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Antimicrobial activity of cefepime/zidebactam (WCK 5222), a β-lactam/β-lactam enhancer combination, against clinical isolates of Gram-negative bacteria collected worldwide (2018–19)

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Background: Zidebactam, a bicyclo-acyl hydrazide β-lactam 'enhancer' antibiotic, in combination with cefepime (WCK 5222) is under clinical development for the treatment of resistant Gram-negative infections.

Objectives: To evaluate the *in vitro* activity of cefepime/zidebactam and comparators against 24 220 Gram-negative bacteria.

Methods: Organisms were consecutively collected in 2018–19 from 137 medical centres located in the USA ($n=9140$), Western Europe (W-EU; $n=5929$), Eastern Europe (E-EU; $n=3036$), the Asia-Pacific region (APAC; $n=3791$) and Latin America (LATAM; $n=2324$). The isolates were susceptibility tested using the broth microdilution method as part of the SENTRY Program. Cefepime/zidebactam was tested at a 1:1 ratio.

Results: Cefepime/zidebactam was highly active against Enterobacterales ($MIC_{50/90}$ 0.03/0.25 mg/L; 99.9% inhibited at ≤8 mg/L) and retained potent activity against carbapenem-resistant Enterobacterales (CRE) isolates (97.8% inhibited at ≤8 mg/L). CRE rates varied widely from 1.1% in the USA to 1.9% in W-EU, 3.6% in APAC and 14.6% in E-EU (3.9% overall). The most common carbapenemase genes observed overall were bla_{KPC} (37.6% of CRE), bla_{OXA-48}-like (30.0%) and bla_{NDM} (23.8%). Resistance to ceftazidime/avibactam among CRE was elevated in APAC (64.8%), E-EU (25.5%) and LATAM (20.7%). Against *Pseudomonas aeruginosa*, cefepime/zidebactam inhibited 99.2% of isolates at ≤8 mg/L and susceptibility to ceftazidime/avibactam and ceftolozane/tazobactam was lowest in E-EU (83.9% and 82.0%, respectively). Cefepime/zidebactam exhibited good activity against *Stenotrophomonas maltophilia* (80.0% inhibited at ≤8 mg/L) and *Burkholderia cepacia* (89.4% inhibited at ≤8 mg/L).

Conclusions: Cefepime/zidebactam demonstrated potent *in vitro* activity against a large worldwide collection of contemporary clinical isolates of Gram-negative bacteria.

Introduction

The rapid evolution of β-lactamases represents one of the main factors driving the increase in resistance to the β-lactam class of antibiotics among clinically relevant Gram-negative bacteria. In light of discovery challenges in identifying β-lactamase-stable β-lactams, the last two decades have seen discovery teams focusing on identifying novel β-lactamase inhibitors (BLIs).[1] These efforts led to the approval of structurally diverse BLIs, such as avibactam, relebactam and vaborbactam.[2] While these recently approved BLIs represent an advance over older BLIs in terms of expanded coverage of class C and KPC β-lactamases, they are not able to comprehensively inhibit class D OXA β-lactamases and MBLs.[3]

Zidebactam ($C_{13}H_{21}N_5O_7S$) is the first described Gram-negative β-lactam enhancer that belongs to the bicyclo-acyl hydrazide (BCH) series.[3] Although derived from a diazabicyclooctane scaffold, BCHs were designed to enhance PBP2 binding in Gram-negatives, including *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Thus, zidebactam is a non-β-lactam antibiotic with a dual mode of action involving selective and high-affinity Gram-negative PBP2 binding and β-lactamase inhibition. Because zidebactam is not a β-lactam, it is not hydrolysed by β-lactamases, including MBLs and class D enzymes; thus, it provides direct antibiotic activity against organisms that produce those enzymes by binding to PBP2. Moreover, β-lactamase-independent synergy or an 'enhancer effect' is obtained when zidebactam is combined with a PBP3-targeting β-lactam, such as cefepime, thus rendering the combination active against isolates producing class D OXA β-lactamases and/or MBLs.[4–7]

Zidebactam in combination with cefepime (WCK 5222) with a dose regimen of 2 g of cefepime and 1 g of zidebactam every 8 h is under clinical development for the treatment of Gram-negative infections (NCT02707107 and NCT02674347; www.clinicaltrials.gov). We evaluated the *in vitro* activity of cefepime combined with zidebactam against a large worldwide collection of contemporary clinical isolates of Gram-negative organisms collected during 2018–19 through the SENTRY Antimicrobial Surveillance Program.

Materials and methods

A total of 24 220 Gram-negative organisms were collected consecutively via the SENTRY Antimicrobial Surveillance Program[8] in 2018 and 2019 from 137 medical centres located in the USA ($n=9140$; 69 centres), Western Europe [W-EU; $n=5929$; 28 centres in 10 countries (Belgium, France, Germany, Ireland, Italy, Portugal, Spain, Sweden, Switzerland and the UK)], Eastern Europe [E-EU; $n=3036$; 12 centres in 9 countries (Belarus, the Czech Republic, Greece, Hungary, Poland, Romania, Russia, Slovenia and Turkey)], the Asia-Pacific region [APAC; $n=3791$; 18 centres in 9 countries (Australia, Japan, Malaysia, New Zealand, the Philippines, South Korea, Taiwan, Thailand and Vietnam)] and Latin America [LATAM; $n=2324$; 10 centres in 6 countries (Argentina, Brazil, Chile, Costa Rica, Mexico and Panama)].

Isolates were obtained from patients hospitalized with pneumonia (36.1%; 8737), urinary tract infection (31.5%; 7632), bloodstream infection (24.1%; 5840), intra-abdominal infection (8.1%; 1954) and skin and soft tissue infection (0.2%; 57).

MIC values of cefepime/zidebactam and comparator agents were determined using the broth microdilution method described by CLSI.[9] Cefepime was combined with zidebactam at a fixed ratio of 1:1 (weight:weight) and an MIC value indicates the concentration of each compound. Thus, a cefepime/zidebactam MIC of 8 mg/L means 8 mg/L cefepime and 8 mg/L zidebactam. Cefepime-susceptible breakpoints published by the US FDA and CLSI for high dosage (≤8 mg/L; 2 g every 8 h) were applied to cefepime/zidebactam as a preliminary cut-off for comparison purposes.[5,6,10,11] Susceptibility interpretations published by CLSI, the US FDA and EUCAST were used for comparator agents when available.[10–12]

Carbapenem-resistant Enterobacterales (CRE) isolates were defined as displaying imipenem or meropenem MIC values ≥4 mg/L. Imipenem was not applied to *Proteus mirabilis* or indole-positive Proteeae due to their intrinsically elevated MIC values. The ESBL-phenotype group included *Escherichia coli*, *Klebsiella pneumoniae* and *P. mirabilis* isolates with elevated MIC values (MIC ≥2 mg/L) for aztreonam, ceftazidime or ceftriaxone that were categorized as susceptible (MIC ≤1 mg/L) to meropenem. The CRE isolates were assessed for β-lactamase-encoding genes using WGS, as previously described.[13]

Ethical approval

Not required.

Results

Cefepime/zidebactam was highly active against Enterobacterales ($MIC_{50/90}$ 0.03/0.25 mg/L; 99.9% inhibited at ≤8 mg/L) and retained potent activity against CRE ($MIC_{50/90}$ 1/2 mg/L; 97.8% inhibited at ≤8 mg/L) and ESBL-phenotype isolates ($MIC_{50/90}$ 0.12/0.25 mg/L; highest MIC 2 mg/L; Tables 1 and 2). In contrast, ceftazidime/avibactam and amikacin were only active against 72.6% and 62.1% of CRE isolates per CLSI criteria, respectively (Table 2).

Against all Enterobacterales isolates combined, cefepime/zidebactam was the most active agent tested, followed by ceftazidime/avibactam, amikacin and meropenem (Table 2). Enterobacterales isolates with an elevated cefepime/zidebactam MIC (>8 mg/L) were only detected in Belarus (four isolates), Greece (one isolate), Mexico (one isolate), Romania (one isolate), Russia (five isolates), Turkey (two isolates) and Vietnam (one isolate) and included eight *K. pneumoniae*, four *Serratia marcescens*, two *Providencia stuartii* and one *Providencia rettgeri*.

Cefepime/zidebactam was also the most active agent tested against *P. aeruginosa* ($MIC_{50/90}$ 1/4 mg/L; 99.2% inhibited at ≤8 mg/L; Tables 1 and 2), followed by ceftazidime/avibactam [$MIC_{50/90}$ 2/8 mg/L; 94.5% susceptible (S)], ceftolozane/tazobactam (93.7% S) and tobramycin (88.9%/87.0% S per CLSI/EUCAST; Table 2). Moreover, cefepime/zidebactam retained potent activity against piperacillin/tazobactam-non-susceptible *P. aeruginosa* isolates (96.5% inhibited at ≤8 mg/L), whereas ceftazidime/avibactam (78.2% S), ceftolozane/tazobactam (75.1% S) and tobramycin (65.4%/62.1% S per CLSI/EUCAST) showed only moderate activity against these organisms (Table 2). Cefepime/zidebactam was also active against *P. aeruginosa* isolates non-susceptible to meropenem (96.6% inhibited at ≤8 mg/L) or ceftazidime (96.0% inhibited at ≤8 mg/L). Notably, cefepime/zidebactam retained activity (MIC of ≤8 mg/L) against 89.0% and 90.9% of *P. aeruginosa* isolates non-susceptible to ceftazidime/avibactam and ceftolozane/tazobactam, respectively (Tables 1 and 2).

The antimicrobial agents active against *A. baumannii-calcoaceticus* species complex were tobramycin (49.5% S per CLSI and EUCAST), cefepime/zidebactam (47.4%/77.1% inhibited at ≤8/≤16 mg/L) and amikacin (43.3%/41.4% S per CLSI/EUCAST; Table 2). Cefepime/zidebactam exhibited good activity against *Stenotrophomonas maltophilia* (80.0% inhibited at ≤8 mg/L) and *Burkholderia cepacia* species complex (89.8% inhibited at ≤8 mg/L; Tables 1 and 2).

Cefepime/zidebactam activity against Enterobacterales and *P. aeruginosa* was very consistent across the geographic regions evaluated, with percentage values for isolates inhibited at ≤8 mg/L of ≥99.9% for Enterobacterales and ≥98.8% for *P. aeruginosa* (Table S1, available as Supplementary data at *JAC* Online). In contrast, susceptibility rates for the comparator agents varied markedly among geographic regions. Susceptibility rates for Enterobacterales and *P. aeruginosa* were generally higher in the USA and W-EU and lowest in E-EU (Table S1). When tested against CRE, the activity of cefepime/zidebactam was marginally lower against isolates from E-EU (95.6% inhibited at ≤8 mg/L) compared with the other regions, where cefepime/zidebactam inhibited 99.0%–100.0% of isolates at ≤8 mg/L (Table S1).

CRE rates varied widely from 1.1% in the USA to 14.6% in E-EU (3.9% overall; Table S2). A carbapenemase gene was identified in 613 of 681 (90.0%) CRE isolates. The most common carbapenemase genes overall were bla_{KPC} (256 isolates), followed by bla_{OXA-48}-like (204 isolates), bla_{NDM} (162 isolates), bla_{VIM} (20 isolates), bla_{IMP} (2 isolates) and bla_{SME-2} (1 isolate). Notably, at least two carbapenemase genes were identified in 32 isolates and no known carbapenemase gene was identified in 69 isolates. Moreover, the frequencies of the carbapenemase types varied among geographic regions, with KPC predominating in the USA, W-EU and LATAM (71.2% to 75.0% of CRE), OXA predominating

Table 1. Antimicrobial activity of cefepime/zidebactam tested against the main organisms and organism groups

Organism/organism group (number of isolates)	Number and cumulative percentage of isolates inhibited at an MIC (mg/L) of:															MIC_{50} (mg/L)	MIC_{90} (mg/L)
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64		
Enterobacterales (17 524)	**104**	**963**	**8287**	**3939**	**2398**	**1019**	**354**	**226**	**177**	**32**	**10**	**8**	**4**	**1**	**2**	0.03	0.25
	0.6	6.1	53.4	75.9	89.5	95.4	97.4	98.7	99.7	99.9	99.9	>99.9	>99.9	>99.9	100.0		
CRE (681)	**1**	**1**	**0**	**4**	**47**	**158**	**119**	**162**	**134**	**30**	**10**	**8**	**4**	**1**	**2**	1	2
	0.1	0.3	0.3	0.9	7.8	31.0	48.5	72.2	91.9	96.3	97.8	99.0	99.6	99.7	100.0		
ESBL phenotype (2889)	**1**	**12**	**85**	**399**	**1543**	**625**	**159**	**39**	**26**							0.12	0.25
	<0.1	0.4	3.4	17.2	70.6	92.2	97.8	99.1	100.0								
Citrobacter freundii complex (282)	**2**	**36**	**126**	**55**	**45**	**13**	**3**	**0**	**0**	**2**						0.03	0.12
	0.7	13.5	58.2	77.7	93.6	98.2	99.3	99.3	99.3	100.0							
Citrobacter koseri (210)	**3**	**47**	**138**	**15**	**7**											0.03	0.06
	1.4	23.8	89.5	96.7	100.0												
Enterobacter cloacae complex (1219)	**4**	**28**	**448**	**334**	**190**	**143**	**43**	**13**	**14**	**1**	**1**					0.06	0.25
	0.3	2.6	39.4	66.8	82.4	94.1	97.6	98.7	99.8	99.9	100.0						
E. coli (8413)	**69**	**557**	**4654**	**1692**	**1209**	**194**	**24**	**9**	**4**	**1**						0.03	0.12
	0.8	7.4	62.8	82.9	97.2	99.5	99.8	99.9	>99.9	100.0							
Klebsiella aerogenes (413)	**1**	**9**	**227**	**88**	**60**	**15**	**5**	**5**	**3**							0.03	0.12
	0.2	2.4	57.4	78.7	93.2	96.9	98.1	99.3	100.0								
Klebsiella oxytoca (611)	**0**	**63**	**372**	**87**	**50**	**24**	**10**	**2**	**2**	**1**						0.03	0.12
	0.0	10.3	71.2	85.4	93.6	97.5	99.2	99.5	99.8	100.0							
K. pneumoniae (4060)	**20**	**116**	**1719**	**614**	**456**	**524**	**235**	**184**	**152**	**25**	**7**	**3**	**4**	**1**		0.06	0.5
	0.5	3.3	45.7	60.8	72.0	85.0	90.7	95.3	99.0	99.6	99.8	99.9	>99.9	100.0			
Morganella morganii (208)	**1**	**17**	**139**	**37**	**8**	**6**										0.03	0.06
	0.5	8.7	75.5	93.3	97.1	100.0											
P. mirabilis (906)	**2**	**11**	**219**	**549**	**77**	**38**	**6**	**2**	**0**	**1**	**1**					0.06	0.12
	0.2	1.4	25.6	86.2	94.7	98.9	99.6	99.8	99.8	99.9	100.0						
Providencia spp. (124)	**1**	**22**	**38**	**36**	**15**	**4**	**1**	**4**	**0**	**0**	**0**	**1**	**0**	**0**	**2**	0.06	0.12
	0.8	18.5	49.2	78.2	90.3	93.5	94.4	97.6	97.6	97.6	97.6	98.4	98.4	98.4	100.0		
S. marcescens (754)	**0**	**10**	**48**	**348**	**257**	**54**	**23**	**7**	**2**	**1**	**0**	**4**				0.06	0.25
	0.0	1.3	7.7	53.8	87.9	95.1	98.1	99.1	99.3	99.5	99.5	100.0					
other Enterobacterales (324)	**1**	**47**	**159**	**84**	**24**	**4**	**4**	**0**	**0**	**0**	**1**					0.03	0.12
	0.3	14.8	63.9	89.8	97.2	98.5	99.7	99.7	99.7	99.7	100.0						
P. aeruginosa (4808)	**1**	**2**	**3**	**8**	**43**	**107**	**489**	**1889**	**1000**	**844**	**382**	**34**	**5**	**1**		1	4
	<0.1	0.1	0.1	0.3	1.2	3.4	13.6	52.9	73.7	91.2	99.2	99.9	>99.9	100.0			
piperacillin/tazobactam non-susceptible (>16 mg/L) (1122)						**0**	**7**	**32**	**227**	**481**	**336**	**33**	**5**	**1**		4	8
						0.0	0.6	3.5	23.7	66.6	96.5	99.5	99.9	100.0			
meropenem non-susceptible (>2 mg/L) (1147)				**0**	**1**	**1**	**18**	**104**	**236**	**449**	**299**	**33**	**5**	**1**		4	8
				0.0	0.1	0.2	1.7	10.8	31.4	70.5	96.6	99.5	99.9	100.0			
ceftazidime non-susceptible (>8 mg/L) (953)						**0**	**2**	**23**	**204**	**398**	**288**	**32**	**5**	**1**		4	8
						0.0	0.2	2.6	24.0	65.8	96.0	99.4	99.9	100.0			

A. baumannii-calcoaceticus complex (1139)	**0**	**1**	**2**	**0**	**1**	**10**	**69**	**121**	**138**	**198**	**338**	**199**	**52**	**9**	16	32		
	0.0	0.1	0.3	0.3	0.4	1.2	7.3	17.9	30.0	47.4	77.1	94.6	99.1	100.0				
B. cepacia complex (113)				**0**	**2**	**1**	**4**	**34**	**32**	**28**	**8**	**2**	**2**		4	16		
				0.0	1.8	2.7	6.2	36.3	64.6	89.4	96.5	98.2	100.0					
S. maltophilia (636)						**0**	**20**	**97**	**211**	**181**	**98**	**22**	**6**	**1**	4	16		
						0.0	3.1	18.4	51.6	80.0	95.4	98.9	99.8	100.0				

in E-EU (52.7% of CRE) and NDMs predominating in APAC (62.9% of CRE; Table S2).

Discussion

The results of this investigation clearly demonstrated that cefepime/zidebactam has potent *in vitro* activity against Enterobacterales and *P. aeruginosa* isolates and, based on the translational *in vivo* pharmacokinetic/pharmacodynamic studies, it may exhibit a therapeutically relevant activity against *A. baumannii* independent of geographic region or resistance to the antimicrobial agents currently available to treat infections caused by these organisms.[5,6,14–17] Cefepime/zidebactam showed almost complete activity against Enterobacterales (99.9% inhibited at ≤8 mg/L) independent of carbapenem resistance mechanisms prevalent across the geographic regions evaluated. These include even those regions where the activity of ceftazidime/avibactam has been compromised by the increased frequency of MBLs, such as E-EU, APAC and LATAM. In those regions, CRE susceptibility to ceftazidime/avibactam varied from 35.2% (APAC) to 74.5% (E-EU) and 79.3% (LATAM), whereas MBL frequencies among CRE were 64.8% (APAC), 25.2% (E-EU) and 20.7% (LATAM). Cefepime/zidebactam also showed remarkable *in vitro* activity against *P. aeruginosa*, including isolates resistant to most active BLI combinations currently used to treat *P. aeruginosa* infections, such as ceftazidime/avibactam and ceftolozane/tazobactam.

Like other β-lactams and most antimicrobial agents tested, cefepime/zidebactam showed relatively higher $MIC_{50/90}$ values (16/32 mg/L) for *Acinetobacter* spp. when compared with other Gram-negative organisms; nevertheless, cefepime/zidebactam (47.4% inhibited at ≤8 mg/L) and tobramycin (49.5% S per CLSI) were the most active compounds tested against these organisms. It is also important to note that the potent *in vivo* bactericidal activity of human-simulated cefepime/zidebactam exposure against carbapenem-resistant *A. baumannii* strains (OXA-23 or OXA-24 producers) with cefepime/zidebactam MIC values of 16 to 64 mg/L has been shown in a neutropenic murine thigh and lung infection model.[14] The *in vivo* and *in vitro* efficacy of cefepime/zidebactam against *Acinetobacter* spp. isolates with elevated cefepime/zidebactam MIC values also has been shown by other investigators and was attributed to the β-lactam enhancer function of zidebactam that improves the *in vivo* activity of cefepime by reducing the magnitude of its pharmacodynamically relevant exposures.[15,18] Pharmacokinetic/pharmacodynamic investigations have established that zidebactam-mediated reduction in the requirement of $\%fT_{>MIC}$ of cefepime leads to therapeutically relevant coverage of high-MIC strains by cefepime/zidebactam as evidenced by 2 to 3 $\log_{10}$ kill of *P. aeruginosa* and *A. baumannii* with cefepime/zidebactam MICs up to 64 mg/L in translational animal models.[19] In the present study, 94.6% and 99.1% of *A. baumannii* isolates were inhibited at cefepime/zidebactam MICs of ≤32 and ≤64 mg/L, respectively.

In summary, cefepime/zidebactam demonstrated potent *in vitro* activity against a large worldwide collection of contemporary (2018–19) clinical isolates of Gram-negative bacteria. This investigation also showed that cefepime/zidebactam possesses strong *in vitro* antimicrobial activity against organisms that produce β-lactamases that are not well inhibited by zidebactam, which is

Table 2. Antimicrobial activity of cefepime/zidebactam and comparator agents tested against Gram-negative organisms from all regions combined

	MIC (mg/L)		CLSI[a]			EUCAST[a]		
Antimicrobial agent (number of isolates)	MIC_{50}	MIC_{90}	% S	% I	% R	% S	% I	% R
Enterobacterales (17 524)								
cefepime/zidebactam	0.03	0.25	(99.9)[b]					
ceftazidime/avibactam	0.12	0.5	98.9		1.1	98.9		1.1
ceftolozane/tazobactam	0.25	2	91.7	1.5	6.8	91.7		8.3
piperacillin/tazobactam	2	64	87.2	4.3	8.5	83.2		16.8
ampicillin/sulbactam	16	>64	43.7	14.6	41.7	43.7[c]		56.3
ceftriaxone	≤0.06	>8	75.2	0.8	24.0	75.2	0.8	24.0
ceftazidime	0.25	>32	79.5	2.0	18.4	75.9	3.6	20.5
meropenem	0.03	0.06	96.1	0.4	3.5	96.5	1.0	2.5
ertapenem	≤0.008	0.25	94.2	0.9	4.9	94.2		5.8
amikacin	2	4	97.6	0.6	1.8	95.9[d]		4.1
gentamicin	0.5	>16	86.1	0.7	13.2	85.5[d]		14.5
levofloxacin	0.06	16	73.3	2.9	23.8	73.4	2.9	23.8
CRE (681)[e]								
cefepime/zidebactam	1	2	(97.8)[b]					
ceftazidime/avibactam	1	>32	72.6		27.4	72.6		27.4
ceftolozane/tazobactam	>16	>16	2.1	1.7	96.3	2.1		97.9
amikacin	8	>32	62.1	7.9	30.0	50.1[d]		49.9
gentamicin	16	>16	42.9	3.5	53.6	41.1[d]		58.9
levofloxacin	32	>32	12.2	4.7	83.1	12.2	4.7	83.1
ESBL-phenotype Enterobacterales (2889)[f]								
cefepime/zidebactam	0.12	0.25	(100.0)[b]					
ceftazidime/avibactam	0.12	0.5	99.8		0.2	99.8		0.2
ceftolozane/tazobactam	0.5	8	85.1	4.1	10.8	85.1		14.9
piperacillin/tazobactam	8	>128	74.5	12.1	13.4	62.1		37.9
meropenem	0.03	0.06	100.0	0.0	0.0	100.0	0.0	0.0
ertapenem	0.03	0.5	93.6	2.2	4.2	93.6		6.4
amikacin	4	8	95.5	1.2	3.2	90.3[d]		9.7
gentamicin	1	>16	56.9	1.4	41.6	55.9[d]		44.1
levofloxacin	8	32	27.9	6.0	66.2	27.9	6.0	66.2
P. aeruginosa (4808)								
cefepime/zidebactam	1	4	(99.2)[b]					
ceftazidime/avibactam	2	8	94.5		5.5	94.5		5.5
ceftolozane/tazobactam	0.5	4	93.7	1.5	4.8	93.7		6.3
piperacillin/tazobactam	4	128	76.7	10.9	12.4	[g]	76.7	23.3
ceftazidime	2	32	80.2	5.1	14.7	[g]	80.2	19.8
meropenem	0.5	16	76.1	5.6	18.2	76.1	11.2	12.6
tobramycin	0.5	8	88.9	1.2	9.9	87.0[d]		13.0
levofloxacin	0.5	32	64.6	10.4	25.0	[g]	64.6	35.4
ciprofloxacin	0.25	16	72.5	6.3	21.2	[g]	72.5	27.5
Piperacillin/tazobactam-non-susceptible *P. aeruginosa* (MIC >16 mg/L; 1122)								
cefepime/zidebactam	4	8	(96.5)[b]					
ceftazidime/avibactam	4	32	78.2		21.8	78.2		21.8
ceftolozane/tazobactam	2	>16	75.1	6.2	18.8	75.1		24.9
piperacillin/tazobactam	128	>128	0.0	46.7	53.3	[g]	0.0	100.0
ceftazidime	32	>32	20.1	19.1	60.9	[g]	20.1	79.9
meropenem	8	>32	35.7	7.7	56.7	35.7	20.7	43.7
tobramycin	1	>16	65.4	2.8	31.8	62.1[d]		37.9
levofloxacin	4	>32	29.6	13.3	57.1	[g]	29.6	70.4
ciprofloxacin	2	>16	39.9	8.6	51.5	[g]	39.9	60.1
Ceftazidime/avibactam-non-susceptible *P. aeruginosa* (MIC >8 mg/L; 264)								
cefepime/zidebactam	8	16	(89.0)[b]					
ceftazidime/avibactam	32	>32	0.0		100.0	0.0		100.0
ceftolozane/tazobactam	>16	>16	21.2	8.7	70.1	21.2		78.8
piperacillin/tazobactam	128	>128	7.6	36.0	56.4	[g]	7.6	92.4

Continued

Table 2. *Continued*

Antimicrobial agent (number of isolates)	MIC (mg/L)		CLSI[a]			EUCAST[a]		
	MIC_{50}	MIC_{90}	% S	% I	% R	% S	% I	% R
ceftazidime	>32	>32	0.4	11.0	88.6	[g]	0.4	99.6
meropenem	>32	>32	6.8	4.9	88.3	6.8	6	82.6
tobramycin	>16	>16	33.0	3.4	63.6	29.5[d]		70.5
levofloxacin	32	>32	6.8	8.0	85.2	[g]	14.8	85.2
ciprofloxacin	16	>16	11.8	5.3	82.8	[g]	11.8	88.2
Ceftolozane/tazobactam-non-susceptible *P. aeruginosa* (MIC >4 mg/L; 286)								
cefepime/zidebactam	4	8	(90.9)[b]					
ceftazidime/avibactam	32	>32	36.4		63.6	36.4		63.6
ceftolozane/tazobactam	>16	>16	0.0	24.1	75.9	0.0		100.0
piperacillin/tazobactam	128	>128	8.0	29.7	62.2	[g]	8.0	92.0
ceftazidime	>32	>32	3.5	7.0	89.5	[g]	3.5	96.5
meropenem	32	>32	9.4	4.5	86.0	9.4	15.7	74.8
tobramycin	>16	>16	26.9	4.5	68.5	21.7[d]		78.3
levofloxacin	32	>32	10.5	6.6	82.9	[g]	17.1	82.9
ciprofloxacin	16	>16	10.6	6.0	83.4	[g]	10.6	89.4
A. baumannii-calcoaceticus complex (1139)								
cefepime/zidebactam	16	32	(47.4)[b]					
ceftazidime/avibactam	16	>32	(35.0)[b]					
piperacillin/tazobactam	>128	>128	28.5	2.7	68.9			
ampicillin/sulbactam	32	>64	32.8	6.1	61.1			
ceftazidime	>32	>32	31.7	3.3	65.0			
meropenem	>32	>32	34.5	0.3	65.2	34.5	1.1	64.4
imipenem	>8	>8	34.8	0.4	64.8	34.8	0.4	64.8
amikacin	>32	>32	43.3	2.8	53.9	41.4[d]		58.6
gentamicin	>16	>16	40.7	3.6	55.7	40.7[d]		59.3
tobramycin	8	>16	49.5	1.2	49.3	49.5[d]		50.5
levofloxacin	16	>32	32.6	2.1	65.3	31.0	1.1	68.0
ciprofloxacin	>16	>16	31.1	0.8	68.1	[g]	31.1	68.9
S. maltophilia (636)								
cefepime/zidebactam	4	16	(80.0)[b]					
ceftazidime/avibactam	32	>32	(31.9)[b]					
ceftazidime	>32	>32	20.8	8.5	70.8			
levofloxacin	1	8	75.2	10.8	14.0			
minocycline	0.5	2	98.9	1.1	0.0			
trimethoprim/sulfamethoxazole	0.25	1	94.9		5.1	[g]	97.3	2.7
B. cepacia complex (113)								
cefepime/zidebactam	4	16	(89.4)[b]					
ceftazidime/avibactam	2	8	(93.8)[b]					
ceftazidime	4	16	80.5	9.7	9.7			
meropenem	2	8	89.4	7.1	3.5			
levofloxacin	2	32	55.8	21.2	23.0			
minocycline	4	16	72.5	14.7	12.8			
trimethoprim/sulfamethoxazole	1	4	78.8		21.2			

[a]Criteria as published by CLSI[10] and EUCAST.[12] S, susceptible; I, intermediate; R, resistant.
[b]Percentage inhibited at ≤8 mg/L for comparison.
[c]These breakpoints for oral administration are relevant for uncomplicated urinary tract infections only.
[d]For infections originating from the urinary tract. For systemic infections, aminoglycosides must be used in combination with other active therapy.
[e]Organisms include *C. freundii* species complex (6), *E. cloacae* species complex (43), *E. coli* (21), *Hafnia alvei* (1), *K. aerogenes* (7), *K. oxytoca* (11), *K. pneumoniae* (561), *P. mirabilis* (3), *P. rettgeri* (3), *P. stuartii* (3), *S. marcescens* (21) and unspeciated *Raoultella* (1).
[f]Organisms include *E. coli* (1742), *K. pneumoniae* (1046) and *P. mirabilis* (101) isolates with elevated MIC values (MIC ≥2 mg/L) of aztreonam, ceftazidime or ceftriaxone that are considered susceptible (MIC ≥1 mg/L) to meropenem.
[g]An arbitrary susceptible breakpoint of ≤0.001 mg/L and/or >50 mm has been published by EUCAST indicating that susceptible should not be reported for this organism/agent combination and intermediate should be interpreted as susceptible increased exposure.[12]

due to the β-lactam enhancer activity. Clinical studies on the efficacy of zidebactam in combination with cefepime are warranted to establish the potential of this combination to provide therapeutic coverage against infections caused by MDR Gram-negative organisms, including MBL-producing Enterobacterales.

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Supplementary data

Tables S1 and S2 are available as Supplementary data at *JAC* Online.

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