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SUSCEPTIBILITY

In Vitro Activity of Cefepime-Zidebactam, Ceftazidime-Avibactam, and Other Comparators against Clinical Isolates of *Enterobacterales*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*: Results from China Antimicrobial Surveillance Network (CHINET) in 2018

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ABSTRACT This study evaluated the *in vitro* activity of cefepime-zidebactam in comparison with that of ceftazidime-avibactam and other comparators against clinically significant Gram-negative bacillus isolates. A total of 3,400 nonduplicate Gram-negative clinical isolates were collected from 45 medical centers across China in the CHINET Program in 2018, including *Enterobacterales* ($n = 2{,}228$), *Pseudomonas aeruginosa* ($n = 657$), and *Acinetobacter baumannii* ($n = 515$). The activities of cefepime-zidebactam and 20 comparators were determined by broth microdilution as recommended by the Clinical and Laboratory Standards Institute. Cefepime-zidebactam demonstrated potent activity against almost all *Enterobacterales* ($MIC_{50/90}$, 0.125/1 mg/liter) and good activity against *P. aeruginosa* ($MIC_{50/90}$, 2/8 mg/liter). Among the 373 carbapenem-resistant *Enterobacteriaceae* isolates, 57.3% (213/373) and 15.3% (57/373) were positive for bla_{KPC-2} and bla_{NDM}, respectively. Cefepime-zidebactam showed a MIC of ≤2 mg/liter for 92.0% (196/213) of bla_{KPC-2} producers and 79.7% (47/59) of bla_{NDM} producers. Ceftazidime-avibactam showed good *in vitro* activity against *Enterobacterales* ($MIC_{50/90}$, 0.25/2 mg/liter; 94.0% susceptible) and *P. aeruginosa* ($MIC_{50/90}$, 4/16 mg/liter; 86.9% susceptible). Ceftazidime-avibactam was active against 9.1% of carbapenem-resistant *Escherichia coli* isolates (63.6% were bla_{NDM} producers) and 84.6% of *Klebsiella pneumoniae* isolates (74.3% were bla_{KPC} producers). Most (90.1%) bla_{KPC-2} producers were susceptible to ceftazidime-avibactam. Cefepime-zidebactam demonstrated limited activity ($MIC_{50/90}$, 16/32 mg/liter) against the 515 *A. baumannii* isolates (79.2% were carbapenem resistant), and ceftazidime-avibactam was less active ($MIC_{50/90}$, 64/>64 mg/liter). Cefepime-zidebactam was highly active against clinical isolates of *Enterobacterales* and *P. aeruginosa*, including bla_{KPC-2}-positive *Enterobacterales* and bla_{NDM}-positive *Enterobacterales* and carbapenem-resistant *P. aeruginosa*. And ceftazidime-avibactam was highly active against bla_{KPC-2}-positive *Enterobacterales* and carbapenem-resistant *P. aeruginosa*.

KEYWORDS *Enterobacterales*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, cefepime-zidebactam, ceftazidime-avibactam, bla_{KPC}, bla_{NDM}, bla_{OXA-48}

In the past decades, both the CDC and WHO have emphasized that carbapenem-resistant Gram-negative pathogens, including *Enterobacterales*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*, were the major health care threats worldwide (1–3). Therapeutic options for such pathogens are limited because of their multidrug-resistant

Citation Yang Y, Guo Y, Yin D, Zheng Y, Wu S, Zhu D, Hu F, on behalf of the China Antimicrobial Surveillance Network (CHINET) Study Group. 2021. *In vitro* activity of cefepime-zidebactam, ceftazidime-avibactam, and other comparators against clinical isolates of *Enterobacterales*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*: results from China Antimicrobial Surveillance Network (CHINET) in 2018. Antimicrob Agents Chemother 65:e01726-20. https://doi.org/10.1128/AAC.01726-20.

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Received 27 August 2020
Returned for modification 24 September 2020
Accepted 23 October 2020
Accepted manuscript posted online 2 November 2020
Published 16 December 2020

nature, which may result in death of the infected patients. This situation makes the development of novel and active antimicrobial agents against these pathogens a primary priority (4).

Studies on one class of β-lactamase inhibitors, the diazabicyclooctanes, have identified novel compounds termed β-lactam enhancers, for their potent PBP2 affinity in important Gram-negative pathogens. Ceftazidime-avibactam was approved by the U.S. Food and Drug Administration (FDA) for the treatment of complicated urinary tract infections and complicated intra-abdominal infections in February 2015 (5). Avibactam can inhibit the activity of AmpC cephalosporinases, extended-spectrum β-lactamases (ESBLs), KPC carbapenemases, and some Ambler class D β-lactamases (OXA-48), and it is able to restore or enhance the bactericidal activity of ceftazidime against β-lactamase-producing organisms. Zidebactam, another new β-lactamase inhibitor under clinical evaluation, also demonstrates potent activity against a wide spectrum of Gram-negative pathogens possessing ESBLs, AmpC-type β-lactamases, KPC β-lactamases, and metallo-β-lactamases (MBLs) by combining with cefepime. Unlike avibactam, without inherent activity by itself, zidebactam has antibacterial activity against *Enterobacterales* and *P. aeruginosa*, including carbapenemase-producing isolates (6).

There have been several reports on the *in vitro* activity of ceftazidime-avibactam against *Enterobacterales* and *P. aeruginosa* in China (7, 8), but no study has been conducted to evaluate cefepime-zidebactam against isolates from Chinese patients. Our continuing surveillance study aims to assess the *in vitro* activity of cefepime-zidebactam and ceftazidime-avibactam against clinical strains which were recently isolated in 2018 through the China Antimicrobial Surveillance Network (CHINET). These collective susceptibility data on different carbapenemase-producing organisms might improve rational use of these novel β-lactam combinations in clinical practice.

RESULTS

***In vitro* activity of cefepime-zidebactam, ceftazidime-avibactam, and comparator agents.** Cefepime-zidebactam exhibited potent antibacterial activity against almost all *Enterobacterales* (MIC_{50}, 0.125 mg/liter). Overall, 86.1% of the carbapenem-resistant *Enterobacteriaceae* (CRE) strains and 89.8% of carbapenem-resistant *Klebsiella pneumoniae* strains were inhibited at 2 mg/liter. Ceftazidime-avibactam also demonstrated good antibacterial activity against *Enterobacterales* clinical isolates, evidenced by inhibiting 94.0% of *Enterobacterales* at 8 mg/liter, specifically, inhibiting 95.5% of *Escherichia coli* strains, 94.7% of *K. pneumoniae* strains, and 85.0% of *Enterobacter cloacae* strains. And 69.7% of CRE strains were susceptible to ceftazidime-avibactam. The majority (90.9%) of carbapenem-resistant *E. coli* isolates were resistant to ceftazidime-avibactam, but cefepime-zidebactam showed a 2-mg/liter or lower MIC against 81.8% of carbapenem-resistant *E. coli* isolates. The distribution of cefepime-zidebactam MICs against CRE is shown in terms of genotype in Fig. S1 in the supplemental material. Cefepime-zidebactam and ceftazidime-avibactam were highly active against *E. coli* strains (>95% susceptible), similar to polymyxin B and tigecycline. Cefepime-tazobactam, ceftolozane-tazobactam, and piperacillin-tazobactam also displayed potent activity against *E. coli*, and about 90% of the test strains were susceptible. More than 60% of *E. coli* isolates were resistant to ceftriaxone, ciprofloxacin, and levofloxacin, and 33.2% were resistant to cefepime, but only 4.6% (33/719) were resistant to carbapenems. More than 80% of the carbapenem-resistant *K. pneumoniae* strains were susceptible to cefepime-zidebactam, ceftazidime-avibactam, polymyxin B, and tigecycline. The majority of carbapenem-resistant *Klebsiella aerogenes* and *Serratia marcescens* isolates were susceptible to ceftazidime-avibactam, but few carbapenem-resistant *E. cloacae* and *Citrobacter freundii* isolates were susceptible to ceftazidime-avibactam. Tables 1 and 2 and Fig. 1 provide the MIC frequency distribution of cefepime-zidebactam and ceftazidime-avibactam to *Enterobacterales* clinical isolates, including carbapenemase-positive and -negative isolates.

TABLE 1 *In vitro* activities of cefepime-zidebactam and comparators tested against 719 isolates of *E. coli* and 33 isolates of carbapenem-resistant *E. coli* collected in China, 2018[a]

	E. coli (*n* = 719)					Carbapenem-resistant *E. coli* (*n* = 33)				
	MIC (mg/liter)					MIC (mg/liter)				
Antimicrobial agent	Range	50%	90%	R, %	S, %	Range	50%	90%	R, %	S, %
Cefepime-zidebactam	≤0.03 to 32	0.06	0.125	0.4	99	0.06 to 32	0.125	8	9.1	81.8
Ceftazidime-avibactam	≤0.03 to >64	0.125	0.5	4.5	95.5	0.25 to >64	>64	>64	90.9	9.1
Ceftolozane-tazobactam	≤0.06 to >128	0.25	4	9	89.6	4 to >128	>128	>128	97	0
Cefepime-tazobactam	≤0.03 to >64	0.06	0.5	4.3	94.7	8 to >64	>64	>64	90.9	0
Piperacillin-tazobactam	≤2 to >256	≤2	32	10.6	86.4	128 to >256	>256	>256	100	0
Cefoperazone-sulbactam	≤1 to >128	8	64	10.4	75.2	32 to >128	>128	>128	97	0
Cefazolin	1 to >32	>32	>32	71.9	15.4	>32 to >32	>32	>32	100	0
Cefuroxime	≤0.5 to >32	>32	>32	62.4	33.7	>32 to >32	>32	>32	100	0
Ceftriaxone	0.5 to >32	>32	>32	61.3	38.2	>32 to >32	>32	>32	100	0
Ceftazidime	≤0.25 to >32	2	>32	26.8	63.3	8 to >32	>32	>32	97	0
Cefepime	≤0.06 to >128	4	128	33.2	45.1	16 to >128	>128	>128	100	0
Moxalactam	≤0.06 to >128	0.5	16	63.1	36.5	8 to >128	>128	>128	100	0
Aztreonam	≤1 to >128	8	64	41.4	47.6	≤1 to >128	64	>128	75.8	21.2
Imipenem	≤0.06 to >128	0.125	0.5	4.3	94.9	2 to >128	16	64	93.9	0
Meropenem	≤0.03 to >64	≤0.03	≤0.03	4.2	95.3	2 to >64	16	64	90.9	0
Amikacin	≤1 to >128	2	8	5.1	88.3	≤1 to >128	4	>128	30.3	57.6
Ciprofloxacin	≤0.06 to >8	>8	>8	64.3	26.4	0.25 to >8	>8	>8	93.9	6.1
Levofloxacin	≤0.125 to >16	8	32	60.2	33.5	0.5 to >16	16	32	90.9	6.1
Trimethoprim-sulfamethoxazole	≤0.25 to >32	>32	>32	64.8	35.2	≤0.25 to >32	>32	>32	84.8	15.2
Polymyxin B	≤0.125 to >16	0.5	1	0.8	98.5	0.25 to >16	0.5	16	12.1	87.9
Tigecycline	≤0.06 to 4	0.125	0.25	0	99.7	0.125 to 4	0.25	1	0	97

[a]R, resistant; S, susceptible.

P. aeruginosa isolates were inhibited by cefepime-zidebactam ($MIC_{50/90}$, 2/8 mg/liter) at 2 mg/liter (35.6%) and 4 mg/liter (29.7%). The proportions of carbapenem-resistant *P. aeruginosa* strains inhibited at 4 and 8 mg/liter were 20.5% and 34.5%, respectively. Ceftazidime-avibactam also demonstrated good antibacterial activity against most *P. aeruginosa* strains, 8 mg/liter of ceftazidime-avibactam could inhibit 88.5% of *P. aeruginosa* strains, and 64.3% of carbapenem-resistant *P. aeruginosa* isolates were susceptible to ceftazidime-avibactam. The $MIC_{50}/_{90}$ values of cefepime-

TABLE 2 *In vitro* activities of cefepime-zidebactam and comparators tested against 788 isolates of *K. pneumoniae* and 272 isolates of carbapenem-resistant *K. pneumoniae* collected in China, 2018

	K. pneumoniae (*n* = 788)					Carbapenem-resistant *K. pneumoniae* (*n* = 272)				
	MIC (mg/liter)					MIC (mg/liter)				
Antimicrobial agent	Range	50%	90%	R, %	S, %	Range	50%	90%	R, %	S, %
Cefepime-zidebactam	≤0.03 to 32	0.125	2	0.5	96.3	0.06 to 32	1	4	1.5	89.7
Ceftazidime-avibactam	≤0.03 to >64	0.25	4	5.3	94.7	0.125 to >64	2	64	15.4	84.6
Ceftolozane-tazobactam	≤0.06 to >128	1	128	39.2	58.1	0.5 to >128	64	>128	97.1	1.5
Cefepime-tazobactam	≤0.03 to >64	0.125	>64	32.5	65	0.06 to >64	64	>64	91.5	3.3
Piperacillin-tazobactam	≤2 to >256	16	>256	44.4	49.7	≤2 to >256	>256	>256	96.3	2.9
Cefoperazone-sulbactam	≤1 to >128	16	>128	40.7	51	≤1 to >128	>128	>128	94.5	3.7
Cefazolin	1 to >32	>32	>32	62.8	37.2	2 to >32	>32	>32	97.8	2.2
Cefuroxime	≤0.5 to >32	>32	>32	61.2	34.9	2 to >32	>32	>32	98.2	1.5
Ceftriaxone	0.5 to >32	>32	>32	60.3	38.8	0.5 to >32	>32	>32	97.1	2.2
Ceftazidime	≤0.25 to >32	8	>32	48.5	47.3	≤0.25 to >32	>32	>32	96.3	2.2
Cefepime	≤0.06 to >128	8	>128	46.3	45.1	≤0.06 to >128	128	>128	96.7	1.5
Aztreonam	≤1 to >128	16	>128	52.4	44.8	≤1 to >128	>128	>128	95.6	4
Imipenem	≤0.06 to >128	0.5	64	33.6	63.6	0.25 to >128	32	128	97.4	0.7
Meropenem	≤0.03 to >64	≤0.03	>64	33.1	65.7	≤0.03 to >64	64	>64	96	2.6
Amikacin	≤1 to >128	≤1	>128	26.9	72.6	≤1 to >128	>128	>128	67.6	30.9
Ciprofloxacin	≤0.06 to >8	2	>8	57.4	34.1	≤0.06 to >8	>8	>8	95.6	4
Levofloxacin	≤0.125 to >16	1	32	49.9	39.8	≤0.125 to >16	>16	>16	92.3	5.1
Trimethoprim-sulfamethoxazole	≤0.25 to >32	16	>32	52.4	47.6	≤0.25 to >32	>32	>32	72.1	27.9
Polymyxin B	≤0.125 to >16	0.5	1	3	96.3	≤0.125 to >16	0.5	1	5.9	93.8
Tigecycline	≤0.06 to 16	0.5	2	0.5	95.7	0.125 to 8	1	2	0.4	93.4

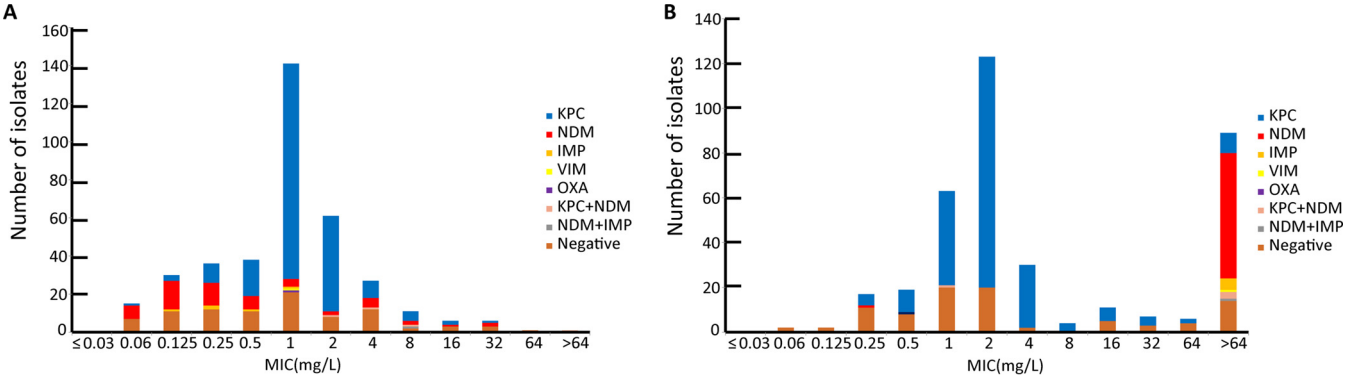

FIG 1 Distribution of cefepime-zidebactam (A) and ceftazidime-avibactam (B) MIC against carbapenem-resistant *Enterobacteriaceae* species in terms of carbapenemase genotype.

zidebactam and ceftazidime-avibactam against *A. baumannii* isolates were 16/32 mg/liter and 64/>64 mg/liter, respectively. About 26.0% (171/657) of *P. aeruginosa* isolates were resistant to carbapenems. *P. aeruginosa* isolates were mostly susceptible to cefepime-zidebactam (97.4%), ceftazidime-avibactam (86.9%), ceftolozane-tazobactam (89.5%), and polymyxin B (85.4%) (Table 3). As for carbapenem-resistant *P. aeruginosa*, 34.5% and 32.2% of isolates were susceptible to ceftazidime and cefepime and 64.3% and 93.0% were susceptible to ceftazidime-avibactam and cefepime-zidebactam, respectively. Overall, 79.2% (408/515) of *A. baumannii* isolates were resistant to carbapenems. Polymyxin B and tigecycline were the only agents showing relatively low MICs and susceptibility higher than 90% (Table 4).

Detection of carbapenemase genes. In this study, 16.7% (373/2228) of the *Enterobacterales* strains were carbapenem resistant, including *K. pneumoniae* (72.9% [272/373]), *E. coli* (8.8% [33/373]), and *E. cloacae* (5.9% [22/373]). Most (74.3% [277/373]) CRE strains had a single carbapenemase, 1.3% (5/373) were positive for dual carbapenemases, and 23.9% (89/373) were negative for all five common carbapenemase genes. More than half (57.1% [213/373]) of the CRE strains were bla_{KPC-2} positive, while 6.7% (25/373) and 8.1% (30/372) were bla_{NDM-1} and bla_{NDM-5} positive, respectively. Four

TABLE 3 *In vitro* activities of cefepime-zidebactam and comparators tested against 657 isolates of *P. aeruginosa* and 171 isolates of carbapenem-resistant *P. aeruginosa* collected in China, 2018

	P. aeruginosa (*n* = 657)					Carbapenem-resistant *P. aeruginosa* (*n* = 171)				
	MIC (mg/liter)					MIC (mg/liter)				
Antimicrobial agent	Range	50%	90%	R, %	S, %	Range	50%	90%	R, %	S, %
Cefepime-zidebactam	0.06 to 64	2	8	1.1	97.4	1 to 64	4	8	2.3	93
Ceftazidime-avibactam	0.125 to >64	4	16	13.1	86.9	1 to >64	8	64	35.7	64.3
Ceftolozane-tazobactam	0.25 to >128	1	8	7.5	89.5	0.5 to >128	2	128	23.4	69.6
Cefepime-tazobactam	≤0.03 to >64	4	32	14.8	72.3	2 to >64	16	>64	36.3	38.6
Piperacillin-tazobactam	≤2 to >256	16	256	42.9	41.1	≤2 to >256	64	>256	78.4	9.4
Cefoperazone-sulbactam	≤1 to >128	16	128	23.9	56.8	≤1 to >128	64	>128	50.9	18.1
Cefazolin	32 to >32	>32	>32	100	0	>32 to >32	>32	>32	100	0
Cefuroxime	16 to >32	>32	>32	99.8	0	>32 to >32	>32	>32	100	0
Ceftriaxone	1 to >32	>32	>32	82	1.5	16 to >32	>32	>32	95.3	0
Ceftazidime	≤0.25 to >32	8	>32	26	63	2 to >32	32	>32	50.9	34.5
Cefepime	0.125 to >128	8	32	19.6	67.6	4 to >128	16	>128	45	32.2
Aztreonam	≤1 to >128	8	64	33.6	51.3	≤1 to >128	32	>128	73.1	16.4
Meropenem	≤0.03 to >64	2	16	26	60.1	8 to >64	16	64	100	0
Amikacin	≤1 to >128	4	16	10.8	64.1	≤1 to >128	8	64	23.4	45
Ciprofloxacin	≤0.06 to >8	0.25	8	22.4	67	≤0.06 to >8	1	>8	46.8	36.3
Levofloxacin	≤0.125 to >16	1	16	27.2	62.3	0.25 to >16	4	32	56.7	27.5
Trimethoprim-sulfamethoxazole	≤0.25 to >32	16	>32	96.7	3.3	≤0.25 to >32	16	>32	96.5	3.5
Polymyxin B	0.25 to >16	2	4	3.8	85.4	0.25 to >16	2	4	5.3	86
Tigecycline	≤0.06 to >32	8	16	NA[a]	NA	0.125 to >32	16	32	NA	NA

[a]NA, not available; R, resistant; S, susceptible.

TABLE 4 *In vitro* activities of cefepime-zidebactam and comparators tested against 515 isolates of *A. baumannii* and 408 isolates of carbapenem-resistant *A. baumannii* collected in China, 2018[a]

	A. baumannii (*n* = 515)					Carbapenem-resistant *A. baumannii* (*n* = 408)				
	MIC (mg/liter)					MIC (mg/liter)				
Antimicrobial agent	Range	50%	90%	R, %	S, %	Range	50%	90%	R, %	S, %
Cefepime-zidebactam	≤0.03 to >64	16	32	36.5	26	2 to >64	16	32	46.1	8.8
Ceftazidime-avibactam	0.125 to >64	64	>64	84.9	15.1	4 to >64	64	>64	98.8	1.2
Ceftolozane-tazobactam	≤0.06 to >128	32	128	80.6	17.9	0.5 to >128	64	128	99	0.7
Cefepime-tazobactam	≤0.03 to >64	64	>64	78.1	20	2 to >64	>64	>64	97.8	1
Piperacillin-tazobactam	≤2 to >256	>256	>256	81.4	16.3	8 to >256	>256	>256	98.5	1
Cefoperazone-sulbactam	≤1 to >128	128	>128	79.8	18.3	4 to >128	128	>128	96.8	1.5
Cefazolin	4 to >32	>32	>32	99.6	0	>32 to >32	>32	>32	100	0
Cefuroxime	4 to >32	>32	>32	95.1	1.2	8 to >32	>32	>32	99.8	0.2
Ceftriaxone	0.5 to >32	>32	>32	82.3	8.5	8 to >32	>32	>32	98.8	0.2
Ceftazidime	≤0.25 to >32	>32	>32	81.9	17.3	2 to >32	>32	>32	98.3	1.2
Cefepime	≤0.06 to >128	128	>128	79.8	18.4	2 to >128	128	>128	98.3	0.7
Aztreonam	≤1 to >128	64	128	86.8	4.7	8 to >128	64	128	97.5	0.2
Imipenem	0.125 to >128	64	128	78.8	20	4 to >128	64	128	99.5	0
Meropenem	≤0.03 to >64	64	>64	78.8	19.8	2 to >64	64	>64	99.5	0.2
Amikacin	≤1 to >128	>128	>128	76.1	23.5	≤1 to >128	>128	>128	92.2	7.6
Ciprofloxacin	≤0.06 to >8	>8	>8	82.5	17.5	0.125 to >8	>8	>8	98.3	1.7
Levofloxacin	≤0.125 to >16	8	32	78.3	17.9	≤0.125 to >16	8	32	94.6	1.5
Trimethoprim-sulfamethoxazole	≤0.25 to >32	>32	>32	69.3	30.7	≤0.25 to >32	>32	>32	82.4	17.6
Polymyxin B	0.25 to >16	1	2	2.5	97.5	0.25 to >16	1	2	3.2	96.8
Tigecycline	≤0.06 to 16	1	2	NA	NA	0.125 to 16	1	2	NA	NA

[a]NA, not available; R, resistant; S, susceptible.

isolates were positive for both bla_{KPC-2} and bla_{NDM}. For other metallo-β-lactamases, five isolates were positive for bla_{IMP-4}, one isolate was positive for bla_{VIM-1}, and another isolate was positive for both bla_{NDM-1} and bla_{IMP-1}. Additionally, $bla_{OXA-232}$ was detected in only one isolate, and bla_{KPC-2} was mostly detected in *K. pneumoniae* (94.8% [202/213]). The prevalences of bla_{NDM} were 36.8% (21/57) in *E. coli* isolates, 22.8% (13/57) in *K. pneumoniae* isolates, and 22.8% (13/57) in *E. cloacae* isolates. The results of antimicrobial susceptibility testing indicated that 92% of bla_{KPC}-positive and 82.5% of bla_{NDM}-positive *Enterobacterales* were susceptible to cefepime-zidebactam. However, 90.1% of bla_{KPC}-positive *Enterobacterales* were susceptible, while 98.2% of bla_{NDM}-positive *Enterobacterales* were resistant, to ceftazidime-avibactam.

DISCUSSION

The spread of drug-resistant Gram-negative bacteria, especially CRE strains, *P. aeruginosa*, and *A. baumannii*, has substantially increased morbidity and mortality rates worldwide. There is an urgent need to develop new antimicrobial agents for clinical use (4, 9). Results from the CHINET Antimicrobial Surveillance Network showed that more than 25% of the *K. pneumoniae* strains isolated from 44 hospitals across China were resistant to imipenem and meropenem (10), nearly a 10-fold increase since 2005 (http://www.chinets.com/Data/GermYear). In China, KPC-2, NDM, and OXA-48-like carbapenemases were predominant among clinical CRE isolates. The most prevalent carbapenemase gene was bla_{KPC-2} among the carbapenem-resistant *K. pneumoniae* isolates from adult patients, whereas bla_{NDM}, bla_{KPC-2}, and bla_{OXA-48} were the predominant carbapenemase genes among the carbapenem-resistant *K. pneumoniae* isolates from pediatric patients. The predominant carbapenemase gene was bla_{NDM} in the carbapenem-resistant *E. coli* isolates from both adults and children (11).

Currently, tigecycline, polymyxins (including polymyxin B and colistin), and ceftazidime-avibactam are available for the treatment of infections caused by carbapenem-resistant Gram-negative bacilli. In this study, more than 87.9% of the carbapenem-resistant *E. coli*, carbapenem-resistant *K. pneumoniae*, and carbapenem-resistant *A. baumannii* strains tested were susceptible to tigecycline and polymyxin B. Additionally, 86% of carbapenem-resistant *P. aeruginosa* strains were susceptible to polymyxin B. Ceftazidime-avibactam has been approved by the Center for Drug Evaluation in China

for the treatment of infections caused by multidrug-resistant or extensively drug-resistant Gram-negative bacilli, including bla_{KPC}- or bla_{OXA-48}-positive strains. The prevalence of CRE strains was 13.9% in the present study, which was similar to that in the CHINET 2017 study (7) and higher than another national surveillance study of isolates collected in 2012 to 2014 (8). The bla_{KPC}-positive isolates still showed a low (<10%) rate of resistance to ceftazidime-avibactam, but the majority (98.2%) of the isolates possessing bla_{NDM} were resistant to ceftazidime-avibactam. As reported previously (12, 13), a novel L169P mutation in KPC-2 and D179Y/T243M mutation in KPC-3 confer reduced susceptibility to ceftazidime-avibactam.

Unlike avibactam, without inherent antimicrobial activity and with no effect on metallo-β-lactamase, zidebactam has antibacterial activity against *Enterobacterales* and *P. aeruginosa*, including carbapenemase-producing isolates (6). Previous studies have demonstrated that the new antibacterial combination cefepime-zidebactam is active against multidrug-resistant Gram-negative pathogens, especially metallo-β-lactamase-producing *Enterobacterales*, *P. aeruginosa*, and OXA-carbapenemase-positive *A. baumannii* (6, 14, 15). According to a study by Khan et al. (16), cefepime-zidebactam had a MIC of ≤2 mg/liter against more than 99% of *E. coli*, *K. pneumoniae*, and *Enterobacter* strains. In the present study, 99% of the *E. coli* and 96.3% of *K. pneumoniae* isolates were inhibited by cefepime-zidebactam at the same breakpoint (≤2 mg/liter). Furthermore, 92% of bla_{KPC}-positive and 82.5% of bla_{NDM}-positive *Enterobacterales* were susceptible to cefepime-zidebactam. Additionally, cefepime-zidebactam could inhibit 97.4% of *P. aeruginosa* and 93.0% of carbapenem-resistant *P. aeruginosa* isolates (MIC ≤ 8 mg/liter), consistent with the study by Khan et al. (16), in which 98% of *P. aeruginosa* isolates and 78% of carbapenem-resistant isolates were inhibited by cefepime-zidebactam at ≤8 mg/liter. Only 26% of the *A. baumannii* isolates and 8.8% of the carbapenem-resistant isolates were inhibited by cefepime-zidebactam at ≤8 mg/liter. Cefepime-zidebactam did not show good *in vitro* activity against *A. baumannii*, though in the neutropenic mouse thigh and lung infection models (17), considerable activity was still demonstrable for cefepime-zidebactam (MIC range of 16 to 64 mg/liter) against carbapenem-resistant *A. baumannii*. Our study showed MICs comparable to those in several other studies (14, 15, 18), and the clinical role of cefepime-zidebactam would be determined on breakpoints based on further clinical investigations.

In conclusion, this study demonstrated that both cefepime-zidebactam and ceftazidime-avibactam show excellent *in vitro* antibacterial activity against recent clinical isolates of *Enterobacterales* and *P. aeruginosa*. Ceftazidime-avibactam exhibited activity against bla_{KPC-2}-producing strains, and cefepime-zidebactam showed lower MICs against both bla_{KPC}- and bla_{MBL}-producing strains. Diazabicyclooctane β-lactamase inhibitors provide a new therapeutic alternative for the infections caused by carbapenem-resistant *Enterobacterales*.

MATERIALS AND METHODS

Clinical strains. A total of 3,400 nonduplicate sequential isolates of Gram-negative bacilli were collected from 45 medical centers in 28 provinces or cities across China in 2018, including *Klebsiella pneumoniae* ($n = 788$), *Escherichia coli* ($n = 719$), *P. aeruginosa* ($n = 657$), *A. baumannii* ($n = 515$), *Enterobacter cloacae* ($n = 140$), *Proteus mirabilis* ($n = 134$), *Serratia marcescens* ($n = 110$), *Klebsiella aerogenes* ($n = 106$), *Morganella morganii* ($n = 92$), *Citrobacter freundii* ($n = 85$), and *Proteus vulgaris* ($n = 54$). Among the 3,400 clinical strains, 41.8% were isolated from the respiratory tract, 20.6% from the urinary tract, and 11.2% and 6.9% from blood and wounds, respectively. Species identification was performed at each participating site and confirmed by the central laboratory using the Vitek-2 compact system (bioMérieux, France) or matrix-assisted laser desorption ionization–time-of-flight mass spectrometry (Vitek MS; bioMérieux).

Antimicrobial susceptibility testing. MICs were determined by the reference broth microdilution method recommended by the Clinical and Laboratory Standards Institute (CLSI) (19). Cefepime-zidebactam, ceftazidime-avibactam, ceftolozane-tazobactam, cefepime-tazobactam, cefoperazone-sulbactam, piperacillin-tazobactam, cefepime, ceftazidime, ceftriaxone, cefuroxime, cefazolin, aztreonam, imipenem, meropenem, amikacin, ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, polymyxin B, and tigecycline were tested using a dried customized commercially prepared microdilution panel (Sensititre; Thermo Fisher Scientific). *E. coli* ATCC 25922 and ATCC 35218, *K. pneumoniae* ATCC 700603, and *P. aeruginosa* ATCC 27853 were used as the quality control strains in antimicrobial susceptibility testing. Quality control and interpretation of the results were based on 2019 CLSI break-

points (20) for all the antimicrobial agents with the exception of cefepime-zidebactam and tigecycline, for which CLSI criteria are not available. Tigecycline MICs were interpreted using U.S. FDA MIC breakpoints for *Enterobacterales* (21). Cefepime-zidebactam MICs were interpreted using CLSI breakpoints for cefepime for comparison purposes only.

CRE definition and carbapenemase detection. As defined by the Centers for Disease Control and Prevention (CDC), the *Enterobacterales* isolates that test resistant to at least one of the carbapenems (ertapenem, meropenem, doripenem, or imipenem) or produce a carbapenemase are called carbapenem-resistant *Enterobacteriaceae* (CRE) (https://www.cdc.gov/hai/organisms/cre/technical-info.html#Definition). Some *Enterobacterales* (e.g., *Proteus* spp., *Morganella* spp., and *Providencia* spp.) have intrinsic elevated MICs to imipenem. In such cases, the MIC results of meropenem were used to determine if these organisms meet the CRE definition. The presence of the five most common carbapenemase genes (bla_{KPC}, bla_{NDM}, bla_{IMP}, bla_{VIM}, and bla_{OXA-48}) were confirmed for all the CRE strains by PCR with specific primers and DNA sequencing, as described previously (7).

Study approval. The study protocol was approved by the Institutional Review Board of Huashan Hospital, Fudan University (no. 2018-408).

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.3 MB.

ACKNOWLEDGMENTS

We gratefully acknowledge the contribution of the members of CHINET for collection of the isolates in this study, including the following: Yingchun Xu and Xiaojiang Zhang from Peking Union Medical College Hospital; Zhaoxia Zhang and Ping Ji from the First Affiliated Hospital of Xinjiang Medical University; Mei Kang and Chao He from West China Hospital, Sichuan University; Chuanqing Wang and Leiyan He from Children's Hospital of Fudan University; Yuanhong Xu and Ying Huang from the First Affiliated Hospital of Anhui Medical University; Zhongju Chen and Ziyong Sun from Tongji Hospital, Tongji Medical College, Huazhong University of Science & Technology; Yuxing Ni and Jingyong Sun from Ruijin Hospital, Shanghai Jiaotong University School of Medicine; Yunzhuo Chu and Sufei Tian from the First Affiliated Hospital of China Medical University; Zhidong Hu and Jin Li from Tianjin Medical University General Hospital; Yunsong Yu and Jie Lin from Sir Run Shaw Hospital, Zhejiang University School of Medicine; Bin Shan and Yan Du from the First Affiliated Hospital of Kunming Medical University; Sufang Guo and Yanyan Wang from the First Affiliated Hospital of Inner Mongolia Medical University; Lianhua Wei and Xin Wang from Gansu Provincial Hospital; Hong Zhang and Chun Wang from Children's Hospital of Shanghai; Yunjian Hu and Xiaoman Ai from Beijing Hospital; Chao Zhuo and Danhong Su from the First Affiliated Hospital of Guangzhou Medical University; Ruizhong Wang and Hua Fang from Pudong New Area People's Hospital; Bixia Yu from Zhejiang Ningbo Zhenhai Longsai Hospital; Ping Gong and Miao Song from the People's Hospital of Zigui, Hubei Province; Dawen Guo and Jinying Zhao from the First Affiliated Hospital of Harbin Medical University; Wen'en Liu and Yanming Li from Xiangya Hospital, Central South University; Yan Jin and Yueling Wang from Shandong Provincial Hospital; Kaizhen Weng and Yirong Zhang from Jinjiang Municipal Hospital; Xuesong Xu and Chao Yan from China-Japan Union Hospital, Jilin University; Xiangning Huang and Hua Yu from Sichuan Provincial People's Hospital; Yi Li and Shanmei Wang from Henan Provincial People's Hospital; Lixia Zhang and Juan Ma from Shaanxi Provincial People's Hospital; Shuping Zhou and Jiangwei Ke from Jiangxi Provincial Children's Hospital; Lei Zhu and Jinhua Meng from Children's Hospital of Shanxi; Wenqi Song and Fang Dong from Beijing Children's Hospital, Capital Medical University; Han Shen and Wanqing Zhou from Nanjing Drum Tower Hospital, Affiliated Hospital of Nanjing; Gang Li and Wei Jia from General Hospital of Ningxia Medical University; Jinsong Wu and Yuemei Lu from Shenzhen People's Hospital; Jihong Li from the Second Hospital of Hebei Medical University; Jiangshan Liu from Jinchang Hospital of Integrated Traditional Chinese and Western Medicine; Longfeng Liao from the People's Hospital of Ganxian; Hongqin Gu from Guangrao County People's Hospital; Lin Jiang from the People's Hospital of Huixian, Henan Province; Wen He from Central Hospital of Yingkou Development Zone, Liaoning Province; Shunhong Xue from Huzhu County People's Hospital, Qinghai Province; Jiao Feng from the

People's Hospital of Linshui, Sichuan Province; Rui Dou from Lixin County People's Hospital; and Chunlei Yue from Jiutai People's Hospital.

This work was supported by National Mega-project for Innovative Drugs (2019ZX09721001-006-004), the National Natural Science Foundation of China (81871690, 81902100, and 81902101), the Science and Technology Innovation Action Plan of Shanghai Science and Technology Committee (17DZ1910403), Shanghai Antimicrobial Surveillance Network (3030231003), and the China Antimicrobial Surveillance Network (WI207259).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

We declare that we have no conflict of interest.

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