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Review

Infections by multidrug-resistant Gram-negative Bacteria: What's new in our arsenal and what's in the pipeline?

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ABSTRACT

The spread of multidrug-resistant bacteria is an ever-growing concern, particularly among Gram-negative bacteria because of their intrinsic resistance and how quickly they acquire and spread new resistance mechanisms. Treating infections caused by Gram-negative bacteria is a challenge for medical practitioners and increases patient mortality and cost of care globally. This vulnerability, along with strategies to tackle antimicrobial resistance development, prompts the development of new antibiotic agents and exploration of alternative treatment options. This article summarises the new antibiotics that have recently been approved for Gram-negative bacterial infections, looks down the pipeline at promising agents currently in phase I, II, or III clinical trials, and introduces new alternative avenues that show potential in combating multidrug-resistant Gram-negative bacteria.

1. Introduction

Antibiotic-resistant bacteria are spreading fast and stealthily around the world and are an ever-increasing health concern. Some estimates indicate that 700000 deaths per year can be attributed to antimicrobial resistance [1]. Although quantification of future excess morbidity and mortality is challenging, by 2050, mortality attributed to antibiotic resistance is estimated to increase to 10 million deaths annually and a cost of 100 trillion USD [1,2].

Gram-negative bacteria (GNBs) are of particular concern. One study placed the mortality risk ratio of healthcare-associated infections by multidrug-resistant (MDR) vs. non-MDR GNBs at 1.42 [95%-confidence interval (CI) 1.31-1.54%] at 30 days and 1.48 [95%CI 1.39-1.57%] at 90 days showing significant elevation in mortality risk [3]. Another study of hospital-acquired infections reported that for patients infected with antibiotic-resistant GNBs, the median length of hospital stay was increased by 5 days, and hospital cost was increased by 35.9% compared with non-resistant GNBs ($144 414 and $106 293 USD, respectively; $P<0.0001$) [4]. The special concern about GNBs arises partly from their efficiency at upregulating or acquiring new genes encoding a diverse range of antibiotic resistance mechanisms. GNBs can develop resistance through DNA mutations under selective pressure from antimicrobial agents (e.g. point mutations in DNA gyrase conferring fluoroquinolone resistance), or by acquisition from horizontal gene transfer (usually via mobile genetic elements, such as plasmids, transposons or integrons) [5]. These acquired resistance genes may produce antibiotic-inactivating enzymes, such as extended-spectrum β-lactamases (ESBLs), and carbapenemases [5]. Carbapenem-resistant Enterobacteriaceae (CRE) are particularly challenging to treat and usually become carbapenem-resistant by acquisition of carbapenemases. The most common (so called "Big Five") carbapenemases include *Klebsiella pneumoniae* carbapenemase (KPC), oxacillinase-type carbapenemase (OXA), and metallo-beta-lactamases (MBLs), which include imipenemase MBL (IMP), New Delhi MBL (NDM) and Verona integron-encoded MBL (VIM) [6]. NDM-1, most frequently encountered in *Escherichia coli* or *K. pneumoniae*, was first described in Sweden from a traveller returning from India in 2008,

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Table 1
Global priority list of antibiotic-resistant Gram-negative bacteria to guide research, discovery, and development of new antibiotics. World Health Organization. 2017 [13].

Priority 1: Critical	**Resistance spectrum**
Acinetobacter baumannii	carbapenem-resistant
Pseudomonas aeruginosa	carbapenem-resistant
Enterobacteriaceae	carbapenem-resistant, third-generation cephalosporin-resistant
Priority 2: High	
Helicobacter pylori	clarithromycin-resistant
Campylobacter	fluoroquinolone-resistant
Salmonella spp.	fluoroquinolone-resistant
Neisseria gonorrhoeae	third-generation cephalosporin-resistant, fluoroquinolone-resistant
Priority 3: Medium	
Haemophilus influenzae	ampicillin-resistant
Shigella spp.	fluoroquinolone-resistant

and NDM genes have since rapidly spread among different clonal lineages and across a diverse range of Gram-negative species and are now globally distributed [7,8].

Unfortunately, despite the implementation of strategies to tackle antibiotic resistance development, the rate of antibacterial resistance is expected to increase inexorably [9,10]. The widespread use of antibiotics in animals and humans, the increasing global population and the rise of globalisation has helped disseminate resistance throughout the world [11]. On the other hand, the rate of new antibiotic development has been decreasing every decade since the 1980s and drastically after the 2000s [12]. This led to initiatives, such as the '10 x 20 initiative' set by the Infectious Diseases Society of America (IDSA) to encourage more antibiotic research with the goal of having 10 new antibiotic treatments by 2020 [12]. In the World Health Organization (WHO) Priority Pathogens List for Research & Development of New Antibiotics published in 2017 (Table 1), all bacteria in the Priority 1 Critical category are carbapenem-resistant GNB strains, including carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa*, and third-generation cephalosporin-resistant Enterobacteriaceae, which includes common pathogens such as *E. coli, Enterobacter* spp. and *K. pneumoniae* [13,14]. Due to the emergence of GNB strains that cannot be treated with any existing marketed antibiotics, GNBs are designated by the WHO as the most critical priority for antibiotic research and development [15].

This review introduces some recently approved novel antibiotics that can combat existing MDR GNBs, with drug information summarised in Table 2 and chemical structures summarised in the Supplementary material [16]. These novel antibiotics include ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, plazomicin and eravacycline. The review also explores some novel antibiotics that are currently in clinical trials or development, and discusses alternative/complementary management approaches that could potentially prove useful in the battle against MDR GNBs [16]. Finally, pharmacokinetic/pharmacodynamic (PK/PD) strategies to optimise the use of our currently available antibiotics against GNBs will be briefly described.

2. Novel approved antibiotics

2.1. β-Lactam/β-lactamase inhibitor combinations

2.1.1. Ceftolozane/tazobactam

Ceftolozane/tazobactam (trade name Zerbaxa, developed by Merck/MSD) is a combination of ceftolozane, a novel oxyimino-aminothiazolyl cephalosporin, and the β-lactamase inhibitor tazobactam [17,18]. Ceftolozane resembles the third-generation cephalosporin ceftazidime but has a modified side chain that gives a more potent inhibition profile towards penicillin-binding proteins (PBPs) [19]. Tazobactam is a penicillanic acid sulfone derivative and an irreversible inactivator of β-lactamase [18]. It is exclusively cleared renally [20].

Ceftolozane has a minimum inhibitory concentration (MIC) against *P. aeruginosa* that is 8- to 16-fold lower compared with ceftazidime, imipenem, and ciprofloxacin [21]. The effectiveness of ceftolozane is limited by the production of ESBLs and AmpC β-lactamases, although stability to hydrolysis by AmpC enzymes may be dependent on the level of expression as well as the specific organism and enzyme type [22,23]. To overcome this barrier, tazobactam has been used to increase the coverage of ceftolozane. The addition of tazobactam to ceftolozane elevates in vitro activity against β-lactamase-producing microorganisms and ESBL-producers, such as *E. coli, K. pneumoniae*, and *Proteus mirabilis*, as well as some inhibition against AmpC de-repressed Enterobacter and Citrobacter strains [17,24]. Ceftolozane/tazobactam has also demonstrated higher in vitro activity than available cephalosporins against Enterobacteriaceae but remains susceptible to hydrolysis by MBLs and KPC enzymes [25,26]. One in vitro study also showed that ceftolozane/tazobactam is effective against *P. aeruginosa* in the planktonic state, not the biofilm state [27].

In vivo activities against neutropenic murine thigh infection models showed a 2:1 ratio of ceftolozane/tazobactam was the most effective formulation for both efficacy and MIC reduction [28]. In a prospective, randomised, double-blind, phase II trial (ClinicalTrials.gov Identification Number: NCT01147640), ceftolozane/tazobactam in combination with metronidazole was compared against meropenem for complicated intra-abdominal infections (cIAIs) [29]. The combination had microbiological success against *E. coli* (89.5%), *P. aeruginosa* (100%), and *K. pneumoniae* (100%), and was found to be well tolerated with similar adverse event rates (50% vs. 48.8% in meropenem) [30]. In a randomised, double-blind, phase III trial (NCT01345929), ceftolozane/tazobactam was superior to levofloxacin for complicated urinary tract infections (cUTIs) [31]. The microbiological eradication at the test-of-cure visit 5 to 9 days after treatment was 88.9% for ceftolozane/tazobactam compared with 77.4% [95%CI 5.8-17.1%] for levofloxacin, and both were well tolerated with 34.7% and 34.4% adverse event rates, respectively [31,32]. In 2014, the U.S. Food and Drug Administration (FDA) approved the use of Zerbaxa for cUTIs and its combination with metronidazole was approved for cIAIs [18]. In 2015, the European Medicines Agency (EMA) approved ceftolozane/tazobactam for cIAIs, acute pyelonephritis, and cUTIs [33]. A randomised, double-blind, phase III trial (NCT02070757) of ceftolozane/tazobactam compared with meropenem for patients with ventilator-acquired pneumonia (VAP) completed its recruitment recently, and results are pending [34]. It should be noted that the dose used in the above trial is double the approved dose for cIAIs and cUTIs as the epithelial lining fluid (ELF)/plasma ratio is 50% [35].

In summary, ceftolozane/tazobactam has good in vitro activity against most Enterobacteriaceae (including ESBL-producers) and notable effectiveness against *P. aeruginosa* [36].

2.1.2. Ceftazidime/avibactam

Ceftazidime/avibactam (trade name Avycaz (Allergan) in US and Canada; Zavicefta (Pfizer) outside US and Canada) is a combination of the cephalosporin ceftazidime and the non-β-lactam β-lactamase inhibitor avibactam [37]. Ceftazidime is an established third-generation cephalosporin with predominant activity against Gram-negative bacilli, but ceftazidime-resistant GNBs have become increasingly more common [38]. Ceftazidime is resistant to hydrolysis by many of the older narrow-spectrum β-lactamases (such as TEM-1 or SHV-1); however, it is not stable against ES-

Table 2
Summary of novel antibiotics approved by FDA and EMA since 2010.

Drug	Approval time	Antibiotic class	Company	Inhibitor provides stability to β-lactamase[1]					Spectrum against organisms [15]		Indication	Dosage[5]
				ESBL	KPC	OXA[2]	AmpC	MBLs[3]	Effective against	Ineffective against		
Ceftolozane/ Tazobactam (Zerbaxa)	FDA: December 2014; EMA: September 2015	Cephalosporin/ β-lactamase inhibitor	Merck & Co. (US, Canada); Merck Sharp & Dohme (MSD) (outside US & Canada)	+	-	-	+/-	-	MDR-*P. aeruginosa*[4], Enterobacteriaceae (including some ESBL and AmpC producers)	NDM- or IMP-producing Enterobacteriaceae, CRAB	FDA: cIAI, cUTI; EMA: cIAI, cUTI	1 g/0.5 g by IV infusion over 1 h every 8 h [18,33]
Ceftazidime/ Avibactam (Avycaz in US, Canada; Zavicefta outside US & Canada)	FDA: February 2015; EMA: June 2016	Cephalosporin/ β-lactamase inhibitor	Allergan Inc. (US, Canada); Pfizer (outside US & Canada)	+	+	+	+	-	Enterobacteriaceae (including ESBL, AmpC, KPC and OXA-48 producers), MDR-*P. aeruginosa*[4]	NDM- or IMP-producing Enterobacteriaceae, CRAB	FDA: cIAI, cUTI; EMA: cIAI, cUTI, HAP, VAP	2 g/0.5 g by IV infusion over 2 h every 8 h [54,55]
Meropenem/ Vaborbactam (Vabomere)	FDA: August 2017	Carbapenem/ β-lactamase inhibitor	Rempex Pharmaceuticals Inc.	+	+	-	+	-	Enterobacteriaceae (including KPC, ESBL and AmpC producers, and CRE)	MDR-*P. aeruginosa*[4] (including CRPA), CRAB	FDA: cUTI	2 g/2 g by IV infusion over 3 h every 8 h [57]
Plazomicin (Zemdri)	FDA: June 2018	Aminoglycoside	Achaogen Inc.	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	Enterobacteriaceae (including CRE)	Organisms producing 16S rRNA methyltransferases, CRAB, CRPA	FDA: cUTI	15 mg/kg by IV infusion over 30 min every 24 h [80]
Eravacycline (Xerava)	FDA: August 2018; EMA: October 2018	Tetracycline	Tetraphase Pharmaceuticals Inc.	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	Enterobacteriaceae (including CRE), *A. baumannii* (including CRAB)	*P. aeruginosa* (including CRPA), *B. cenocepacia*	FDA: cIAI; EMA: cIAI	1 mg/kg by IV infusion over 1 h every 12 h [90,91]

Note:
[1] '+' indicates positive protection, '-' indicates no protection and '+/-' indicates possible protection against β-lactamases.
[2] OXA (oxacillinase) refers to OXA carbapenemases, e.g. OXA-48.
[3] MBLs (metallo-beta-lactamases) include NDM (New Delhi metallo-β-lactamase), IMP (Imipenemase metallo-β-lactamase) and VIM (Verona integron-encoded metallo-β-lactamase).
[4] MDR (multidrug-resistant)-*P. aeruginosa* utilises chromosomal AmpC β-lactamase, porin loss, and efflux pumps for its antibiotic resistant mechanisms.
[5] Dosage refers to patients 18 years or older of age; For ceftolozane/tazobactam and ceftazidime/avibactam: dosage is for patients with CrCl greater than 50 mL/min. For meropenem/vaborbactam: dosage is for patients with eGFR equal or greater than 50 mL/min/1.73 m^2. For plazomicin: dosage is for patients with CrCl equal or greater than 60 mL/min. For eravacycline: dosage is for patients without severe (Child-Pugh C) hepatic impairment.
Abbreviations: cIAI (complicated intra-abdominal infection), CRAB (carbapenem-resistant *Acinetobacter baumannii*), CrCl (creatinine clearance), eGFR (estimated glomerular filtration rate), CRPA (carbapenem-resistant *Pseudomonas aeruginosa*), cUTI (complicated urinary tract infection), EMA (European Medicines Agency), ESBL (extended spectrum β-Lactamase), EU (European Union), FDA (United States Food and Drug Administration), HAP (hospital-acquired pneumonia), IMP (imipenemase metallo-β-lactamase), IV (intravenous), KPC (*Klebsiella pneumoniae* carbapenemase), MBL (metallo-β-lactamase), MDR (multidrug-resistant), NDM (New Delhi metallo-β-lactamase), OXA (oxacillinase), rRNA (ribosomal ribonucleic acid), US (the United States), VAP (ventilator-acquired pneumonia), VIM (Verona integron-encoded metallo-β-lactamase).
Bacteria abbreviations: *A. baumannii* (*Acinetobacter baumannii*), *B. cenocepacia* (*Burkholderia cenocepacia*), *P. aeruginosa* (*Pseudomonas aeruginosa*).

BLs, class C (AmpC-type) enzymes and carbapenemases, such as KPCs and MBLs [39]. To protect against this susceptibility, ceftazidime has been paired with avibactam, which is a diazabicyclooctane that provides protection against class A and C β-lactamases by binding covalently and inhibiting their actions [39]. Of note, avibactam (in contrast to tazobactam) binds reversibly to β-lactamases [37]. Ceftazidime/avibactam is primarily cleared by the kidneys [40]. In vitro studies of ceftazidime/avibactam have demonstrated inhibition against >99.9% of Enterobacteriaceae and *P. aeruginosa* isolates that were resistant to meropenem, ceftazidime and piperacillin/tazobactam [41]. Ceftazidime/avibactam had activity against 100% of KPC and OXA-48 producers in urine isolates, the most prevalent carbapenemases in the study [42]. Ceftazidime/avibactam also had coverage against ESBLs and most KPCs but not MBLs [43-45].

A randomised, double-blind, superiority phase III trial (NCT01595438) comprising 1033 hospitalised adult patients who were given either ceftazidime/avibactam or doripenem for cUTIs has been completed [46]. Ceftazidime/avibactam showed non-inferiority for the co-primary endpoints of symptom resolution and combined resolution/microbiological cure; superiority was shown in the EMA endpoint (using a 5% significance level, which indicated superiority on the microbiological endpoint) [47]. In an open-label, randomised, non-inferiority phase III trial (NCT01644643) of patients with cUTIs or cIAIs due to ceftazidime-resistant pathogens, ceftazidime/avibactam demonstrated similar cure rates at 91% for test-of-cure visits compared with best available therapy (97% of the time this was a carbapenem) [48,49]. The adverse event rate was 31% for ceftazidime/avibactam and 39% for carbapenem, with gastrointestinal disorders the most frequently reported [49]. A randomised, double-blind, phase III study (NCT01726023) from Asia comparing ceftazidime/avibactam plus metronidazole to meropenem in the treatment of cIAIs showed comparative effectiveness with clinical cure rates of 93.8% and 94.0%, respectively [50]. A randomised, double-blind, non-inferiority phase III trial (NCT01808092) for hospital-acquired pneumonia (HAP)/VAP showed 77.4% cure rate in the ceftazidime/avibactam-treated group compared with 78.1% in the meropenem-treated group, which shows ceftazidime/avibactam as non-inferior and a potential alternative to meropenem [51,52]. In 2015, ceftazidime/avibactam was approved by the FDA to treat cUTIs, and its combination with metronidazole was approved to treat cIAIs [53,54]. The EMA approved ceftazidime/avibactam in 2016 for the indications of cUTIs, cIAIs, HAP/VAP, and infections by GNBs when other treatments might not work [55]. It should be highlighted that the infusion time of ceftazidime/avibactam is 2 h and this can be considered an extended infusion and might contribute to its effectiveness [54].

In summary, ceftazidime/avibactam has a wide range of activity against GNBs, including most of the KPC- and OXA-48-producers [45,56].

2.1.3. Meropenem/vaborbactam

Meropenem/vaborbactam (trade name Vabomere, previously named Carbovance; vaborbactam developed by Rempex Pharmaceuticals Inc., acquired by Melinta Therapeutics) is a combination of the broad-spectrum carbapenem meropenem with the β-lactamase inhibitor vaborbactam [57]. Meropenem is a bactericidal β-lactam that inhibits cell wall synthesis by binding to PBPs. Meropenem/vaborbactam is primarily excreted by the kidneys [57]. Meropenem is effective against both Gram-positive and Gram-negative bacteria, and it is resistant to hydrolysis by many β-lactamases, except carbapenemases such as KPCs [58,59]. To resist degradation against these enzymes, a novel cyclic boronate β-lactamase inhibitor vaborbactam has been added. Vaborbactam by itself has no antibacterial activity but it protects meropenem from destruction by serine β-lactamases that target carbapenems [60,61]. When tested in vitro against KPC-positive Enterobacteriaceae, meropenem/vaborbactam inhibited 99.0% of the isolates [62]. Another study showed similar success at inhibiting KPC-positive Enterobacteriaceae and reported a 98.5% inhibition rate [63]. However, when tested against *A. baumannii* producing primarily class D (OXA-type) carbapenemases and *P. aeruginosa* with MDR phenotypes mediated by porin changes and efflux mechanisms, the addition of vaborbactam did not increase bacterial susceptibility [63].

In a randomised, double-blind, phase III trial (NCT02166476; 'TANGO I') comparing meropenem/vaborbactam against piperacillin/tazobactam in an intent-to-treat study against cUTIs, patients who received meropenem/vaborbactam achieved a clinical success rate of 98.4% compared with 94.0% for piperacillin/tazobactam [64]. Additionally, the endpoint for the FDA (overall success at the end of the intravenous treatment visit), and the endpoint for the EMA (microbiological eradication) were both met in this study [64]. Another open-label, randomised, phase III trial (NCT02168946; 'TANGO II') was completed in 2017, and meropenem/vaborbactam demonstrated increased clinical cure rate and decreased 28-day all-cause mortality compared with the best available treatment for cUTIs, HAP/VAP, and bacteraemia caused by CRE [65]. Vabomere was approved by the FDA in 2017 for cUTIs [57]. The EMA has recommended granting a marketing authorisation for Vabomere in September 2018 [66]. A randomised, double-blind, comparative phase III trial (NCT03006679; 'TANGO III') comparing meropenem/vaborbactam against piperacillin/tazobactam in HAP/VAP is ongoing [67].

In summary, meropenem/vaborbactam has demonstrated success against a wide range of KPC-positive Enterobacteriaceae and it is a viable option against MDR GNBs.

2.2. Aminoglycosides

2.2.1. Plazomicin

Plazomicin (trade name Zemdri, developed by Achaogen) is a new aminoglycoside derivative of sisomicin that inhibits bacterial protein synthesis [68]. The half-life of plazomicin is 2-3 h, and its lung penetration is quite poor; the ratio of ELF to plasma area under the concentration-time curve (AUC) is approximately 13%, which is similar to that of amikacin (14%) [69,70]. Plazomicin is eliminated via the kidneys [71]. Adverse effects associated with plazomicin include dizziness, hypoaesthesia, somnolence, nausea and transient mild-to-moderate hypotension [69]. No clinically significant impairment of vestibular, cochlear or renal function was observed [69]. The antibacterial spectrum of plazomicin covers GNBs, including CRE, with minimal activity against *P. aeruginosa* and *Acinetobacter* spp. [72]. Plazomicin is active in vitro against CRE and aminoglycoside-resistant Enterobacteriaceae containing aminoglycoside-modifying enzymes [73-76]. The combination of plazomicin with colistin, meropenem or fosfomycin showed synergistic activity against VIM-1- and KPC-2-producing *K. pneumoniae* isolates [76]. However, it is not active against bacteria containing ribosomal methyltransferases found in most NDM-1-producing Enterobacteriaceae (*E. coli, K. pneumoniae, Enterobacter* spp.) that are also resistant to amikacin, gentamicin and tobramycin [73,74,77].

In a multinational, randomised, double-blind, non-inferiority phase III study (NCT02486627; Evaluating Plazomicin in cUTI [EPIC]), 388 (64%) of 609 enrolled patients were analysed in the microbiological modified intent-to-treat (mMITT) population [78]. At test-of-cure visit, in patients with cUTIs, microbiological eradication by plazomicin vs. meropenem was 86.9% vs. 75.6% (95%CI 0.4-21.7%), and in patients with acute pyelonephritis was 85.7% vs. 71.8% [95%CI 0.4-27.1%] [78]. Once-daily plazomicin also demonstrated non-inferiority compared with meropenem, with a clinical

cure rate of 87.9% vs. 91.6% in patients with cUTIs and 90.5% vs. 88.5% in patients with acute pyelonephritis [78]. Plazomicin was generally well-tolerated, with the most common adverse events reported to be diarrhoea, hypertension, headache, nausea and vomiting [78]. The EPIC study supports the use of plazomicin as a potential new treatment option for cUTIs and acute pyelonephritis [78]. Another multicentre, randomised, open-label phase III trial (NCT01970371; Combating Antibiotic-Resistant Enterobacteriaceae [CARE]) compared the efficacy of plazomicin with that of colistin in the treatment of bloodstream infections (BSIs) or HAP/VAP due to CRE based on day 28 all-cause mortality or significant disease-related complications [79]. Both plazomicin and colistin were administered in combination with adjunctive therapy of meropenem or tigecycline [79]. In 39 patients with BSIs or HAP/VAP, plazomicin showed reduced all-cause mortality of 11.8% at day 28 compared with 40.0% for colistin (90%CI 0.7-52.5%) [79]. In BSI patients, plazomicin also demonstrated favourable microbiological response rate compared with colistin (92.9% vs. 60.0% at End-of-Treatment; 92.9% vs. 53.3% at Test-of-Cure) [79]. In June 2018, the FDA approved plazomicin for the indication of adult cUTIs including pyelonephritis but not BSI [80]. The EMA also accepted an application from Achaogen in the same month [81].

In summary, plazomicin is potent and has good synergistic activity with colistin, meropenem or fosfomycin against VIM-1 and KPC-2 producing GNBs. However, plazomicin should be used only as a last resort when there are limited or no alternative treatment options available [80].

2.3. Tetracyclines

2.3.1. Eravacycline

Eravacycline (trade name Xerava, developed by Tetraphase Pharmaceuticals Inc.) is a novel fluorocycline with broad-spectrum antibacterial activity; it is a synthetic tigecycline analogue with a pair of modifications to the D-ring core at C-7 and C-8 that widens its activity [82,83]. In vitro studies have demonstrated broad-spectrum antimicrobial activity against GNBs with the exception of *P. aeruginosa* and *Burkholderia cenocepacia* [83]. Eravacycline is resistant against expression of tetracycline-targeting efflux channels, ribosomal protection mechanisms, and β-lactamases [83]. It is notably successful against carbapenem-resistant *A. baumannii* and was more potent than any other drug tested in an in vitro study [84]. Eravacycline is also effective against biofilms formed by uropathogenic *E. coli* [85].

In a randomised, double-blind, non-inferiority phase III trial (NCT01844856; 'IGNITE1') comparing eravacycline with ertapenem, the intent-to-treat populations receiving eravacycline had a cure rate of 86.8% vs. a cure rate of 87.6% for ertapenem, indicating non-inferiority and demonstrating eravacycline as a promising alternative option for patients with cIAIs with MDR GNBs [86,87]. A recently published post hoc analysis of the IGNITE1 trial and another similar phase III trial (NCT02784704; 'IGNITE4') demonstrated a favourable microbiological response rate of 88.9% and 100% for eravacycline against ESBL-producing Enterobacteriaceae and *A. baumannii*, respectively [88,89]. The FDA and the EMA approved eravacycline for the indication of adult cIAIs in August and October 2018, respectively [90,91]. Meanwhile, a randomised phase III trial (NCT03032510; 'IGNITE3') comparing eravacycline with ertapenem for cUTIs was recently completed and results are pending [92].

In summary, although not effective against *P. aeruginosa*, the effectiveness of eravacycline against a wide variety of GNBs and the problematic organism *A. baumanni* has made it a helpful tool in fighting MDR GNBs.

A summary of the newly approved antibiotics ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, plazomicin and eravacycline is presented in Table 2.

3. Antibiotics in phase III clinical trials

3.1. β-Lactams or β-lactam/β-lactamase inhibitor combinations

3.1.1. Sulopenem

Sulopenem (CP-70,429, developed by Pfizer Japan) is a new broad-spectrum carbapenem that is potent against both Gram-positive and Gram-negative bacteria. It is not active against *Stenotrophomonas maltophilia* or *P. aeruginosa*, which exhibit high intrinsic resistance to sulopenem [93,94]. In vitro, sulopenem showed bactericidal activities against ESBL-producing Enterobacteriaceae (MIC_{50} 0.015–0.125 μg/mL), and Gram-positive and Gram-negative anaerobes [95,96]. In four different animal models, sulopenem demonstrated dose-dependent activity, and was active against ESBL-producing *K. pneumoniae* and *E. coli* [97,98]. Pfizer Japan completed an extensive preclinical program, followed by a phase II trial of intravenous formulation of sulopenem in Japan and a phase II trial of its oral prodrug in community-acquired pneumonia (CAP) in the US [99]. Although the results were encouraging, the development of sulopenem by Pfizer was abandoned, and Iterum Therapeutics obtained the license of sulopenem and its prodrugs and restarted the development program in 2015 [99]. Although most carbapenems are administered intravenously, sulopenem can be administered both orally as a tablet form or intravenously with good bioavailability [99]. Iterum Therapeutics is commencing three phase III studies for the treatment of uncomplicated urinary tract infections (uUTIs) (NCT03354598), cUTIs (NCT03357614), and cIAIs (NCT03358576) by the end of 2018, with a plan to file a New Drug Application (NDA) by late 2019 [99-102].

3.1.2. Imipenem/cilastatin + relebactam (MK-7655)

Relebactam (developed by Merck/MSD) is a novel β-lactamase inhibitor that inhibits class A and C β-lactamases [103]. It is administered intravenously in combination with imipenem, a β-lactam cell wall inhibitor, and cilastatin, a dehydropeptidase inhibitor, to prolong the antibiotic effect of imipenem [104]. Imipenem/relebactam was active against Enterobacteriaceae and non-fermenting GNBs. They include *E. coli* (ESBL- and KPC-producing strains), *K. pneumoniae* (ESBL, KPC, AmpC and OXA-positive strains), imipenem-resistant *K. pneumoniae* expressing AmpC β-lactamases or KPC carbapenemases, and *P. aeruginosa* isolates with either outer membrane porin protein D (OprD) deficiency or expression of AmpC [105,106]. However, imipenem/relebactam is not active against imipenem-resistant Enterobacteriaceae expressing IMPs, VIMs or NDM MBLs, *A. baumannii*, or IMP- or VIM-producing *P. aeruginosa* [106].

In two recently completed randomised non-inferiority phase II trials in patients with cIAIs or cUTIs caused by imipenem-resistant GNBs, imipenem-cilastatin/relebactam demonstrated non-inferiority compared with imipenem-cilastatin with similar tolerability and safety profiles [107,108]. Notably, both studies included only a very low number of imipenem-resistant strains, which represented an important limitation and highlighted the need for further trials, particularly involving patients with CRE infections [107,108]. Specifically, in the cIAI study (NCT01506271) only 36 patients (13% of the MITT population) had at-baseline GNB strains non-susceptible to imipenem, whereas in the cUTI study (NCT01505634) only 10% of the isolated strains were imipenem-non-susceptible [107,108]. Moreover, in both studies, the addition of relebactam did not restore susceptibility to imipenem, presumably due to mechanisms other than β-lactamases vulnerable to relebactam inhibition [107,108]. In a randomised, double-blind, phase III trial (NCT02452047) testing imipenem-cilastatin/relebactam against imipenem-cilastatin/colistimethate sodium combination in the treatment of imipenem-resistant infections (HAP, VAP, cIAIs, cUTIs),

imipenem-cilastatin/relebactam demonstrated a higher favourable clinical response (71.4% vs. 40%) and a lower all-cause mortality (9.5% vs. 30%) compared with cilastatin/colistimethate sodium [109]. Two phase III trials (NCT03583333, NCT02493764) are currently recruiting, investigating imipenem-cilastatin/relebactam vs. piperacillin/tazobactam for treatment of HAP/VAP in China and multiple countries, respectively [110,111]. Specifically targeting β-lactamase-producing MDR GNBs, relebactam has exhibited great potential in treating nosocomial infections. In 2014, the FDA designated imipenem-cilastatin/relebactam fast track status for the treatment of bacterial HAP, VAP, cIAIs and cUTIs [112].

3.1.3. Cefiderocol or S-649266

Cefiderocol (developed by Shionogi & Co. Ltd.) is a novel siderophore cephalosporin with a catechol at the third position side chain [113]. Cefiderocol displays antibiotic activity against aerobic GNBs as it binds to ferric ion, utilises the iron uptake system and bypasses their outer membrane barriers [113]. Cefiderocol is also stable against β-lactamases, including metallo- and serine-carbapenemases, via passive diffusion through porin channels [114]. Cefiderocol has demonstrated potent in vitro activity against a large spectrum of GNBs, including Enterobacteriaceae and *Vibrio* spp., and non-fermenting bacteria, such as *Acinetobacter* spp., *Pseudomonas* spp., and *Burkholderia* spp. [115]. Cefiderocol was potent in vitro as well as in vivo in a neutropenic murine thigh model against *P. aeruginosa* resistant to other siderophore cephalosporins [116].

There are two ongoing phase III trials and one completed phase II trial. The completed randomised, double-blind, phase II trial (NCT02321800) compared cefiderocol with imipenem/cilastatin for cUTIs in hospitalised patients and demonstrated superiority of cefiderocol against GNBs while being well tolerated [117]. One ongoing randomised, open-label phase III trial (NCT02714595) comparing cefiderocol against best available therapy is set to test the treatment with cefiderocol against a variety of severe infections (BSIs, cUTIs, HAP/VAP) by carbapenem-resistant GNBs [118]. A second ongoing randomised, double-blind, phase III trial (NCT03032380) comparing cefiderocol with meropenem for HAP/VAP is estimated to be completed in 2019 [119]. The company plans to submit an NDA in late 2018 followed by a marketing authorisation application to the EMA [120]. The wide spectrum of activity of cefiderocol against siderosphore-resistant bacteria and non-fermenting bacteria demonstrates its great potential in fighting GNB infections.

3.1.4. Cefepime/AAI101

Cefepime, a fourth-generation cephalosporin with a wide range of Gram-positive and Gram-negative activity, is combined with the β-lactamase inhibitor **AAI101** (developed by Allecra) [121]. Cefepime is an established cephalosporin; however, there has been an increase of resistance in β-lactamase-producing Enterobacteriaceae [121]. AAI101 is a novel β-lactamase inhibitor that has inhibitory activities on a wide array of β-lactamases as well as some class A and class B carbapenemases [121]. The combination of cefepime/AA101 has been tested in vitro against highly resistant *K. pneumoniae* and *E. coli* strains, and AA101 restored the susceptibility of these organisms against cefepime [121]. A randomised, double-blind, non-inferiority, phase II trial (NCT03680612) comparing cefepime/AAI101 with cefepime in hospitalised adults with cUTIs has been completed, pending results [122]. A randomised, double-blind, non-inferiority phase III trial (NCT03687255) comparing cefepime/AAI101 with piperacillin/tazobactam in the treatment of cUTIs is currently recruiting [123].

3.2. Outer Membrane Protein Targeting Antibiotics (OMPTAs)

3.2.1. Murepavadin (POL7080)

Murepavadin (POL7080, developed by Polyphor Pharmaceuticals) is a protein epitope mimetic belonging to a novel class of antibiotics called the Outer Membrane Protein Targeting Antibiotics (OMPTAs). It targets the lipopolysaccharide transport protein D (LptD) on the outer membrane of *P. aeruginosa*, and is critical for lipopolysaccharide synthesis [124,125]. Therefore, it is highly specific for *P. aeruginosa*, and has demonstrated activity against MDR *P. aeruginosa* in a murine pneumonia model [126]. A phase I clinical trial showed that murepavadin was safe and well-tolerated in healthy volunteers [127]. In a phase II study (NCT02096328), murepavadin demonstrated good lung penetration and showed encouraging results when given on top of standard-of-care in patients with VAP, with a cure rate of 80% and a 28-day all-cause mortality of 8% [128]. A randomised, parallel phase III trial (NCT03409679) to compare murepavadin combined with one anti-pseudomonal antibiotic with the combination of two anti-pseudomonal antibiotics in treating VAP is currently recruiting [129].

A summary of the antibiotics in phase III clinical trials is presented in Table 3.

4. Antibiotics in phase II and phase I clinical trials

4.1. Phase II drugs

4.1.1. LYS228

LYS228 (developed by Novartis Pharmaceuticals) is a new monobactam that strongly binds PBP-3 and inhibits bacterial peptidoglycan synthesis [130]. It is stable against NDM-1, KPCs, and most ESBLs, resulting in retained potency against ESBLs and CRE [131]. In vitro, LYS228 is potent against both wild-type and β-lactamase-producing Enterobacteriaceae, regardless of β-lactamases produced, and has potency similar to tigecycline [131]. With a broad spectrum against MDR GNBs, LYS228 has great potential in treatment of nosocomial infections. It is currently in two phase II trials (NCT03377426, NCT03354754) testing its PK, clinical response, safety and tolerability in patients with cUTIs and cIAIs, respectively [132,133].

4.1.2. Sulbactam/ETX2514 (ETX2514SUL)

ETX2514SUL (developed by Entasis Therapeutics Inc.) is a combination of sulbactam, a β-lactam antibiotic, and ETX2514, a diazabicyclooctane with wide-spectrum inhibition of class A, B, and D β-lactamases, and potent in vivo efficacy against MDR *A. baumannii* [134]. A phase I trial of ETX2514SUL has demonstrated positive PK and drug tolerance results, and a phase II trial (NCT03445195) evaluating the safety and efficacy of intravenous ETX2514SUL in patients with cUTIs was concluded and results are pending [135,136]. ETX2514SUL has been awarded Fast Track status by the FDA, and a plan to move to phase III trials in early 2019 is underway [135].

4.2. Phase I drugs

4.2.1. WCK5222

WCK5222 (developed by Wockhardt Discovery) is a combination of cefepime, a cephalosporin, and zidebactam, which binds to Gram-negative PBP-2 and inhibits β-lactamases [137]. In vitro, WCK5222 was potent against β-lactamase-producing Enterobacteriaceae and *P. aeruginosa* [137]. WCK5222 is potentially indicated for HAP/VAP, BSI/sepsis, cIAIs and cUTIs [138]. A phase I study (NCT02707107) evaluating the safety, tolerability and PK of intravenous WCK5222 has been completed, and results are pending for

Table 3
Summary of antibiotics with activity against Gram-negative bacteria currently in clinical trials.

Drug name	Phase	Company	Drug class and MOA	Spectrum against Gram-negative bacteria and enzymes [15]		Potential indications	Ongoing clinical trials (ClinicalTrial.gov No.)
				Effective against	Ineffective against		
Sulopenem	III	Pfizer and Iterum Therapeutics Ltd.	β-lactam	ESBL-producing Enterobacteriaceae	CRE, *P. aeruginosa*, *S. maltophilia*	cIAI, cUTI, uUTI	NCT03354598, NCT03357614, NCT03358576
Imipenem/cilastatin + Relebactam (MK-7655)	III	Merck Sharp & Dohme Corp.	β-lactamase inhibitor + β-lactam/ dehydropeptidase inhibitor	Enterobacteriaceae producing class A and C β-lactamases: *E. coli* (ESBL- and KPC strains), *K. pneumoniae* (ESBL, KPC, AmpC and OXA type carbapenemase strains) and *P. aeruginosa* isolates with either porin deficiency or over-expression of chromosomal AmpC	Imipenem-resistant Enterobacteriaceae expressing IMP, VIM or NDM MBLs, *A. baumannii*, IMP- or VIM-producing *P. aeruginosa*	cIAI, cUTI, HAP, VAP	NCT02493764, NCT03583333
Cefiderocol or S-649266	III	Shionogi & Co. Ltd.	Cephalosporin	ESBL and AmpC-producing Enterobacteriaceae, CRE (irrespective of carbapenemase-production), carbapenem-resistant *Acinetobacter* spp., MDR-*Pseudomonas* spp., *S. maltophilia* and *Burkholderia* spp.		BSI, cUTI, HAP, VAP	NCT02714595, NCT03032380
Cefepime/AAI101	III	AAI101: Allecra	β-lactam + β-lactamase inhibitor	ESBL and carbapenemase-producing Enterobacteriaceae	CRAB, CRPA	cUTI	NCT03687255
Murepavadin or POL7080	III	Polyphor Ltd.	OMPTA	CRPA	CRAB, CRE	HAP, VAP by *P. aeruginosa*	NCT03409679
LYS228	II	Novartis Ag.	β-lactam	Enterobacteriaceae-producing NDM-1, KPC, most ESBLs, CRE	CRAB, CRPA	cIAI, cUTI	NCT03377426, NCT03354754
Sulbactam/ETX2514 (ETX2514SUL)	II	Entasis Therapeutics Inc.	β-lactam + β-lactamase inhibitor	Class A, B, and D β-lactamases, CRAB	CRE, CRPA		NCT03445195
Cefepime/Zidebactam (WCK 5222)	I	Wockhardt Ltd.	Cephalosporin + β-lactamase inhibitor	ESBL-producing Enterobacteriaceae, CRE, CRPA		BSI, cIAI, cUTI, HAP, VAP	NCT02707107, NCT02942810, NCT03554304 [191], NCT03630094 [192]
SPR741	I	Spero Therapeutics Inc.	Polymyxin				NCT03376529, NCT03022175 [193]
SPR994 (Tebipenem)[1]	I	Spero Therapeutics Inc.	β-lactam	ESBL-producing *E. coli* and *K. pneumoniae* [194]		cUTI [194]	NCT03395249 [195][2]
Nacubatam or OP0595/RG6080[1]	I	Meiji Seika Pharma Co. Ltd.; Fedora Pharmaceuticals Inc.	β-lactamase inhibitor	CRE, Class A and C β-lactamases [196]	CRAB		NCT03182504 [197][2]
VNRX-5133[1]	I	VenatoRX Pharmaceuticals	β-lactamase inhibitor	Serine β-lactamases, MBLs [198]			NCT02955459 [199][2], NCT03332732 [200], NCT03690362 [201]
GSK3342830[1]	I	GlaxoSmithKline plc	Cephalosporin β-lactam	CRAB, CRE, CRPA			NCT02751424 [202][2]
TP-6076[1]	I	Tetraphase Pharmaceuticals	Tetracycline	CRAB, Enterobacteriaceae, *E. coli, K. pneumoniae* [203]	CRPA		NCT03691584 [204]

Note:
[1] SPR994 (Tebipenem), Nacubactam (OP0595/RG6080), VNRX-1533, GSK3342830 and TP-6076 are not included in the main text.
[2] These clinical trials have been concluded as of 11 October 2018.
Abbreviations: BSI (blood stream infection), cIAI (complicated intra-abdominal infection), cUTI (complicated urinary tract infection), CRAB (carbapenem-resistant *Acinetobacter baumannii*), CRE (carbapenem-resistant Enterobacteriaceae), CRPA (carbapenem-resistant *Pseudomonas aeruginosa*), ESBL (extended spectrum β-Lactamase), GNBs (Gram-negative bacteria), HAP (hospital-acquired pneumonia), IMP (imipenemase metallo-β-lactamase), KPC (*Klebsiella pneumoniae* carbapenemase), MBL (metallo-β-lactamase), MDR (multidrug-resistant), MOA (mechanism of action), NDM (New Delhi metallo-β-lactamase), OMPTA (outer membrane protein-targeting antibiotic), OXA (oxacillin carbapenemases), uUTI (uncomplicated urinary tract infection), VAP (ventilator-acquired pneumonia), VIM (Verona integron-encoded metallo-β-lactamase).
Bacteria abbreviations: *A. baumannii* (*Acinetobacter baumannii*), *E. coli* (*Escherichia coli*), *K. pneumoniae* (*Klebsiella pneumoniae*), *P. aeruginosa* (*Pseudomonas aeruginosa*), *S. maltophilia* (*Stenotrophomonas maltophilia*).

another phase I study (NCT02942810) that investigates the PK of WCK5222 in patients with renal impairment [139,140].

4.2.2. SPR741

SPR741 (developed by Spero Therapeutics Inc.) is a polymyxin derivative with little antibiotic activity but it enhances other antibiotics [141]. Polymyxins are five cationic charged lipopeptides that attack the cell membrane of GNBs, and SPR741 is a derivative of polymyxin B with the same cyclic portion but lacking the two-cationic charged fatty acid tail [141]. A randomised phase I trial (NCT03376529) was completed in 2018 investigating combinations of SPR741 with ceftazidime, piperacillin/tazobactam, or aztreonam showing favourable tolerability and PK profiles [142,143].

4.2.3. Others

Other phase I drugs that are currently being developed include **SPR994** (a broad-spectrum β-lactam), **Nacubactam** (OPO595/RG6080, a serine β-lactamase inhibitor), **VNRX-5133**, (an injectable β-lactamase inhibitor), **GSK3342830** (a new siderophore cephalosporin β-lactam) and **TP-6076** (a tetracycline), as summarised in Table 3.

5. Emerging alternative management options for GNB infections

Although antibiotics represent a significant avenue in infectious disease management, exploring new treatment options is imperative to enhance the arsenal against MDR organisms. Areas of development include targeting quorum-sensing systems, lectin inhibition, bacteriophage-mediated endolysin delivery, and antibody immune therapy.

5.1. Quorum-sensing inhibitors (QSI)

Developed by Nanyang Technological University, Singapore, quorum sensing (QS) is utilised by bacteria to communicate in response to stimuli. Bacteria may be triggered to synthesise small molecules that contribute to regulating gene expression [144]. The regulation of various virulence factors by QS has led to investigations into QS as a therapeutic target. Two major mechanisms have been proposed for the disruption of QS: intercepting the small signalling molecules with quorum-quenching enzymes (QQEs) and inhibiting QS receptors with quorum-sensing inhibitors (QSIs) [144]. *Las* and *rhl*, two homologues of the largely conserved acylhomoserine lactone-based QS signals, function in QS pathways in *P. aeruginosa*. One in vitro study explored using QQEs and QSIs to inhibit gene expression regulated by *las* and *rhl*, and it found significant reduction in the pathogenicity of *P. aeruginosa* with a combination therapy [144]. Another study on *P. aeruginosa* explored the effects of blocking *las* and *rhl* receptors with meta-bromo-thiolactone, which was shown to have protective effects on *Caenorhabditis elegans* and human lung epithelium against killing and biofilm formation by *P. aeruginosa* [145]. The promising results produced in vitro encourage progression to in vivo studies. Pending future results, potential clinical trials may emerge involving QSI/QQE for HAP/VAP.

5.2. Lectin inhibitors

P. aeruginosa expresses cell surface proteins called lectins. They play a key pathogenic role in two ways: by binding galactose and fructose, respectively, in the glycocalyx of mammalian airways leading to adhesion, and by inactivating the mucociliary elevator [146]. A small clinical trial showed that inhalation of fructose and galactose reduced *P. aeruginosa* count in the sputum of cystic fibrosis (CF) patients without impairing lung function [147]. This indicates that the competitive inhibition of lectins is effective at facilitating the removal of bacteria via the mucociliary elevator and may provide an adjunctive treatment option, pending further research [147]. However, since this trial, investigations into lectin inhibition have stagnated.

5.3. Bacteriophages

Use of bacteriophages to target certain bacteria was a very early idea that has recently undergone a renaissance. Bacteriophages expressing endolysins can enter target cells when combined with permeabilisers [148]. More recently, effective reduction of *P. aeruginosa* load in a biofilm-associated murine model of CF has been demonstrated with nebulised phage therapy [149]. Nebulisation has been shown to be an effective delivery method for bacteriophages, and has potential to be trialled in HAV/VAP cases [150]. A phase I/II clinical trial investigating bacteriophages (NCT02116010; 'PhagoBurn'; Pherecydes Pharma) was launched in June 2013, and was funded by the European Commission under the Seventh Framework Programme for Research and Development [151]. However, it was stopped prematurely in January 2017 due to insufficient efficacy of anti-*P. aeruginosa* bacteriophage PP1131 [152]. A major limitation of the study was that stability issues resulted in a lower than expected dose (1000-fold to 10 000-fold) of PP1131 in the phage group [152]. At low doses, PP1131 induced a slower clinical response than standard-of-care, and treatment-resistant bacteria were also isolated in patients with failed treatments [152]. However, some positive findings from this study, such as a clinically-relevant reduced bacterial burden and fewer serious adverse events in the phage group, warrant further investigations with increased doses and a larger sample size [152].

5.4. Immunotherapy

Use of monoclonal antibodies (MABs) has great potential for highly targeted antibiotic therapy. The development of polymerase chain reaction (PCR) for use in diagnosing infections has overcome the barrier of traditional culturing techniques [153]. A small phase II trial (NCT00851435, Kenta Biotech Ltd, n=31) was conducted on patients with serotype O11 *P. aeruginosa* pneumonia [154]. The study demonstrated that panobacumab, a MAB targeted against pseudomonal lipopolysaccharides, combined with conventional therapy, decreased time to clinical resolution with no associated immunogenicity, which may justify further research into adjunctive immunotherapy for HAP/VAP [155]. Another trial, sponsored by KaloBios Pharmaceuticals, has investigated a fusion antibody (FAB) KB001 targeted to another pseudomonal virulence factor, the type-3 secretion system needle-tip protein PcrV [156]. This trial indicated that the FAB KB001 was safe, with a favourable PK profile, but was not powered to explore clinical outcome [156]. A subsequent phase II trial (NCT01695343, Humanigen, Inc.) has investigated the clinical efficacy of KB001 in CF patients with associated pseudomonal infection [157]. In this study, KB001 demonstrated moderately improved forced expiratory volume in one second (FEV_1) and reduced inflammatory marker IL-8 compared with placebo [158]. Further immunotherapeutic research has yielded MEDI3902, which is in a phase II trial (NCT02696902, Medimmune LLC) [159]. This MAB also targets the PcrV component of the pseudomonal type III secretion system and is administered prophylactically in VAP patients [160]. Outcomes for the trial will include safety and efficacy in reducing incidence of pseudomonal VAP and may direct further research [160].

6. New dosing strategies to optimise efficacy of existing antibiotics against Gram-negative bacteria

The rapid rise of MDR pathogens combined with a drying antibiotic pipeline has created an urgent need to optimise the use of currently available antibiotics. The traditional goals of antibiotic therapy were previously focused on maximising clinical and microbiological outcomes, but not on minimising the emergence of bacterial resistance [161]. Emerging PK/PD data indicate that the magnitude of antibiotic exposures for resistance suppression is generally higher than the thresholds needed for optimal clinical and bacteriological outcomes [162-167]. Therefore, conventional antibiotic dosing, which primarily seeks to attain clinical success, may potentially amplify bacterial resistance by selecting mutant bacterial strains with reduced drug susceptibility [168-170]. Furthermore, as most antibiotic dosing recommendations have been derived from healthy volunteers, different dosing approaches may be needed in patients with severe infections [171]. The altered dosing approaches may not only increase the likelihood of PK/PD target attainment and therapeutic success but may also prolong the clinical lifespan of our existing antibiotic armamentarium. By way of example, maintaining effective β-lactam exposure for extended periods via prolonged infusion (either continuous or extended infusion) has been associated with the likelihood of clinical success and resistance suppression and, thus, would be particularly suitable in critically ill patients with severe infections [162,172-174]. The theoretical basis for prolonged β-lactam infusion in critically ill patients is well established with numerous preclinical and PK/PD data supporting this method of administration over traditional bolus dosing in such a population [172]. Through robust PK/PD analysis, newer β-lactam antibiotics (and their combinations), such as ceftazidime/avibactam, doripenem and meropenem/vaborbactam, have been recognised to benefit from prolonged infusions in the earlier phase of development. Furthermore, a recent individual patient data meta-analysis of three multicentre randomised controlled trials [175-177] comparing continuous and intermittent infusion of β-lactam antibiotics reported lower hospital mortality in the continuous infusion group, with the greatest benefits observed in patients with a higher level of sickness severity who were not receiving renal replacement therapy and were infected with non-fermenting GNBs [178]. Eight recent meta-analyses have also reported significant patient benefits with prolonged β-lactam infusions [179-186]. Importantly, the BLING III trial (NCT03213990; a prospective, multinational, multicentre, open-labelled, phase III trial) is currently underway aiming to recruit 7000 patients to determine whether continuous infusion of a β-lactam antibiotic results in significant patient benefits compared with intermittent dosing in critically ill patients with severe sepsis [187].

However, there are currently limited data describing the PK/PD exposure needed to prevent the emergence of resistance and urgent research is clearly needed to identify these exposures for most antibiotic classes [161]. In the context of resistance prevention, rationally optimised combination therapy may restrict the amplification of resistant mutants [188-190]. In the current situation, it is likely that we have to strongly consider this approach, particularly in critically ill patients with severe infections. Applying combination therapy is likely to be important earlier in the course of infection where the inoculum of the infecting pathogens is the highest. To date, however, no randomised clinical trial has shown that this approach reduces the emergence of resistance, and more clinical comparative studies are needed to evaluate the outcomes of antibiotic monotherapy vs. combination therapy, particularly in patients with severe infections.

7. Conclusions

Despite increased efforts to develop new antibiotics, the number of drug approvals has dwindled in the last few years. Since 2010, only five new agents with activity against MDR Gram-negative strains have been approved by the FDA and/or the EMA, namely ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, plazomicin and eravacycline. To safeguard these antibiotics from resistance development, it is crucial to use them only as last-resort treatments when infections caused by microorganisms resistant to alternative options are confirmed or strongly suspected. Also, it should be noted that for the difficult-to-treat GNBs (such as MBL/NDM-1 producers, MDR-*A. baumanni*, etc.) the available options are still very limited and are expected to remain limited in the near future. Although there is a variety of agents currently in clinical trials, the vast majority of them are modifications of existing antibiotic classes addressing specific resistant mechanisms and are active only against specific pathogens or limited subsets of resistant strains [15]. On the other hand, new alternative treatments, such as immunotherapy, bacteriophages, QSIs and lectin inhibitors, are in their infancy for the management of GNB infections, and their potential is yet to be explored. Finally, further research is needed to assess the PK/PD, efficacy, and applicability of these novel antibiotics in clinical practice.

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Ethical approval

Not required.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2018.10.011.

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