In Vitro Activities of Ceftazidime-Avibactam and Aztreonam-Avibactam against 372 Gram-Negative Bacilli Collected in 2011 and 2012 from 11 Teaching Hospitals in China

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Ceftazidime-avibactam, aztreonam-avibactam, and comparators were tested by reference broth microdilution against 372 non-repetitive Gram-negative bacilli (346 unselected plus 26 selected meropenem-nonsusceptible *Enterobacteriaceae* isolates) collected from 11 teaching hospitals in China in 2011 and 2012. Meropenem-nonsusceptible isolates produced extended-spectrum β -lactamases (ESBLs; e.g., CTX-M-14/3), AmpCs (e.g., CMY-2), and/or carbapenemases (e.g., KPC-2 and NDM-1). Avibactam potentiated the activity of ceftazidime against organisms with combinations of ESBLs, AmpCs, and KPC-2. Aztreonam-avibactam was active against all β -lactamase producers (including producers of NDM-1 and IMP-4/8) except *bla*_{OXA}-containing *Acinetobacter baumannii* and some *Pseudomonas aeruginosa* isolates.

Avibactam is a member of a class of inhibitors called diazabicyclooctanes (DBOs) that does not contain a β -lactam core but maintains the capacity to covalently acylate its β -lactamase targets (1, 2, 3). Avibactam alone has very little intrinsic antimicrobial activity but has been shown to efficiently restore the *in vitro* activities of cephalosporins (including ceftazidime and cefartoline) (4, 5) against Ambler class A, class C, and some class D β -lactamases (6, 7, 8, 9, 10), excluding metallo- β -lactamases (MBLs) and *Acinetobacter* OXA carbapenemases (2). The combination of aztreonam and avibactam has been proposed as a principal candidate for the treatment of infections with MBL-producing Gram-negative organisms (8, 11). To date, few data have been available in China describing the *in vitro* activities of ceftazidime-avibactam and aztreonam-avibactam against clinical Gram-negative bacilli, especially *Enterobacteriaceae*. In this study, we evaluated the *in vitro* activities of ceftazidime and aztreonam alone and combined with a fixed concentration of 4 mg/liter of avibactam against routinely collected clinical Gram-negative bacilli, including *Enterobacteriaceae*, *Acinetobacter* spp., and *Pseudomonas aeruginosa*, from two national surveillance programs in China, the Chinese Meropenem Susceptibility Surveillance (CMSS) program in 2012 and the Chinese Antimicrobial Resistance Surveillance of Nosocomial Infections (CARES) in 2011.

A total of 372 nonrepetitive, routinely collected isolates (from 2011 and 2012) were obtained from 11 teaching hospitals representing the south, north, northwest, east, and middle districts of mainland China. The 372 organisms included the following. (i) Two hundred ninety-one routinely collected but otherwise unselected *Enterobacteriaceae* isolates (from CMSS) and 26 carbapenem-nonsusceptible *Enterobacteriaceae* isolates (meropenem MIC, ≥ 2 mg/liter; 19 isolates from CARES and the remainder from CMSS) were tested. Of the 26 carbapenem-nonsusceptible *Enterobacteriaceae* isolates, 10 produced KPC-2, 11 produced IMP β -lactamases (10 isolates produced IMP-4 and 1 isolate produced IMP-8), and 3 produced NDM-1. The remaining 2 isolates possessed TEM-1 and CTX-M, enzymes that are not regarded as carbapenemases. Most of the carbapenemase producers coharbored other β -lactamases (ACT-14/15, CMY-2, DHA-1, and SHV-12/

11/107) (Table 1). (ii) Thirty routinely collected but otherwise unselected *Acinetobacter* isolates (from CMSS), including 11 carbapenem-nonsusceptible isolates in which coexisting genes were detected encoding OXA-23-like, OXA-51-like, and TEM-1 β -lactamases, were tested. (iii) Twenty-five routinely collected but otherwise unselected *P. aeruginosa* isolates (from CMSS), including 11 carbapenem-nonsusceptible bacteria that harbored genes encoding OXA-50-like and/or TEM-1 β -lactamases, were tested. All the isolates, obtained from intra-abdominal, urinary tract, respiratory tract, or bloodstream infections, were sent to the central laboratory (Laboratory Medicine, Peking University People's Hospital, Beijing, China) for reidentification and antibiotic susceptibility testing. The Vitek GNI system (bioMérieux Vitek Inc., Hazelwood, MO) or API20E or API20NE (bioMérieux, Marcy l'Etoile, France) was used for bacterial identification.

MIC measurements were performed by the reference broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI) M7-A9 (2012) (12). MICs of ceftazidime and aztreonam alone and in combination with avibactam (AstraZeneca Pharmaceuticals) at a fixed concentration of 4 mg/liter (CLSI M100-S23, 2013) (13) were measured. Antibiotic solutions for susceptibility testing were prepared fresh; i.e., dried panels were not used in this study. MICs of ceftazidime, aztreonam, and comparator agents were interpreted according to CLSI criteria in M100-S23, 2013 (13).

For meropenem-nonsusceptible Gram-negative bacilli (Table 1), PCR was used to amplify carbapenemase genes (*bla*_{KPC}, *bla*_{NDM}, *bla*_{IMP}, *bla*_{VIM}, *bla*_{SIM}, *bla*_{SPM}, *bla*_{GIM}, *bla*_{OXA-48}, *bla*_{OXA-23-like}, *bla*_{OXA-24-like}, *bla*_{OXA-51-like}, *bla*_{OXA-58-like}, and *bla*_{OXA-50-like}) and

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TABLE 1 *In vitro* activities of cefazidime-avibactam, aztreonam-avibactam, and comparators against 48 meropenem-nonsusceptible β -lactamase-producing bacteria^a

Organism (no. of isolates)	Year of isolation	City ^b	MLST ^d	β-Lactamase(s) for which acquired genes were detected	MIC/MIC ₉₀ of:		MIC/MIC ₉₀ reduction (fold)	MIC/MIC ₉₀ of:		MIC/MIC ₉₀ reduction (fold)	MIC/MIC ₉₀ of:					
					CAZ	CAZ-AVI		ATM	ATM-AVI		FEP	TZP	MEM	POL	AMK	LVX
Enterobacteriaceae																
<i>Enterobacter freundii</i> (3)	2011	BJ	ND	KPC-2, TEM-1	64	0.5	128	>128	0.5	>256	16	128	1	0.25	256	ND
	2011	BJ	ND	KPC-2, TEM-1	64	1	64	>128	0.5	>256	16	128	2	0.25	256	ND
	2011	BJ	ND	KPC-2, TEM-1, CMV-2	128	0.5	256	>128	1	>128	16	128	2	0.25	256	ND
	2011	ZJ	11	KPC-2, TEM-1b	128	2	64	>128	0.5	>256	4	256	16	0.25	2	16
	2011	SH	11	KPC-2, TEM-1, SHV-12	>128	1	>128	>128	0.25	>512	8	256	16	0.25	>256	128
<i>Klebsiella pneumoniae</i> (7)	2011	ZJ	11	KPC-2, TEM-1, SHV-11, CTX-M-14	64	1	64	>128	0.25	>512	128	256	>32	0.25	>256	>64
	2012	ZJ	11	KPC-2, TEM-1, SHV-11, CTX-M-14	64	0.5	128	>128	0.25	>512	128	256	>32	0.25	>256	>64
	2012	GZ	11	KPC-2, CMV-2, SHV-11, CTX-M-14	>128	1	>128	>128	1	>128	256	>256	128	0.125	16	16
	2011	GZ	11	KPC-2, CMV-2, SHV-11, CTX-M-14	>128	2	>64	>128	2	>64	256	>256	128	0.125	32	16
	2011	ZJ	11	KPC-2, SHV-11, CTX-M-14	128	2	64	>128	0.5	>256	128	>256	256	0.25	>256	32
<i>Citrobacter freundii</i> (1)	2011	BJ	ND	IMP-4, TEM-1	>128	>128	1	128	0.5	256	8	4	4	0.5	2	ND
<i>Escherichia coli</i> (2)	2011	BJ	ND	IMP-4	>128	>128	1	2	≤0.064	>32	8	4	4	0.25	8	ND
	2011	BJ	ND	IMP-4, TEM-1, CTX-M-14	>128	>128	1	64	0.125	512	32	4	1	0.125	8	ND
<i>Enterobacter cloacae</i> (2)	2012	SY	ND	IMP-4, ACT-14	>128	>128	1	1	0.25	4	64	8	4	0.125	1	2
	2011	GZ	ND	IMP-4, ACT-15, TEM-1, SHV-12, CTX-M-14	>128	>128	1	>128	0.125	>1,024	32	64	2	0.125	4	128
<i>Klebsiella pneumoniae</i> (5)	2011	BJ	147	IMP-4, TEM-1	64	1	64	>128	0.5	>256	64	16	1	0.25	8	ND
	2011	BJ	876	IMP-4, TEM-1	>128	>128	1	8	0.125	64	16	32	4	0.25	1	ND
	2011	BJ	1100	IMP-4, SHV-11	0.25	0.25	1	≤0.064	0.125	128	16	16	2	0.25	2	ND
	2011	BJ	876	IMP-4, DHA-1	>128	>128	1	16	0.125	1	8	16	2	0.125	1	0.064
	2011	SY	876	IMP-4, SHV-107	>128	>128	1	0.125	0.125	256	32	64	0.5	0.125	1	ND
<i>Enterobacter cloacae</i> (1)	2011	FZ	ND	NDM-1, SHV-12	128	1	128	>128	0.5	>256	32	64	>32	0.25	2	32
<i>Klebsiella pneumoniae</i> (3)	2012	SX	147	NDM-1, SHV-12, TEM-1	>128	>128	1	>128	0.5	>256	128	>256	16	0.25	1	32
	2012	SX	147	NDM-1, SHV-12, TEM-1, CTX-M-3	>128	>128	1	>128	0.5	>256	128	>256	8	0.125	2	16
	2012	SX	147	NDM-1, SHV-12, TEM-1, CTX-M-3	>128	>128	1	>128	0.5	>2,000	128	>256	16	0.125	4	64
<i>Enterobacter aerogenes</i> (1)	2011	BJ	ND	TEM-1, ACT-15, CTX-M-3	128	4	32	>128	2	>64	128	256	16	0.125	4	64
<i>Escherichia coli</i> (1)	2011	BJ	ND	TEM-1, CTX-M-14	>128	4	>32	>128	2	>64	256	>256	4	0.125	2	32
Nonfermenters																
<i>Aerobacter baumannii</i> (11)	2012	NA ^c	NA	OXA-23-like, TEM-1	>128	32	>4	>128	64	>2	256	>256	64	0.25	>256	16
<i>Pseudomonas aeruginosa</i> (8)	2012	NA	NA	Only resident <i>bla</i> genes detected	8	8	1	>128	>128	1	32	>256	32	2	>256	16
	2012	SH	ND	TEM-1	8	2	4	32	32	1	32	>256	32	0.25	>256	0.25
<i>Pseudomonas aeruginosa</i> (3)	2012	SH	ND	TEM-1	8	4	2	128	64	2	64	>256	>32	0.5	>256	16
	2012	SH	ND	TEM-1	8	2	4	32	16	2	32	256	16	0.5	>256	0.5

^a MICs were determined in milligrams per liter. The 48 isolates consisted of 11 *P. aeruginosa* and 11 *A. baumannii* isolates listed in Table 2 and 26 additional *Enterobacteriaceae* isolates not included in the collection for which data are shown in Table 2. The *Enterobacteriaceae* are listed by acquired carbapenem resistance mechanism as follows: first *bla*_{KPC}-containing isolates, then isolates that contained genes encoding metallo- β -lactamases, and finally isolates in which no acquired carbapenemase-encoding gene could be detected. CAZ, cefazidime; ATM, aztreonam; AVI, avibactam; FEP, cefepime; TZP, piperacillin-tazobactam; MEM, meropenem; POL, polymyxin; AMK, amikacin; LVX, levofloxacin.

^b BJ, Beijing; ZJ, Zhejiang; SH, Shanghai; GZ, Guangzhou; SY, Shenyang; FZ, Fuzhou; SX, Shanxi.

^c NA, not applicable for more than one isolate.

^d MLST, multilocus sequence type; ND, not detected.

TABLE 2 MIC₅₀s, MIC₉₀s, and ranges of MICs of ceftazidime-avibactam and aztreonam-avibactam for 346 Gram-negative bacilli isolated from clinical specimens^a

Organism(s) and drug resistance phenotype(s) ^b (no. of isolates)	CAZ			CAZ-AVI			CAZ-AVI MIC ₉₀ reduction (fold)	ATM			ATM-AVI			ATM-AVI MIC ₉₀ reduction (fold)
	MIC ₅₀	MIC ₉₀	Range	MIC ₅₀	MIC ₉₀	Range		MIC ₅₀	MIC ₉₀	Range	MIC ₅₀	MIC ₉₀	Range	
<i>Escherichia coli</i> (25)	1	64	0.064–>128	0.125	0.5	0.064–0.5	128	8	128	0.064–>128	0.064	0.125	0.064–0.5	1,024
CAZ-NS and/or CTX-NS (18)	2	64	0.5–>128	0.25	0.5	0.064–0.5	128	32	>128	1–>128	0.064	0.5	0.064–0.5	>256
<i>Klebsiella oxytoca</i> (25)	0.25	2	0.064–4	0.25	0.5	0.064–0.5	4	0.5	8	0.064–>128	0.064	0.064	0.064–0.25	128
<i>Klebsiella pneumoniae</i> (25)	1	64	0.125–>128	0.125	1	0.064–2	64	1	64	0.064–>128	0.064	0.125	0.064–0.25	512
CAZ-NS and/or CTX-NS (14)	4	64	0.5–>128	0.125	1	0.064–2	64	8	128	1–>128	0.064	0.125	0.064–0.25	1,024
<i>Citrobacter diversus</i> (27)	0.125	0.5	0.064–64	0.125	0.25	0.064–0.5	2	0.064	0.25	0.064–128	0.064	0.064	0.064–0.125	4
<i>Citrobacter freundii</i> (24)	8	128	0.064–>128	0.25	1	0.064–2	128	2	64	0.064–128	0.064	0.5	0.064–1	128
CAZ-NS and/or CTX-NS (13)	32	>128	1–256	0.5	1	0.125–2	>128	32	64	2–128	0.125	0.5	0.064–1	128
<i>Enterobacter aerogenes</i> (26)	0.5	64	0.064–128	0.25	0.5	0.064–0.5	128	0.5	32	0.064–32	0.064	0.125	0.064–0.5	256
CAZ-NS and/or CTX-NS (13)	16	64	0.5–128	0.25	0.5	0.125–0.5	128	16	32	0.064–32	0.125	0.25	0.064–0.5	128
<i>Enterobacter cloacae</i> (26)	0.5	64	0.125–128	0.25	0.5	0.125–1	128	0.25	32	0.064–64	0.064	0.25	0.064–1	128
CAZ-NS and/or CTX-NS (10)	32	128	0.125–128	0.5	1	0.125–1	128	16	64	0.25–64	0.125	0.25	0.064–1	256
<i>Morganella morganii</i> (25)	1	64	0.064–128	0.125	1	0.064–1	64	0.5	16	0.064–64	0.064	0.25	0.064–1	64
CAZ-NS and/or CTX-NS (10)	8	128	0.5–128	0.125	1	0.064–1	128	2	32	0.5–64	0.064	0.5	0.064–1	64
<i>Proteus mirabilis</i> (24)	0.064	64	0.064–>128	0.064	0.25	0.064–1	256	0.064	4	0.064–>128	0.064	0.064	0.064–0.125	64
CAZ-NS and/or CTX-NS (11)	0.25	>128	0.064–>128	0.064	0.25	0.064–1	>512	0.5	64	0.064–>128	0.064	0.064	0.064–0.125	1,024
<i>Proteus vulgaris</i> (27)	0.064	0.5	0.064–1	0.064	0.125	0.064–0.125	4	0.064	0.125	0.064–32	0.064	0.064	0.064–0.064	2
<i>Providencia</i> spp. ^c (12)	0.5	256	0.064–>128	0.5	1	0.064–>128	256	0.125	64	0.064–>128	0.064	0.125	0.064–>128	512
CAZ-NS and/or CTX-NS (4)	NA ^d	NA	>128–>128	NA	NA	0.5–>128	NA	NA	NA	16–>128	NA	NA	0.064–>128	NA
<i>Serratia marcescens</i> (25)	0.25	8	0.125–8	0.125	1	0.125–1	8	0.25	64	0.064–128	0.064	0.25	0.064–0.25	256
CAZ-NS and/or CTX-NS (4)	NA	NA	8–8	NA	NA	0.25–1	NA	NA	NA	64–128	NA	NA	0.25–0.25	NA
<i>Pseudomonas aeruginosa</i> (25)	4	16	0.5–64	4	8	1–16	2	16	128	4–>128	16	64	4–>128	2
MEM-NS (11)	8	8	2–16	4	8	2–8	1	32	>128	4–>128	32	>128	8–>128	1
MDR (6)	8	8	1–16	4	8	1–8	1	32	>128	4–>128	32	>128	4–>128	1
CAZ-NS and/or ATM-NS (18)	8	16	2–64	4	8	2–16	2	32	>128	16–>128	32	>128	8–>128	1
<i>Acinetobacter baumannii</i> (28)	8	>128	2–>128	8	32	1–>128	>4	32	>128	8–>128	16	64	4–>128	>2
MEM-NS (11)	128	>128	32–>128	16	32	16–128	>4	64	>128	8–>128	32	64	32–64	>2
MDR (12)	128	>128	32–>128	16	32	16–>128	>4	64	>128	8–>128	32	64	>32–>128	>2
CAZ-NS (13)	128	>128	32–>128	16	32	4–128	>4	64	>128	8–>128	32	64	16–64	>2
<i>Acinetobacter calcoaceticus</i> (2)	NA	NA	>128–>128	NA	NA	>128–>128	NA	NA	NA	>128–>128	NA	NA	>128–>128	NA

^a MICs are expressed in milligrams per liter. Organisms were isolated in 2011 or 2012 and tested using freshly prepared panels.

^b CAZ, ceftazidime; ATM, aztreonam; AVI, avibactam; CTX, cefotaxime; MEM, meropenem; NS, nonsusceptible; MDR, multidrug resistant. Multidrug-resistant isolates were defined as isolates demonstrating resistance to at least one antimicrobial agent from three or more different classes.

^c Four *Providencia rettgeri* isolates were ceftazidime nonsusceptible and aztreonam nonsusceptible; avibactam restored the activities of ceftazidime and aztreonam against 3 of these isolates with 128- and 256- to 1,000-fold MIC reduction, respectively.

^d NA, not applicable. MIC₅₀s and MIC₉₀s are not presented for groups of fewer than 6 isolates.

other β -lactamase genes (*bla*_{TEM}, *bla*_{SHV}, *bla*_{CTX-M}, *bla*_{AmpC}, *bla*_{DHA}, and *bla*_{CMY}) according to procedures described in previous studies (14). All PCR products were sequenced with an ABI7570 sequencer (Applied Biosystems, Foster City, CA).

In this study, avibactam potentiated the activities of ceftazidime and aztreonam *in vitro* against most species of clinical isolates of *Enterobacteriaceae* tested. For isolates of *Enterobacteriaceae* that were nonsusceptible to ceftazidime and/or cefotaxime (33%; 97 of 291), the addition of 4 mg/liter avibactam greatly increased the activities of ceftazidime and aztreonam against most species (64- to 1,024-fold MIC₉₀ reduction) (Table 2). For the ceftazidime- and/or cefotaxime-nonsusceptible isolates of *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Providencia rettgeri* in the present study, both clavulanic acid (data not shown) and avibactam restored the activity of ceftazidime. For the isolates of *Citrobacter freundii*, *Enterobacter aerogenes*, *Enterobacter cloacae*, and *Morganella morganii* that were nonsusceptible to ceftazidime and/or cefotaxime, the activity of ceftazidime could not be protected by clavulanic acid (with no MIC₉₀ reduction; data not shown) but avibactam retained its protection of ceftazidime and aztreonam, with clear MIC₉₀ reductions (64- to 256-fold). It is possible that a large proportion of the ceftazidime/cefotaxime-

nonsusceptible isolates of these species produced stably derepressed AmpC β -lactamases (15–17).

Avibactam potentiated the activities of ceftazidime and aztreonam against carbapenem-nonsusceptible *Enterobacteriaceae* that harbored genes encoding KPC-2 and other class A enzymes (CTX-M-14/3, SHV-11/12, and TEM-1/1b) or class C enzymes (ACT-15, and CMY-2) (Table 1). Against carbapenem-nonsusceptible *Enterobacteriaceae* that carried genes encoding MBLs, such as IMP-4/8 and NDM-1, avibactam did not restore the activity of ceftazidime; however, the aztreonam-avibactam combination remained active (8).

The MIC₉₀ of ceftazidime-avibactam for 25 unselected clinical isolates of *P. aeruginosa* was 8 mg/liter (Table 2), as was found previously in studies from Canada (18) and France (19). The MIC of ceftazidime-avibactam was $\leq$ 8 mg/liter for 24 of 25 isolates (96%) (data not shown). For 18 *P. aeruginosa* isolates that were ceftazidime and/or aztreonam nonsusceptible, the addition of avibactam reduced the MIC₉₀ of ceftazidime from 16 to 8 mg/liter (Table 2; Fig. 1). The MIC of aztreonam alone was $\leq$ 8 mg/liter for 7 of 25 *P. aeruginosa* isolates (28%), and the MIC of aztreonam-avibactam was $\leq$ 8 mg/liter for 9 of 25 isolates (36%) (data not shown). Eleven *P. aeruginosa* isolates were phenotypically identi-

FIG 1 Ceftazidime, ceftazidime-avibactam, aztreonam, and aztreonam-avibactam MIC distributions for 291 *Enterobacteriaceae* isolates (excluding meropenem-nonsusceptible isolates), 30 *Acinetobacter* spp. isolates, and 25 *P. aeruginosa* isolates.

fied as meropenem nonsusceptible; however, the mechanisms of nonsusceptibility were not clarified by *bla* gene analysis. The only nonresident β -lactamase gene identified was *bla*_{TEM-1} in 3 of the isolates (Table 1). Regardless of mechanism, more than 90% of ceftazidime-avibactam MICs for these 11 carbapenem-nonsusceptible *P. aeruginosa* isolates were ≤ 8 mg/liter (Table 1).

MIC₉₀s of ceftazidime and aztreonam against *Acinetobacter baumannii* were lowered by >4 -fold and >2 -fold, respectively, upon combining with avibactam at 4 mg/liter (Table 2). For the 11 meropenem-nonsusceptible *A. baumannii* isolates that harbored nonresident genes encoding OXA-23-like and TEM-1 β -lactamases, the ranges of MICs of ceftazidime-avibactam and aztreonam-avibactam were relatively high, at 16 to 128 and 32 to 64 mg/liter, respectively, even though avibactam reduced the MIC₉₀s somewhat (Tables 1 and 2).

In conclusion, the *in vitro* activity of ceftazidime-avibactam against bacteria isolated from patients in China supports further evaluation of ceftazidime-avibactam in clinical studies against ESBL-, AmpC-, and serine carbapenemase-producing *Enterobacteriaceae* isolates. *In vitro*, ceftazidime-avibactam showed more activity than a carbapenem against carbapenem-nonsusceptible and KPC-producing isolates. At the same time, aztreonam-avibactam could serve as a candidate for the treatment of infections with MBL-producing *Enterobacteriaceae*, especially NDM-producing organisms (Table 1) (19). In both cases, additional studies are needed to establish what the potential roles of ceftazidime-avibactam and

aztreonam-avibactam might be as substitutes for carbapenems to reduce the dissemination of carbapenemases in the future.

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