Review Article

An Update on Antimicrobial Resistance and the Role of Newer Antimicrobial Agents for *Pseudomonas aeruginosa*

Agila Kumari Pragasam, Balaji Veeraraghavan, E. Nalini, Shalini Anandan, Keith S. Kaye[1]

Department of Clinical Microbiology, Christian Medical College, Vellore, Tamil Nadu, India, [1]Division of Infectious Diseases, University of Michigan Medical School, Ann Arbor, MI, USA

Abstract

Infections due to *Pseudomonas aeruginosa* is a major health concern, especially hospital-acquired infections, in critically ill individuals. Antimicrobial resistance (AMR) increases the morbidity and mortality rates associated with pseudomonal infections. In this review, we aim to address two major aspects of *P. aeruginosa*. The first part of the review will focus on the burden of AMR and its prevailing mechanisms seen in India, while the second part will focus on the challenges and approaches in the management with special emphasis on the role of newer antimicrobial agents.

Keywords: Antimicrobial resistance, India, newer antimicrobials, *Pseudomonas aeruginosa*, treatment

Introduction

Pseudomonas aeruginosa is a non-fermenting Gram-negative pathogen that causes severe infections. This includes bacteraemia, pneumonia, urinary tract infections and skin and soft-tissue infections. It occurs more frequently in critically ill patients particularly in immunocompromised and hospitalised patients. In critically ill patients, *P. aeruginosa* contributes 3%–15% of blood stream infections with high mortality rate of about 27%–48%. In spite of recent advances in therapy, *P. aeruginosa* bacteraemia remains fatal in more than 20% of cases. Over 50% of deaths happen within a few days of infection. Selection of appropriate empirical therapy reduces the mortality rates, while inappropriate empirical therapy leads to the development of resistance, results in clinical failure.[1]

Antimicrobial Resistance in *Pseudomonas aeruginosa*

P. aeruginosa is well known for its intrinsic ability to resist wide range of antipseudomonal agents. Antimicrobial resistance (AMR) in *P. aeruginosa* is mediated by chromosomal/intrinsic and plasmid/acquired-mediated mechanisms.[2] Chromosomal mechanisms include the following: (i) mutational derepression of the chromosomally encoded *ampc* beta-lactamase (penicillins and cephalosporins), (ii) mutational modification of antimicrobial targets such as gyrase and topoisomerase (fluoroquinolones – *gyrA, gyrB, parC* and *parE*), (iii) presence of mutated and/or loss of outer membrane proteins preventing the uptake of antimicrobials (carbapenems-*OprD*) and (iv) overexpression of efflux systems (beta-lactams, fluoroquinolones and aminoglycoside resistance – *mexAB, mexCD, mexEF* and *mexXY*).[3] Whereas the acquisition of plasmid-mediated resistance genes coding for various beta-lactamases and aminoglycoside-modifying enzymes have been identified and reported. This includes beta-lactamases (bla_{PSE}, bla_{SHV}, bla_{VEB}, bla_{PER}, bla_{IMP}, bla_{VIM}, bla_{NDM} and bla_{SPM}), aminoglycosides-modifying enzymes (aminoglycoside acetyltransferases [*AAC*], aminoglycoside nucleotidyltransferase [*ANT*] and aminoglycoside phosphotransferase [*APH*]) and 16S rRNA methylases (*armA, rmtA-rmtH* and *npmA*). The various mechanisms along with its specific substrates described here are summarised in Table 1.[4,5]

Address for correspondence: Dr. Keith S. Kaye, Division of Infectious Diseases, University of Michigan Medical School, 5510A MSRB I, SPC 5680, 1150 W. Medical Center Drive, Ann Arbor, MI 48109-5680, Michigan, USA.
E-mail: keithka@med.umich.edu

Access this article online

Quick Response Code:

Website: www.ijmm.org

DOI: 10.4103/ijmm.IJMM_18_334

How to cite this article: Pragasam AK, Veeraraghavan B, Nalini E, Anandan S, Kaye KS. An update on antimicrobial resistance and the role of newer antimicrobial agents for *Pseudomonas aeruginosa*. Indian J Med Microbiol 2018;36:303-16.

Table 1: Antimicrobial resistance mechanisms described in *Pseudomonas aeruginosa*

	Cephalosporins		Beta-lactam/ beta-lactamase inhibitor		Monobactam	Carbapenems			Fluoroquinolones	Aminoglycosides		
	CZD	CPI	P/T	C/S	AZT	IMI	MERO	DORI	LEVO	AMK	NET	TOB
Chromosomal-mediated mechanisms												
Efflux mediated resistance (pre-dominant mechanisms in *Pseudomonas aeruginosa*)												
mexAB	√ (R)	√ (R)			√ (R)		√ (R)	√ (I/R)	√ (R)			
mex*CD*		√ (R)			√ (R)				√ (R)			
mexEF						√ (R)	√ (R)		√ (R)			
mexXY		√ (R)							√ (R)	√ (R)	√ (R)	√ (R)
Outer membrane porins												
oprD						√ (R)						
Altered drug binding sites (quinolone resistance determining regions)												
GyrA, GyrB, ParC									√ (R)			
Chromosomally encoded *AmpC*	√ (I/R)	√ (I/R)	√ (I/R)		√ (I/R)							
Plasmid mediated mechanisms												
Extended spectrum beta lactamases (SHV, PER, TEM, VEB, OXA, CTX-M)	√ (R)	√ (R)	√ (S/I)		√ (R)							
Carbapenemases: Class A (GES, KPC); Class B (SPM, IMP, VIM, NDM)	√ (R)	√ (R)	√ (R)	√ (R)	√ (R) (except class B)	√ (R)	√ (R)	√ (R)				
Aminoglycosides (16 S RMTases)										√ (R)	√ (R)	√ (R)

√: The targets for each of the AMR determinants contributing resistance. S: Susceptible, I: Intermediate, R: Resistant; P/T: Piperacillin/tazobactam, C/S: Cefoperazone/sulbactam, CZD: Ceftazidime, CPI: Cefepime, IMI: Imipenem, MERO: Meropenem, AZT: Aztreonam, LEVO: Levofloxacin, AMK: Amikacin, NET: Netilmicin, DOR: Doripenem, TOB: Tobramycin

Phenotypes of multidrug resistant (MDR), extensive drug resistant (XDR) and pan drug resistant (PDR) are frequently encountered in *P. aeruginosa* causing nosocomial infections. Strains are categorised as MDR, XDR and PDR when resistance is observed for antipseudomonal agents of ≥1 agent in ≥3 classes, all agents in ≥3 classes and resistant to all agents in all classes, respectively.[6] Notably, the emergence of phenotype from MDR to XDR to PDR in *P. aeruginosa* occurs in a timely fashion using the complex regulatory mechanisms accumulated by intrinsic and extrinsic determinants as detailed above.

Current Status of Antimicrobial Resistance in *Pseudomonas aeruginosa* in India

Phenotypic resistance

In 2017, Government of India has included *P. aeruginosa* as one of the important pathogens to National Programme for the Containment of Antimicrobial Resistance (within the 12th 5-year plan, 2012–2017) under National Centre for Disease control. World health organisation in 2017 published a list of bacterial pathogens in which carbapenem-resistant *P. aeruginosa* stands second as a critical pathogen for which identification of new antibiotic is essential to overcome its MDR properties. Pan India susceptibility profile of *P. aeruginosa* varies from one region to other. The interquartile range of antibiotic susceptibility for various therapeutic agents are Ceftazidime-24 (lower quartile –31 and Upper quartile –55), Cefepime-32.75 (26–58.75), Beta-lactam/beta lactamase inhibitor-piperacillin/tazobactam-38 (36.5–74.5), under carbapenems, interquartile range for imipenem - 29.5 (43–72.5) and meropenem - 36 (33–69), for azithromycin only limited data are available, for fluoroquinolone levofloxacin - 28.5 (39–67.5) and ciprofloxacin-28.5, in aminoglycoside for amikacin-36 (33.25–69.25), netilmicin - 43.5 (42.25–85.75),

gentamicin- 22.5 (24–46.5) and in polymyxin for colistin - 3.75 (96.25–100). Antibiotic susceptibility percentage of *P. aeruginosa* from different regions varies with the presence of different antibiotic-resistant genes. Among different antipseudomonas drugs tested, almost all are highly susceptible to colistin whereas less susceptible to gentamicin, ceftazidime and cefepime. Table 2 summarises the current scenario of antimicrobial susceptibility rates reported by Indian studies.[7-16]

Molecular resistance

P. aeruginosa has intrinsic resistance mediated through chromosomal gene expression which promotes specific structural and compositional features that protect bacteria from various antimicrobials. Lie *et al*., 2015, observed constitutive protection with MexAB-OprM efflux pump by expelling multiple antibiotics.[17] AmpC expression plays an important role in intrinsic resistance as it is induced by exposure to aminopenicillin and cephalosporins.[18] Acquired resistance through horizontal transfer of resistance genes also aids in survival of the pathogen under different antibiotic stress.[19] Mutations in regulatory regions contribute to increased expression of antibiotic-resistant genes. Mutations in ampD and ampR regulatory proteins led to increased expression of *ampC*.[18,20] Hence, the prevalence of carbapenem resistance and *ampC* expression varies with influence of antibiotic exposure, environmental-influenced horizontal gene transfer and also on mutations on regulatory regions. In case of pan-India Scenario, studies by Bharti *et al*., 2016, showed increased percentage of bla_{NDM-1}.[21] Paul *et al*., 2015, have reported co-occurrence of bla_{KPC-2} + $_{NDM-1}$ which is an unusual phenotype.[22] Table 3 summarises Indian reports on molecular mechanisms of AMR in *P. aeruginosa*.[8,10,21-28]

Approaches to overcome resistance

The emergence of resistance in *P. aeruginosa* during treatment is of great concern which limits treatment options.[29] It is mainly due to the inappropriate definite therapy that results in poor clinical outcomes. One main approach to be addressed is the use of combination therapy.[30] The potential clinical outcome of treatment with monotherapy and combination therapy remains controversial particularly for infections that are caused by MDR *P. aeruginosa*.[31,32] However, several studies addressed the importance and effectiveness of combination therapies than monotherapy. Importantly, increased rate of survival is achieved upon adequate combination therapy.

Combination therapy includes two agents either β-lactams with aminoglycosides and/or with fluoroquinolones to achieve better clinical outcome.[33] The rationale behind the theory of combination therapy is to reduce the emergence of resistance rate during therapy and to achieve synergy, where the minimum inhibitory concentrations (MIC) can be achieved with two antibiotics with different spectrum of activity. Eric chamot *et al.,* recommend the direction of empirical therapy with two antipseudomonal agents.[34] Later, combination therapy could be deescalated to monotherapy based on susceptibility pattern of the isolate.

Table 2: Antibiotic susceptibility pattern of *Pseudomonas aeruginosa* in India

Reference (study period)	Cephalosporins (%)		βL/βLI (%)		Carbapenems (%)		Monobactam (%)	FQ (%)	Aminoglycoside (%)			Polymyxin (%)
	CZD	CPI	P/T	C/S	IMI	MERO	AZT	LEVO	AMK	NET	GEN	COL
Gandra *et al*., 2016[7] (January 2008-December 2014)	32		38	-	53		-	-	43			100*
Gupta *et al*., 2016[8] (February 2012-October 2013)	32	26#	37	-	-		-	37#	37	-	29	-
Kotwal *et al*., 2016[9] (January 2010-December 2012)	60	26	93*	43	72	-	-	18 (Cip)	40	-	23	-
Ellappan *et al*., 2018[10] (January 2014-February 2016)	0#	-	-	-	0#	0#	-	5# (Cip)	21#	-	3#	88#
Agarwal and Sankar, 2016[11] (July 2011-February 2014)	53		-		69		-	-	-			-
Dhaneria *et al*., 2018[12] (June 2012-January 2014)	17	-	33#	-	-		-	-	67	-	33	-
Senthamarai *et al*., 2014[13] (February 2012-January 2013)	34	-	60	62	80*	-	-	-	70	86*	48	-
CDDEP: Antibiotic resistance MAP[14] year: 2014	31	-	36		53		-	45	42#			100
Scoping document[5] (ICMR data) year: 2015	55		73	-	58		-	45*	-			99
CMC year: 2014-2016 (unpublished)	76*	76*	76	69*	73	74*	68	75*	77*	85*		99
	74-77	73-80	75-76	68-70	70-75	71-77	65-70	73-77	75-79	78-89		98-99
Wattal *et al*., 2014[16] (January 2008-December 2011)	42	40 1	45	36#	33		-	29* (Cip)	32	27		100

#Lowest percentage, *Highest percentage. FQ: Fluoroquinolones, GEN: Gentamicin, COL: Colistin, P/T: Piperacillin/tazobactam, C/S: Cefoperazone/sulbactam, CZD: Ceftazidime, CPI: Cefepime, IMI: Imipenem, MERO: Meropenem, AZT: Aztreonam, LEVO: Levofloxacin, AMK: Amikacin, NET: Netilmicin, βL: Beta lactamase, βLI: Beta lactamase inhibitor

Table 3: Molecular profile of beta lactamases reported in India

References	Study period/place	Number of isolates	Findings (%)
Ellappan *et al*., 2018[10]	January 2014-February 2016	156	bla_{VIM} - 23.1 bla_{NDM}-1-17.3 bla_{VIM} + bla_{NDM}-1-7.1 bla_{IMP} - 1.3 bla_{VEB} - 4.5
Bharti and Sharma, 2016[21]	-	180	bla_{TEM} - 25 bla_{SHV} - 1.78 bla_{CTX-M} - 10.71 bla_{TEM} + Bla_{CTX-M} - 5.35 bla_{NDM} - 37.93 bla_{PDC} - 21.15
Mohanam and Menon, 2017[23]	November 2013-December 2014	213	bla_{VIM} - 32 bla_{NDM} - 27 bla_{VIM} + bla_{NDM} - 14 bla_{IMP} + bla_{NDM} - 9 bla_{VIM} + bla_{IMP} - 5 bla_{IMP} + bla_{VIM} +bla_{NDM} - 4.5
Naim *et al*., 2017[24]	February 2014-December 2015	24	bla_{NDM}-1-29.16
Paul *et al*., 2015[22]	July 2012-June 2013	88	bl_{aKPC-2} + $_{NDM}$-1-2.27 bla_{NDM}-1-10.22
Paul *et al*., 2016[25]	October 2012-September 2013	18	bla_{NDM}-1-18.18
Paul *et al*., 2016[26]	October 2012-September 2013	17	bla_{VIM}-2 + bla_{NDM}-1-11.76
Rahman *et al*., 2018[27]	July-December 2012	130	bla_{NDM}-1-29.23
Gupta *et al*., 2016[8]	February 2012-October 2013	35	bla_{CTX-M} - 11.4 bla_{AmpC} - 42.8
Pragasam *et al*., 2016[28]	January 2014-December 2015	240	bla_{VEB} (23%), bla_{TEM} (5%) and bla_{SHV} (0.4%) bla_{VIM} (37%), bla_{NDM} (14%), bla_{GES} (8%) and bla_{IMP} (2%)

Challenges in laboratory

In vitro antimicrobial susceptibility testing determines and guides clinical decision-making on antimicrobial therapy for the management. Unlike *Enterobacteriaceae*, interpreting susceptibility to *P. aeruginosa* is challenging.[35] Due to complex chromosomally encoded resistance mechanisms, differential susceptibility phenotypes are being increasingly noted. This includes resistance to imipenem and susceptible to meropenem within the carbapenem agents.[36,37] Similarly, ceftazidime being susceptible, while carbapenems showing resistance.[38,39] Such discrepant susceptibility profile appears due to chromosome-mediated resistance mechanisms. Therefore, clinical decisions must be made based on *in vitro* susceptibility of each agent. Due to these reasons, extrapolation of one agent's susceptibility to another agent within the same group must be strictly avoided especially for *P. aeruginosa*.

Challenges in management of *P. aeruginosa* infections

The differences exist in the clinical breakpoints for *Enterobacteriaceae* and *P. aeruginosa*. This is especially for all antipseudomonal agents belonging to β-lactams (ceftazidime and cefepime), β-lactam/β-lactamase inhibitor (pip/tazo), fluoroquinolones (ciprofloxacin and levofloxacin), aminoglycosides (amikacin, gentamicin and tobramycin) and polymyxins (colistin). With respect to clinical breakpoint differences, dosage of the agent suggested for the treatment of *P. aeruginosa* also varies.[40] In case of ceftazidime, for *Enterobacteriaceae*, MIC of ≤4 μg/ml is considered susceptible with the dosage recommended being 1 g every 8 h. In contrast, for *P. aeruginosa*, MIC of ≤8 μg/ml is considered susceptible with a recommended dosage of 1 g every 6 h or 2 g every 8 h because, *P. aeruginosa* infections requires high drug dosage. One of the main challenges in the management of *P. aeruginosa* infections is the MIC of an antipseudomonal agent. Studies have shown that MIC of an antimicrobial for an *Enterobacteriaceae* isolates are usually less than the clinical susceptibility breakpoints.[41] Whereas, in *P. aeruginosa*, MIC is generally very near to susceptible breakpoints. This, in turn, requires high dosage for therapy and/or addition of the second agent for a combined effect to reduce MIC of the first agent.[42,43]

New Agents with Antipseudomonal Activity

Table 4 summarises list of newer antimicrobial agents and its clinical indications for use.

Table 5 summarises data evidences for the activity of newer agents.

Table 4: Newer antimicrobial agents with anti-pseudomonal activity

Agents	Phase	Indications for use	Dosing
Ceftazidime/avibactam	FDA approved for clinical use	Complicated UTI and IAI	2.5 g IV q8h
Ceftolozane/tazobactam	FDA approved for clinical use	Complicated UTI and IAI	1.5 g IV q8h
Meropenem/varborbactam	FDA approved for clinical use	Complicated UTI	Meropenem 2 g, vaborbactam 2 g, IV q8h
Plazomicin	FDA approved for clinical use	Complicated UTI	500 mg/10 mL once daily
Imipenem/relebactam	Phase 3	-	-
Cefiderocol	Phase 2	-	-

UTI: Urinary tract infection, IAI: Intra-abdominal infections, FDA: Food and Drug Administration, IV: Intravenous

Ceftolozane/tazobactam

Ceftolozane/tazobactam (C/T) combination of a fifth-generation cephalosporin, with a beta-lactamase inhibitor. Ceftolozane has an antipseudomonal activity which was stable against AmpC enzymes and remained unaffected by porins and efflux systems of *P. aeruginosa*.[62] This combination was approved by the Food and Drug Administration (FDA) in December 2014, includes ceftolozane, which is a novel cephalosporin active against bacterial ampC enzymes, efflux system and membrane impermeability. However, it can be hydrolysed by extended-spectrum beta-lactamases (ESBLs) and carbapenemase. Therefore, the addition of tazobactam broadens the spectrum of activity against ESBL producers. It is licensed for use in adults for the treatment of complicated intra-abdominal infections (cIAIs) and complicated urinary tract infections (cUTI) including pyelonephritis.[63] It is approved for infections caused by *Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, P. aeruginosa, Proteus mirabilis, Bacteroides fragilis and Streptococcus* spp.

Table 5: Susceptibility of newer agents in *Pseudomonas aeruginosa* as reported by various studies

Study	Number of isolates	Study	Period	Source of specimen	MIC50 (μg/ml)	MIC90 (μg/ml)
Ceftolozane/tazobactam						
Sader *et al*., 2014[44]	*n*=2191	European Countries, Turkey, Israel surveillance collection	2011-2012	BSI, PNM, SSSI, UTI, IAI and others	1	>32
Farrell *et al*., 2013[45]	*n*=1971	US census region surveillance collection	2011-2012	BSI, PNM, SSSI, UTI, IAI	0.5	2
Buehrle *et al*., 2016[46]	*n*=38	University of Pitsburg Medical Centre, USA	-	BSI, RTI	-	4
Farrell *et al*., 2014[47]	*n*=1019	US and Europe	2012	Pneumonia	0.4	4
Farrell *et al*., 2014[47]	*n*=269	US and Europe	2012	Pneumonia	4	>32
Livermore *et al*., 2017[48]	*n*=1099	Europe	2011-2015	BSI	-	0.5
Pfaller *et al*., 2017[49]	*n*=603	Europe	2012-2015	UTI and IAI	-	4
Giani *et al*., 2017[50]	*n*=935	Italy	2013-2014	BSI, LRTI	-	4
Grupper *et al*., 2017[51]	*n*=290	US	2013-2014	BSI, LRTI, wound infections	-	4
Seifert *et al*., 2018[52]	*n*=497	Germany	2014-2015	-	-	2
Ceftazidime/avibactam						
Buehrle DJ *et al*., 2016[46]	*n*=38	University of Pitsburg Medical Centre, USA	-	BSI, RTI	-	8
Sader HS *et al*., 2015[53]	*n*=3902	INFORM Program, USA	2012-2013	BSI, PNM, SSSI, UTI, IAI and others	2	4
	MDR (*n*=580)				4	16
	XDR (*n*=338)				8	32
Levasseur *et al*., 2012[54]	*n*=126	South Paris Hospital	December 2006-April 2007	-	4	8
Walkty *et al*., 2011[55]	*n*=470	CANWARD study	January-December 2009	BSI, PNM, SSSI and UTI	2	8
Imipenem/relebactam						

Contd...

Table 5: Contd...

Study	Number of isolates	Study	Period	Source of specimen	MIC50 (μg/ml)	MIC90 (μg/ml)
Livermore *et al*., 2013[56]	Imipenem susceptible isolates (*n*=8) Imipenem non-susceptible (OprD-) (*n*=4/8) Multi drug resistant (*n*=ND)	Isolates from UK hospitals studied at HPA antimicrobial resistance and healthcare -associated infections unit			0.25-0.5 μg/ml ≤2 μg/ml 4-8 μg/ml	-
Lapuebla *et al*., 2015[57]	Imipenem susceptible (*n*=490) Imipenem non-susceptible (*n*=144)	Isolated from single patient from 11 different hospitals, Brooklyn and Queens, NewYork			0.5/4 μg/ml 1/4 μg/ml	2/4 μg/ml 2/4 μg/ml
Meropenem/vaborbactam						
Lapuebla *et al*., 2015[58]	*n*=98	Single patient isolate, Brooklyn and Queens, NewYork	November 2014-January 2014	-	8/8 μg/ml	32/8 μg/ml
Cefiderocol						
Ito *et al*., 2016[59]	*n*=104	Randomly collected clinical isolates, USA	One set from 2009 to 2011, second set from 2000 to 2009		≤0.063 mg/L	1 mg/L
Plazomicin						
Landman *et al*., 2011[60]	*n*=679	Single patient isolates from 15 Brooklyn hospitals, Newyork 1 in Staten island, Newyork	2009	Routine microbiological sample	8 mg/L	32 mg/L
Aggen *et al*., 2010[61]	*n*=51	Different geographic location	2004-2006	-	8 μg/ml	64 μg/ml

BSI: Bloodstream infection, UTI: Urinary tract infection, IAI: Intra-abdominal infections, RTI: Respiratory tract infection, LRTI: Lower respiratory tract infections, MIC: Minimum inhibitory concentration, MDR: Multidrug resistant, XDR: Extensive drug resistant, PNM: Pneumonia, HPA: Health protection agency, ND: Not determined, SSSI: Skin and skin structure infection

The safety and efficacy of this drug have not been established for use in paediatric population.[64] C/T has been shown to demonstrate better *in vitro* activity against ceftazidime-resistant *E. coli, K. pneumoniae* and *P. aeruginosa* than other antimicrobials such as ceftriaxone, cefepime and piperacillin/tazobactam. The antimicrobial is available for intravenous (iv) use as injection and is administered at a dose of 1.5 g (1 g/0.5 g) every 8 h by IV infusion over 1 h for patients 18 years or older with creatinine clearance >50 mL/min.[63] Dosage in patients with impaired renal function varies according to the renal clearance rate.

Since ceftolozane overcomes efflux mechanism present in the bacteria, it is more effective against *P. aeruginosa* where efflux contributes to a majority of drug resistance.[65] However, in *Enterobacteriaceae*, the resistance mechanisms are mostly enzymatic inactivation of the beta-lactam antibiotics. This could be a possible reason for C/T being highly effective against *P. aeruginosa* compared to *Enterobacteriaceae*.[66]

At present, FDA approved C/T for the treatment of cIAI and cUTI. However, it was not approved for its use in bacteraemia. Recently, Patel *et al*., 2016, have used C/T for a 66-year-old bacteraemic patient with MDR *P. aeruginosa* infection.[67] *In vitro*, the isolate was susceptible to C/T with MIC of 2/4 μg/ml. 375 mg of C/T monotherapy was given for about 25 days, and the clinical outcome was successful. The concentration of the drug achieved in the serum was higher than the MIC of the organism and signifies the utility of C/T in bacteraemic cases. However, further studies need to be carried out to warrant the use of C/T in bacteraemia.

In due course of evaluating C/T as active antipseudomonal agents, Gangcuangco *et al*., 2016, have reported the case report of C/T resistance.[67] A 68-year-old male with persistent sepsis developed resistance during therapy. This report alerts clinicians, and microbiologist to perform repeated cultures and susceptibility testing for *P. aeruginosa*, as it develops resistance during therapy resulting in clinical failure. Although C/T is a new agent, routine susceptibility testing warrants its clinical success.

Studies have proven that tazobactam does not directly influence the activity of ceftolozane, yet it showed excellent activity

against strains-producing ESBLs. Notably, Ceftolozane *in vitro* activity was proved to be 8-fold higher than ceftazidime.[68] Further, C/T was found to be superior than imipenem and piperacillin/tazobactam.[69] More importantly, against ceftazidime-resistant *P. aeruginosa*, C/T retained its activity; underlining the clinical utility of C/T against *P. aeruginosa* infections.

Further, studies have proven that, MICs of *P. aeruginosa* producing AmpC beta-lactamases are 2 and 4 μg/ml, suggesting the stability of C/T against *AmpC* enzymes. This was supported by Moya *et al*., wherein a common resistance mechanism in P. *aeruginosa* does not influence the MIC of C/T.[70] In contrary, Cabot *et al*., 2014, have reported that mechanisms of resistance to be due to the mutated and altered structure of *ampC* which could hydrolyse Ceftolozane.[71] More importantly, cross-resistance associated with C/T was not observed in any of the studies reported. Strains that are resistant to antipseudomonal agents retained its susceptibility against C/T. Table 5 summarises MIC_{50} and MIC_{90} reported by various studies.

Ceftazidime/avibactam

Ceftazidime/avibactam combination was formerly known as "NXL104." It is a coformulation of an antipseudomonal cephalosporin (ceftazidime) and a novel non-β-lactam-based β-lactamase inhibitor (avibactam). It is stable against clinical isolates producing β-lactamases such as Class A (TEM, SHV, CTX-M), Class C (AmpC), Class D (Oxa) and carbapenemase (KPC). In *P. aeruginosa,* ceftazidime resistance is contributed by the production of β-lactamases (AmpC and ESBLs). Addition of avibactam restores the activity of ceftazidime, whereas clavulanic acid and tazobactam, either lacks or partially restores ceftazidime activity. This combination of ceftazidime/avibactam was found to have an excellent antibacterial activity against a multidrug-resistant Gram-negative isolates.[72] However, it lacks activity against metallo β-lactamase-producing organisms.

This combination was approved by the FDA in February 2015 for the treatment of cIAIs in combination with metronidazole and cUTI including pyelonephritis. Dosage was formulated in the ratio of 4:1, with 2 g of ceftazidime and 0.5 g of avibactam. It is available for IV use, administered every 8 h over 2-h infusion period. However, the dosage varies for patients with impaired renal function such as 1.25 g IV q8 h (CLcr 30–50 mL/min), 0.94 g IV q12 h (CLcr 15–29 mL/min), 0.94 g IV q24 h (CLcr 6–15 mL/min) and 0.94 g IV q48 h (CLcr <5 mL/min). Safety of using this combination in paediatric population has not been established.

In a Phase 2 trial of ceftazidime/avibactam versus imipenem/cilastatin groups, cure rates observed were 70.4% and 71.4%, respectively. Similarly, for ceftazidime/avibactam+metronidazole versus meropenem, the cure rates were 91.2% and 93.4%, respectively. However, in patients with impaired renal function, clinical cure rates were 45% and 74%, respectively. Furthermore, mortality rates were 25.8% and 8.6% between the groups, respectively. Clinical trials of REPRISE study showed promising results wherein ceftazidime/avibactam is a better alternative to carbapenems for treating infections due to ceftazidime-resistant Gram-negative organisms. Against Class A carbapenemase (KPC)-producing organism in US, MIC_{50} and MIC_{90} of Avycaz were found to be 0.5 and 2 μg/ml, respectively. Interestingly, studies have reported reduction in the MIC_{90} of ceftazidime from 128 to 4 μg/ml upon addition of avibactam.[73]

FDA recommended breakpoint criteria were ≤8/4 and ≥16 μg/ml for interpreting susceptible and resistant for *Enterobacteriaceae* and *P. aeruginosa,* respectively. A number of studies evaluated the *in vitro* activity of ceftazidime/avibactam against clinical isolates across various sites. The results are summarised in Table 5.[46,53-55] Of all the reports, MIC_{50} and MIC_{90} were ranging from 2 to 8 μg/ml and 4 to 32 μg/ml, respectively. Notably, MIC_{50} and MIC_{90} were found to be 4 and 16 μg/ml for MDR and 8 and 32 μg/ml for XDR *P. aeruginosa,* respectively. This is comparatively lesser than the MIC of ceftazidime alone.[74]

Resistance to ceftazidime/avibactam is reported by Winkler *et al*., in the archived isolates of their collection.[75] It was reported that the mechanism of resistance is due to the chromosomal-mediated porin and efflux pumps.[75] This is a major concern, as resistances due to chromosomal-mediated mechanisms are difficult to treat, while this mechanism could not be transferred to another strain as they are chromosomal mediated. However, the addition of fosfomycin to this combination has been proven to improve the clinical outcome when more than one agent targeting the cell wall synthesis pathways is prescribed.

Imipenem/relebactam

Relebactam or MK-7655 is bicyclic diazabicyclooctane, non-beta lactam and a beta-lactamase inhibitor.[76] Physically, it resembles avibactam but contains an additional piperdine ring. It is stable in the pH range of 4–8 under aqueous environment.[77] Piperdine possesses positive charge under this pH, which resists efflux from bacteria.[78] Relebactam is effective against Class A β-lactamases (e.g., KPC) and Class C (eg: ampC) but is inactive against Class B metallo-β-lactamases (e.g., VIM, NDM and IMP) and Class D (e.g., OXA) β-lactamases.[56,57,79] Relebactam inhibits β-lactamases by acetylation and is highly reactive against β-lactamase PER-2 of *P. aeruginosa*.[80,81] It is also effective against *P. aeruginosa* PDC-3, ESBL.[82] Addition of relebactam to imipenem inhibits the action of carbapenemase (β-lactamases) along with cell wall synthesis inhibition by imipenem providing potent protection against MDR pathogens. Zhanel *et al*. (2017) observed multiple-fold (8 fold) decrease in MIC against imipenem non-susceptible, β-lactamase-producing *Enterobacteriaceae* and in *P. aeruginosa*.[83]

Livermore *et al*., 2013, found that MIC value (1–2 mg/L) of imipenem susceptible *P. aeruginosa* with intrinsic AmpC imposed resistance was highly reduced to 0.25–0.5 mg/L with imipenem-relebactam combinations.[56] In case of

imipenem-resistant isolates, concentration of relebactam is comparatively higher than that used in susceptible isolates. For different OprD absent isolates without any other resistant mechanisms, addition of relebactam has reduced MIC values from 16–64 to 2–8 mg/L, whereas in MDR isolates MIC was around 4–8 mg/L. Imipenem-relebactam combination is not significant in reducing MIC of isolates with metallo-carbapenemases as relebactam is inactive against it. Lapuebla *et al*., 2016, found that in 490 isolates of *P. aeruginosa*, imipenem-relebactam combination has reduced MIC from 2–16 to 0.5–2 μg/ml.[57] In imipenem non-susceptible isolates (n = 144), imipenem-relebactam combination reduced MIC as 1–2 μg/ml. In case of 30 carbapenemase-negative isolates, six of these isolates with OprD and AmpC as that of wild-type controls, MIC's reduced from 2 to 4 μg/ml to 1 μg/ml after addition of relebactam to imipenem. In 14 of the carbapenem-negative isolates, with AmpC as control but with reduced OprD, MIC's reduced from 1–>16 to 0.25–8 μg/ml. Remaining ten with elevated AmpC but with reduced OprD has its MIC reduced from 2–>16 to 1–8 μg/ml.[84]

In case of cIAIs, a non-inferiority, randomised, double-blinded, Phase II clinical trial (NCT01506271) used imipenem relebactam. Pathogens isolated were *E. coli* (n = 171), *Klebsiella pneumoniae* (n = 38) and *P. aeruginosa* (n = 37), in which 40 were imipenem non-susceptible. The primary outcome of the study revealed that discontinuous IV infusion with two different arms of relebactam 250 mg and 125 mg showed increased response variation of 1.1% and 3.7%, respectively, against imipenem alone. Overall response in curing disease with two different doses of relebactam along with the same dose of imipenem showed 86.5% (250 mg relebactam), 89.6% (125 mg relebactam) against 84.8% with imipenem alone for all tested pathogens.[85]

A global, double-blinded, randomised, non-inferiority Phase II trial, tested imipenem-cilastatin/relebactam (500–500/250 mg), imipenem-cilastatin/relebactam (500–500/125 mg) with imipenem-cilastatin alone (500–500 mg) in patients suffering with cUTI and acute pyelonephritis (AP). Pathogens isolated at baseline included *E. coli* (n = 143), *K. pneumoniae* (n = 34) and *P. aeruginosa* (n = 16). About 25 isolates were non-susceptible to imipenem while 15 were non-susceptible to imipenem-relebactam. Microbial response to the treatment in microbiologically evaluable population showed a primary outcome of 95.5% to 250 mg of relebactam while it was 98.7% with imipenem alone group. In case of 125 mg of relebactam primary outcome was 98.6% while it was 98.7% in imipenem alone. Hence, the trial showed both are non-inferior to imipenem alone. In microbiological response also, the outcome was same.

Two Phase III study, NCT02452047 (RESTORE-IMI 1) and NCT02493764 (RESTORE-IMI 2), which got over on September 2017 (results not yet published) and May 2019, use imipenem-relebactam in comparison with colistimethate sodium-imipenem and imipenem-relebactam in comparison with piperacillin tazobactam, respectively. The first trial tested in patients with hospital-associated bacterial pneumonia, ventilator-associated bacterial pneumonia, cIAIs and cUTI whereas the second trail deals with hospital-associated bacterial pneumonia and ventilator-associated bacterial pneumonia. Results from these studies would prove that imipenem-relebactam as the drug of choice to treat imipenem non-susceptible Enterobactericeae and also multiple drug-resistant *P. aeruginosa.*

Meropenem/vaborbactam

Vaborbactam is a non-β-lactam, with high propensity towards serine β-lactamases. Similar to relebactam, vaborbactam is active against Class A (e.g., KPCs) and Class C β-lactamases but are inactive against Class B and Class D β-lactamases.[86,87] Boron atom of vaborbactam is electrophilic, forms covalent bond with serine of β-lactamases.[76,86] As this is a reversible reaction, there is no hydrolysis of the antibiotic; hence, its action is more of inhibition.[88] Meropenems high activity against Gram-negative pathogens is because of its inclination to bind PBP2 followed with PBP1a, 1b and 3. Meropenem low affinity to PBP3 is its significant property as it results in enhanced bacterial cell lysis but not filamentation. This leads to decreased cell mass before lysis and also reduced endotoxin (lipopolysaccharide) release.[89]

Vaborbactam showed the increased activity when combined with meropenem in inhibiting KPC beta-lactamases in *K. pneumoniae* isogenic strains that showed multiple resistance such as ESBL, AmpC production along with less porin intake because of mutations in OmpK35 and OmpK36.[90] AcrAB-TolC efflux system involved in multiple drug resistance had less influence on vaborbactam activity. Vaborbactam restored meropenem activity at 8 μg/ml with the MIC of ≤2 μg/ml in isogenic strains with maximum mutations. There is no significant MIC reduction for *P. aeruginosa* and *Acinetobacter baumanii* with meropenem-relebactam combination.[58,91]

In a Phase III clinical trial (TANGO I– NCT02166476), which was a randomised, multicentred, double-blinded, non-inferiority trial, meropenem-vaborbactam (2000/2000 mg), through IV infusion 3 h, every 8-h interval for 5–10 days, was tested along with piperacillin/tazobactam combination. Patients (n = 550) under the study were grouped as 1:1 based on geographical location and infection type such as AP, cUTI either with or without removable source. Patients were followed with oral levofloxacin for 5 days after discontinuation of IV (DCIV) of above-mentioned drug combinations. The primary outcome calculated based on microbiologic-modified intention to treat (m-MITT) or m-MITT after DCIV. Treatment success is defined by microbiological cure with baseline microbial load decreased to $<10^4$ CFU/ml as per FDA. m-MITT evaluation showed 98.4% for meropenem-vaborbactam and 94.0% for piperacillin/tazobactam. Hence, there is a significant difference of 4.5% with 95% confidence interval, thus proved non-inferiority of meropenem-vaborbactam.

In case of specific disease condition, m-MITT after DCIV was 100% for both complicated urinary tract infection with either removable or non-removable source, whereas it was 97% in case of AP. m-MITT for the above three complications were 92.1% and 95.3% for complicated urinary tract disease with removable and non-removable source, respectively, whereas it was 94.1% in acute pyelonephritis. Pathogens isolated in above three complications were Enterobactericeae (n = 333) and *P. aeruginosa* (n = 15). The secondary outcome was measured as test of cure (TOC) for 15–19 days. The baseline pathogen eradication should be $<10^3$ CFU/ml according to education maintenance allowance criteria. Hence, m-MITT at TOC was 66.7% for meropenem-vaborbactam and 57.7% for piperacillin/tazobactam, showing a significant variation of 9.0% at 95% confidence interval. Adverse events reported were 39% and 35.5% in meropenem-relebactam and piperacillin/tazobactam.[92]

Cefiderocol

Cefiderocol or CFDC (S-649266), is a new siderophore-drug conjugate with catechol siderophore conjugated with antibiotic cephalosporin, inhibits bacterial cell wall synthesis. It is phenotypically different from MB-1, BAL30072 and MC-1 with hydroxypyridone substituted monobactam siderophore. Cefiderocol showed high antibacterial activity against carbapenem-resistant *P. aeruginosa*, *Enterobacteriaceae* and *A. baumannii* with reduced MIC.[59] MIC90 of *P. aeruginosa* and beta-lactam-resistant (including metallo-beta-lactamase-VIM, GIM-1, SPM-1 and IMP) *P. aeruginosa* is 1 and 4 mg/L, respectively.[59]

Cefiderocol chelates extracellular ferric iron through catechol siderophore, gets transported intracellularly by iron transport pathways.[93] Catalytic efficiency (K_{cat} and K_m) of cefiderocol was tested against many carbapenemases such as OXA-23, KPC-3, IMP-1, VIM-2 and NDM-1 and found that Kcat/Km of metallo-β-lactamases (L1, VIM-2 and IMP-1) is the lowest among other tested antibiotics. High Km value for cefiderocol with OXA-23 and KPC-3 than meropenem reflects its increased activity against pathogens that produced these enzymes. Kinetics of cefiderocol in comparison with ceftazidime was similar against tested β-lactamases but showed variations in antibacterial activities against OXA-23 positive *A. baumannii.* This variation could be the result of different antibiotic uptake mechanisms for cefiderocol and ceftazidime.

Dosage of 2 g in IV with 8-h interval for 10 days was good in healthy patients without any typical adverse side effects.[94,95] Katsube *et al*., 2017, found that the dosage of cefiderocol in patients with different grades of augmented renal function as 2 g for every 6 h with 3-h infusion which showed a >90% (PTA) probability of target attainment with plasma drug concentration exceeding MIC of ≤4 μg/ml. The SIDERO-WT-2014 study tested *in vitro* broth microdilution method to determine MIC_{90} values for both carbapenem susceptible and carbapenem non-susceptible Enterobacteriaceae and *P. aeruginosa.* Cefiderocol MIC_{90} of *P. aeruginosa* was 0.5 μg/ml (n = 765, North America and Europe), with MIC of ≤4 μg/ml for 99.9% of isolates except a single isolate from North America had MIC of 8 μg/ml. In case of meropenem non-susceptible isolates (MIC ≥4 μg/ml, n = 353) with MIC_{90} values for cefiderocol in North America isolates (n = 151) was 0.5 and 1 μg/ml in case of Europe (n = 202) with overall MIC of ≤4 μg/ml. In case of meropenem susceptible isolates, MIC_{90} for cefiderocol was 0.5 μg/ml (n = 614) for North America and 0.5 μg/ml (n = 563) with 99.9% of these meropenem susceptible isolates had MIC's at ≤4 μg/ml. Variations in MIC values in these isolates could be due to either because of reduced expression of iron uptake components or might be due to mutations that disrupt siderophore-antibiotic conjugate attachment and entry as identified with previously studied siderophore-antibiotic conjugates.

Adaptation-based resistance with native siderophore competition as in MB-1 drug resistance was not identified with cefiderocol.[96] In another study with carbapenem non-susceptible isolates collected from 52 countries from the period of 2014–2016, *in vitro* antibacterial activity of cefiderocol showed MIC_{90} of *P. aeruginosa* (n = 262) was 1 μg/ml with 99.2% (260/262) with an MIC of ≤4 μg/ml.[97]

Saisho *et al*., 2018, studied the pharmacokinetics, tolerability and safety of cefiderocol in Phase 1 trial with healthy Japanese and Caucasian males and Japanese females, as a single-centred, double-blinded, randomised, placebo-controlled study that was done in two groups with single ascending dose and with multiple ascending doses. This study indicated that healthy subjects given with cefiderocol in different dosage pattern tolerated it well without any significant adverse events.

A Phase II study on efficacy/safety of IV cefiderocol versus imipenem/cilastatin in cUTI with or without pyelonephritis or acute uncomplicated pyelonephritis caused by Gram-negative pathogens (APEKS-cUTI/NCT02321800), was an interventional, multicentred, randomised, open-label clinical study. Patients were administered with 2 g of drug by IV, 3 h of infusion for every 8 h for 7–14 days. Clinical and microbiological outcome of the study proposed the effectiveness of the tested drug cefiderocol, which resulted in reduced number of colony-forming units ($<10^4$) after 7 days from the end of treatment. Kawaguchi *et al*., 2018, tested population pharmacokinetics for cefiderocol and found that the dosage of 2 g with 1-h IV infusion for every 8-h interval for 7 or 14 days was efficient to treat complicated urinary tract infection and acute uncomplicated pyelonephritis.[98] Drug exposure or concentration of drug in patients with infection is comparatively lower which could be balanced by shortened dosing interval.

A Phase III clinical trial (CREDIBLE-CR/NCT02714595), is a multicentred, randomised, open-label clinical study of cefiderocol to treat patients with carbapenem-resistant Gram-negative pathogen is in progress from September 2016 and will get over in October 2018. Serious infections such as hospital-acquired pneumonia, healthcare-associated

pneumonia, ventilator-associated pneumonia, bloodstream infections, cUTI and sepsis are treated with 2 g of cefiderocol as IV with 3 h of infusion time, every 8 h for 7–14 days. Thus, cefiderocol is one of the drugs of choice to treat carbapenem-resistant Gram-negative pathogens causing complicated urinary tract infection, bloodstream infections and nosocomial pneumonia.

Plazomicin

Plazomicin or ACHN-490 is basically a modified sisomicin (SIS) with improved activity against aminoglycoside-degrading enzymes of *Enterobacteriaceae*, *P. aeruginosa* and *A. baumannii* and *Staphylococcus aureus*. This property is because of the presence of hydroxymethyl group in 6' position in ACHN-490.[61] Prevalent aminoglycoside-resistant enzymes are AAC (N-acetylation), APH (O-phosphorylation) and by ANT (O-adenylylation).[99] MIC values of strains with different aminoglycoside resistance mechanisms with either single or multiple AG-resistant enzymes showed increased fold reductions in MIC values with plazomicin. *E. coli* with ANT (2")-I with an MIC of 32 μg/ml with SIS and AMK showed effective reduction with an MIC of 0.25 μg/ml whereas a strain with AAC (3) 1 showed MIC of 2 μg/ml when compared to >64 μg/ml with SIS and GEN.

In case of *P. aeruginosa* with AAC (3)-I and AAC (6')-II reduced from 32 μg/ml (SIS), 64 μg/ml (GEN) to 8 μg/ml to plazomicin and 32 μg/ml (SIS and GEN) to 2 μg/ml, respectively.[61] Pankuch *et al*., 2011, studied the activity of plazomicin along with cefepime, imipenem, doripenem and piperacillin/tazobactam on *P. aeruginosa* by synergy time-kill assay.[100] MIC of plazomicin for all 25 isolates at 24 h ranges from 0.5 to 256 μg/ml, which included four strains with aminoglycoside-modifying enzymes. Combination of plazomicin with cefepime, doripenem, imipenem and piperacillin/tazobactam revealed synergism against ≥70%, ≥80% at 6 and 12 h, respectively, whereas at 24-h synergism is high for all strains. Among different combinations, MIC levels of plazomicin and piperacillin/tazobactam combination showed high synergism with 92% of isolates. Walkty *et al*., 2014, studied *in vitro* activity of plazomicin against both Gram-positive and Gram-negative pathogens isolated from Canadian hospitals as a part of CANWARD study from 2011 to 2012.[101] MIC_{50} and MIC_{90} for plazomicin and amikacin were 4 and 16 μg/ml and 4 and 8 μg/ml, respectively, whereas in case of MDR *P. aeruginosa* it was 8 and 32 μg/ml. When compared to other tested aminoglycosides, such as gentamicin and tobramycin, MIC_{90} of plazomicin is 2 and 8 times low, but according to *in vivo* studies, plazomicin showed effective serum concentration than gentamicin and tobramycin.[102,103]

Cass *et al*., (2011) conducted two randomised, double-blinded, placebo-controlled Phase 1 clinical trial to study pharmacokinetics, tolerability and safety of plazomicin injection in healthy individuals.[103] In the first study, parallel group design was followed with increasing single and double doses. Totally, 39 individuals (30 with drug and 9 as placebo) were administered with single dose of 1 mg/kg (10 min IV) body weight of plazomicin, proceeded with single and multiple doses of 4,7,11 and 15 mg/kg for about 10,10,5 and 3 days, respectively. In study, 2 and 8 individuals (8 drugs and 2 places) received 15 mg/kg for 5 days. In both the studies, drug was well tolerated without major adverse effects.

In a multicentre, multinational double-blinded randomised, comparator-controlled Phase II clinical study (NCT01096849), plazomicin was administered intravenously and compared with levofloxacin in case of cUTI and in AP patients. Isolated baseline pathogens included *Enterobacteriaceae* ($n = 68$) MIC of ≤0.12–8 μg/ml for plazomicin, MIC of ≤0.12 to >4 μg/ml for levofloxacin and two other Gram-negative pathogen, *E. coli* and *P. aeruginosa* were with MIC of >4 μg/ml for plazomicin. Patients randomised as 1:1:1 and were given with 10 mg/kg ($n = 22$) and also 15 mg/kg ($n = 76$) of plazomicin, daily by IV (30 min) and comparator group with 750 mg/kg ($n = 47$) of levofloxacin IV daily for 5 consecutive days, respectively. The primary outcome of the study evaluated as microbiological eradication rate with TOC determined at 5–12 days after last dose of treatment in MITT and microbiological evaluable (ME) population groups. Microbiological eradication at TOC based on primary diagnosis baseline pathogen of the ME population in AP was 100% (2 is the number of patients with eradication at TOC/2 number of patients with the following primary diagnosis), 88.9% (16/18) and 80.0%(12/15), and in cUTI, it was 80.0% (4/5), 88.2 (15/17) and 83.3 (5/6), respectively, in all three groups. Number of patients with eradication at TOC to the number of patients infected with different pathogens for all three conditions were like for *P. aeruginosa* was 50% in case of 15 mg/kg group.[104] Hence, this study propound the administration of plazomicin either as 10 mg/kg or 15 mg/kg once daily for 5 days in patients with AP and other AP.

A Phase III clinical trial (NCT02486627), EPIC was a randomised multicentre, multinational, double-blind study comparing the efficacy and safety of plazomicin in comparison to meropenem with oral therapy of levofloxacin. A total of 609 participants with cUTI and PA were administered with plazomicin 15 mg/kg once daily and meropenem 1 g for every 8 h, through IV for 4–7 days followed with oral therapy with levofloxacin against ESBL-positive Enterobactericeae, *E. coli, K. pneumoniae, Enterobacter cloacea and P. mirabilis*.[105] MMITT values of Enterobactericeae were 97.3%(220/226), ESBL 35.0%(79/226), aminoglycoside non-susceptible 34.5%(78/226) in cUTI cases, and it was 100% (162/162), 17.35% (28/162) and 14.2%(23/162) in AP. Microbiological eradication rates at TOC for plazomicin were 86.9%($n = 93$), for meropenem 75.6% ($n = 90$) in cUTI and 73.1%($n = 57$) for plazomicin and 73.1%($n = 69$) for meropenem in AP. Hence, plazomicin was well tolerated in both tested disease conditions with higher microbiological eradication rates and thus could be the drug of choice to treat MDR Enterobacteriaceae.

Conclusion

Although new agents are being developed, it is well known that efflux pumps play a major role in the AMR in *P. aeruginosa*. It will pose a great challenge for the development of any antipseudomonal agent to bypass this mechanism. This could be achievable by the use of efflux inhibitors as therapeutic purposes. Henceforth, efflux inhibitors for clinical use are the need of hour to achieve clinical success in the treatment of *P. aeruginosa* infections. Further, randomised controlled trials evaluating the syndrome-specific combination of agents would support improved clinical success rates.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Micek ST, Lloyd AE, Ritchie DJ, Reichley RM, Fraser VJ, Kollef MH, *et al. Pseudomonas aeruginosa* bloodstream infection: Importance of appropriate initial antimicrobial treatment. Antimicrob Agents Chemother 2005;49:1306-11.
2. Strateva T, Yordanov D. *Pseudomonas aeruginosa* – A phenomenon of bacterial resistance. J Med Microbiol 2009;58:1133-48.
3. Lister PD, Wolter DJ, Hanson ND. Antibacterial-resistant *Pseudomonas aeruginosa*: Clinical impact and complex regulation of chromosomally encoded resistance mechanisms. Clin Microbiol Rev 2009;22:582-610.
4. Breidenstein EB, de la Fuente-Núñez C, Hancock RE. *Pseudomonas aeruginosa*: All roads lead to resistance. Trends Microbiol 2011;19:419-26.
5. El Zowalaty ME, Al Thani AA, Webster TJ, El Zowalaty AE, Schweizer HP, Nasrallah GK, *et al. Pseudomonas aeruginosa*: Arsenal of resistance mechanisms, decades of changing resistance profiles, and future antimicrobial therapies. Future Microbiol 2015;10:1683-706.
6. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, *et al.* Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: An international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18:268-81.
7. Gandra S, Mojica N, Klein EY, Ashok A, Nerurkar V, Kumari M, *et al.* Trends in antibiotic resistance among major bacterial pathogens isolated from blood cultures tested at a large private laboratory network in India, 2008-2014. Int J Infect Dis 2016;50:75-82.
8. Gupta R, Malik A, Rizvi M, Ahmed M. Presence of metallo-beta-lactamases (MBL), extended-spectrum beta-lactamase (ESBL) & AmpC positive non-fermenting gram-negative bacilli among Intensive Care Unit patients with special reference to molecular detection of bla CTX-M & bla AmpC genes. Indian J Med Res 2016;144:271-5.
9. Kotwal A, Biswas D, Kakati B, Singh M. ESBL and MBL in cefepime resistant *Pseudomonas aeruginosa*: An update from a rural area in Northern India. J Clin Diagn Res 2016;10:DC09-11.
10. Ellappan K, Belgode Narasimha H, Kumar S. Coexistence of multidrug resistance mechanisms and virulence genes in carbapenem-resistant *Pseudomonas aeruginosa* strains from a tertiary care hospital in South India. J Glob Antimicrob Resist 2018;12:37-43.
11. Agarwal R, Sankar J. Characterisation and antimicrobial resistance of sepsis pathogens in neonates born in tertiary care centres in Delhi, India: A cohort study. Lancet Glob Health 2016;4:e752-60.
12. Dhaneria M, Jain S, Singh P, Mathur A, Lundborg CS, Pathak A, *et al.* Incidence and determinants of health care-associated blood stream infection at a neonatal Intensive Care Unit in Ujjain, India: A prospective cohort study. Diseases 2018;6. pii: E14.
13. Senthamarai S, Reddy AS, Sivasankari S, Anitha C, Somasunder V, Kumudhavathi MS, *et al.* Resistance pattern of *Pseudomonas aeruginosa* in a tertiary care hospital of Kanchipuram, Tamilnadu, India. J Clin Diagn Res 2014;8:DC30-2.
14. Centre for Disease Dynamics, Economics and Policy. Available from: https://www.resistancemap.cddep.org/. [Last accessed on 2018 Sep 08].
15. Gandra S, Joshi J, Trett A, Lamkang AS, Laxminarayan R. Scoping Report on Antimicrobial Resistance in India. Washington, DC: Center for Disease Dynamics, Economics & Policy; 2017.
16. Wattal C, Raveendran R, Goel N, Oberoi JK, Rao BK. Ecology of blood stream infection and antibiotic resistance in Intensive Care Unit at a tertiary care hospital in North India. Braz J Infect Dis 2014;18:245-51.
17. Li XZ, Plésiat P, Nikaido H. The challenge of efflux-mediated antibiotic resistance in gram-negative bacteria. Clin Microbiol Rev 2015;28:337-418.
18. Juan C, Maciá MD, Gutiérrez O, Vidal C, Pérez JL, Oliver A, *et al.* Molecular mechanisms of beta-lactam resistance mediated by ampC hyperproduction in *Pseudomonas aeruginosa* clinical strains. Antimicrob Agents Chemother 2005;49:4733-8.
19. Poole K. *Pseudomonas aeruginosa*: Resistance to the max. Front Microbiol 2011;2:65.
20. Balasubramanian D, Schneper L, Kumari H, Mathee K. A dynamic and intricate regulatory network determines *Pseudomonas aeruginosa* virulence. Nucleic Acids Res 2013;41:1-20.
21. Bharti NM, Sharma PC. Molecular characterization of *Pseudomonas aeruginosa* isolates recovered from human patients in Himachal Pradesh (India) for selective genes: Extended spectrum β-lactamase (ESBL), ampicillin class c (AMPC) and metallo β-lactamase (MBL) genes. Int J Pharm Sci Res 2016;7:4905-16.
22. Paul D, Dhar Chanda D, Maurya AP, Mishra S, Chakravarty A, Sharma GD, *et al.* Co-carriage of blaKPC-2 and blaNDM-1 in clinical isolates of *Pseudomonas aeruginosa* associated with hospital infections from India. PLoS One 2015;10:e0145823.
23. Mohanam L, Menon T. Coexistence of metallo-beta-lactamase-encoding genes in *Pseudomonas aeruginosa*. Indian J Med Res 2017;146:S46-52.
24. Naim H, Rizvi M, Azam M, Gupta R, Taneja N, Shukla I, *et al.* Alarming emergence, molecular characterization, and outcome of blaNDM-1 in patients infected with multidrug-resistant gram-negative bacilli in a tertiary care hospital. J Lab Physicians 2017;9:170-6.
25. Paul D, Maurya AP, Chanda DD, Sharma GD, Chakravarty A, Bhattacharjee A, *et al.* Carriage of blaNDM-1 in *Pseudomonas aeruginosa* through multiple Inc type plasmids in a tertiary referral hospital of Northeast India. Indian J Med Res 2016;143:826-9.
26. Paul D, Dhar D, Maurya AP, Mishra S, Sharma GD, Chakravarty A, *et al.* Occurrence of co-existing bla VIM-2 and bla NDM-1 in clinical isolates of *Pseudomonas aeruginosa* from India. Ann Clin Microbiol Antimicrob 2016;15:31.
27. Rahman M, Prasad KN, Gupta S, Singh S, Singh A, Pathak A, *et al.* Prevalence and molecular characterization of New Delhi metallo-beta-lactamases in multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* from India. Microb Drug Resist 2018;24:792-8.
28. Pragasam AK, Vijayakumar S, Bakthavatchalam YD, Kapil A, Das BK, Ray P, *et al.* Molecular characterisation of antimicrobial resistance in *Pseudomonas aeruginosa* and *Acinetobacter baumannii* during 2014 and 2015 collected across India. Indian J Med Microbiol 2016;34:433-41.
29. Bassetti M, Vena A, Croxatto A, Righi E, Guery B. How to manage *Pseudomonas aeruginosa* infections. Drugs Context 2018;7:212527.
30. Tschudin-Sutter S, Fosse N, Frei R, Widmer AF. Combination therapy for treatment of *Pseudomonas aeruginosa* bloodstream infections. PLoS One 2018;13:e0203295.
31. Traugott KA, Echevarria K, Maxwell P, Green K, Lewis JS 2nd. Monotherapy or combination therapy? The *Pseudomonas aeruginosa* conundrum. Pharmacotherapy 2011;31:598-608.
32. Hu Y, Li L, Li W, Xu H, He P, Yan X, *et al.* Combination antibiotic therapy versus monotherapy for *Pseudomonas aeruginosa* bacteraemia: A meta-analysis of retrospective and prospective studies. Int J Antimicrob Agents 2013;42:492-6.
33. Vardakas KZ, Tansarli GS, Bliziotis IA, Falagas ME. B-lactam plus aminoglycoside or fluoroquinolone combination versus β-lactam

monotherapy for *Pseudomonas aeruginosa* infections: A meta-analysis. Int J Antimicrob Agents 2013;41:301-10.
34. Chamot E, Boffi El Amari E, Rohner P, Van Delden C. Effectiveness of combination antimicrobial therapy for *Pseudomonas aeruginosa* bacteremia. Antimicrob Agents Chemother 2003;47:2756-64.
35. Juan C, Conejo MC, Tormo N, Gimeno C, Pascual Á, Oliver A, *et al.* Challenges for accurate susceptibility testing, detection and interpretation of β-lactam resistance phenotypes in *Pseudomonas aeruginosa*: Results from a Spanish multicentre study. J Antimicrob Chemother 2013;68:619-30.
36. Pragasam AK, Raghanivedha M, Anandan S, Veeraraghavan B. Characterization of *Pseudomonas aeruginosa* with discrepant carbapenem susceptibility profile. Ann Clin Microbiol Antimicrob 2016;15:12.
37. Pragasam AK, Raghanivedha M, Anandan S, Veeraraghavan B. Molecular characterization of imipenem-resistant, meropenem-susceptible *Pseudomonas aeruginosa* with blaVIM-2 phenotype: Potential for dissemination. Jpn J Infect Dis 2016;69:159-60.
38. Zeng ZR, Wang WP, Huang M, Shi LN, Wang Y, Shao HF, *et al.* Mechanisms of carbapenem resistance in cephalosporin-susceptible *Pseudomonas aeruginosa* in China. Diagn Microbiol Infect Dis 2014;78:268-70.
39. Campana EH, Xavier DE, Petrolini FV, Cordeiro-Moura JR, Araujo MR, Gales AC, *et al.* Carbapenem-resistant and cephalosporin-susceptible: A worrisome phenotype among *Pseudomonas aeruginosa* clinical isolates in Brazil. Braz J Infect Dis 2017;21:57-62.
40. Frei CR, Wiederhold NP, Burgess DS. Antimicrobial breakpoints for gram-negative aerobic bacteria based on pharmacokinetic-pharmacodynamic models with Monte Carlo simulation. J Antimicrob Chemother 2008;61:621-8.
41. Yang Q, Zhang H, Wang Y, Xu Z, Zhang G, Chen X, *et al.* Antimicrobial susceptibilities of aerobic and facultative gram-negative bacilli isolated from Chinese patients with urinary tract infections between 2010 and 2014. BMC Infect Dis 2017;17:192.
42. Jean SS, Lee WS, Yu KW, Liao CH, Hsu CW, Chang FY, *et al.* Rates of susceptibility of carbapenems, ceftobiprole, and colistin against clinically important bacteria collected from Intensive Care Units in 2007: Results from the surveillance of multicenter antimicrobial resistance in Taiwan (SMART). J Microbiol Immunol Infect 2016;49:969-76.
43. Veeraraghavan B, Jesudason MR, Prakasah JA, Anandan S, Sahni RD, Pragasam AK, *et al.* Antimicrobial susceptibility profiles of gram-negative bacteria causing infections collected across India during 2014-2016: Study for monitoring antimicrobial resistance trend report. Indian J Med Microbiol 2018;36:32-6.
44. Sader HS, Farrell DJ, Castanheira M, Flamm RK, Jones RN. Antimicrobial activity of ceftolozane/tazobactam tested against *Pseudomonas aeruginosa* and *Enterobacteriaceae* with various resistance patterns isolated in European hospitals (2011–12). J Antimicrob Chemother 2014;69:2713-22.
45. Farrell DJ, Flamm RK, Sader HS, Jones RN. Antimicrobial activity of ceftolozane/tazobactam tested against *Enterobacteriaceae* and *Pseudomonas aeruginosa* with various resistance patterns isolated in US hospitals (2011-2012). Antimicrob Agents Chemother 2013;57: 6305–10:AAC-01802.
46. Buehrle DJ, Shields RK, Chen L, Hao B, Press EG, Alkrouk A, *et al.* Evaluation of the *in vitro* activity of ceftazidime-avibactam and ceftolozane-tazobactam against meropenem-resistant *Pseudomonas aeruginosa* isolates. Antimicrob Agents Chemother 2016;60:3227-31.
47. Farrell DJ, Sader HS, Flamm RK, Jones RN. Ceftolozane/tazobactam activity tested against gram-negative bacterial isolates from hospitalised patients with pneumonia in US and European medical centres (2012). Int J Antimicrob Agents 2014;43:533-9.
48. Livermore DM, Mushtaq S, Meunier D, Hopkins KL, Hill R, Adkin R, *et al.* Activity of ceftolozane/tazobactam against surveillance and 'problem' *Enterobacteriaceae*, *Pseudomonas aeruginosa* and non-fermenters from the British Isles. J Antimicrob Chemother 2017;72:2278-89.
49. Pfaller MA, Bassetti M, Duncan LR, Castanheira M. Ceftolozane/tazobactam activity against drug-resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa* causing urinary tract and intraabdominal infections in Europe: Report from an antimicrobial surveillance programme (2012-15). J Antimicrob Chemother 2017;72:1386-95.
50. Giani T, Arena F, Pollini S, Di Pilato V, D'Andrea MM, Henrici De Angelis L, *et al.* Italian nationwide survey on *Pseudomonas aeruginosa* from invasive infections: Activity of ceftolozane/tazobactam and comparators, and molecular epidemiology of carbapenemase producers. J Antimicrob Chemother 2017;73:664-71.
51. Grupper M, Sutherland C, Nicolau DP. Multicenter evaluation of ceftazidime-avibactam and ceftolozane-tazobactam inhibitory activity against meropenem-nonsusceptible *Pseudomonas aeruginosa* from blood, respiratory tract, and wounds. Antimicrob Agents Chemother 2017;61. pii: e00875-17.
52. Seifert H, Körber-Irrgang B, Kresken M; German Ceftolozane/Tazobactam Study Group. *In vitro* activity of ceftolozane/tazobactam against *Pseudomonas aeruginosa* and *Enterobacteriaceae* isolates recovered from hospitalized patients in Germany. Int J Antimicrob Agents 2018;51:227-34.
53. Sader HS, Castanheira M, Mendes RE, Flamm RK, Farrell DJ, Jones RN, *et al.* Ceftazidime-avibactam activity against multidrug-resistant *Pseudomonas aeruginosa* isolated in U.S. medical centers in 2012 and 2013. Antimicrob Agents Chemother 2015;59:3656-9.
54. Levasseur P, Girard AM, Claudon M, Goossens H, Black MT, Coleman K, *et al. In vitro* antibacterial activity of the ceftazidime-avibactam (NXL104) combination against *Pseudomonas aeruginosa* clinical isolates. Antimicrob Agents Chemother 2012;56:1606-8.
55. Walkty A, DeCorby M, Lagacé-Wiens PR, Karlowsky JA, Hoban DJ, Zhanel GG, *et al. In vitro* activity of ceftazidime combined with NXL104 versus *Pseudomonas aeruginosa* isolates obtained from patients in Canadian hospitals (CANWARD 2009 study). Antimicrob Agents Chemother 2011;55:2992-4.
56. Livermore DM, Warner M, Mushtaq S. Activity of MK-7655 combined with imipenem against *Enterobacteriaceae* and *Pseudomonas aeruginosa*. J Antimicrob Chemother 2013;68:2286-90.
57. Lapuebla A, Abdallah M, Olafisoye O, Cortes C, Urban C, Landman D, *et al.* Activity of imipenem with relebactam against gram-negative pathogens from New York city. Antimicrob Agents Chemother 2015;59:5029-31.
58. Lapuebla A, Abdallah M, Olafisoye O, Cortes C, Urban C, Quale J, *et al.* Activity of meropenem combined with RPX7009, a novel β-lactamase inhibitor, against gram-negative clinical isolates in New York city. Antimicrob Agents Chemother 2015;59:4856-60.
59. Ito A, Kohira N, Bouchillon SK, West J, Rittenhouse S, Sader HS, *et al. In vitro* antimicrobial activity of S-649266, a catechol-substituted siderophore cephalosporin, when tested against non-fermenting gram-negative bacteria. J Antimicrob Chemother 2016;71:670-7.
60. Landman D, Kelly P, Bäcker M, Babu E, Shah N, Bratu S, *et al.* Antimicrobial activity of a novel aminoglycoside, ACHN-490, against *Acinetobacter baumannii* and *Pseudomonas aeruginosa* from New York city. J Antimicrob Chemother 2011;66:332-4.
61. Aggen JB, Armstrong ES, Goldblum AA, Dozzo P, Linsell MS, Gliedt MJ, *et al.* Synthesis and spectrum of the neoglycoside ACHN-490. Antimicrob Agents Chemother 2010;54:4636-42.
62. Zhanel GG, Chung P, Adam H, Zelenitsky S, Denisuik A, Schweizer F, *et al.* Ceftolozane/tazobactam: A novel cephalosporin/β-lactamase inhibitor combination with activity against multidrug-resistant gram-negative bacilli. Drugs 2014;74:31-51.
63. U.S. Food and Drug Administration. Zerbaxa ®. Full Prescribing Information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206829lbl.pdf. [Last accessed on 2018 Sep 12].
64. Larson K, Johnson MG, Rizk ML, Caro L, Bradley JS, Ang J, *et al.* Ceftolozane/tazobactam dose evaluation for pediatric subjects with complicated intra-abdominal infection and complicated urinary tract infection. Open Forum Infect Dis 2017;4:S528-9.
65. Takeda S, Nakai T, Wakai Y, Ikeda F, Hatano K. *In vitro* and *in vivo* activities of a new cephalosporin, FR264205, against *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 2007;51:826-30.
66. Pragsam AK, Kumar DT, Doss CG, Iyadurai R, Satyendra S, Rodrigues C,

et al. In silico and *In vitro* activity of ceftolozane/tazobactam against *Pseudomonas aeruginosa* collected across Indian hospitals. Indian J Med Microbiol 2018;36:127-30.
67. Patel UC, Nicolau DP, Sabzwari RK. Successful treatment of multi-drug resistant *Pseudomonas aeruginosa* bacteremia with the recommended renally adjusted ceftolozane/tazobactam regimen. Infect Dis Ther 2016;5:73-9.
68. Goodlet KJ, Nicolau DP, Nailor MD. Ceftolozane/tazobactam and ceftazidime/avibactam for the treatment of complicated intra-abdominal infections. Ther Clin Risk Manag 2016;12:1811-26.
69. Sorbera M, Chung E, Ho CW, Marzella N. Ceftolozane/Tazobactam: A new option in the treatment of complicated gram-negative infections. P T 2014;39:825-32.
70. Moya B, Zamorano L, Juan C, Pérez JL, Ge Y, Oliver A, *et al.* Activity of a new cephalosporin, CXA-101 (FR264205), against beta-lactam-resistant *Pseudomonas aeruginosa* mutants selected *in vitro* and after antipseudomonal treatment of Intensive Care Unit patients. Antimicrob Agents Chemother 2010;54:1213-7.
71. Cabot G, Bruchmann S, Mulet X, Zamorano L, Moyà B, Juan C, *et al. Pseudomonas aeruginosa* ceftolozane-tazobactam resistance development requires multiple mutations leading to overexpression and structural modification of AmpC. Antimicrob Agents Chemother 2014;58:3091-9.
72. Neuner EA, Bonomo RA. Ceftazidime-avibactam: A novel cephalosporin/β-lactamase inhibitor. Lung Cancer 2018;15:5.
73. Hackel M, Kazmierczak KM, Hoban DJ, Biedenbach DJ, Bouchillon SK, de Jonge BL, *et al.* Assessment of the *in vitro* activity of ceftazidime-avibactam against multidrug-resistant *Klebsiella* spp. collected in the INFORM global surveillance study, 2012 to 2014. Antimicrob Agents Chemother 2016;60:4677-83.
74. van Duin D, Bonomo RA. Ceftazidime/Avibactam and ceftolozane/Tazobactam: Second-generation β-lactam/β-lactamase inhibitor combinations. Clin Infect Dis 2016;63:234-41.
75. Winkler ML, Papp-Wallace KM, Hujer AM, Domitrovic TN, Hujer KM, Hurless KN, *et al.* Unexpected challenges in treating multidrug-resistant gram-negative bacteria: Resistance to ceftazidime-avibactam in archived isolates of *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 2015;59:1020-9.
76. Olsen I. New promising β-lactamase inhibitors for clinical use. Eur J Clin Microbiol Infect Dis 2015;34:1303-8.
77. Mangion IK, Ruck RT, Rivera N, Huffman MA, Shevlin M. A concise synthesis of a β-lactamase inhibitor. Org Lett 2011;13:5480-3.
78. Blizzard TA, Chen H, Kim S, Wu J, Bodner R, Gude C, *et al.* Discovery of MK-7655, a β-lactamase inhibitor for combination with primaxin®. Bioorg Med Chem Lett 2014;24:780-5.
79. Lob SH, Hackel MA, Kazmierczak KM, Hoban DJ, Young K, Motyl MR, *et al. In vitro* activity of imipenem-relebactam against gram-negative bacilli isolated from patients with lower respiratory tract infections in the United States in 2015 – Results from the SMART global surveillance program. Diagn Microbiol Infect Dis 2017;88:171-6.
80. Shlaes DM. New β-lactam-β-lactamase inhibitor combinations in clinical development. Ann N Y Acad Sci 2013;1277:105-14.
81. Barnesa MD, Papp-Wallace KM, Alsop J, Domitrovic TN, Becka SA, Hujer AM, *et al*. Determining resistance mechanisms in *Pseudomonas aeruginosa* clinical isolates that demonstrate altered susceptibility profiles to b-lactam-relebactam (REL) vs. b-lactam-avibactam (AVI) combinations [abstract no. P0235 plus poster]. In: 27th European Congress of Clinical Microbiology and Infectious Diseases. Vienna: 2017.
82. Barnesb MD, Bethel CR, Alsop J, Becka SA, Rutter JD, Papp- Wallace KM, *et al*. Relebactam (REL) inhibits the PDC-3 blactamase and restores the susceptibility of imipenem (IMI) against *Pseudomonas aeruginosa* [abstract no. 2780 plus poster]. In: 2nd ASM Microbe. New Orleans; 2017.
83. Zhanel GG, Lawrence CK, Adam H, Schweizer F, Zelenitsky S, Zhanel M, *et al*. Imipenem–relebactam and meropenem–vaborbactam: Two novel carbapenem-β-lactamase inhibitor combinations. Drugs 2018;78:1-34.
84. Quale J, Bratu S, Gupta J, Landman D. Interplay of efflux system, ampC, and oprD expression in carbapenem resistance of *Pseudomonas aeruginosa* clinical isolates. Antimicrob Agents Chemother 2006;50:1633-41.
85. Lucasti C, Vasile L, Sandesc D, Venskutonis D, McLeroth P, Lala M, *et al.* Phase 2, dose-ranging study of relebactam with imipenem-cilastatin in subjects with complicated intra-abdominal infection. Antimicrob Agents Chemother 2016;60:6234-43.
86. Hecker SJ, Reddy KR, Totrov M, Hirst GC, Lomovskaya O, Griffith DC, *et al.* Discovery of a cyclic boronic acid β-lactamase inhibitor (RPX7009) with utility vs. class A serine carbapenemases. J Med Chem 2015;58:3682-92.
87. Wong D, van Duin D. Novel beta-lactamase inhibitors: Unlocking their potential in therapy. Drugs 2017;77:615-28.
88. Drawz SM, Papp-Wallace KM, Bonomo RA. New β-lactamase inhibitors: A therapeutic renaissance in an MDR world. Antimicrob Agents Chemother 2014;58:1835-46.
89. Zhanel GG, Wiebe R, Dilay L, Thomson K, Rubinstein E, Hoban DJ, *et al.* Comparative review of the carbapenems. Drugs 2007;67:1027-52.
90. Lomovskaya O, Sun D, Rubio-Aparicio D, Nelson K, Tsivkovski R, Griffith DC, *et al.* Vaborbactam: Spectrum of beta-lactamase inhibition and impact of resistance mechanisms on activity in *Enterobacteriaceae*. Antimicrob Agents Chemother 2017;61. pii: e01443-17.
91. Castanheira M, Huband MD, Mendes RE, Flamm RK. Meropenem-vaborbactam tested against contemporary gram-negative isolates collected worldwide during 2014, including carbapenem-resistant, KPC-producing, multidrug-resistant, and extensively drug-resistant *Enterobacteriaceae*. Antimicrob Agents Chemother 2017;61. pii: e00567-17.
92. Kaye KS, Bhowmick T, Metallidis S, Bleasdale SC, Sagan OS, Stus V, *et al.* Effect of meropenem-vaborbactam vs. piperacillin-tazobactam on clinical cure or improvement and microbial eradication in complicated urinary tract infection: The TANGO I randomized clinical trial. JAMA 2018;319:788-99.
93. Ito-Horiyama T, Ishii Y, Ito A, Sato T, Nakamura R, Fukuhara N, *et al.* Stability of novel siderophore cephalosporin S-649266 against clinically relevant carbapenemases. Antimicrob Agents Chemother 2016;60:4384-6.
94. Shimada J, Saisho Y, Katsube T, White S, Fukase H. S-649266, a novel siderophore cephalosporin for gram negative bacterial infections: Pharmacokinetics, safety and tolerability in healthy subjects, abstr F-1564. Abstr 54th Intersci Conf Antimicrob Agents Chemother. 2014.
95. Echols R, Katsube T, Arjona Ferreira JC, Krenz HK. S-649266, a siderophore cephalosporin for gram negative bacterial infection: Pharmacokinetics and safety in subjects with renal impairment, abstr ECCMD-1174. Eur Cong Clin Microbiol Infect Dis 2015.
96. Hackel MA, Tsuji M, Yamano Y, Echols R, Karlowsky JA, Sahm DF, *et al. In vitro* activity of the siderophore cephalosporin, cefiderocol, against a recent collection of clinically relevant gram-negative bacilli from North America and Europe, including carbapenem-nonsusceptible isolates (SIDERO-WT-2014 study). Antimicrob Agents Chemother 2017;61. pii: e00093-17.
97. Hackel MA, Tsuji M, Yamano Y, Echols R, Karlowsky JA, Sahm DF, *et al. In vitro* activity of the siderophore cephalosporin, cefiderocol, against carbapenem-nonsusceptible and multidrug-resistant isolates of gram-negative bacilli collected worldwide in 2014 to 2016. Antimicrob Agents Chemother 2018;62. pii: e01968-17.
98. Kawaguchi N, Katsube T, Echols R, Wajima T. Population pharmacokinetic analysis of cefiderocol, a parenteral siderophore cephalosporin, in healthy subjects, subjects with various degrees of renal function, and patients with complicated urinary tract infection or acute uncomplicated pyelonephritis. Antimicrob Agents Chemother 2018;62. pii: e01391-17.
99. Jana S, Deb JK. Molecular understanding of aminoglycoside action and resistance. Appl Microbiol Biotechnol 2006;70:140-50.
100. Pankuch GA, Lin G, Kubo A, Armstrong ES, Appelbaum PC, Kosowska-Shick K, *et al.* Activity of ACHN-490 tested alone and in combination with other agents against *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 2011;55:2463-5.
101. Walkty A, Adam H, Baxter M, Denisuik A, Lagacé-Wiens P,

Karlowsky JA, *et al. In vitro* activity of plazomicin against 5,015 gram-negative and gram-positive clinical isolates obtained from patients in Canadian hospitals as part of the CANWARD study, 2011-2012. Antimicrob Agents Chemother 2014;58:2554-63.
102. Zhanel GG, Lawson CD, Zelenitsky S, Findlay B, Schweizer F, Adam H, *et al.* Comparison of the next-generation aminoglycoside plazomicin to gentamicin, tobramycin and amikacin. Expert Rev Anti Infect Ther 2012;10:459-73.
103. Cass RT, Brooks CD, Havrilla NA, Tack KJ, Borin MT, Young D, *et al.* Pharmacokinetics and safety of single and multiple doses of ACHN-490 injection administered intravenously in healthy subjects. Antimicrob Agents Chemother 2011;55:5874-80.
104. Connolly LE, Riddle V, Cebrik D, Armstrong ES, Miller LG. A multicenter, randomized, double-blind, phase 2 study of the efficacy and safety of plazomicin compared with levofloxacin in the treatment of complicated urinary tract infection and acute pyelonephritis. Antimicrob Agents Chemother 2018;62. pii: e01989-17.
105. Cloutier DJ, Miller LG, Komirenko AS, Cebrik DS, Krause DM, Keepers TR. Plazomicin versus meropenem for the treatment of complicated urinary tract infection and acute pyelonephritis: Results of the EPIC study. In: Abstract no. Oral presentation presented at 27th European Congress of Clinical Microbiology and Infectious Diseases; April, 2017.