In Vitro Activity of New β-Lactam–β-Lactamase Inhibitor Combinations and Comparators against Clinical Isolates of Gram-Negative Bacilli: Results from the China Antimicrobial Surveillance Network (CHINET) in 2019

Yan Guo, a,b Renru Han, a,b Bo Jiang, c Li Ding, a,b Fengzhen Yang, d Beijia Zheng, e Yang Yang, a,b Shi Wu, a,b Dandan Yin, a,b Demei Zhu, a,b Fupin Hu, a,b on behalf of the China Antimicrobial Surveillance Network (CHINET) Study Group

a Institute of Antibiotics, Huashan Hospital, Fudan University, Shanghai, China
b Key Laboratory of Clinical Pharmacology of Antibiotics, Ministry of Health, Shanghai, China
c First Affiliated Hospital of Kunming Medical University, Yunnan, China
d Yantai Yuhuangding Hospital, Shandong, China
e Taizhou Central Hospital, Zhejiang, China

Yan Guo, Renru Han, and Bo Jiang contributed equally to this work. Author order was determined both alphabetically and in order of increasing seniority.

ABSTRACT Novel β-lactam–β-lactamase inhibitor combinations (BLBLIs) are in clinical development for the treatment of infections caused by carbapenem-resistant and difficult-to-treat resistant (DTR) (defined as resistance to all tested β-lactams and fluoroquinolones) Gram-negative bacilli. This study evaluated the in vitro activities of cefepime-zidebactam, ceftazidime-avibactam, cefepime-tazobactam, ceftolozane-tazobactam, and other comparators against 4,042 nonduplicate Gram-negative clinical isolates collected from different regions of China (46 hospitals) in 2019. Based on the pharmacokinetic-pharmacodynamic (PK-PD) breakpoints, cefepime-zidebactam inhibited 98.5% of Enterobacterales and 98.9% of Pseudomonas aeruginosa isolates, respectively. Against carbapenem-resistant and difficult-to-treat resistant Gram-negative bacilli, cefepime-zidebactam demonstrated better activity against Enterobacterales (96% and 97.2%, respectively) and P. aeruginosa (98.2% and 96.9%, respectively). Among the 379 carbapenem-resistant Enterobacterales isolates, the most common carbapenemase genes detected were blaKPC-2 (64.1%) and blaNDM (30.9%). Cefepime-zidebactam showed an MIC90 of ≤2 mg/L for 98.8% of blaKPC-positive isolates and 89.7% of blaNDM-positive isolates. Ceftazidime-avibactam also showed efficient in vitro activity against Enterobacterales (93.6%) and P. aeruginosa (87.7%). Ceftazidime-avibactam was active against 97.5% of blaKPC-positive isolates and 100% of blaOXA-23-family-positive isolates. Cefepime-zidebactam inhibited 97.3% of Acinetobacter baumannii isolates with an MIC50/90 of 16/32 mg/L. Our study systematically evaluated the in vitro activities of these new BLBLIs against a variety of Gram-negative bacilli, provided preclinical data for the approval of these BLBLIs in China, and supported cefepime-zidebactam and ceftazidime-avibactam as potential efficient therapies for infections caused by carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant P. aeruginosa (CRPA), and DTR isolates.

IMPORTANCE Enterobacterales, Pseudomonas aeruginosa, and Acinetobacter baumannii are the most common Gram-negative bacilli to cause nosocomial infections throughout the world. Due to their large public health and societal implications, carbapenem-resistant A. baumannii (CRAB), carbapenem-resistant P. aeruginosa (CRPA), and carbapenem-resistant and third-generation-cephalosporin-resistant Enterobacteriaceae were regarded by the World Health Organization (WHO) as a global priority for investment in new drugs in 2017. The present study showed the potent in vitro...
activity of these novel BLBLIs and other comparators against Gram-negative bacillus isolates, including carbapenem-resistant or difficult-to-treat resistant phenotypes. Polymyxins, tigecycline, and ceftazidime-avibactam (except for blq_{outer}-positive isolates) were available for the treatment of infections caused by CRE isolates. Currently, cefepime-zidebactam and other BLBLIs have not yet been approved for use in China. Here, our study aimed to evaluate the in vitro activities of BLBLIs against Gram-negative bacillus isolates, especially CRE, before clinical use.

**KEYWORDS** β-lactam–β-lactamase inhibitor combinations, difficult-to-treat resistance, cefepime-zidebactam, ceftazidime-avibactam, carbapenemase

Gram-negative bacilli are causative pathogens in many infections, including pneumonia, bloodstream infections, wound or surgical site infections, and meningitis, in health care settings, which have become a significant public health threat globally (1–3). Results from the China Antimicrobial Surveillance Network (CHINET) (www.chinets.com) for 2021 showed that more than 25% of *Klebsiella pneumoniae*, 20% of *Pseudomonas aeruginosa*, and 69% of *Acinetobacter baumannii* isolates are resistant to imipenem and meropenem. Carbapenem-resistant Gram-negative bacilli have rapidly increased worldwide in the last decade, which is related to the emergence and prevalence of plasmid-mediated extended-spectrum β-lactamases (ESBLs), AmpC cephalosporinases, and carbapenemases among these isolates, conferring resistance to β-lactam antibiotics, and make difficulties in empirical treatment for clinicians (3, 4). Recently, the difficult-to-treat resistant (DTR) phenotype, defined as resistance to all tested β-lactams and fluoroquinolones, has caught attention as it is associated with clinical therapeutic options and patient outcomes. Antimicrobial resistance in these bacteria has significant potential impacts on antibiotic use and patient outcomes (1). Currently, aminoglycosides, polymyxins (colistin and polymyxin B), and tigecycline are the antibiotics available for the treatment of infections caused by these intractable isolates in China but are problematic in their clinical efficacy, their safety profile, and emerging resistance (3, 5–7). New therapeutic development is urgently needed to combat these intractable pathogens. To date, several new β-lactam–β-lactamase inhibitor combinations (BLBLIs) in different stages of development, including ceftazidime-avibactam, ceftolozane-tazobactam, cefepime-zidebactam, meropenem-vaborbactam, and imipenem-relebactam, inhibit class A and class C β-lactamases, and some are active against class B and class D β-lactamases (3, 8, 9). In this study, based on data from the CHINET Antimicrobial Surveillance Network, we evaluated the in vitro activity of these newly developed BLBLIs against Gram-negative bacilli and strengthened the epidemiological surveillance of resistance of Gram-negative bacilli to confront an emerging global epidemic.

**RESULTS**

**Strain characteristics.** The results of antimicrobial susceptibility testing indicated that 61% of *Escherichia coli*, 51% of *K. pneumoniae*, and 44.5% of *Proteus mirabilis* isolates were resistant to ceftriaxone.

Among the tested *Enterobacterales* isolates, 379/2,656 (14.3%) were carbapenem-resistant *Enterobacterales* (CRE), including *K. pneumoniae* (74.1%; 281/379), *E. coli* (10.6%; 40/379), and *Enterobacter cloacae* (4.5%; 17/379).

For glucose-nonfermenting bacteria, 228/756 (30.2%) and 471/630 (74.8%) were carbapenem-resistant *P. aeruginosa* (CRPA) and carbapenem-resistant *A. baumannii* (CRAB), respectively, and 11.9% (316/2,656) of *Enterobacterales* isolates and 8.6% (65/756) of *P. aeruginosa* isolates were difficult-to-treat resistant (DTR) isolates.

**Susceptibility of Gram-negative bacilli.** The in vitro activities of cefepime-zidebactam, ceftazidime-avibactam, cefepime-tazobactam, ceftolozane-tazobactam, and other comparator agents against 4,042 clinical isolates are summarized in Tables 1 to 3. Cefepime-zidebactam exhibited potent antibacterial activity against all *Enterobacterales* isolates (*n* = 2,656) with an MIC\textsubscript{90} of 0.06/1 mg/L. A total of 98.5% of isolates were inhibited at the provisional cefepime-zidebactam pharmacokinetic-pharmacodynamic (PK-PD)
| Antibacterial agent     | MIC range (mg/L) | MIC\(_{50}\) (mg/L) | MIC\(_{90}\) (mg/L) | % R | % S |
|------------------------|------------------|----------------------|---------------------|-----|-----|
| **Enterobacterales (n = 2,656)** |                  |                      |                     |     |     |
| Cefepime-zidebactam    | ≤0.03 to >64     | 0.06                 | 1                   | NA  | 98.5 |
|                        |                  |                      |                     |     |     |
| Ceftazidime-avibactam  | ≤0.03 to >64     | 0.25                 | 4                   | 64  | 93.5 |
|                        |                  |                      |                     |     |     |
| Cefepime-tazobactam    | ≤0.03 to >64     | 0.06                 | 64                  | NA  | 85.8 |
|                        |                  |                      |                     |     |     |
| Ceftolozane-tazobactam| ≤0.06 to >128    | 0.5                  | 128                 | 23.9| 74.2 |
|                        |                  |                      |                     |     |     |
| Tigecycline            | ≤0.06 to >32     | 0.25                 | 2                   | 0.8 | 96.5 |
|                        |                  |                      |                     |     |     |
| Polymyxin B            | ≤0.125 to >16    | 0.5                  | >16                 | 18.6| 81.4 |
|                        |                  |                      |                     |     |     |
| Imipenem               | ≤0.06 to >128    | 0.5                  | 32                  | 18  | 74.6 |
|                        |                  |                      |                     |     |     |
| Meropenem              | ≤0.03 to >64     | ≤0.03                | 64                  | 14  | 85.6 |
|                        |                  |                      |                     |     |     |
| Piperacillin-tazobactam| 1 to >256        | 4                    | >256                | 19.6| 75.5 |
|                        |                  |                      |                     |     |     |
| Cefoperazone-sulbactam | ≤1 to >128       | 4                    | >128                | 21.7| 78.3 |
|                        |                  |                      |                     |     |     |
| Cefepime               | ≤0.06 to >128    | 0.5                  | >128                | 36.6| 63.4 |
|                        |                  |                      |                     |     |     |
| Ceftazidime            | ≤0.25 to >32     | 1                    | >32                 | 34.2| 65.8 |
|                        |                  |                      |                     |     |     |
| Ceftriaxone            | ≤0.5 to >32      | 4                    | >32                 | 52.1| 47.9 |
|                        |                  |                      |                     |     |     |
| Cefuroxime             | ≤0.25 to >32     | >32                  | 62.9                | 33.5| 66.5 |
|                        |                  |                      |                     |     |     |
| Cefazolin              | ≤0.5 to >32      | >32                  | 72                  | 20.1| 79.9 |
|                        |                  |                      |                     |     |     |
| Amikacin               | 0.5 to >128      | 2                    | >16                 | 9.3 | 90.7 |
|                        |                  |                      |                     |     |     |
| Aztreonam              | ≤1 to >128       | 2                    | >128                | 41.5| 58.5 |
|                        |                  |                      |                     |     |     |
| Ciprofloxacin          | ≤0.06 to >8      | 1                    | >8                  | 50.4| 49.6 |
|                        |                  |                      |                     |     |     |
| Levofloxacin           | ≤0.125 to >16    | 1                    | >16                 | 43.5| 56.5 |
|                        |                  |                      |                     |     |     |
| Trimethoprim-sulfamethoxazole | ≤0.25 to >32 | 1 | >32 | 46.3 | 53.7 |

**CRE, carbapenem-resistant *Enterobacterales*; DTR, difficult-to-treat resistant; % R, percentage of resistant isolates; % S, percentage of susceptible isolates.

b NA, not available.
c Cefepime-zidebactam MICs were interpreted using a provisional breakpoint of ≤8 mg/L based on the PK-PD breakpoint.
d Cefepime-tazobactam MICs were interpreted using a provisional breakpoint of ≤16 mg/L based on the PK-PD breakpoint.
e Polymyxin B MICs were interpreted using the EUCAST breakpoint of colistin (≤2 mg/L, susceptible; ≥2 mg/L, resistant).
| Antibacterial agent                  | P. aeruginosa (n = 756) | CRPA (n = 228) | DTR P. aeruginosa (n = 65) |
|-------------------------------------|-------------------------|----------------|---------------------------|
|                                     | MIC range (mg/L) | MIC\(_{50}\) (mg/L) | % R | % S | MIC\(_{50}\) (mg/L) | MIC\(_{90}\) (mg/L) | % R | % S | MIC\(_{50}\) (mg/L) | MIC\(_{90}\) (mg/L) | % R | % S |
| Cefepime-zidebactam                | ≤0.03 to >64     | 2              | 8          | NA\(^{b}\) | 98.9\(^{c}\) | 4              | 8          | NA | 98.2\(^{c}\) | 8              | 16             | NA | 96.9\(^{c}\) |
| Ceftazidime-avibactam             | ≤0.03 to >64     | 2              | 16         | 12.3 | 87.7 | 4              | 64         | 32 | 68 | 16              | >64            | 66.2 | 33.8 |
| Cefepime-tazobactam               | ≤0.03 to >64     | 4              | 32         | NA   | 87.7\(^{d}\) | 16             | 64         | NA | 68.4\(^{d}\) | 32             | >64            | NA | 23.1\(^{d}\) |
| Ceftolozane-tazobactam           | ≤0.06 to >128    | 1              | 4          | 7.1  | 90.2 | 2              | >128       | 18 | 76.3 | 8              | >128           | 38.5 | 49.2 |
| Polymyxin B\(^{e}\)               | 0.25 to >16      | 1              | 2          | 4.4  | 95.6 | 1              | 1          | 3.1 | 96.9 | 1              | 1             | 1.5  | 98.5 |
| Imipenem                           | 0.125 to >128    | 2              | 32         | 29.4 | 70.6 | 16             | 64         | 97.4 | 0.9 | 32             | >128           | 100  | 0   |
| Meropenem                          | ≤0.03 to >64     | 0.5            | 16         | 18.5 | 81.5 | 8              | 64         | 61.4 | 38.6 | 32             | >64            | 93.8 | 0   |
| Piperacillin-tazobactam           | ≤2 to >256       | 8              | 256        | 16.7 | 63.3 | 32             | >256       | 37.3 | 62.7 | 256            | >256           | 87.7  | 0   |
| Cefoperazone-sulbactam            | ≤1 to >128       | 8              | 64         | 19.8 | 80.2 | 32             | >128       | 44.3 | 55.7 | 128            | >128           | 92.3  | 0   |
| Cefepime                           | ≤0.06 to >128    | 4              | 32         | 14.2 | 85.8 | 16             | 128        | 35.5 | 64.5 | 32             | >128           | 83.1  | 0   |
| Ceftazidime                        | ≤0.25 to >32     | 4              | >32        | 22.1 | 77.9 | 16             | >32        | 44.3 | 55.7 | >32            | >32           | 92.3  | 0   |
| Amikacin                           | ≤1 to >128       | 4              | 8          | 3.8  | 96.2 | 4              | 32         | 9.6  | 90.4 | 8              | >128           | 26.2  | 73.8 |
| Aztreonam                          | ≤1 to >128       | 8              | 64         | 32.7 | 67.3 | 32             | 128        | 53.9 | 46.1 | 64             | >128           | 90.8  | 0   |
| Ciprofloxacin                      | ≤0.06 to >8      | 0.25           | 8          | 22   | 78.8 | 1              | >8         | 37.3 | 62.7 | >8             | >8             | 76.9  | 0   |
| Levofloxacin                       | ≤0.125 to >16    | 1              | 16         | 28.4 | 71.6 | 2              | >16        | 49.6 | 50.4 | 16             | >16            | 95.4  | 0   |

\(^{a}\)CRPA, carbapenem-resistant P. aeruginosa; DTR, difficult-to-treat resistant.

\(^{b}\)NA, not available.

\(^{c}\)Cefepime-zidebactam MICs were interpreted using a provisional breakpoint of ≤32 mg/L based on the PK-PD breakpoint.

\(^{d}\)Cefepime-tazobactam MICs were interpreted using a provisional breakpoint of ≤16 mg/L based on the PK-PD breakpoint.

\(^{e}\)Polymyxin B MICs were interpreted using the EUCAST breakpoint of colistin (≤2 mg/L, susceptible; >2 mg/L, resistant).
| Antibacterial agent                     | A. baumannii (n = 630) | CRAB (n = 471) |
|---------------------------------------|------------------------|----------------|
|                                       | MIC range (mg/L)       | MIC$_{50}$ (mg/L) | % R | % S | MIC range (mg/L) | MIC$_{50}$ (mg/L) | % R | % S |
| Cefepime-zidebactam                   | ≤0.03 to >64           | 16              | 32  | NA  | 16              | 64              | NA  | 97.3 |
| Cefepime-tazobactam                   | ≤0.03 to >64           | 64              | >64 | NA  | 64              | >64             | NA  | 30.6 |
| Tigecycline                           | ≤0.06 to >32           | 1               | 4   | 4   | 1               | 4               | 1   | 89.5 |
| Polymyxin B                          | ≤0.125 to >16          | 0.5             | 1   | 3.2 | 0.5             | 0.5             | 3.4 | 96.6 |
| Imipenem                              | ≤0.06 to >128          | 64              | 128 | 74.4 | 64             | 128           | 99.6 | 0.2 |
| Meropenem                             | ≤0.03 to >64           | 64              | >64 | 74.3 | 64             | >64             | 99.4 | 0.6 |
| Cefepime                              | ≤0.06 to >128          | 64              | >128 | 74  | 128           | >128           | 99.4 | 0.6 |
| Ceftazidime                           | ≤0.25 to >32           | >32             | >32 | 74.4 | >32          | >32             | 99.4 | 0.6 |
| Ceftriaxone                           | ≤0.5 to >32            | >32             | >32 | 75.4 | >32          | >32             | 99.4 | 0.6 |
| Piperacillin-tazobactam               | ≤2 to >256             | 256             | >256 | 74.1 | >256        | >256           | 99.4 | 0.6 |
| Cefoperazone-sulbactam                | ≤1 to >128             | 64              | >128 | 67.6 | 128          | >128           | 89.2 | 4 |
| Amikacin                              | ≤1 to >128             | 64              | >128 | 61.7 | 128          | >128           | 81.3 | 18.7 |
| Ciprofloxacin                         | ≤0.06 to >8            | >8              | >8   | 74.4 | >8           | >8             | 96.2 | 3.2 |
| Levofloxacin                          | ≤0.125 to >16          | 8               | >16  | 63.8 | 16           | >16            | 82.6 | 4.2 |
| Trimethoprim-sulfamethoxazole         | ≤0.25 to >32           | 32              | >32  | 60.8 | >32          | >32            | 76.9 | 23.1 |

*CRAB, carbapenem-resistant A. baumannii; DTR, difficult-to-treat resistant.

*NA, not available.

*Cefepime-zidebactam MICs were interpreted using a provisional breakpoint of ≤64 mg/L based on the PK-PD breakpoint.

*Cefepime-tazobactam MICs were interpreted using a provisional breakpoint of ≤16 mg/L based on the PK-PD breakpoint of P. aeruginosa.

*Polymyxin B MICs were interpreted using the EUCAST breakpoint of colistin (≤2 mg/L, susceptible; ≥2 mg/L, resistant).
breakpoint (≤8 mg/L), with 24 E. coli, 4 K. pneumoniae, 7 Proteus rettgeri, 3 P. mirabilis, 1 E. cloacae, and 1 Serratia marcescens isolates showing MICs of ≥16 mg/L among the various genera of Enterobacterales. Besides cefepime-zidebactam, ceftazidime-avibactam was also active against all Enterobacterales clinical isolates with an MIC\(_{50/90}\) of 0.25/4 mg/L. Among 171 ceftazidime-avibactam-resistant isolates, cefepime-zidebactam showed an MIC of 8 mg/L or lower against 84.1% of the tested isolates (data not shown). Apart from cefepime-zidebactam and ceftazidime-avibactam, tigecycline (96.5% susceptible) and amikacin (90.4% susceptible) also displayed potent activity against Enterobacterales. The rate of susceptibility to cefepime-tazobactam was 85.8%, similar to those for polymyxin B (81.4% susceptible) and meropenem (85.6% susceptible), which showed good activity against the tested isolates. More than 60% of the Enterobacterales isolates were susceptible to ceftolozane-tazobactam (74.2% susceptible), imipenem (74.6% susceptible), piperacillin-tazobactam (75.5% susceptible), cefoperazone-sulbactam (69.8% susceptible), and ceftazidime (60.5% susceptible). The following other comparator agents showed limited activity: cefepime (55.3% susceptible), ceftriaxone (46.1% susceptible), aztreonam (54.7% susceptible), ciprofloxacin (42.1% susceptible), levofl oxacin (48.1% susceptible), and trimethoprim-sulfamethoxazole (53.7% susceptible) (Table 1).

A total of 756 clinical isolates of P. aeruginosa were highly inhibited by cefepime-zidebactam with an MIC\(_{50/90}\) of 2/8 mg/L at a PK-PD breakpoint of ≤32 mg/L (98.9% susceptible). The rate of susceptibility of P. aeruginosa to cefepime-zidebactam was similar to or slightly higher than those for ceftazidime-avibactam (87.7% susceptible), ceftolozane-tazobactam (90.2% susceptible), polymyxin B (95.6% susceptible), and amikacin (95.4% susceptible) (Table 2). The rates of susceptibility to many commonly used broad-spectrum β-lactams, i.e., cefepime-tazobactam, cefepime, ceftazidime, and meropenem, of P. aeruginosa ranged from 70% to 80%, and those for other comparator agents, i.e., imipenem, old BLBLIs, aztreonam, and fluoroquinolones, ranged from 50% to 70%.

The MIC\(_{50/90}\) value of cefepime-zidebactam against 630 A. baumannii isolates was 16/32 mg/L (Table 3). Among the tested isolates, 97.3% were susceptible to cefepime-zidebactam based on ≤64 mg/L. Polymyxin B and tigecycline were the available agents showing excellent activity against A. baumannii isolates, with susceptibilities of 89.5% and 96.8%, respectively. The rates of susceptibility to amikacin and trimethoprim-sulfamethoxazole were around 40%. These isolates were highly resistant to other β-lactams, with or without BLBLIs, as well as the fluoroquinolones tested, with susceptibility rates of less than 30%.

Susceptibility of carbapenem-resistant organisms. Overall, the CRE isolates were inhibited by cefepime-zidebactam with an MIC\(_{50/90}\) of 1/4 mg/L at ≤8 mg/L. Cefepime-zidebactam retained good activity with an MIC\(_{90}\) in the range of 0.125 to 16 mg/L against bla\(_{KPC}\)-positive (n = 243), bla\(_{VIM}\)-positive (n = 117), bla\(_{NDM}\)-positive (n = 8), bla\(_{OXA-232}\)-positive (n = 7), bla\(_{IMI}\)-positive (n = 1), as well as carbapenemase-negative (n = 3) isolates (Table 4). The MIC\(_{90}\) value of ceftazidime-avibactam was lower than the susceptibility breakpoint, with 97.5% and 100% susceptible bla\(_{KPC}\)-positive and bla\(_{OXA-232}\)-positive isolates, respectively. Tigecycline and polymyxin B showed good in vitro activity against CRE, with susceptibilities of 95.5% and 90.5%, respectively. The rates of susceptibility to amikacin and trimethoprim-sulfamethoxazole were around 40%. These isolates were highly resistant to other β-lactams, with or without BLBLIs, as well as the fluoroquinolones tested, with susceptibility rates of less than 30%.

Moreover, the rate of susceptibility to cefepime-zidebactam of CRPA was higher than those for amikacin (98.2% versus 89%) and polymyxin B (98.2% versus 96.9%), whereas the rates of susceptibility were 76.3% for ceftolozane-tazobactam and 68% for ceftazidime-avibactam as the most active comparators. Except for imipenem and meropenem, CRPA isolates were moderately resistant to other β-lactams, aztreonam, and fluoroquinolones, with susceptibility rates of 30% to 50%.

For CRAB, cefepime-zidebactam, tigecycline, and polymyxin B showed high susceptibility rates of 96.6%, 88.5%, and 96.6%, respectively, and amikacin and trimethoprim-sulfamethoxazole showed limited activity, with susceptibility rates of 18.7% and 23.1%, respectively. The MICs of other agents were higher, with MIC\(_{90}\) values of >32 mg/L.
### TABLE 4 In vitro activities of cefepime-zidebactam and comparator agents against isolates of carbapenem-resistant *Enterobacterales* carrying carbapenemase genes

| Group (no. of isolates) | Cefepime-zidebactam<sup>a</sup> | Ceftazidime-avibactam  | Cefepime-tazobactam<sup>b</sup> | Ceftolozane-tazobactam | Tigecycline | Polymyxin B<sup>c</sup> |
|------------------------|---------------------------------|------------------------|---------------------------------|-----------------------|------------|------------------------|
|                        | MIC<sub>50</sub> (mg/L) | MIC<sub>90</sub> (mg/L) | % S                | MIC<sub>50</sub> (mg/L) | MIC<sub>90</sub> (mg/L) | % S     | MIC<sub>50</sub> (mg/L) | MIC<sub>90</sub> (mg/L) | % S     | MIC<sub>50</sub> (mg/L) | MIC<sub>90</sub> (mg/L) | % S     |
| MBL<sup>d</sup> positive |                     |                        |                   |                      |            |                        |                      |            |                   |                      |            |
| NDM (117)              | 0.25                | 16                     | 89.7               | >64                   | >64         | 0.9    | >64                   | >64         | 6.8    | >128               | >128         | 1.7    |
| IMP (8)                | 0.125               | 0.5                    | 100                | >64                   | >64         | 12.5   | 16                   | >64         | 50     | >128               | >128         | 12.5   |
| VIM (1)                | 0.125               | 0.125                  | 100                | 32                    | 32          | 0      | 4                    | 4           | 100    | >128               | >128         | 0      |
| MBL negative, serine carbapenemase positive |                     |                        |                   |                      |            |                        |                      |            |                   |                      |            |
| KPC (243)              | 1                   | 2                      | 98.8               | 2                     | 4           | 97.5   | 64                   | >64         | 10.7   | 128                | >128         | 0      |
| OXA-232 (7)            | 1                   | 2                      | 100                | 1                     | 2           | 100    | 64                   | >64         | 100    | 128                | >128         | 0      |
| MBL negative, serine carbapenemase negative (3) |                     |                        |                   |                      |            |                        |                      |            |                   |                      |            |
|                        | 4                   | 8                      | 100                | 32                    | >64     | 33.3   | 64                   | >64         | 100    | >128               | >128         | 33.3   |

<sup>a</sup>Cefepime-zidebactam MICs were interpreted using a provisional breakpoint of ≤8 mg/L based on the PK-PD breakpoint.

<sup>b</sup>Cefepime-tazobactam MICs were interpreted using a provisional breakpoint of ≤16 mg/L based on the PK-PD breakpoint.

<sup>c</sup>Polymyxin B MICs were interpreted using the EUCAST breakpoint of colistin (≤2 mg/L, susceptible; ≥2 mg/L, resistant).

<sup>d</sup>MBL, metallo-β-lactamase.
**Susceptibility of DTR isolates.** Cefepime-zidebactam inhibited 97.2% of DTR *Enterobacterales* isolates with an MIC50/90 of 1/4 mg/L at ≤8 mg/L, and 74.7% of DTR *Enterobacterales* isolates were susceptible to ceftazidime-avibactam with an MIC50/90 of 2/>64 mg/L. Only tigecycline (95.9% susceptible) and polymyxin B (92.4% susceptible) displayed greater *in vitro* activity than cefepime-zidebactam and ceftazidime-avibactam against all DTR *Enterobacterales* isolates (Table 1).

A total of 96.9% of DTR *P. aeruginosa* isolates were susceptible to cefepime-zidebactam with an MIC50/90 of 8/16 mg/L at ≤32 mg/L. The rates of susceptibility to amikacin, cefotolozane-tazobactam, and ceftazidime-avibactam of DTR *P. aeruginosa* isolates were 70.8%, 49.2%, and 33.8%, respectively. Only polymyxin B (98.5% susceptible) demonstrated greater *in vitro* activity than the above-described agents against DTR *P. aeruginosa* isolates (Table 2).

**Detection of carbapenemase genes.** In this study, 99.2% (376/379) of the CRE isolates had a single carbapenemase gene, and only 3 isolates were negative for all five common carbapenemase genes (Table 4). Among these carbapenemase genes, 64.1% (243/379) of isolates were *bla*KPC-2 positive, 18.5% (70/379) were *bla*NDM-5 positive, 12.4% (47/379) were *bla*NDM-1 positive, 2.1% (8/379) were *bla*ARM positive, 1.8% (7/379) were *bla*OXA-32 positive, and 0.3% (1/379) were *bla*VIM positive, respectively. Additionally, *bla*KPC-2 was mainly detected in *K. pneumoniae* (80.1%; 225/281), *S. marcescens* (90.9%; 10/11), *Citrobacter freundii* (44.4%; 4/9), and *Morganella morganii* (100%; 1/1). The highest prevalences of *bla*NDM-5 were 82.5% (33/40) in *E. coli* and 55.6% (5/9) in *Klebsiella aerogenes* isolates. *bla*NDM-1 was the predominant type of carbapenemase gene among *E. cloacae* (70.6%; 12/17) and *P. rettgeri* (100%; 9/9) isolates.

**DISCUSSION.** Of particular concern is the spread of antimicrobial-resistant Gram-negative bacillus isolates, especially CRE, *P. aeruginosa*, and *A. baumannii*, which has substantially increased morbidity and mortality rates and caused nosocomial outbreaks (10, 11). The emergence of antimicrobial resistance continues to outpace the development of new agents (12). Novel BLBLIs such as ceftazidime-avibactam and cefotolozane-tazobactam significantly reduce the disease burden for patients and improve serious adverse outcomes against Gram-negative bacilli as effective treatment options. Surveillance of resistance to these novel BLBLIs has been continuously performed in the Chinese mainland since 2017, although they were not approved by the National Medical Products Administration.

In this study, 98.5% of *Enterobacterales* and 98.9% of *P. aeruginosa* isolates were inhibited by cefepime-zidebactam based on PK-PD breakpoints of ≤8 mg/L and ≤32 mg/L (13), respectively. In a lab of International Health Management Associates (IHMA) study (12), the authors observed that cefepime-zidebactam inhibited 98.5% of *Enterobacterales* and 59.6% of *P. aeruginosa* isolates. There are currently no Clinical and Laboratory Standards Institute (CLSI), European Committee on Antimicrobial Susceptibility Testing (EUCAST), or U.S. Food and Drug Administration (FDA) clinical breakpoints of cefepime-zidebactam, so according to its PK-PD breakpoint (≤32 mg/L), *P. aeruginosa* had a rate of susceptibility to cefepime-zidebactam of 99.6%, whereas it was 98.9% in our study. The potent activity of cefepime-zidebactam against CRE, *P. aeruginosa*, and *A. baumannii* isolates harboring carbapenemase genes has been previously reported. In another study of a worldwide surveillance program, Sader et al. (14) reported that 99.3% of CRE isolates (n = 153) had cefepime-zidebactam MICs of ≤8 mg/L, similar to the results of this study (98.5%).

The DTR phenotype, a novel category in the study of Gram-negative bacteremia, focuses on treatment-limiting resistance to all first-line agents. The DTR phenotype was defined as an isolate that tests not susceptible (intermediate or resistant) to all β-lactam categories, including carbapenems and fluoroquinolones, and it was demonstrated that isolates that were not susceptible to first-line agents were associated with increased patient mortality and clinical failure. Karlowsky et al. (12) studied 13,248
Gram-negative clinical isolates at 26 U.S. hospitals from 2015 to 2017 for the SMART global surveillance program and found that overall, 1% of infections exhibited DTR. Specific DTR rates observed in that study were 0.3% for *E. coli*, 0.6% to 1.0% for *Enterobacter* spp., 0.6% to 3.0% for *Klebsiella* spp., and 8.4% for *P. aeruginosa* (data not shown). In our study, we observed slightly higher DTR rates of 1.2% for *E. coli*, 0.04% to 0.5% for *Enterobacter* spp., 9.3% for *Klebsiella* spp., and 8.6% for *P. aeruginosa*. The differences in DTR rates between the 2 studies may reflect the characteristics of the strains among different regions and different specimen sources. Kadri et al. reported mortality was significantly higher for DTR than for carbapenem-resistant, extended-spectrum-cephalosporin-resistant, or fluoroquinolone-resistant infections (15). The *in vitro* effect was also observed in our CRE as well as *P. aeruginosa* isolates. But cefepime-zidebactam still showed good activity against these carbapenem-resistant organisms (CROs) (96% to 98.2%) and DTR isolates (96.9% to 97.2%).

In this study, more than 89.5% of the CRE and CRAB isolates tested were susceptible to tigecycline and polymyxin B. Additionally, 96.9% of CRPA isolates were susceptible to polymyxin B. Ceftazidime-avibactam has been used for the treatment of infections caused by *P. aeruginosa* (98.9% and 87.7%, respectively) and **NDM-positive isolates were resistant to ceftazidime-avibactam.** The major resistance mechanisms that confer reduced susceptibility to ceftazidime-avibactam are as follows: the production of metallo-β-lactamases (MBLs) such as NDM, VIM, or IMP; *bla*<sub>TEM</sub> variants; and the transposition of KPC with porin deficiency (3, 16). During the clinical use of ceftazidime-avibactam, several researchers have observed a change from the KPC-2 to the KPC-33 carbapenemase of CRE isolates but lower MICs of carbapenems (often restoring susceptibility to imipenem and low-level resistance to meropenem) because the KPC variants exhibiting single-amino-acid substitutions in their Ω-loop (positions 164 to 179, particularly the Asp179Tyr substitution) and two additional regions (one close to the hinge loop at positions 240 to 243 and one covering positions 263 to 277) lead to an enhanced affinity for ceftazidime and reduced binding to avibactam (16–19). Similar to avibactam, zidebactam lacks direct β-lactamase-inhibitory activity against MBLs. But cefepime-zidebactam exhibited potent activity against MBL-producing isolates, contingent on zidebactam’s unique penicillin binding protein 2 (PBP2) binding activity (20). Due to high-affinity Gram-negative bacterial PBP2 binding, zidebactam demonstrates antibacterial activity against various *Enterobacteriaceae* and *P. aeruginosa* isolates (14).

There were limitations to our study. First, some new agents that also show potent activity, such as meropenem-vaborbactam, imipenem-relebactam, and cefiderocol, have not been evaluated at this time due to difficulties in the ordering process. Second, a homology analysis of resistant isolates, especially CRO isolates, has not been carried out to clarify the characteristics of their spread in China.

**Conclusion.** We studied a recent nationwide collection of Gram-negative bacilli and observed that new BLBLIs, especially cefepime-zidebactam and ceftazidime-avibactam, demonstrated potent *in vitro* activity against *Enterobacteriales* (susceptibility rates of 98.5% and 93.6%, respectively) and *P. aeruginosa* (98.9% and 87.7%, respectively) isolates producing important β-lactamases, including MBLs (except for ceftazidime-avibactam), KPCs, and OXA-232, for which treatment agents are limited. The results from this study support the use of cefepime-zidebactam and ceftazidime-avibactam as potential therapies for infections caused by CRE, CRPA, and DTR isolates.

**MATERIALS AND METHODS**

**Compliance with ethical standards.** The study protocol was approved by the Institutional Review Board of Huashan Hospital, Fudan University (no. 2019-460).

**Clinical isolates.** The China Antimicrobial Surveillance Network (CHINET) is a multicenter bacterial resistance surveillance program in operation since 2005 in China. In 2019, 46 hospitals in 28 provinces or cities collected up to 4,042 nonduplicate, clinically significant Gram-negative isolates from CHINET, including *Klebsiella pneumoniae* (*n* = 979), *Escherichia coli* (*n* = 900), *P. aeruginosa* (*n* = 756), *A. baumannii* (*n* = 630), *Enterobacter cloacae* (*n* = 172), *Proteus mirabilis* (*n* = 119), *Serratia marcescens* (*n* = 118), *K. pneumoniae* (*n* = 126), and *Acinetobacter* spp. (data not shown). The China Antimicrobial Surveillance Network (CHINET) is a multicenter bacterial resistance surveillance program in operation since 2005 in China. In 2019, 46 hospitals in 28 provinces or cities collected up to 4,042 nonduplicate, clinically significant Gram-negative isolates from CHINET, including *Klebsiella pneumoniae* (*n* = 979), *Escherichia coli* (*n* = 900), *P. aeruginosa* (*n* = 756), *A. baumannii* (*n* = 630), *Enterobacter cloacae* (*n* = 172), *Proteus mirabilis* (*n* = 119), *Serratia marcescens* (*n* = 118), *K. pneumoniae* (*n* = 126), and *Acinetobacter* spp. (data not shown).
aerogenes (n = 103), Morganella morganii (n = 89), Citrobacter freundii (n = 84), Proteus vulgaris (n = 51), Proteus rettgeri (n = 29), and Klebsiella oxytoca (n = 12). Among the tested clinical isolates, 23.6% of the isolates were isolated from patients in the intensive care unit, followed by outpatient and emergency departments (18.5%), urology surgery (6.7%), respiratory medicine (5.6%), neurosurgery departments (4.2%), and other departments. A total of 33.9% of the tested isolates were isolated from sputum, followed by urine (22.5%), blood (12.1%), secreta (7.7%), bronchoalveolar lavage fluid (3.9%), pus (2.8%), wound (2.7%), abdominal fluid (2.0%), bile (1.7%), shunt fluid (1.3%), drain (1.2%), and other sources (8.2%). Species identification was performed at each participating site and confirmed by the central laboratory using matrix-assisted laser desorption ionization–time of flight mass spectrometry (Vitek MS; bioMérieux, France). Quality control was performed according to Clinical and Laboratory Standards Institute (CLSI) guidelines using E. coli ATCC 25922 and ATCC 35218, K. pneumoniae ATCC 700603, and P. aeruginosa ATCC 27853 for antimicrobial susceptibility testing.

Antimicrobial susceptibility testing. MICs were determined by the reference broth microdilution method recommended by the CLSI. Cefepime-zydabactam, ceftazidime-avibactam, cefepime-tazobactam, ceftolozane-tazobactam, and other comparators were tested using a dried customized commercial microdilution panel (Sensititre; Thermo Fisher Scientific) in the study. Quality control and test results were interpreted according to 2021 CLSI breakpoints (21) for all agents tested except for cefepime-zydabactam, tigecycline, and polymyxin B, for which CLSI criteria were not available. Tigecycline MICs were interpreted using the U.S. Food and Drug Administration (FDA) MIC breakpoints for Enterobacteriales (22). Cefepime-zydabactam MICs were interpreted using provisional breakpoints based on anticipated clinical data (13, 23) (≤8 mg/L for Enterobacteriales, ≤32 mg/L for P. aeruginosa, and ≤0.04 mg/L for A. baumannii). Cefepime-tazobactam MICs were interpreted using provisional breakpoints of ≤16 mg/L for Enterobacteriales and P. aeruginosa based on PK-PD studies (24). Polymyxin B was explained by European Committee on Antimicrobial Susceptibility Testing (EUCAST) MIC interpretative breakpoints of colistin (25).

In this study, isolates with meropenem or imipenem resistance phenotypes were considered carbapenem-resistant organisms (CROs). Difficult-to-treat resistance phenotypes were defined by testing resistance to all tested β-lactams (including carbapenems and β-lactamase inhibitor combinations) and fluoroquinolones (15).

Detection of carbapenemase genes. Carbapenem-resistant Enterobacteriales (CRE) isolates were selected for analysis of carbapenemase. The five most common carbapenemase genes (blaTEM, blaPER, blaOXA, blaKPC, and blaVIM) were confirmed for all of the CRE isolates by PCR with specific primers and DNA sequencing, as described previously (26).

ACKNOWLEDGMENTS

We gratefully acknowledge the contribution of the members of CHINET for collection of the isolates in this study, including Yingchun Xu and Xiaojia 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; Chuangqing Wang and Leiyian He from Children’s Hospital of Fudan University; Yuhanhong 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 and Technology; Yuxing Ni and Jingyong Sun from Ruijin Hospital, Shanghai Jiaotong University School of Medicine; Yinhuo 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 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 Zuo 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; 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; JiJong Li from the Second Hospital of Hebei Medical University; Jiangshan Liu from JinJiang Hospital of integrated traditional Chinese and Western Medicine; Longfeng Liao from the People’s Hospital of Ganzian; Hongquin 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 Linxi County People’s Hospital; Chunlei Yue from Jiutai People’s Hospital; Ruyi Guo and Yan Jin from Quanzhou First Hospital, Fujian; Xiaobo Ma and Yanping Zheng from The First Affiliated Hospital of Xiamen University; Fangfang Hu from GuiZhou Provincial People’s Hospital; and Yunsheng Chen and Qing Meng from Shenzhen Children’s Hospital.

We declare that we have no conflict of interest.

This publication was supported by the National Natural Science Foundation of China (81871690, 81272311, 81902100, and 32141002), the Three-Year Action Plan for the Construction of Shanghai Public Health System (GWV-10.2-XD02), and the China Antimicrobial Surveillance Network (independent medical grants from Pfizer [2020QD049]). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

REFERENCES

1. Poirel L, Madec J-Y, Lupo A, Schink A-K, Kieffer N, Nordmann P, Schwarz S. 2018. Antimicrobial resistance in Escherichia coli. Microbiol Spectr 6:ARBA-0026-2017. https://doi.org/10.1128/microbiolspec.ARBA-0026-2017.

2. Holmén CL, Andersson DI, Moberly HLT, Boehman MA. 2021. Pathogenesis of Gram-negative bacteremia. Clin Microbiol Rev 34:e00234-20. https://doi.org/10.1128/CMR.00234-20.

3. Yahav D, Giske CG, Gramatziene A, Abodakpi H, Tam VH, Leiboivici L. 2021. New β-lactam–β-lactamase inhibitor combinations. Clin Microbiol Rev 34:e00115-20. https://doi.org/10.1128/CMR.00115-20.

4. Bush K, Bradford PA. 2020. Epidemiology of β-lactamase-producing pathogens. Clin Microbiol Rev 33:e00047-19. https://doi.org/10.1128/CMR.00047-19.

5. He T, Wang R, Liu D, Walsh TR, Zhang R, Lv Y, Ke Y, Ji Q, Wei R, Liu Z, Shen Y, Wang G, Sun L, Lei L, Lv Z, Li Y, Fang M, Wang L, Sun Q, Fu Y, Song H, Hao Y, Shen Z, Wang S, Chen G, Wu C, Shen J, Wang Y. 2019. Emergence of plasmid-mediated high-level tigecycline resistance genes in animals and humans. Nat Microbiol 4:1450–1456. https://doi.org/10.1038/s41564-019-0445-2.

6. Nang SC, Azad MAK, Velkov T, Zhou QT, Li JI. 2021. Rescuing the last-line polymyxins: achievements and challenges. Pharmacol Rev 73:679–728. https://doi.org/10.1124/pbr.120.000209.

7. Rodriguez-Bano J, Gutierrez-Gutierrez B, Machuca I, Pascual A. 2018. Treatment of infections caused by extended-spectrum–β-lactamase-, AmpC-, and carbapenemase-producing Enterobacteriaceae. Clin Microbiol Rev 31:e00079-17. https://doi.org/10.1128/CMR.00079-17.

8. Yin D, Wu S, Yang Y, Shi Q, Dong D, Zhu D, Hu F, China Antimicrobial Surveillance Network (CHINET) Study Group. 2019. Results from the China Antimicrobial Surveillance Network (CHINET) in 2017 of the in vitro activities of ceftazidime-avibactam and cefotolozane-tazobactam against clinical isolates of Enterobacteriaceae and Pseudomonas aeruginosa. Antimicrob Agents Chemother 63:e02431-18. https://doi.org/10.1128/AAC.02431-18.

9. Yang Y, Guo Y, Yin D, Zheng Y, Wu S, Zhu D, Hu F. 2021. In vitro activity of cefepime-zidebactam, ceftazidime-avibactam, and other comparators against clinical isolates of Enterobacteriales, 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.

10. Bonomo RA, Burd EM, Conly J, Limbagho BM, Poirel L, Segre JA, Westblade LF. 2018. Carbapenemase-producing organisms: a global scourge. Clin Infect Dis 66:1290–1297. https://doi.org/10.1093/cid/cix983.

11. Tacconelli E, Carrara E, Savoldi A, Barhabat S, Mendelson M, Monnet DL, Pulcini C, Kahlmeter G, Klymians J, Carmeli Y, Oueltette M, Outterson K, Patel J, Cavaleri M, Cox EM, Houchens CR, Grayson ML, Hansen P, Singh N, Theuretzbacher U, Magnirni N, WHO Pathogens Priority List Working Group. 2018. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis 18:318–327. https://doi.org/10.1016/S1473-3099(17)30753-3.

12. Karlovsky JA, Lob SH, Raddatz J, DePestel DD, Young K, Motyl MR, Sahm DF. 2021. In vitro activity of imipenem/relebactam and ceftolozane/tazobactam against clinical isolates of Gram-negative bacilli with difficult-to-treat resistance and multidrug-resistant phenotypes—study for monitoring antimicrobial resistance trends, United States 2015–2017. Clin Infect Dis 72:2112–2120. https://doi.org/10.1093/cid/ciaa381.

13. Karlovsky JA, Hackel MA, Bouchillon SK, Sahm DF. 2020. In vitro activity of WCK 5222 (cefezipem-zidebactam) against worldwide collected Gram-negative bacilli not susceptible to carbapenems. Antimicrob Agents Chemother 64:e01432-20. https://doi.org/10.1128/AAC.01432-20.

14. Sader HS, Castanheira M, Huband M, Jones RN, Flamm RK. 2017. WCK 5222 (cefezipem-zidebactam) antimicrobial activity against clinical isolates of Gram-negative bacteria collected worldwide in 2015. Antimicrob Agents Chemother 61:e0072-17. https://doi.org/10.1128/AAC.0072-17.

15. Karle S, Adjayem J, Lai YL, Spaulding AB, Ricotta E, Prevorts DR, Palmore TN, Rhee C, Klompas M, Dekker JP, Powers JH, III, Suffredini AF, Hooper DC, Friddkin S, Danner RL, National Institutes of Health Antimicrobial Resistance Outcomes Research Initiative (NIH-ARORI). 2018. Difficult-to-treat resistance in Gram-negative bacteremia at 173 US hospitals: retrospective cohort analysis of prevalence, predictors, and outcome of resistance to all first-line agents. Clin Infect Dis 67:1803–1814. https://doi.org/10.1093/cid/ciy378.

16. Shi Y, Yin D, Han R, Guo Y, Zheng Y, Wu S, Yang Y, Li S, Zhong R, Hu F. 2020. Emergence and recovery of ceftazidime-avibactam resistance in blaKPC-33-harboring Klebsiella pneumoniae sequence type 11 isolates in China. Clin Infect Dis 71:5436–5439. https://doi.org/10.1093/cid/ciaa1521.

17. Sader HS, Castanheira M, Duncan LR, Mendes RÉ. 2021. Antimicrobial activities of ceftazidime/avibactam, cefotolozane/tazobactam, imipenem/relebactam, meropenem/vaborbactam, and comparators against Pseudomonas aeruginosa from patients with skin and soft tissue infections. Int J Infect Dis 113:279–281. https://doi.org/10.1016/j.ijid.2021.10.022.

18. Li X, Quan J, Ke H, Wu W, Feng Y, Yu Y, Jiang Y. 2019. Emergence of a KPC variant conferring resistance to ceftazidime-avibactam in a widespread ST11 carbapenem-resistant Klebsiella pneumoniae clone in China. Front Microbiol 12:24272. https://doi.org/10.3389/fmicb.2021.724272.

19. Venditti C, Butera O, Meledandri M, Balice MP, Coccilli GC, Fontana C, D’Arezzo S, De Giuli C, Antonini M, Capone A, Messina F, Nisi C, Di Caro A. 2020. Molecular analysis of clinical isolates of ceftazidime-avibactam-resistant Klebsiella pneumoniae. Clin Microbiol Infect 27:1040.e1–1040.e6. https://doi.org/10.1016/j.cmi.2021.03.001.
20. Bhagwat SS, Hariharan P, Joshi PR, Palwe SR, Shrivastava R, Patel MV, Devanga Ragupathi NK, Bakthavatchalam YD, Ramesh MS, Somn R, Veeraraghavan B. 2020. Activity of cefepime/zidebactam against MDR Escherichia coli isolates harbouring a novel mechanism of resistance based on four-amino-acid inserts in PBP3. J Antimicrob Chemother 75: 3563–3567. https://doi.org/10.1093/jac/dkaa353.

21. Clinical and Laboratory Standards Institute. 2021. Performance standards for antimicrobial susceptibility testing, M100, 31st ed. Clinical and Laboratory Standards Institute, Wayne, PA.

22. US Food and Drug Administration. 2019. Tigecycline—Injection products. US Food and Drug Administration, Silver Spring, MD. https://www.fda.gov/drugs/development-resources/tigecycline-injection-products.

23. Bhagwat SS, Legakis NJ, Skalidis T, Loannidis A, Goumenopoulos C, Joshi PR, Shrivastava R, Palwe SR, Periasamy H, Patel MV, Chatzipanagiotou S, Hellenic Cefepime/Zidebactam Study Group. 2021. In vitro activity of cefepime/zidebactam (WCK 5222) against recent Gram-negative isolates collected from high resistance settings of Greek hospitals. Diagn Microbiol Infect Dis 100:115327. https://doi.org/10.1016/j.diagmicrobio.2021.115327.

24. Lasko MJ, Abdelraouf K, Nicolau DP. 2021. In vivo activity of WCK 4282 (high-dose cefepime/tazobactam) against serine-β-lactamase-producing Enterobacterales and Pseudomonas aeruginosa in the neutropenic murine lung infection model. Antimicrob Agents Chemother 65:e02193-20. https://doi.org/10.1128/AAC.02193-20.

25. European Committee on Antimicrobial Susceptibility Testing. 2021. Breakpoint tables for interpretation of MICs and zone diameters, Version 11.0. https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_11.0_Breakpoint_Tables.pdf.

26. Poirel L, Walsh TR, Cuvillier V, Nordmann P. 2011. Multiplex PCR for detection of acquired carbapenemase genes. Diagn Microbiol Infect Dis 70: 119–123. https://doi.org/10.1016/j.diagmicrobio.2010.12.002.