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Review

What's new in the treatment of multidrug-resistant gram-negative infections?

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ABSTRACT

Eradicating multi-drug resistant (MDR) organisms has been a major challenge in healthcare settings worldwide. Newly approved drugs and those currently in the pipeline may have a promising solution to this issue. The purposes of this review are to describe the various resistance mechanisms of Gram-negative bacteria and to provide a summary of the current literature available on the newer agents, such as ceftazidime/avibactam, ceftolozane/tazobactam, meropenem/vaborbactam, and other emerging agents used for the treatment of MDR Gram-negative infections. Given that MDR organisms confer resistance to treatment by various methods, including enzymatic degradation, efflux pumps, and porin mutation, an understanding of mechanisms of bacterial resistance combined with information on newer antimicrobial agents against MDR Gram-negative bacteria will further assist clinicians in determining the best suitable therapy for the treatment of various complicated infections.

1. Introduction

Emerging antibiotic-resistant pathogens have been a significant threat to global public health (Boucher et al., 2009). Given that few candidate antibiotics were in the pipeline to treat infections caused by "ESKAPE" pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* species) in 2010, the Infectious Diseases Society of America (IDSA) launched the 10 x '20 initiative, a global commitment to develop 10 new antibiotics by 2020 (The 10 × '20 Initiative: Pursuing a Global Commitment to Develop 10 New Antibacterial Drugs by 2020, 2010). A recent report from the World Health Organization (WHO) has shown that multidrug-resistant (MDR) Gram-negative pathogens including carbapenem-resistant *Enterobacteriaceae* (CRE), *A. baumannii*, and *P. aeruginosa* are considered to be the highest priority for future drug development efforts (World Health Organization (WHO)). So far, four drugs with clinical activity against Gram-negative pathogens, ceftolazane/tazobactam (C/T) (December 2014), ceftazidime/avibactam (CAZ/AVI) (February 2015), meropenem/vaborbactam (MER/VAB) (August 2017), and plazomicin (June 2018) have been approved by the Food and Drug Administration (FDA). Furthermore, there are several antibiotic candidates against Gram-negative bacteria in the development pipelines: imipenem/cilastatin/relebactam, aztreonam/avibactam, cefiderocol, eravacycline, and cefepime/VNRX-5133.

The purposes of this review are: (1) to describe mechanisms of antimicrobial resistance in Gram-negative bacteria, and (2) to review some of the newly approved agents active against MDR Gram-negative pathogens or those in clinical development.

1.1. Mechanisms of antibiotic resistance in MDR gram-negative bacterial infections

Mechanisms of resistance to any antibiotic can be categorized into one of the following four major mechanisms: enzymatic degradation of the antibiotic, modification of the antibiotic target, efflux of antibiotic from the bacteria, and prevention of absorption or intake of the antibiotic (Opal and Pop-Vicas, 2015). However, in regards to β-lactams, the predominant mechanisms of resistance to Gram-negative bacteria are mediated through enzymatic degradation, efflux pumps, and porin loss. In those Gram-negative bacteria resistant to carbapenems, namely *A. baumannii, P. aeruginosa*, and some *Enterobacteriaceae*, specific mechanisms can be attributed to these phenomena (Lister et al., 2009; Martirosov and Lodise, 2016; Peleg et al., 2008).

β-Lactamases are responsible for the hydrolyzation and subsequent inactivity of β-lactam antibiotics and can be expressed with a wide variety of substrates, from narrow spectrum penicillinases to carbapenemases capable of nearly pan-β-lactam hydrolyzation

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(Drawz and Bonomo, 2010). These enzymes concentrate in the periplasmic space of bacteria and can be chromosomally mediated or encoded on plasmids capable or horizontal transfer between similar species of bacteria and can be expressed in an inducible manner or constitutively (Drawz and Bonomo, 2010). β-lactamases are classified by two schemes, the Ambler classification and the Bush-Jacoby classification (Ambler, 1980; Bush and Jacoby, 2010). The Ambler classification groups β-lactamases into 4 classes (A-D; Table 1) according to their amino acid sequences and is preferred in most clinical settings (Drawz and Bonomo, 2010). The Bush-Jacoby classification scheme represents an attempt to correlate enzyme substrates with structural similarities and may have a benefit in regards to correlating a specific enzyme with phenotypic resistance identified in a particular bacteria (Bush and Jacoby, 2010). For the purposes of this review, the Ambler classification will be used throughout.

Porin loss and efflux pumps are two major mechanisms of resistance across Gram-negative rods. Select porins serve to transport β-lactams antibiotics, among other things, into the periplasmic space of the organism where the antibiotic can access the penicillin-binding protein (PBP) to which it displays an affinity (Opal and Pop-Vicas, 2015). The loss or low expression of porins can dramatically change drug susceptibilities to an organism, and in regards to β-lactams, the addition of a β-lactamase inhibitor will not improve susceptibility to a particular agent (Tsai et al., 2011). In general, porins that impact carbapenem susceptibility vary by bacterial species, and have varying impacts on the change in minimum inhibitory concentration (MIC) (Lister et al., 2009; Mussi et al., 2005; Sugawara et al., 2016). Few β-lactams are not impacted by porin loss and bacteria with such mutations, while potentially less virulent than their wild-type counterparts, represent a difficult subset of drug-resistant bacteria to overcome (Tsai et al., 2011).

Efflux pumps are capable of removing antibiotics from their site of activity and contributing to decreased drug susceptibility. Efflux pumps represent a similar challenge to porin loss mutants with a wide diversity expressed in various bacteria with varying substrate affinities. It is important to note that while a single porin loss or efflux pump expression may have minimal impact on susceptibility to a certain agent, their expression in conjunction with other mechanisms of resistance can commonly lead to MDR organisms. The non-enzymatic resistance mechanisms in Gram-negative rods are shown in Table 2.

Table 2
Non-enzymatic resistance mechanisms with impact on carbapenem susceptibility (Lister et al., 2009; Mussi et al., 2005; Sugawara et al., 2016).

Organism	Porin mutation of loss	Efflux pump system
Klebsiella spp.	OmpK35 OmpK36	+/−
E. coli	OmpF OmpC	+/−
P. aeruginosa	OprD	MexAB-OprM MexXY MexCD-OprJ
A. baumannii	CarO	AdeABC

1.1.1. Carbapenem-resistant Enterobacteriaceae (CRE)

While carbapenems remain stable to most β-lactamases, carbapenemases are readily able to hydrolyze these compounds and can be produced by a variety of Gram-negative organisms. Carbapenem-resistant *Enterobacteriaceae* (CRE) initially described, were secondary to a high level of AmpC production in conjunction with a porin loss or efflux pumps. However, carbapenemases have been primarily responsible for the increasing frequency of CRE (Mammeri et al., 2008; Tzouvelekis et al., 2012). Particularly concerning in the U.S. is the dissemination of class A carbapenemases in *Enterobacteriaceae* across the country with only a single state not reporting isolation of a *K. pneumoniae* carbapenemase (KPC) producing isolate as of August 2017 (Martirosov and Lodise, 2016; Tracking Carbapenem-resistant Enterobacteriaceae; Tzouvelekis et al., 2012). Metallo-β-lactamases have led to the isolation of pan-β-lactam resistant isolates with relatively limited treatment options, and while infrequently found in *Enterobacteriaceae* in the U.S., they have become widely disseminated abroad (Boucher et al., 2009; Deshpande et al., 2010; Queenan and Bush, 2007). Currently the Centers for Disease Control and Prevention (CDC) has only recorded less than 500 isolates producing metallo-β-lactamases in the U.S. as of December 2017, with the New Delhi Metallo-β-lactamase (NDM) being the most frequently implicated enzyme in *Enterobacteriaceae*, representing nearly 400 of these isolates in the U.S. (Tracking Carbapenem-resistant *Enterobacteriaceae*). The high proportion of the NDM among metallo-β-lactamase producing *Enterobacteriaceae* is a trend that is seen on a global scale, with this enzyme representing the majority of metallo-β-lactamases in one global surveillance study (Kazmierczak et al., 2016). While *Klebsiella* species (spp.) and *Escherichia coli* can be found to have porin loss mutations, these mutations rarely yield non-susceptibility to carbapenems and more often affect cephalosporin susceptibility (Sugawara et al., 2016). In *K. pneumoniae,* isolates with a loss of the porin OmpK36 in conjunction with extended-spectrum beta-lactamase (ESBL) production has been noted to cause markedly elevated MICs to ertapenem (16-32 μg/mL), and non-susceptibility to imipenem and meropenem under the current Clinical and Laboratory Standards Institute guidelines (Clinical and Laboratory Standards Institute, 2010; Wang et al., 2009). Similarly, efflux pumps in *Enterobacteriaceae*, the best characterized being the AcrAB-TolC operon, do not impact carbapenem MICs and does not act synergistically with other mechanisms of resistance to carbapenems (Doumith et al., 2009).

1.1.2. Carbapenem-Resistant Pseudomonas aeruginosa

P. aeruginosa already represents an organism with limited treatment options because of many resistance mechanisms it can contain (Lister et al., 2009; Meletis et al., 2012). *P. aeruginosa* ubiquitously produces Class-C β-lactamases. While carbapenems will remain relatively stable to hydrolysis with these enzymes, when produced in conjunction with other mechanisms of resistance, carbapenem susceptibility can be

Table 1
Summary of β-lactamases by Ambler Classification (Ambler, 1980; Bush and Jacoby, 2010; Drawz and Bonomo, 2010).

Ambler Class	Active Site	β-lactamases	Examples of enzymes	Typical Producers	Effective inhibitors	Substrate
A	Serine	Pencillinases	TEM, SHV, CTX-M	*Enterobacteriaceae*	Clavulanate, tazobactam, sulbactam,	Pencillins, cephalosporins
A	Serine	Carbapenemases	KPC, GES	*Enterobacteriaceae*	Vaborbactam, avibactam, relebactam	β-lactams
B	Metal ions (usually Zinc)	Metallo-β-lactamases	NDM, VIM, IMP, L1	*S. maltophilia, A. baumannii, Enterobacteriaceae, Pseudomonas* spp.		β-lactams except aztreonam
C	Serine	Cephalosporinases	AmpC, CMY	SPICE organisms*, *Pseudomonas* spp., *A. baumannii*	Vaborbactam, avibactam, relebactam	Cephalosporins, penicillins
D	Serine	Oxacillinases	OXA	*Enterobacteriaceae, A. baumannii*	Avibactam, relebactam (variable inhibition)	β-lactams to varying degrees

* *Serratia*, *Providencia*, "Indole-positive" *Proteus* species, *Citrobacter*, and *Enterobacter* species.

affected (Quale et al., 2006). However, *P. aeruginosa* can enzymatically mediate carbapenem resistance via production of Class-B enzymes, most commonly producing the Verona-Integron-Metallo-β-lactamase (VIM) (Queenan and Bush, 2007). This trend is seen in the U.S. as well as internationally, with VIM representing greater than 80% of all metallo-β-lactamases produced by *P. aeruginosa.*[20] The OprD porin acts as an important channel for the influx of carbapenems in *P. aeruginosa* and loss of this channel can mediate high-level resistance to carbapenems when compared with wild type isolates (Sakyo et al., 2006). In isolates with only OprD loss, carbapenems are the only β-lactams expected to be affected; however, clinical isolates with decreased porin expression very possibly will have other mechanisms affecting other β-lactams (Lister et al., 2009; Sakyo et al., 2006). An important mechanism of resistance in *P. aeruginosa* is that of efflux pump systems, the first characterized and possibly most notable of which being the MexAB-OprM system (Mex- multiple efflux; Opr- outer membrane protein) (Lister et al., 2009; Meletis et al., 2012). There are a wide variety of reported efflux pump systems all with characteristic substrates and varying impact on drug susceptibility. For example, the MexAB-OprM system represents the broadest substrate profile for β-lactams sparing few β-lactams (e.g., imipenem, ceftolozane). On the other hand, MexXY (which pairs with OprM but is not linked intrinsically), has a narrower substrate for β-lactams (e.g., it impacts cefepime but not ceftazidime) possibly due to its lack of a linked gene encoding an outer membrane protein but readily extrudes aminoglycosides (Masuda et al., 2000). It is important to highlight that while a specific mutation may produce one pattern of resistance, multiple mechanisms expressed in conjunction can produce multi- and pan-drug resistant isolates.

1.1.3. Carbapenem-resistant Acinetobacter baumannii

While most *A. baumannii* strains produce a non-inducible AmpC and have been reported to produce a wide array of non-carbapenemase Class-A enzymes, the enzymes with carbapenemase activity in *A. baumannii* are the OXA type Class-D enzymes (Peleg et al., 2008). This subgroup of enzymes, termed carbapenem-hydrolyzing class D β-lactamases (CHDLs), have high affinities for imipenem, but not always meropenem and have been isolated from *A. baumannii* on a global scale (Poirel and Nordmann, 2006). This subset of enzymes can be characterized by a lower level of resistance produced to carbapenems when compared with Class-B producing isolates, may be present in up to 75% of carbapenem resistant isolates, and have historically been challenging to detect in clinical microbiology labs (Mendes et al., 2009; Peleg et al., 2008; Poirel and Nordmann, 2006; Quinones et al., 2015). *Acinetobacter* can also develop carbapenem resistance via non-enzymatic mechanisms including porin loss (CarO, Omp33/36, OprD), efflux pumps (AdeABC efflux system), and modification of penicillin binding proteins (Morán-Barrio et al., 2017; Poirel and Nordmann, 2006; Xiao et al., 2016). The non-enzymatic mechanisms of resistance have been less frequently studied when compared with the impact of OXA type enzymes on carbapenem susceptibility.

1.2. Newer antimicrobial agents against MDR gram-negative bacteria

Table 3 summarizes selected clinical trials of newer antimicrobial agents against MDR Gram-negative bacteria. The doses and spectrum of activities of newly FDA-approved antimicrobial agents against Gram-negative bacteria are compared in Table 4.

1.2.1. Ceftazidime/avibactam (Avycaz®; Allergan plc, Dublin, Ireland)

CAZ/AVI is a combination of a 3rd generation oxyimino cephalosporin with a diazabicyclooctane non-β-lactam β-lactamase inhibitor (van Duin and Bonomo, 2016). CAZ/AVI has been approved by the FDA for the treatment of complicated intra-abdominal infections (cIAI), in combination with metronidazole, and complicated urinary tract infections (cUTIs) including pyelonephritis (Avycaz® [prescribing information], 2015). In February 2018, the FDA extended its approval for the treatment of hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) (Allergan plc, 2018). CAZ/AVI is available as a 2.5 g (CAZ 2 g/ AVI 0.5 g) strength powder for intravenous (IV) injection (Avycaz® [prescribing information], 2015). Both ceftazidime and avibactam are extensively excreted by the kidney with an approximate half-life of 2 hours (Zasowski et al., 2015; Zhanel et al., 2013). In-vitro experiments showed a ceftazidime MIC of 64 mg/L or higher against KPC producing *Enterobacteriaceae* but reduction to a CAZ/AVI MIC of 4 mg/L or lower (Zasowski et al., 2015). Additionally, CAZ/AVI demonstrated bactericidal activity against all strains at concentrations between 2 and 8 mg/L, while ceftazidime alone was bactericidal only when given at 256 mg/L against the *K. pneumoniae* expressing a non-ESBL (Zhanel et al., 2013).

A new β-lactamase inhibitor, avibactam acts uniquely in comparison with other available β-lactamase inhibitors as it binds covalently and reversibly to β-lactamases, allowing itself to recycle its β-lactamase inhibitor activity (Ehmann et al., 2012). The reversible and recyclable effect of avibactam allows for more potent and reliable inhibition of some β-lactamases including AmpC, KPC, and some OXA-like enzymes than irreversible β-lactamase inhibitors. However, avibactam is not able to effectively inhibit metallo-β-lactamases (Castanheira et al., 2015; Li et al., 2015). CAZ/AVI offers a promising option to combat β-lactamase producing *Enterobacteriaceae,* including KPCs, which are serine β-lactamases belonging to Ambler Class A, capable of carbapenem hydrolysis, commonly plasmid mediated, and found in organisms expressing multiple mechanisms of resistance (Tzouvelekis et al., 2012; van Duin et al., 2018). A recent surveillance study observed this enhanced CAZ/AVI susceptibilities of *Enterobacteriaceae* (Sader et al., 2018). Sader and colleagues observed 100% CAZ/AVI susceptibility against 2151 *Enterobacteriaceae* tested, representing the most active agent tested against MDR strains (defined as non-susceptibility to ≥1 agent in ≥3 antimicrobial classes) whereas only 78.6% of these isolates were susceptible to meropenem.

Although CAZ/AVI may represent a potent option in the treatment of *P. aeruginosa*, the addition of avibactam is unlikely to impact the susceptibilities of ceftazidime non-susceptible isolates because MDR *P. aeruginosa* isolates commonly display non-β-lactamase mediated β-lactam resistance due to porin loss and efflux pump expression (Lister et al., 2009; Wi et al., 2018). Therefore, CAZ/AVI susceptibilities are often less than that seen with C/T, for example in 42 non-carbapenemase producing carbapenem resistant *P. aeruginosa*, only 71.4% of isolates were susceptible to CAZ/AVI where C/T retained susceptibility to 95.2% of isolates (Wi et al., 2018). Susceptible isolates of *P. aeruginosa* to CAZ/AVI commonly have MICs that are several fold higher than C/T comparatively (Buehrle et al., 2016; Pitart et al., 2015; Sader et al., 2015). The clearest example of this is provided by Buehrle and colleagues in an investigation of the comparative susceptibilities of C/T and CAZ/AVI in non-carbapenemase producing meropenem-resistant *P. aeruginosa*, while the authors noted only 8% resistance to either agent in the 38 isolates tested, the median MICs were 4 μg/mL and 1 μg/mL for CAZ/AVI and C/T respectively (Buehrle et al., 2016). In general, 'highly susceptible' isolates with MICs below the breakpoints and 'borderline susceptible' isolates with MICs equal to the breakpoints can be addressed in dosing strategies; however, given that the experience to date with either of these agents is fairly limited, this trend towards higher frequencies of 'borderline susceptible' isolates with CAZ/AVI should be seen as concerning and interpreted with caution. The main reason for this is that most microbiologic surveillance studies to date have used broth microdilution and it is currently unknown to what degree automated antimicrobial susceptibility testing will agree with a reference standard such as broth microdilution (Buehrle et al., 2016; Pitart et al., 2015; Sader et al., 2015). Among *P. aeruginosa* tested in the previously mentioned recent surveillance study, CAZ/AVI, amikacin, and colistin maintained greater than 90% susceptible at 96.8%, 96.2%, and 99.8%, respectively. Those fell slightly but far less than other drugs tested when selecting out MDR P. aeruginosa. Percent susceptibility fell to 88.1%,

Table 3
Selected clinical trials of newer antimicrobial agents against MDR Gram-negative bacteria.

Study (year)	Design	Indication	Study drugs	Results (Drug versus comparator)
Ceftazidime/avibactam(CAZ/AVI)				
RECAPTURE (Wagenlehner et al., 2016)	Phase III, R, DB, Non-Inferiority	cUTI/acute pyelonephritis	CAZ/AVI 2.5 g q8hrs vs. doripenem 500 mg q8hrs, up to 10 or 14 days	-Patient-reported symptomatic resolution at 5 days (70.2% vs. 66.2%) -Combined symptomatic resolution/microbiological eradication at TOC (71.2% vs. 64.5%) -Microbiological eradication at TOC (77.4% vs. 71%)
REPRISE (Carmeli et al., 2016)	Phase III, R, open-label	cUTI or cIAI due to ceftazidime-resistant Gram-negative pathogens	CAZ/AVI 2.5 g q8 hrs vs. BAT, for 5–21 days	-Clinical cure at TOC (91% vs. 91%)
RECLAIM (Mazuski et al., 2016)	Phase III, R, DB, Non-Inferiority	cIAI	CAZ/AVI 2.5 g q8 hrs (+ metronidazole 500 mg q8hrs) vs. meropenem (1 g q8 hrs) for 5–14 days	-Clinical cure at TOC in mMITT population (81.6% vs. 85.1%) -Clinical cure at TOC in MITT population (82.5% vs. 84.9%) -Clinical cure at TOC in CE population (91.7% vs. 92.5%)
REPROVE (Torres et al., 2018)	Phase III, R, DB, Non-Inferiority	HABP or VABP	CAZ/AVI 2.5 g q8hrs vs. meropenem 1 g q8hrs, for 7–14 days	-Clinical cure at TOC in mCITT population (68.8% vs. 73%) -Clinical cure at TOC in CE population (77.4% vs. 78.1%)
Ceftolozane/tazobactam (C/T)				
ASPECT-cUTI (Wagenlehner et al., 2015)	Phase III, R, DB, Non-Inferiority	cUTI	C/T 1.5 g q8 hrs vs. levofloxacin 750 mg IV q24hrs for 7 days	-A composite of microbiological eradication and clinical cure in mMITT (76.8% vs. 68.4%)
ASPECT-cIAI (Solomkin et al., 2015)	Phase III, R, DB, Non-Inferiority	cIAI	C/T 1.5 g q8 hrs (+ metronidazole 500 mg q8hrs) vs. meropenem 1 g q8hrs for 4–14 days	-Clinical cure at TOC in MITT population (83% vs. 87.3%) -Clinical cure at TOC in microbiologically evaluable population (94.2% vs. 94.7%)
Meropenem/vaborbactam (MER/VAB)				
TANGO-I (Kaye et al., 2018)	Phase III, R, DB, Non-Inferiority	cUTI/acute pyelonephritis	MER/VAB 4 g q8 hrs vs. piperacillin-tazobactam 4.5 q8 hrs up to 10 days	-Clinical cure or improvement or microbiological eradication at EOIVT (98.4% vs. 94%)
TANGO-II (Kaye et al., 2017; Wunderink et al., 2017)	Phase III, R, open-label	Known or suspected CRE pathogens, cUTI/acute pyelonephritis, cIAI, HABP/VABP, or bacteremia	MER/VAB 4 g q8hrs vs. BAT, for 7–14 days	-Clinical cure at EDT (64.3% vs. 33.3%) -Clinical cure at TOC (57.1% vs. 26.7%) −28-day mortality (17.9% vs. 33.3%)
Plazomicin				
EPIC (Cloutier et al., 2017)	Phase III, R, DB	cUTI/acute pyelonephritis	Plazomicin 15 mg/kg q24hrs vs. MER 1 g q8hrs (± levofloxacin po 500 mg q24hrs), for 7–10 days	-Composite cure in mMITT population at TOC (81.7% vs. 70.1%)
CARE (McKinnell et al., 2017)	Phase III, R, open-label	bloodstream infection or HABP/VABP	Plazomicin 15 mg/kg q24hrs vs. colistin 300-mg lading dose; 5 mg/kg/day divided q8hrs or q12hrs (+ MER or tigecycline), for 7–14 days	-All-cause mortality at day 28 in mMITT population (11.8% vs. 40%)
Imipenem/cilastatin/relebactam (IMI/REL)				
Lucasti et al. (Lucasti et al., 2016)	Phase II, R, DB Dose-ranging study	cIAI	IMI (500 mg) + REL (125 mg or 250 mg) q6hrs vs. IMI (500 mg q6hrs), for 4–14 days	-Clinical response rates at DCIV (98.8% [REL 125 mg] vs. 96.3% [REL 250 mg] vs. 95.2%)
Sims et al. (Sims et al., 2017)	Phase II, R, DB Dose-ranging study	cUTI/acute pyelonephritis	IMI (500 mg) + REL (125 mg or 250 mg) q6hrs vs. IMI (500 mg q6hrs), for 4–14 days	-Microbiological response rate at DCIV in ME population (98.6% [REL 125 mg] vs. 95.5% [REL 250 mg] vs. 98.7%)
Cefiderocol				
APEKS-cUTI (Portsmouth et al., 2017)	Phase II, R, DB Non-inferiority	cUTI/acute uncomplicated pyelonephritis	Cefiderocol (2 g) q8 hrs vs. IMI (1 g) q8 hrs, for 7 to 14 days	-The composite of clinical or microbiological response at TOC in MITT population (72.6% vs. 54.6%) -Clinical response rate in MITT population (89.7% vs. 87.4%)

R = randomized; DB = double blind; cUTI = complicated urinary tract infection; TOC = test of cure; cIAI = complicated intra-abdominal infection; BAT = nest available therapy; mMITT = microbiologically modified intention to treat, HABP = hospital-acquired bacterial pneumonia; VABP = ventilator-associated bacterial pneumonia; mCITT = clinically modified intention-to-treat; clinically evaluable = CE; EOIVT = end of IV therapy; CRE = carbapenem-resistant Enterobacteriaceae; EDT = end of therapy; DCIV = discontinuation of IV therapy; ME = microbiologically evaluable.

Table 4
Comparison of newer antimicrobial agents against Gram-negative bacteria (Avycaz® [prescribing information], 2015; Zerbaxa® [prescribing information], 2014; Vabomere® [prescribing information], 2017).

Generic name	Ceftolozane-tazobactam	Ceftazidime-avibactam	Meropenem-vaborbactam
Brand name	ZERBAXA	AVYCAZ	VABOMERE
FDA indications	cIAI (with metronidazole), cUTI	cIAI (with metronidazole), cUTI, HABP/VABP	cUTI
Usual dose	1.5 g q8h	2.5 g q8h	4 g q8h
Renal dose adjustment	Estimated CrCl 30–50 750 mg q8h 15–29 375 mg q8h ESRD 750 mg ×1 then 150 mg q8h	Estimated CrCl 31–50 1.25 g q8h 16–30 0.94 g q12h 6–15 0.94 g q24h <5 0.94 g q48h	eGFR (ml/min/1.73m^2) 30–49 2 g q8h 15–29 2 g q12h <15 1 g q12h
Spectrum of activity			
Gram-positive			
MSSA	+	+/−	+
MRSA	-	-	-
Enterococcus spp.	-	-	+
Streptococcus spp.	+	+/−	+
Gram-negative			
Pseudomonas spp.	+++	+	+
Acinetobacter spp.	+/−	+/−	+
ESBL	+	+++	+++
CRE	-	+++	+++
Anaerobes	-	-	+

cIAI = complicated Intra-Abdominal Infection; cUTI = complicated Urinary Tract Infection; HABP = Hospital-Acquired Bacterial Pneumonia; VABP = Ventilator-Associated Bacterial Pneumonia; ESRD = End-stage renal disease; HD = hemodialysis; spp. = species; MRSA = Methicillin Resistance Staphylococcus Aureus; MSSA = Methicillin Sensitive Staphylococcus Aureus; ESBL = Extended spectrum beta-lactamase; CRE = carbapenem-resistant *Enterobacteriaceae*.
*Estimated CrCl (ml/min) using Cockcroft-Gault formula.
(+) contains intrinsic activity; (−) lacks intrinsic activity; (+/−) variable activity; (+++) large benefit over current options in MDR strains.

88.4%, and 99.4% for CAZ/AVI, amikacin, and colistin respectively, compared with a drop 74.7% to 44.6% for piperacillin/tazobactam. C/T was only tested against *P. aeruginosa* isolates from 2017, resultingly leaving it difficult to directly compare susceptibility rates.

Additionally, CAZ/AVI does not have high degrees of susceptibility in *Stenotrophomonas or Acinetobacter* spp. and its activity against anaerobic and Gram-positive pathogens is limited (Sader et al., 2018; van Duin and Bonomo, 2016; Zasowski et al., 2015).

1.2.1.1. Clinical trials. The RECAPTURE trial, a phase III randomized study, compared the safety and efficacy of CAZ/AVI (2.5 g every 8 hours over 2 hours) with doripenem (500 mg every 8 hours) in the treatment of cUTI including pyelonephritis (Wagenlehner et al., 2016). After a minimum of 5 days of intravenous (IV) therapy, the antibiotic therapy could be switched to oral and then continued for up to 10–14 days for bacteremic patients. CAZ/AVI was non-inferior to doripenem with regard to patient-reported symptomatic resolution at 5 days (70.2% vs. 66.2%; CI -2.38 to 10.42) and combined symptomatic resolution/microbiological eradication at test of cure (TOC) (71.2% vs. 64.5%; CI 0.30 to13.12), while it demonstrated superiority at the 5% significance level over doripenem for microbiological eradication at TOC (77.4% vs. 71.0%; CI 0.33 to 12.36). It has been concluded that CAZ/AVI could be an effective and safe alternative to a carbapenem for the empiric treatment of cUTI.

Mazuski and colleagues conducted a prospective, double-blinded, randomized trial (RECLAIM study) to determine the safety and efficacy of CAZ/AVI (2.5 g every 8 hours) plus metronidazole (500 mg every 8 hours) versus meropenem (1 g every 8 hours) for the treatment of cIAI (Mazuski et al., 2016). Study drugs were given for 5–14 days. As a primary end point, clinical cure at TOC was assessed 28–35 days after randomization. Clinical cure rates with both regimens (CAZ/AVI + metronidazole vs. meropenem) were similar with regard to microbiologically modified intention-to-treat (mMITT) (82.5% vs. 84.9%; 95% confidence interval (CI) -8.64 to 1.58), the modified intention-to-treat (82.5% vs. 84.9%; 95% CI -6.90 to 2.10), and clinically evaluable (91.7% vs. 92.5%; 95% CI -4.61 to 2.89) populations. Additionally, the safety profile of CAZ/AVI seemed to be similar to that of ceftazidime alone. The RECLAIM study has shown CAZ/AVI plus metronidazole to be non-inferior to meropenem in treating adult patients with cIAI.

Recently, the REPROVE trial, a multinational, phase 3, double-blind study, has been published. Patients with nosocomial pneumonia including VABP were assigned to either CAZ/AVI (2.5 g every 8 hours) or meropenem (1 g every 8 hours) for 7–14 days (Torres et al., 2018). There were similar clinical cure rates between the CAZ/AVI and meropenem groups in the clinically modified intention-to-treat (68.8% vs. 73%; CI -10.8 to 2.5) as well as clinically evaluable populations (77.4% vs. 78.1%; CI -7.9 to 6.4). The findings from this study supported the use of CAZ/AVI as a potential alternative to carbapenems for the treatment of nosocomial pneumonia.

In the REPRISE study, a pathogen-directed, randomized, open-label, phase III trial, CAZ/AVI (2.5 g every 8 hours) was compared with best available therapy (BAT) in patients with ceftazidime-resistant Gram-negative cUTI or cIAI (Carmeli et al., 2016). The duration of antibiotic therapy in both groups was 5–21 days. The clinical cure rates at the TOC in both groups were similar (CAZ/AVI vs. BAT, 91% [95% CI 85.6–94.7] vs. 91% [95% CI 85.9–95]). These results further confirmed the efficacy of CAZ/AVI in the treatment of cUTI or cIAI due to ceftazidime-resistant *Enterobacteriaceae* and *P. aeruginosa*.

In the cIAI trial (RECLAIM trial), patients with moderate kidney impairment (Creatinine Clearance [CrCl] = 30–50 ml/min) treated with CAZ/AVI showed the decreased clinical response compared to meropenem-treated patients due to possible underdosing. However, such a trend was not observed in the cUTI and HABP/VABP trials (REPRISE & REPROVE trials) where currently recommended doses were used for patients with moderate kidney impairment (Avycaz® [prescribing information], 2015).

1.2.1.2. Emergence of resistance to ceftazidime/avibactam. Resistance to CAZ/AVI has been noted in isolates of *Enterobacteriaceae.* Isolates of *K. pneumoniae* producing KPC-3 have previously been reported to produce higher CAZ/AVI MICs than isolates producing KPC-2 (Humphries et al., 2015; Shields et al., 2015). The expression of additional ESBLs along with an *ompK*36 (porin loss) mutation also contributes to elevated CAZ/AVI MICs when in the presence of KPC-2 expression (Shields et al., 2015). While porin loss in conjunction with increased enzymatic activity can lead to CAZ/AVI resistance in clinical isolates, the impact of these porin loss mutations on avibactam influx to the periplasmic space is unclear (Humphries and Hemarajata, 2017; Nelson et al., 2017; Pagès et al., 2015).

In 2017, Shields and colleagues reported a case of in-vivo CAZ/AVI resistance which had developed in 3 of the initial 37 isolates, all KPC-3 producing isolates within a median of 15 days following initial CAZ/AVI exposure (Shields et al., 2016). The isolates which developed resistance underwent genetic sequencing and analysis (Haidar et al., 2017a; Shields et al., 2017a, 2017b). The results of these investigations elucidated new information regarding CAZ/AVI resistance, describing amino acid substitutions in the Ω-loop which led to the return of meropenem susceptibility and bactericidal activity at clinically achievable concentrations (Haidar et al., 2017a; Shields et al., 2017a, 2017b). The described isolates expressed a KPC-3 variant that behaved in a more similar fashion to an ESBL and displayed a higher affinity for ceftazidime than usual (Haidar et al., 2017a; Levitt et al., 2012). The role of carbapenems in treating such isolates is unclear at this point, as exposure to subinhibitory concentrations of meropenem readily selects for carbapenem resistance, yielding pan-β-lactam resistant isolates (Shields et al., 2017b). As expected, CAZ/AVI has been reported to have high rates of resistance when tested against Ambler Class B, metallo-β-lactamase producing isolates (Aitken et al., 2016). However, there has been reported success with the combination of aztreonam with CAZ/AVI (Davido et al., 2017; Marshall et al., 2017). The benefit of this combination is that aztreonam, which is not readily hydrolyzed by Class B enzymes but will be hydrolyzed by any accompanying β-lactamases, can be protected by such β-lactamases by the addition of avibactam (Marshall et al., 2017). The combination of the two drugs could likely be simplified to aztreonam and avibactam in such scenarios. This agent is currently under clinical development and will be discussed further in a later section.

1.2.2. Ceftolozane/tazobactam (Zerbaxa®; Merck & Co., Inc., NJ, USA)

C/T represents the first agent of the IDSA10 by '20 initiative that has significant benefit in the treatment of MDR Gram-negative infections. In 2014, the FDA has approved C/T under the brand name Zerbaxa® pairing a novel β-lactam, ceftolazane with a 1st generation β-lactamase inhibitor, tazobactam for the treatment of cUTI and cIAI (Zerbaxa® [prescribing information], 2014). C/T is available as a vial for injection in a dose of 1.5 g (C 1 g/T 0.5 g). Similar to CAZ/AVI, it is mainly eliminated in the urine and the half-lives of ceftolozane and tazobactam are approximately 3 hours and 1 hour, respectively (Zerbaxa® [prescribing information], 2014).

Ceftolozane represents a significant contribution to the current agents available in the treatment on MDR *P. aeruginosa*, as it has a high binding affinity for PBP1b and PBP3, which are expressed in high concentrations in *P. aeruginosa* (Zhanel et al., 2014). Ceftolozane is minimally impacted by both OprD porin loss and MexAB-OprM efflux pumps, which have traditionally been difficult mechanisms of β-lactam resistance to overcome (Livermore et al., 2009). *P. aeruginosa* isolates displaying these mutations often display elevated carbapenem MICs and broad non-susceptibility to β-lactams in general (Lister et al., 2009). Ceftolozane also possesses increased stability to Amp-C cephalosporinases (Ambler class C) due to a greater degree of steric hindrance in the side chains of ceftolozane when compared with oxyimino cephalosporins (Murano et al., 2008). Tazobactam is a traditional, suicide substrate, β-lactamase inhibitor. The addition of tazobactam to ceftolozane expands the combination's activity against *Enterobacteriaceae* producing Ambler class A β-lactamases with some additional stability against expression of Ambler class C enzymes (van Duin and Bonomo, 2016). This combination is not likely to be highly active against *Stenotrophomonas or Acinetobacter* spp. due to the inability to inhibit (tazobactam) or withstand hydrolyzation (ceftolozane) by Ambler Class B or D β-lactamases commonly produced by these bacterial species (Farrell et al., 2014; Peleg et al., 2008).

1.2.2.1. Clinical trials. Two major studies, ASPECT-cUTI and ASPECT-cIAI, assessed the clinical efficacy of C/T (Solomkin et al., 2015; Wagenlehner et al., 2015). The ASPECT-cUTI study, a randomized, double-blind, double-dummy, non-inferiority trial, was conducted to evaluate the efficacy and safety of C/T in the treatment of patients with cUTI or pyelonephritis (Wagenlehner et al., 2015). Enrolled patients were randomized to receive either C/T (1.5 g every 8 hours) or levofloxacin (750 mg IV every 24 hours) for 7 days. This study found C/T to be non-inferior with regard to the primary endpoint, a composite of microbiological eradication, and clinical cure after 5–9 days of treatment in the mMITT population (C/T, 76.9% vs. levofloxacin, 68.4%; 95% CI 2.3 to 14.6). Additionally, subgroup analyses suggest that the composite cure endpoint favored C/T over levofloxacin in patients with cUTI caused by levofloxacin-resistant or ESBL-producing pathogens. It has been thus concluded that C/T will be a useful addition for the treatment of cUTI, especially with difficult-to-treat pathogens.

The other phase III, randomized trial, ASPECT-cIAI study assessed the efficacy and safety of C/T in the treatment of cIAI (Solomkin et al., 2015). There was no significant differences in clinical cure rates at the TOC between C/T plus metronidazole and meropenem for the treatment of cIAI in both the MITT (94.2% vs. 94.7%; 95% CI -8.91 to .54) and microbiologically evaluable (94.2% vs. 94.7%; 95% CI -4.52 to 2.59) populations. However, C/T (+ metronidazole) was found to have a higher clinical cure rates compared to meropenem in patients with ESBL-producing *Enterobacteriaceae* (95.8% vs. 88.5%). Furthermore, C/T (+ metronidazole) achieved a 100% cure rate for CTX-M-14/15 ESBLs, as compared to 72.7% in the meropenem group. Currently, a clinical trial assessing the efficacy of C/T compared with meropenem for the treatment of ventilated nosocomial pneumonia (ASPECT-NP) is undergoing (Clinicaltrials.gov, https://clinicaltrials.gov/ct2/show/NCT02070757; accessed on January 17, 2018).

1.2.2.2. Emergence of resistance to ceftolozane/tazobactam. Despite the fact that C/T has been available for clinical use for a relatively short time, resistance in *P. aeruginosa* has emerged and mechanisms leading to such resistance have not been fully elucidated. Cabot and colleagues determined the dynamics of resistance development in-vitro to C/T as well as other anti-pseudomonal agents (Cabot et al., 2014). This study found that overexpression of chromosomally mediated AmpC secondary to a large amount of mutations on *ampC* genes was required for development of high-level resistance (Cabot et al., 2014). It is worth noting that resistance developed slower to C/T than to ceftazidime, ciprofloxacin, or meropenem in this in-vitro model (Cabot et al., 2014). In a study involving clinical *P. aeruginosa* isolates collected from patients treated with C/T, three isolates (out of 21) were found to have developed on treatment resistance (Haidar et al., 2017b). Two of the reported resistant isolates and three susceptible isolates had undergone whole genome sequencing and polymerase chain reactions to detect for both chromosomally and non-chromosomally mediated resistance mechanisms (Haidar et al., 2017b). The investigators noted resistance to have developed in isolates overexpressing *ampC*; however, there were no differences in expression of OXA-50 (Ambler class D) or *oprD* porin between susceptible and resistant isolates (Haidar et al., 2017b). Additionally, one resistant isolate was noted to have increased expression of efflux pump transporter genes *mexY, mexB,* and *mexD,* but this wasn't noted in the second resistant isolate (Haidar et al., 2017b). Based on the genetic sequencing, the authors concluded resistance was likely secondary to overexpression of *ampC* (Haidar et al., 2017b). While these reports would suggest chromosomally mediated AmpC overexpression is the leading factor of *P. aeruginosa* resistance to C/T, there have been reports of horizontally acquired resistance (MacVane et al., 2017). Fraile-Ribot and colleagues reported six clinical *P. aeruginosa* isolates with developed C/T resistance mediated by acquisition of various OXA enzymes (Ambler class D) (Fraile-Ribot et al., 2017a, 2017b). In one report of five susceptible/resistant paired isolates, four were identified to be of the sequence type ST175 and one ST179; all of the susceptible isolates expressed mutations conferring inactivation of oprD and AmpR (responsible for AmpC expression) (Fraile-Ribot et al., 2017a). However, it was not until the acquisition of OXA enzymes that resistance

was displayed by these isolates (Fraile-Ribot et al., 2017a). While the impact of these β-lactamases on C/T resistance is less supported than that of overexpressed AmpC due to the multiple other mechanisms of resistance present in these isolates, it is concerning in that OXA-like enzymes represent a common transmissible β-lactamase in *Pseudomonas* (Livermore et al., 2009). Similarly, concerning is the clonal lineage to which these isolates belong, as ST175 has proven to be a successful pathogen across rather broad geographic areas (Cabot et al., 2016). Perhaps most concerning is the frequency of broad antibiotic resistance expressed by the few clinical isolates which have had genetic characterization of their resistance mechanisms (Fraile-Ribot et al., 2017a, 2017b; Haidar et al., 2017b; MacVane et al., 2017).

1.2.3. Meropenem/vaborbactam (Vabomere®; The Medicines Company, NJ, USA)

In August 2017, the FDA has approved MER/VAB under the brand name Vabomere®, for the treatment of cUTI caused by susceptible *Enterobacteriaceae* (*E. coli*, *K. pneumoniae*, and *Enterobacter cloacae species* complex) (Vabomere® [prescribing information], 2017). MER/VAB is available as a 2 g single-dose vial (MER 1 g/ VAB 1 g) (Vabomere® [prescribing information], 2017). Both meropenem and vaborbactam are primarily excreted by kidneys and thereby require dose adjustments in patients with impaired renal dysfunction (Vabomere® [prescribing information], 2017).

The novel component of MER/VAB is vaborbactam, a cyclic, boronic acid-based, β-lactamase inhibitor (Hecker et al., 2015). Vaborbactam has activity against Amber class A including KPC and class C beta-lactamases; however, it has little to no inhibitory activity against OXA-type carbapenemases and metallo-β-lactamases (MBL) (Wright et al., 2017). Therefore, the addition of vaborbactam to meropenem does not appear to expand coverage to carbapenem-resistant *Acinetobacter* or *Pseudomonas*, as these organisms are likely to produce enzymes uninhibited by vaborbactam, or have developed non-enzymatic resistance for which the addition of a β-lactamase inhibitor offers no benefit (Wright et al., 2017).

1.2.3.1. Clinical trials. The efficacy and safety data of MER/VAB are currently available from the TANGO-I and TANGO-II trials (Kaye et al., 2018; Wunderink et al., 2017). The TANGO-III trial comparing MER/VAB to piperacillin-tazobactam (PIP/TAZ) in patients with HABP and VABP is currently underway (Clinicaltrials.gov, https://clinicaltrials.gov/ct2/show/NCT03006679; accessed on January 17, 2018). In the TANGO-I trial, a multi-center, randomized, double-blind, non-inferiority study, MER/VAB (4 g every 8 hours) was compared with PIP/TAZ (4.5 g every 8 hours) for up to 10 days for the treatment of cUTIs including pyenephritis (Kaye et al., 2018). The primary outcome of clinical cure or improvement and microbiological eradication at the end of intravenous therapy in the mMITT population was 98.4% and 94% in the MER/VAB group and PIP/TAZ group, respectively (95% CI 0.70–9.1). It has been concluded that MER/VAB was statistically superior to PIP/TAZ for the treatment of cUITs. Additionally, the overall safety profile of MER/VAB was comparable to PIP/TAZ.

The TANGO II trial was a multi-center, randomized, open-label study comparing the efficacy and safety of MER/VAB with the BAT for the treatment of serious infections due to CRE including cUTI/ pyelonephritis, cIAI, HABP/VABP, and/or bloodstream infection (Kaye et al., 2017; Wunderink et al., 2017). The study randomized patients to either MER/VAB (4 g every 8 hours) or BAT with one or more agents, such as aminoglycosides, carbapenems, CAZ/AVI, polymyxin B, colistin, and tigecycline, for 7–14 days. The TANGO II study was stopped early because of superior efficacy of MER/VAB over BAT. There were significant differences in clinical cure rates ($p = 0.04$ at both TOC and end of therapy) as well as 28-day mortality ($p = 0.03$) favoring MER/VAB over BAT (Kaye et al., 2017). Furthermore, MER/VAB was associated with decreased nephrotoxicity (an increase from baseline serum creatinine of at least 0.5 mg/dL) as compared with BAT (11.1% vs. 24%).

1.2.4. Plazomicin (Zemdri®; Achaogen, CA, USA)

Plazomicin, a next-generation aminoglycoside, was designed to retain activity against bacteria containing aminoglycoside-modifying enzymes (http://www.achaogen.com/plazomicin; accessed on June 21, 2018). Similar to other aminoglycosides, plazomicin produces its bactericidal effect by binding to the bacterial 30s ribosomal subunits and interrupting the process of protein synthesis (Aggen et al., 2010). In June 2018, plazomicin was approved by the FDA for the treatment of cUTI (http://www.achaogen.com/plazomicin; accessed on June 18, 2018). Plazomicin is primarily excreted by the kidney (~90%) and thus requires dose adjustments in patients with impaired renal dysfunction (Plazomicin sulfate Injection Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC)). The recommended dose of plazomicin for the treatment of both cUTI and BSI is 15 mg/kg daily if the CrCl >60 mL/min, 10 mg/kg daily if CrCl >30 to 60 mL/min, and 10 mg/kg once every other day if CrCL >15 to 30 mL/min (Plazomicin sulfate Injection Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC)). Plazomicin has a half-life of 3.5 hours and negligible protein binding (~20%) (Plazomicin sulfate Injection Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC)). The use of aminoglycosides can be limited due to some significant adverse effects including nephrotoxicity and ototoxicity. However, it appears that plazomicin causes less renal toxicity compare to other aminoglycosides (Plazomicin sulfate Injection Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC)).

Plazomicin demonstrates broad-spectrum antimicrobial activity against Gram-negative bacilli and Gram-positive cocci. Plazomicin has potent activity against MDR *Enterobacteriaceae* isolates including CRE, but its activity against *Acinetobacter and Pseudomonas* spp. is limited (http://www.achaogen.com/plazomicin; accessed on June 21, 2018). Plazomicin is also active against both methicillin-susceptible and methicillin-resistant *Staphylococcus Aureus* (MRSA) (http://www.achaogen.com/plazomicin; accessed on June 21, 2018).

1.2.4.1. Clinical trials. The efficacy and safety of plazomicin is being assessed in two phase III clinical trials, EPIC (Evaluating Plazomicin in cUTI) and CARE (Combating Antibiotic Resistant Enterobacteriaceae) (http://www.achaogen.com/plazomicin; accessed on June 18, 2018). The EPIC trial is a randomized, multi-center, double-blind study comparing plazomicin (15 mg/kg IV every 24 hours) with meropenem (1 g IV every 8 hours) for the treatment of cUTI or acute pyelonephritis. Levofloxacin (500 mg PO every 24 hours) or another approved oral treatment was an optional adjunct to any of the treatment groups, used for 1–3 days after the initial 4- to 7-day treatment regimen was completed (Cloutier et al., 2017). The composite of clinical and microbiological cure at TOC in the mMITT population was evaluated as a primary endpoint. It was found that plazomicin achieved significantly higher composite cure rates than meropenem (81.7% vs. 70.1%; CI 2.7–20.3). Although the safety profile in both treatment groups were similar, the incidence of total treatment emergent adverse events related to renal function were higher in the plazomicin group (plazomicin 3.6% vs. meropenem 1.3%) (Cloutier et al., 2017).

The CARE trial, a multi-center, randomized, open-label study, was conducted to assess the efficacy of plazomicin compared with colistin in the treatment of patients with bloodstream infection (BSI) or HABP/VABP due to CRE (McKinnell et al., 2017). Patients were randomized to receive plazomicin (15 mg/kg IV every 24 hours) or colistin (300 mg as a loading dose then 5 mg/kg/d IV divided into 2–3 divided doses) in addition to meropenem, or tigecycline. The all-cause mortality at day 28 was evaluated as a primary endpoint. The results from this trial found that plazomicin had a significantly lower all-cause mortality compared to the colistin therapy (11.8% vs. 40.0%; 90% CI 0.7–52.5). These findings, however, should be interpreted with caution due to a small sample size, no control group, and protocol changes. From a safety standpoint, plazomicin appeared to be well tolerated (McKinnell et al., 2017).

1.2.5. Imipenem/cilastatin/relebactam (MK-7655A; Merck Sharp & Dohme [MSD], NJ, USA)

Relebactam (REL) is a novel β-lactamase inhibitor that is active against class A and C β-lactamases (Lucasti et al., 2016). The addition of REL to imipenem/cilastatin (IMI) may restore the clinical activity of imipenem against many imipenem-resistant isolates such as KPC-producing *Enterobacteriaceae* and AmpC-producing *P. aeruginosa* (Lucasti et al., 2016). The results from 2 phase II trials have shown that IMI/REL (REL 125 mg or 250 mg + IMI 500 mg every 6 hours) was non-inferior to IMI (500 mg every 6 hours) alone for the treatment of cUTI or cIAI (Table 3) (Lucasti et al., 2016; Sims et al., 2017). Additionally, both IMI/REL regimens were well tolerated and demonstrated similar safety profile compared with IMI alone. Two pivotal phase III clinical trials (RESTORE-IMI 1 and RESTORE-IMI 2) are currently underway (Efficacy and Safety of Imipenem+Cilastatin/Relebactam (MK-7655A) Versus Colistimethate Sodium + Imipenem+Cilastatin in Imipenem-Resistant Bacterial Infection (MK-7655A-013) - Full Text View - ClinicalTrials.gov; Imipenem/Relebactam/Cilastatin Versus Piperacillin/Tazobactam for Treatment of Participants With Bacterial Pneumonia (MK-7655A-014) - Full Text View - ClinicalTrials.gov). The RESTORE-IMI 1 trial is designed to evaluate the efficacy of IMI/REL vs. colistimethate sodium plus IMI in imipenem-resistant bacteria infections including HABP/VABP, cIAI, and cUTI (Efficacy and Safety of Imipenem+Cilastatin/Relebactam (MK-7655A) Versus Colistimethate Sodium + Imipenem+Cilastatin in Imipenem-Resistant Bacterial Infection (MK-7655A-013) - Full Text View - ClinicalTrials.gov). In the RESTORE-IMI 2 trial, IMI/REL will be compared with PIP/TAZ in patients with HABP/VABP (Imipenem/Relebactam/Cilastatin Versus Piperacillin/Tazobactam for Treatment of Participants With Bacterial Pneumonia (MK-7655A-014) - Full Text View - ClinicalTrials.gov).

1.2.6. Aztreonam/avibactam (PF 06947387; Allergan plc, Dublin, Ireland)

Although aztreonam, a monobactam antibiotic, is active against many Gram-negative bacteria, it is readily hydrolyzed by most serine ESBLs, carbapenemase enzymes, and class C β-lactamases (Wright et al., 2017). It is of importance to note that aztreonam is stable against class B β-lactamase, also known as metallo-β-lactamase that can inactivate all β-lactams including carbapenems, and are resistant to β-lactamase inhibitors (Wright et al., 2017). Although there are metallo-β-lactamase inhibitors in clinical development, currently metallo-β-lactamases will confer resistance to all β-lactam antibiotics except aztreonam. Given that avibactam has a broad-spectrum coverage against many class A, class C, and some class D β-lactamases, the combination of aztreonam with avibactam appears to be a promising agent for the treatment of complicated infections due to MDR pathogens including ESBLs, KPCs, some class D β-lactamases, and metallo-β-lactamases (Sy et al., 2016). The phase II clinical trial (REJUVENATE trial) evaluating the pharmacokinetics and safety of aztreonam/avibactam (ATM/AVI) in the treatment of patients with cIAI has been completed; however, the results are not available at this time (Determine the PK and Safety and Tolerability of ATM-AVI for the Treatment of cIAIs in Hospitalized Adults (REJUVENATE) - Full Text View - ClinicalTrials.gov). Pfizer Inc. plans to conduct a phase III clinical trial (REVIST trial) to assess the efficacy and safety of ATM/AVI (± metronidazole) versus meropenem ± colistin for the treatment of serious infections caused by Gram-negative bacteria including MBL-producing pathogens (A Study to Determine the Efficacy, Safety and Tolerability of Aztreonam-Avibactam (ATM-AVI) ± Metronidazole (MTZ) Versus Meropenem (MER) ± Colistin (COL) for the Treatment of Serious Infections Due to Gram Negative Bacteria. - Full Text View - ClinicalTrials.gov).

1.2.7. Cefiderocol (S-649266; Shionogi & Co., Osaka, Japan)

Cefiderocol, a novel siderophore cephalosporin antibiotic, is currently in late-stage clinical development. Among antibiotics currently available or in the pipeline, cefiderocol appears to be most promising for serious MDR Gram-negative infections, as it has shown activity against highly resistant various Gram-negative pathogens including *P. aeruginosa* producing metallo-β-lactamases, *A. baumannii* producing OXA-type β-lactamase, KPC- and VIM- producing *Enterobacteriaceae* isolates, and *Stenotrophomonas maltophilia* (Wright et al., 2017). Cefiderocol has a unique mechanism of action compared with currently available antibiotics. The catchol side chain of cefiderocol binds to ferric acid and its complex is actively transported into bacteria via the bacterial iron transporters (Ito et al., 2016). In addition to the ability to efficiently penetrate into pathogens, cefiderocol is highly active against carbapenemase hydrolysis (Wright et al., 2017).

1.2.7.1. Clinical trials. The APEKS-cUTI study was a multicenter, double-blind, randomized trial designed to assess the safety and efficacy of cefiderocol compared with IMI in patients with cUTI or acute uncomplicated pyelonephritis and a positive urine culture (Portsmouth et al., 2017). Patients were randomized to receive either cefiderocol (2 g) or IMI (1/1 g) every 8 hours for 7 to 14 days. The composite of clinical and microbiological response rate at test of cure in the MITT population was evaluated as a primary endpoint. The results from the APEKS-cUTI trial found cefiderocol to have a significantly higher rate of the composite outcome compared to IMI (72.6% vs. 54.6; 95% CI 8.23–28.92). It has been concluded that cefiderocol was well tolerated and met the FDA primary efficacy endpoint for non-inferiority, which demonstrated superiority to IMI in patients with cUTI/acute uncomplicated pyelonephritis due to Gram-negative bacteria. The CREDIBLE-CR trial assessing the efficacy of cefiderocol with the BAT for the severe infections caused by carbepenemase-resistant Gram-negative pathogens and the APEKS-NP trial comparing cefiderocol with meropenem for nosocomial pneumonia due to Gram-negative pathogens are ongoing (Shionogi).

1.2.8. Other new antibiotics in clinical development

Other novel antibiotic candidates against MDR Gram-negative infections include eravacycline (Tetraphase Pharmaceuticals, Inc., MA, USA) and cefepime/VNRX5133(VenatoRx Pharmaceuticals, Inc., Malvern, PA). Eravacycline is a fully-synthetic fluorocycline antibiotic, which is currently in clinical development for the treatment of serious MDR infections (Tetraphase Pharmaceuticals Presents Clinical Data from Oral Eravacycline Development Program at IDWeek 2017). Eravacycline shows a very broad-spectrum activity against ESBLs, CRE, carbapenem-resistant *A. baumannii*, MRSA, vancomycin resistant *Enterococcus*, and anaerobes; however this drug lacks activity against *P. aeruginosa* (Tetraphase Pharmaceuticals Presents Clinical Data from Oral Eravacycline Development Program at IDWeek 2017). Based on positive results from two phase III trials, IGNITE 1 and IGNITE 4, the NDA for eravacycline for the treatment of cIAI was submitted to the FDA in January 2018; however, in the most recent phase III trial, IGNITE 3, eravacycline failed to meet its co-primary efficacy endpoints against ertapenem in the treatment of cUTI (Tetraphase's eravacycline misses endpoints in phase 3 flop | FierceBiotech).

Similar to vaborbactam, VNRX5133 is a novel β-lactamase inhibitor, expected to be further studied in combination with cefepime (Pipeline). Recent data from in-vitro testing demonstrates cefepime/VNRX5133 to have better activity against certain strains of *P. aeruginosa* and *Enterobacteriaceae* when compared to cefepime alone, meropenem, and levofloxacin (Hackel and Sahm, 2018a). It has the potential to combat some of the most difficult to treat *Enterobacteriaceae* and *P. aeruginosa* producing serine or metallo β-lactamase (Hackel and Sahm, 2018b). A Phase III trial for cefepime/VNRX-5133 is expected to start in the near future (Hackel and Sahm, 2018a; Pipeline).

2. Conclusions

The increase in resistance seen in Gram-negative organisms has led to strong advocacy for the research and development of new agents to combat infections caused by such organisms (Boucher et al., 2009; The 10 × '20 Initiative: Pursuing a Global Commitment to Develop 10 New Antibacterial Drugs by 2020, 2010; World Health Organization

(WHO)). While our armamentarium has increased to some degree, the role of these new agents is still unclear, as the clinical data surrounding their use remain scarce. One concerning aspect is the difficulty of studying the clinical efficacy of these agents in treating certain MDR organisms, as there have been relatively low numbers of patients with target MDR organisms included in much of the reported literature. Keeping in mind that resistance has developed to CAZ/AVI and C/T with the first clinical report of treating CRE and MDR *P. aeruginosa*, respectively, clinicians should identify settings in which the use of these important drugs is appropriate to preserve their future efficacy (Haidar et al., 2017b; Shields et al., 2016). Currently the major roles of the newly available drugs are in the treatment of KPC producers (CAZ/AVI, MER/VAB) and MDR *P. aeruginosa* (C/T). While they serve a very niche role, some of the intricacies of their use such as dosing in renal dysfunction, pharmacokinetically derived dosing for non-urinary or intraabdominal infections, and need for combination therapy require further investigation. Unmet needs still exist for the treatment of MDR *A. baumanii, S. maltophilia, Burkholerdia,* and metallo-β-lactamase producing bacteria. While some new drugs may soon be available as useful agents to treat infections caused by these organisms, clinicians should strive to provide innovative therapy in the meantime, as seen with the example of CAZ/AVI with aztreonam (Davido et al., 2017; Marshall et al., 2017).

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