved for complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI). It is, however, inactive against the KPC-producing Enterobacteriaceae isolates and many extended-spectrum β-lactamase (ESBL)-producing *K. pneumoniae* isolates [16–18]. Therefore, it is not discussed in this article.

This article mainly focuses on in vitro and clinical study data on novel anti-CRE antibiotics, and also introduces other novel antibiotics that have shown in vitro activity against other important clinical MDR bacterial pathogens.

2 β-Lactams and β-Lactamase Inhibitor Combinations

Avibactam (formerly NXL104) is a diazabicyclooctane (DBO, non-lactam class) derivative antibiotic. It has very good potency in reversibly inhibiting serine β-lactamase enzymes including Ambler class A (mainly ESBL, KPC), class C, and partial class D (including OXA-1, OXA-10, and OXA-48-like), while sparing the class B enzymes. It has undoubtedly been a key breakthrough in treating CRE infections [19]. Sader et al. reported that the addition of avibactam significantly reduced the minimum inhibitory concentrations (MICs) of ceftazidime and meropenem against most MDR-Enterobacteriaceae species [20, 21]. The overall treatment success rates using ceftazidime-avibactam against several CRE infections ranged between 45 and 76% [18]. With a recommended dose of 2.5 g intravenously every 8 h, ceftazidime-avibactam (4:1 fixed ratio) has an efficacy comparable to carbapenem. One phase III trial comparing the therapeutic efficacy of ceftazidime-avibactam and meropenem (against implicated etiologies mainly including *K. pneumoniae*, *P. aeruginosa*, REPROVE trial, NCT01808092) showed clinical non-inferiority in treating patients with hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP) [22]. In addition, Bassetti et al. have suggested that ceftazidime-avibactam can be combined with gentamicin, fosfomycin, colistin, or plazomicin as a potential alternative treatment regimen in settings with high (> 20%) CRE prevalence rates [18]. The FDA and the European Medicines Agency (EMA) have approved ceftazidime-avibactam in treating cIAI (combined with metronidazole), cUTI, and nosocomial pneumonia [18, 19, 23].

Ceftaroline [a fifth-generation anti-MRSA cephalosporin approved for treatment of community-acquired pneumonia (CAP)] combined with avibactam has also been shown to be active against ESBL, KPC, and AmpC-producing Enterobacteriaceae isolates [24]. Furthermore, ceftaroline-avibactam showed efficacy comparable to doripenem in treating cUTI in a phase II study (NCT01281462).

Aztreonam is active against MβL-producing GNB, while it is readily hydrolyzed by most class A and class C enzymes [1]. A combination of avibactam and aztreonam has exhibited good in vitro potency against most of the ESBL-, KPC-, MβL-, and AmpC-producing Enterobacteriaceae isolates. Nevertheless, aztreonam-avibactam is inactive against the MDR-*P. aeruginosa* and *A. baumannii* strains [18]. A phase III trial comparing the clinical efficacy of aztreonam-avibactam (plus metronidazole in cIAI) and meropenem (plus colistin, if necessary) in various infections (cIAI, HAP/VAP) related to MDR-GNB was initiated in 2018 (NCT03329092) and will end in 2021.

Relebactam (formerly MK-7655A) is another DBO class drug. When combined with imipenem/cilastatin, this β-lactam combination agent displays in vitro activity similar to that of ceftazidime-avibactam [25, 26]. In a phase II trial involving patients with cUTI (including acute pyelonephritis (APN)), imipenem/cilastatin-relebactam at a prescription dose of 500 mg/250 mg, i.e., 125 mg or 250 mg every 6 h, showed non-inferiority compared with imipenem/cilastatin (500 mg every 6 h) for clinical and microbiological endpoints (NCT01506271) [27]. Another phase II multicenter clinical trial involving imipenem/cilastatin-relebactam at a dose of 500 mg, i.e., 125 mg or 250 mg every 6 h, for treatment of patients with cIAI also showed favorable outcomes [25]. The other phase III trial investigating the difference in clinical efficacy between imipenem/cilastatin-relebactam and imipenem/cilastatin plus colistin in patients with serious infections (HAP, VAP, cIAI, and cUTI) due to imipenem-resistant bacterial strains ended in 2017 (NCT02452047) [18], and the results are pending. In addition, it is noteworthy that ceftazidime-avibactam and imipenem/cilastatin-relebactam also have good pulmonary penetration. A phase III study comparing clinical efficacy, tolerability, and safety between imipenem/cilastatin-relebactam and piperacillin-tazobactam for treating patients with HAP or VAP is ongoing (NCT02493764) [18].

Another DBO-type β-lactamase inhibitor zidebactam (formerly WCK 5222; Wockhardt Ltd., Mumbai, India), with a unique high binding affinity to penicillin-binding protein (PBP)-2, remarkably increases the efficacy of cefepime against serine β-lactamase (ESBL, KPC) producers, probably the Ambler class D producers, and CR-*P. aeruginosa* isolates [13, 28, 29]. Nevertheless, reduced susceptibility of cefepime-zidebactam is reported against some MβL-producing organisms [13, 28, 29]. Moreover, the addition of zidebactam did not significantly potentiate the in vitro efficacy of cefepime against MDR-*A. baumannii* [29]. The safety and tolerability of zidebactam (1–2 g intravenously every 8 h), and zidebactam combined with cefepime (2 g intravenously every 8 h) were evaluated among healthy volunteers beginning in 2016 (MAD study NCT02674347, and phase I MED study NCT02707107, respectively), but the formal reports are still pending.

Nacubactam (formerly OP0595; F. Hoffmann-La Roche Ltd., Basel, Switzerland), a new DBO-type compound, has been reported to be a β-lactam (biapenem, cefepime, piperacillin, etc.) enhancer due to good PBP-2 affinity (although weaker than zidebactam). Its antibacterial spectrum is similar to cefepime-zidebactam [13, 30]. The safety and tolerability of nacubactam alone and nacubactam plus meropenem among healthy volunteers showed favorable results [31], and further clinical study about its efficacy in pneumonia is ongoing.

Vaborbactam, a cyclic boronate non-β-lactam agent (structurally distinct from avibactam and relebactam), does not have intrinsic antibacterial activity. However, it potentiates the in vitro activity of meropenem against KPC-, ESBL-, and AmpC-producing Enterobacteriaceae isolates [26]. Meropenem-vaborbactam has also been approved by the FDA in treating cUTI at a recommended dose of 2 g meropenem plus 2 g vaborbactam every 8 h in patients with estimated glomerular filtration rates ≥ 50 ml/min/1.73 m^2 [32]. Although meropenem-vaborbactam lacks in vitro activity against the class B and class D enzymes [26, 33], it demonstrated non-inferior outcomes in the treatment of patients with HAP/VAP/bacteremia and cIAI compared with the currently best available antibiotics in the TANGO II trial (clinical cure rate, 57.1% vs. 33.3%, $P=0.04$, NCT02168946 [34]). The TANGO III trial (phase III study, NCT03006679) comparing the efficacy of meropenem-vaborbactam with piperacillin-tazobactam in HAP/VAP is ongoing.

Another promising boronate-based β-lactamase inhibitor, VNRX-5133 (VenatoRx Pharmaceuticals, Inc., Malvern, PA, USA), also reportedly possesses broad-spectrum activity against Ambler class A, C, and D enzymes and some MβL-producing organisms (including CRE, and possibly some CR-*P. aeruginosa*, CR-*A. baumannii* isolates) [35]. Its clinical safety among 84 healthy volunteers was established in a phase I trial (NCT02955459) [13, 28, 36].

Cefepime/AAI101 (Allerca Therapeutics, Weil am Rhein, Germany), an antimicrobial agent containing the β-lactamase inhibitor AAI101 (with a β-lactam scaffold) was reported to possess acceptable in vitro activity against cefepime-non-susceptible, ESBL- and KPC-producing Enterobacteriaceae strains [13, 28, 37]. A phase II evaluation was conducted in 2017 to compare the clinical efficacy between cefepime/AAI101 (500 or 750 mg) and cefepime (1–2 g) in the treatment of adult patients with cUTI (NCT03680612); the data are pending [38].

Cefiderocol (formerly S-649266; Shionogi & Co. Ltd., Osaka, Japan) is a siderophore (catechol moiety)-containing cephalosporin agent preferentially binding to the PBP-3 in GNB. By taking advantage of the bacterial iron transport system, its entry into the periplasmic space is significantly facilitated (a "Trojan Horse" strategy) [13, 39, 40]. Cefiderocol shows excellent in vitro activity against most class A, B, C, and D β-lactamase-producing GNB (Enterobacteriaceae, non-fermenters). Reduced in vitro activity, however, was noted among a few *P. aeruginosa* isolates with a deficiency in the iron-regulated outer membrane proteins [39]. As seen in the data of Dobias et al., the MIC inhibiting the in vitro growth of 90% of target organisms (MIC_{90}) for cefiderocol ranged from 2 to 4 μg/ml against KPC producers, or class B enzyme variants (including NDM)-producing Enterobacteriaceae isolates. Among the various antibiotics compared, only colistin and tigecycline displayed in vitro

activities equivalent to cefiderocol against overall MDR-GNB [40]. The MIC_{90} values for cefiderocol were 1–2, 4–8, and 0.25 μg/ml against CR-*P. aeruginosa*, *A. baumannii*, and *Stenotrophomonas maltophilia* isolates, respectively [40, 41]. In a population pharmacokinetic study, a high serum concentration of cefiderocol (> 75 μg/ml) was achieved when subjects were administered doses ranging from 2 g every 8 h to 0.75 g every 12 h (with 3-h infusions) depending upon creatinine clearance rates. Approximately two-thirds of administered cefiderocol is excreted by the kidney as unchanged parent drug. Excellent probabilities (> 90%) of target attainment in blood and urine were observed against GNB with a cefiderocol MIC ≤ 4 μg/ml [42]. In the APEKS-cUTI trial, cefiderocol showed composite clinical and microbiological non-inferiority to high-dose imipenem/cilastatin (1 g/1 g with a 1-h intravenous drip every 8 h) in treating patients at high risk of acquiring MDR-GNB [18, 43]. It is also notable that cefiderocol has an acceptable ratio (0.239) for the epithelial lung fluid (ELF)-to-plasma concentration [44]. Two phase III trials [APEKS-NP trial (NCT03032380); and CREDIBLE-CR trial (NCT02714595), respectively] comparing the treatment efficacy of cefiderocol with meropenem (2 g with a 3-h intravenous drip duration every 8 h for both drugs), colistin, and other best available antibiotics in patients with various serious infections (including healthcare-associated pneumonia, HAP, VAP, cUTI, bloodstream infections) are ongoing [15, 18]. Table 1 illustrates the spectra of novel β-lactam combination antibiotics against the Enterobacteriaceae isolates that produce important β-lactamases (including carbapenemases), CR-*P. aeruginosa* and CR-*A. baumannii*.

3 Non-β-Lactam Antibiotics

Plazomicin (formerly ACHN-490; Achaogen Inc., South San Francisco, CA, USA) is a sisomycin derivative that is unaffected by aminoglycoside-modifying enzymes, although it is vulnerable to other aminoglycoside resistance mechanisms. It displays potent in vitro activity against the majority of β-lactamase-producing bacteria (except those containing NDM enzymes) as well as MRSA [20, 45–47]. Prescribed at a dosage of 15 mg/kg intravenously once daily, plazomicin demonstrated efficacy comparable to levofloxacin (phase II trial, NCT01096849) [48] and meropenem (EPIC study, phase III trial) [49] in treating cUTI. A combination of plazomicin with tigecycline or meropenem demonstrated improved efficacy (survival) and a better safety profile than colistin in treating HAP/VAP/cUTI/bacteremia caused by CRE (CARE trial; mortality rate, 23.5% vs. 50%, NCT01970371) [18]. This agent was approved for treatment of cUTI by the FDA in June 2018. It was suggested that plazomicin be combined with ceftazidime-avibactam to provide better therapeutic efficacy in treating serious infections caused by KPC producers [28, 50].

Eravacycline (Tetraphase Pharmaceuticals, Inc., Watertown, MA, USA) is a fluorocycline belonging to the tetracycline class (with structural similarity to tigecycline, but with more chemical modifications). It is available in both intravenous and oral formulations (oral bioavailability in healthy volunteers, > 90%) [18]. Eravacycline has an antibacterial spectrum equivalent to tigecycline but has been shown to be more potent against MDR-Enterobacteriaceae and *A. baumannii* isolates [28, 39, 51]. Eravacycline has shown efficacy

Table 1 Spectra of novel β-lactam and β-lactam combination antibiotics against important multidrug-resistant Gram-negative bacteria

Agents (references)	Company	Activity against indicated enzymes or multidrug-resistant strains						
		ESBL	KPC	MβL	AmpC	OXA	MDR-PA	MDR-Ab
Ceftazidime-avibactam [16–18]	Pfizer	+	+		+	+		
Aztreonam-avibactam [16–18]	Pfizer	+	+	+	+	+		
Ceftaroline-avibactam [20]	Pfizer	+	+		+	+		
Meropenem-vaborbactam [23, 29]	Melinta	+	+		+			
Imipenem/cilastatin-relebactam [21, 23]	Merck	+	+		+		+	
Meropenem-nacubactam [10, 26]	Roche	+	+		+	+[a]	+[a]	
Cefepime-zidebactam [10, 24, 25]	Wockhardt	+	+	+	+	+	±	+
Cefepime-VNRX-5133 [10, 35]	VenatoRx	+	+	+	+	+	+	
Cefepime-AAI101 [10, 24, 32]	Allecra	+	+		+	+		
Cefiderocol [10, 15, 36–38]	Shionogi	+	+	+	+	+	+	+

ESBL extended-spectrum β-lactamase, *KPC Klebsiella pneumoniae* carbapenemase, *MβL* metallo-β-lactamase, *OXA* oxacillinase, *MDR-PA* multidrug-resistant *Pseudomonas aeruginosa*, *MDR-Ab* multidrug-resistant *Acinetobacter baumannii* complex

\+ In vitro active efficacy

± Possible in vitro active efficacy, but data are limited

[a]For AmpC-hyperproducing *P. aeruginosa* only

comparable to ertapenem (86.8% vs. 87.6%) in treating cIAI in a phase III trial (IGNITE 1 study, NCT01844856) [52]. In August 2018, eravacycline was approved for treating cIAI by the FDA. It is noteworthy that eravacycline has better pulmonary penetration for both ELF and alveolar macrophages than tigecycline (6- and 50-fold of serum concentrations, respectively) [39, 53]. Therefore, it is an attractive treatment option in HAP/VAP as well. By contrast, eravacycline (1.5 mg/kg intravenously once daily) failed to show clinical superiority to ertapenem (1 g intravenously once daily) in the treatment of cUTI (IGNITE3 phase III trial) [54]. As of February 2019, no clinical trials had evaluated the role of eravacycline in HAP.

Omadacycline (Paratek Pharmaceuticals, Inc., Boston, MA, USA) is a modified minocycline (aminomethylcycline) antibiotic with a lower plasma protein-binding affinity than tigecycline (20–30% vs. 60%) [28, 55]. It has less potential for inducing nausea and vomiting compared with the glycylcyclines. Although omadacycline has excellent efficacy against MRSA, MDR-*Streptococcus pneumoniae*, and ESBL-producing *Escherichia coli* isolates (but is not active against ESBL-producing *K. pneumoniae*, ceftazidime-nonsusceptible *Enterobacter* spp.), it displays limited in vitro activity against CRE and CR-*A. baumannii* [28, 56]. Initial proof regarding omadacycline in treating urinary tract infections (UTIs) found that it was active in vitro against ESBL-producing Enterobacteriaceae isolates and CR-*E. coli* (but not *K. pneumoniae*) [13, 57]. Omadacycline (100 mg intravenously once daily, followed by 300 mg orally once daily) was shown to have the clinical efficacy comparable to linezolid (600 mg orally every 12 h) in treating complicated skin and skin structure infections (SSSIs) caused by Gram-positive bacteria (OASIS-1 phase III trial; NCT02378480) [58]. The other phase III study (OASIS-2; NCT02877827) involving a new regimen of omadacycline (450 mg on days 1 and 2 orally, then 300 mg orally once daily) for treating adult subjects with acute bacterial SSSI also showed clinical noninferiority as compared with linezolid (600 mg orally every 12 h) [59]. It also showed non-inferior clinical efficacy to moxifloxacin in the treatment of community-acquired pneumonia (CAP) (EudraCT #2013-004071-13, NCT02531438) [13, 60]. In October 2018, omadacycline was approved for the treatment of CAP and acute bacterial SSSI by the FDA [61].

Ciprofloxacin and levofloxacin lose treatment efficacy in an acidic medium. Finafloxacin (Novartis, Basel, Switzerland) is a fluoroquinolone antibiotic (of the 8-cyano subclass) that is being developed in both an intravenous and an oral formulation [13]. It has higher potency (lower MICs) against ESBL-producing *E. coli* and *K. pneumoniae* isolates than the conventional fluoroquinolones owing to a higher binding affinity to DNA gyrase and topoisomerase IV in an acidic environment (pH 5.0–6.5). Thus, it is suitable for infections of the skin, urinary tract, and vagina [13, 39], where the environment is mostly acidic. In a phase II clinical study of cUTI (including APN), finafloxacin (800 mg intravenously or orally once daily) exhibited clinical and microbiological efficacy equivalent to ciprofloxacin (NCT01928433) [62]. Currently, finafloxacin is only available as a topical formulation for treatment of otitis media (ear drops, approved by the FDA).

Another new fluoroquinolone antibiotic, delafloxacin, has additional in vitro activity against levofloxacin-resistant *S. pneumoniae* and MRSA [28, 63, 64]. Compared with vancomycin plus aztreonam, delafloxacin monotherapy showed clinical non-inferiority as well as similar tolerability in the treatment of acute bacterial SSSI (NCT01811732) [65], and was approved by the FDA for this indication [28]. However, these two new fluoroquinolones were not demonstrated to have in vitro activities against CRE.

Murepavadin (formerly POL7080; Polyphor Ltd., Allschwil, Switzerland) is a 14-amino-acid synthetic peptidomimetic that acts on the outer membrane protein involved in the transport of the lipopolysaccharide component [13, 28]. It was proven to be a potent antibiotic highly specific to *P. aeruginosa*, including carbapenemase producers and colistin-resistant strains [66]. Two clinical trials evaluating the efficacy and safety of murepavadin in treating lower respiratory tract infections caused by *P. aeruginosa* (suspected or confirmed) among patients with VAP or bronchiectasis unrelated to cystic fibrosis have been completed (NCT02096315, and NCT02096328, respectively), and formal results are pending.

Table 2 illustrates the spectra of novel non-β-lactam antibiotics against Enterobacteriaceae producers of various β-lactamases (including carbapenemases), isolates of CR-*P. aeruginosa*, CR-*A. baumannii*, and *S. maltophilia*. Table 3 illustrates the clinical indications (or potential indications) for these novel antibiotics in treatment of various infections caused by XDR or MDR Gram-negative pathogens.

4 Arylomycin and Antibiotic Hybrids

There has been a greater degree of difficulty in designing new antibiotics with unique antibacterial mechanisms in the present decade than in previous decades. Arylomycin A-C_{16} exerts antibacterial effects by inhibition of type I signal peptidase, which leads to an insufficient flux of proteins through the secretion pathway. In target bacteria (including nutrient-depleted *S. aureus* isolates, and rapidly growing *E. coli*), arylomycin causes mislocalization of the essential proteins. Although the MIC breakpoints of arylomycin are not established, its unique antibacterial mechanism is significantly different from that of existing antibiotics. Thus, it has great potential [14, 67].

Table 2 Spectra of novel non-β-lactam antibiotics against important multidrug-resistant Gram-negative bacteria

Agents (references)	Company	Activity against indicated enzymes or multidrug-resistant strains								
		ESBL	KPC	MβL	AmpC	OXA	CRE	MDR-PA	MDR-Ab	SM
Plazomicin [17, 44]	Achaogen	+	+	+[a]	+		+	+	+	
Murepavadin [10, 55]	Polyphor							+		
Eravacycline [24, 36, 46]	Tetraphase	+	+	+	NDF	+	+		+	+
Omadacycline [24, 51]	Paratek	+[b]					+[c]			
Finafloxacin [10, 36]	MerLion	+	NDF	NDF	NDF	NDF	NDF	NDF	+[d]	+
Delafloxacin [24]	Melinta	+			+				+[e]	

ESBL extended-spectrum β-lactamase, *KPC Klebsiella pneumoniae* carbapenemase, *MβL* metallo-β-lactamase, *OXA* oxacillinase, *CRE* carbapenem-resistant Enterobacteriaceae, *MDR-PA* multidrug-resistant *Pseudomonas aeruginosa*, *MDR-Ab* multidrug-resistant *Acinetobacter baumannii*, *NDF* no data found, *SM Stenotrophomonas maltophilia*

\+ In vitro active efficacy

[a]Active against producers of Verona integron-encoded metallo-β-lactamase and imipenemase, not for New Delhi metallo-β-lactamase

[b]Limited for ESBL-producing *Escherichia coli* isolates

[c]Pharmaceutical company pursuing indications for *E. coli* only

[d]Enhanced activity demonstrated against ciprofloxacin-resistant strains

[e]Moderate activity against carbapenem-nonsusceptible isolates

Table 3 Clinical indications (or potential indications) for novel antibiotics in treatment of various infections caused by extensively-drug resistant or multidrug-resistant Gram-negative pathogens (data as of 27 February 2019)

Agents (references)	Indications, or potential indications				
	cUTI	cIAI	BSI	Pneumonia	Acute SSSI
Ceftozolane-tazobactam [13, 14]	+[a]	+[a]			
Ceftazidime-avibactam [14, 16, 19, 22]	+[a]	+[a]	+[a]	+[a,c]	
Meropenem-vaborbactam [28, 34]	+[a, b]	+	+	+[c]	
Ceftaroline-avibactam [10]	+				
Imipenem/cilastatin-relebactam [14]	+[b]	+		+[c]	
Aztreonam-avibactam [10]		+			
Meropenem-nacubactam [10, 26]	+[b]				
Cefiderocol [14, 18, 39, 40, 42, 43]	+[b]		+	+[c]	
Eravacycline [10, 36, 47, 52]	+	+[a]		+	
Plazomicin [14, 17, 48, 49]	+[a,b]		+	+[c]	
Omadacycline [10, 53, 59]	+			+[a,d]	+[a]
Delafloxacin [24, 64]					+[a]

cUTI complicated urinary tract infections, *cIAI* complicated intra-abdominal infections, *BSI* bloodstream infections, *SSTI,* skin and skin structure infections

\+ Denotes indication or potential indication in clinical therapy

[a]Approved by the US Food and Drug Administration

[b]Including acute pyelonephritis

[c]Hospital-acquired pneumonia, and ventilator-associated pneumonia

[d]Community-acquired pneumonia

Some antimicrobial peptides to treat XDR-GNB infections are also under development [68]. Research on antibiotic hybrids, defined as synthetic constructs of two or more pharmacophores belonging to an established agent known to produce a desired antimicrobial effect (over the outer membrane, and/or the constitutively over-expressed efflux pumps in bacteria), has opened a new direction in designing powerful antibiotics [15]. An example is a tobramycin-ciprofloxacin hybrid antibiotic that was found to significantly optimize the in vitro efficacy of ciprofloxacin against ciprofloxacin-resistant and MDR-*P. aeruginosa* strains [69].

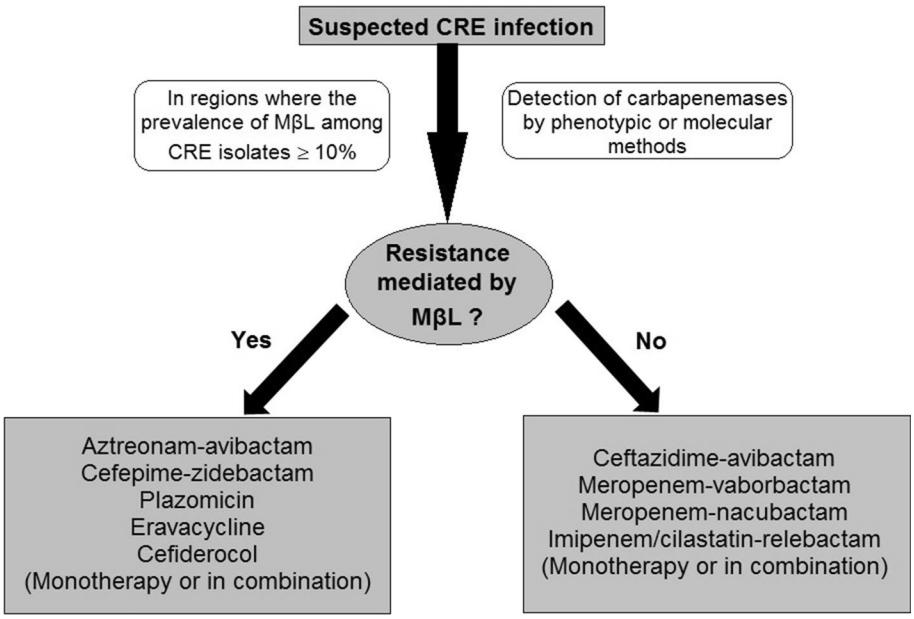

Fig. 1 Antibiotic choices for infections in which carbapenem-resistant Enterobacteriaceae (CRE) isolates are suspected based on the local prevalence of metallo-β-lactamases (MβL), and results of rapid molecular diagnostics

5 Rapid Phenotypic Diagnostics and Molecular Methods for Delineating Carbapenemase Production in Carbapenem-Resistant Enterobacteriaceae

Based on the aforementioned analyses, many new antibiotics (with the exception of omadacycline, finafloxacin, delafloxacin, and murepavadin) are active against CRE related to Ambler class A, C, and/or D enzyme production, while fewer exhibit in vitro activity against class B enzyme-(especially NDM variants) producing CRE [13, 18, 20]. It is alarming that since 2011, NDM-producing Enterobacteriaceae isolates have been detected in patients with cIAI or cUTI in southeastern Asia [2]. To prescribe these novel antibiotics judiciously and expeditiously, we urgently need rapid phenotypic (see below) and molecular diagnostic tools to detect MβL-producing CRE strains early in countries where the MβL prevalence is ≥ 10% [47].

6 Time for Stewardship

In order to achieve precision medicine that avoids erroneous prescription of these novel antibiotics [46], a strict antibiotic stewardship policy should be considered after resistance information on the implicated pathogens is obtained [70]. Effective interventions are of paramount importance in infection control. These include leadership commitment by infection experts, implementation of educational objectives, collaboration between antimicrobial stewardship teams and primary-care physicians, optimization of appropriate doses as well as de-escalation of antibiotics according to culture data and patient condition, and monitoring of in-hospital resistance trends [71]. Despite the arrival of new antibiotics, the consumption of carbapenem class agents has shown a notably positive relationship, with the incidence of Enterobacteriaceae showing non-susceptibility to carbapenems [72]. Consequently, judicious prescription of carbapenem agents is absolutely indicated in hospitals. It is noteworthy that utilization of the modified carbapenem inactivation method (CIM) in combination with the EDTA-modified CIM test could reliably differentiate MβL-producing CRE strains (those displaying a negative result on only the EDTA-modified CIM test) from serine-class carbapenemase producers (showing positive results for both tests) [73, 74]. In addition, polymerase chain reaction tests are of great help in understanding resistance epidemiology and delineating the carbapenemase-encoding alleles in XDR-GNB. An algorithm for antibiotic choices in the treatment of CRE infections is illustrated in Fig. 1.

7 Conclusions

Currently, the global burden of XDR-GNB is remarkably high. This resistance burden boosts the development of new potent antibiotics to combat difficult-to-treat pathogens. Robust clinical trials are warranted to evaluate the spectrum of activity, efficacy, and safety of these novel drugs before they are available clinically. In addition, despite the development of some rapid phenotypic tests to detect carbapenemase-producing GNB strains, rapid genotypic diagnostics are still required to accurately delineate the resistance mechanisms. Finally, from a pharmacoeconomic aspect, further studies of these new antibiotics are needed to

evaluate the benefits of combination therapy compared with monotherapy in further studies.

Acknowledgements The content of this manuscript is partly based on content presented at the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) in Madrid, Spain in April 2018 during the session 'Therapy of MDR/XDR Gram-Negative Bacteria: Dealing with the Devil' (SY026).

Compliance with Ethical Standards

Funding No specific grant from any funding agency in the public, commercial, or not-for-profit sector was obtained for this article.

Conflict of interest Authors SSJ, IMG, WSL, and PRH have no conflicts of interest to declare. Author IMG has served as a speaker on antibiotic resistance and stewardship for Merck, Bayer, Norma Hellas, Pfizer, Basilea, Xelia, and Sanofi and has received consulting honoraria from Merck, Bayer, Basilea, Pfizer, Achaogen, and AstraZeneca.

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