Antimicrobial Activities of Ceftazidime-Avibactam and Comparator Agents against Clinical Bacteria Isolated from Patients with Cancer

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ABSTRACT A total of 521 unique clinical isolates from cancer patients with primarily (>90%) bloodstream infections were tested for susceptibility to ceftazidime-avibactam and comparators using broth microdilution methods. Ceftazidime-avibactam inhibited 97.8% of all *Enterobacteriaceae* ($n = 321$) at the susceptibility breakpoint of $\leq 8/4$ $\mu\text{g/ml}$ (there were 7 nonsusceptible strains). It was also active against *Pseudomonas aeruginosa* (91.7% isolates susceptible, $n = 121$), including many isolates not susceptible to meropenem, cefepime, ceftazidime, piperacillin-tazobactam, or other comparators.

KEYWORDS ceftazidime, avibactam, cancer patients, clinical isolates

Gram-negative bacteria (GNB) cause ~25% to 30% of bacterial infections in neutropenic cancer patients and are associated with greater morbidity and mortality than Gram-positive organisms (1). The provision of potent, empirical Gram-negative coverage when a neutropenic patient develops fever has become an established standard of care (2). Several recent reports have documented the increasing frequency of multidrug-resistant GNB in cancer patients (3–7). The susceptibility of the causative pathogen to the initial regimen is an important determinant of clinical outcome. Thus, empirical therapy of febrile neutropenic patients with currently recommended agents (ceftazidime, cefepime, piperacillin-tazobactam, and carbapenems) may no longer be appropriate against many GNB in this setting (4, 8, 9).

Ceftazidime-avibactam is a novel combination of the non- β -lactam β -lactamase inhibitor avibactam and the extended-spectrum ceftazidime (10). Avibactam protects ceftazidime from being hydrolyzed by many enzymes, including Amber class A (extended-spectrum β -lactamase [ESBL] and *Klebsiella pneumoniae* carbapenemase [KPC]), class C (AmpC), and several class D β -lactamases, but not against metallo- β -lactamases, such as New Delhi metallo- β -lactamase (NDM), Verona integron-encoded metallo- β -lactamase (VIM), and imipenemase (IMP) (11). Its combination with ceftazidime restores the activity of avibactam against organisms producing these enzymes. Ceftazidime-avibactam has been approved by the U.S. FDA for treating complicated urinary tract infections and, in combination with metronidazole, for treating complicated intra-abdominal infections (12). It is also being evaluated for the treatment of hospital-acquired pneumonia. It has not been evaluated for the empirical treatment of cancer patients with fever and neutropenia or for any other indications in this setting. With the increasing frequency of resistant GNB in this patient population, we feel that it may have a potentially important therapeutic role. Consequently, we compared the *in vitro* activity of ceftazidime-avibactam with those of several currently used agents against recent clinical isolates recovered from patients treated at our institution, a National Cancer Institute (NC)-designated comprehensive cancer center.

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TABLE 1 Comparative *in vitro* activities of ceftazidime-avibactam and comparator agents against bacterial isolates from cancer patients

Isolate type and antimicrobial agent	MIC ₅₀ (μg ml ⁻¹)	MIC ₉₀ (μg ml ⁻¹)	Range of MICs (μg ml ⁻¹)	S/R ^a (%)
<i>Escherichia coli</i> (ESBL ⁻) (n = 100)				
Meropenem	0.015	0.06	0.008 to 4	95.0/2.0
Ceftazidime	0.25	32	0.06 to >64	87.0/13.0
Trimethoprim-sulfamethoxazole	>32/608	>32/608	0.06/1.2 to >32/608	39.0/61.0
Tigecycline	0.5	1	0.25 to 8	97.0/1.0
Piperacillin-tazobactam	4/4	128/4	1/4 to >256/4	82.0/13.0
Cefepime	0.06	4	0.015 to >64	87.0/9.0
Ceftazidime-avibactam	0.06/4	0.25/4	0.015/4 to 8/4	100.0/0.0
<i>Escherichia coli</i> (ESBL ⁺) (n = 50)				
Meropenem	0.015	1	0.008 to 8	90.0/2.0
Ceftazidime	8	>64	0.12 to >64	22.0/70.0
Trimethoprim-sulfamethoxazole	0.12/2.4	>32/608	0.06/1.2 to >32/608	38.0/62.0
Tigecycline	0.25	1	0.25 to 1	100.0/0.0
Piperacillin-tazobactam	4/4	>256/4	2/4 to >256/4	64.0/18.0
Cefepime	8	>64	0.03 to >64	14.0/74.0
Ceftazidime-avibactam	0.06/4	1/4	0.015/4 to 16/4	98.0/2.0
<i>Klebsiella</i> spp. (ESBL ⁻) (n = 33)				
Meropenem	0.015	0.03	0.015 to 2	97.0/0.0
Ceftazidime	0.12	0.5	0.03 to >64	90.0/9.1
Trimethoprim-sulfamethoxazole	0.25/4.8	>32/608	0.06/1.2 to >32/608	81.8/18.2
Tigecycline	0.5	2	0.5 to 4	97.0/0.0
Piperacillin-tazobactam	4/4	32/4	0.5/4 to 256/4	87.9/9.1
Cefepime	0.03	0.25	0.008 to >64	90.9/6.1
Ceftazidime-avibactam	0.06/4	0.12/4	0.015/4 to 1/4	100.0/0.0
<i>Klebsiella</i> spp. (ESBL ⁺) (n = 34)				
Meropenem	0.03	0.05	0.012 to 2	97.1/0.0
Ceftazidime	>64	>64	0.12 to >64	14.7/79.4
Trimethoprim-sulfamethoxazole	>32/608	>32/608	0.06/1.2 to >32/608	26.5/73.5
Tigecycline	2	8	0.25 to 8	64.7/11.8
Piperacillin-tazobactam	64/4	>256/4	2/4 to >256/4	35.3/44.1
Cefepime	32	>64	0.12 to >64	35.3/61.8
Ceftazidime-avibactam	0.25/4	1/4	0.03/4 to 4/4	100.0/0.0
<i>Klebsiella</i> spp. (CRE) (n = 28)				
Meropenem	>32	>32	4 to >32	0.0/100.0
Ceftazidime	>64	>64	>64	0.0/100.0
Trimethoprim-sulfamethoxazole	>32/608	>32/608	>32/608	0.0/100.0
Tigecycline	4	8	1 to 32	14.3/35.7
Piperacillin-tazobactam	>256/4	>256/4	>256/4	0.0/100.0
Cefepime	>64	>64	>64	0.0/100.0
Ceftazidime-avibactam	1/4	16/4	0.5/4 to >32/4	82.1/17.9
<i>Enterobacter</i> spp. (n = 42)				
Meropenem	0.03	0.06	0.015 to >32	97.6/2.4
Ceftazidime	0.25	64	0.06 to >64	71.4/28.6
Trimethoprim-sulfamethoxazole	0.25/4.8	2/38	0.12/2.4 to >32/608	88.1/11.9
Tigecycline	1	4	0.25 to 8	85.7/7.1
Piperacillin-tazobactam	4/4	128/4	1/4 to >256/4	71.4/16.7
Cefepime	0.06	2	0.015 to >64	95.2/4.8
Ceftazidime-avibactam	0.25/4	0.5/4	0.015/4 to >32/4	97.6/2.4
<i>Citrobacter</i> spp. (n = 4)				
Meropenem	— ^b	—	0.015 to 32	75.0/25.0
Ceftazidime	—	—	0.25 to >64	50.0/50.0
Trimethoprim-sulfamethoxazole	—	—	0.06/1.2 to >32/608	50.0/50.0
Tigecycline	—	—	0.5 to 4	75.0/0.0
Piperacillin-tazobactam	—	—	4/4 to >256/4	50.0/25.0
Cefepime	—	—	0.06 to >64	75.0/25.0
Ceftazidime-avibactam	—	—	0.06/4 to 0.5/4	100.0/0.0
<i>Serratia marcescens</i> (n = 30)				
Meropenem	0.25	0.5	0.025 to 1	100.0/0.0
Ceftazidime	0.5	1	0.12 to 32	93.3/6.7
Trimethoprim-sulfamethoxazole	0.5/9.5	8/152	0.12/2.4 to >32/608	83.3/16.7

(Continued on following page)

TABLE 1 (Continued)

Isolate type and antimicrobial agent	MIC ₅₀ (μg ml ⁻¹)	MIC ₉₀ (μg ml ⁻¹)	Range of MICs (μg ml ⁻¹)	S/R ^a (%)
Tigecycline	2	4	1 to 8	83.3/6.7
Piperacillin-tazobactam	4/4	8/4	1/4 to >256/4	90.0/3.3
Cefepime	0.5	2	0.06 to 8	90.0/0.0
Ceftazidime-avibactam	0.5/4	1/4	0.12/4 to 1/4	100.0/0.0
<i>Pseudomonas aeruginosa</i> (n = 70)				
Meropenem	0.5	2	0.03 to >32	91.4/7.1
Ceftazidime	2	32	0.5 to >64	87.1/11.4
Trimethoprim-sulfamethoxazole	16/304	32/608	2/38 to >32/608	—
Tigecycline	8	16	2 to >32	—
Piperacillin-tazobactam	4/4	64/4	0.25/4 to >256/4	85.7/7.1
Cefepime	2	16	0.25 to 64	88.6/7.1
Ceftazidime-avibactam	2/4	4/4	0.5/4 to >32/4	98.6/1.4
<i>Pseudomonas aeruginosa</i> , multidrug resistant (n = 51)				
Meropenem	8	>32	0.12 to >32	21.6/62.7
Ceftazidime	8	64	1 to >64	62.7/29.4
Trimethoprim-sulfamethoxazole	>32/608	>32/608	2/38 to >32/608	—
Tigecycline	16	>32	4 to >32	—
Piperacillin-tazobactam	64/4	>256/4	4/4 to >256/4	35.3/49.0
Cefepime	16	64	1 to >64	37.3/29.4
Ceftazidime-avibactam	4/4	>32/4	1/4 to >32/4	82.4/17.6
<i>Stenotrophomonas maltophilia</i> (n = 41)				
Meropenem	>32	>32	1 to >32	—
Ceftazidime	64	>64	1 to >64	24.4/68.3
Trimethoprim-sulfamethoxazole	>32/608	>32/608	0.06/1.2 to >32/608	34.1/65.9
Tigecycline	4	8	0.1 to 16	—
Piperacillin-tazobactam	>256/4	>256/4	16/4 to >256/4	—
Cefepime	64	>64	2 to >64	22.0/78.0
Ceftazidime-avibactam	32/4	>32/4	0.5/4 to >32/4	34.1/65.9
<i>Acinetobacter</i> spp. (n = 14)				
Meropenem	0.25	>32	0.015 to >32	64.3/28.6
Ceftazidime	16	>64	0.06 to >64	42.9/50.0
Trimethoprim-sulfamethoxazole	0.5/9.5	>32/608	0.06/1.2 to >32/608	78.6/21.4
Tigecycline	2	8	0.25 to 16	—
Piperacillin-tazobactam	64/4	>256/4	0.125/4 to >256/4	42.9/50.0
Cefepime	8	>64	0.06 to >64	50.0/50.0
Ceftazidime-avibactam	16/4	>32/4	0.12/4 to >32/4	42.9/57.1
Methicillin-susceptible <i>Staphylococcus aureus</i> (n = 24)				
Meropenem	0.06	0.12	0.06 to 0.25	100.0/0.0
Ceftazidime	8	16	8 to 16	100.0/0.0
Trimethoprim-sulfamethoxazole	0.06/1.2	0.06/1.2	0.06/1.2 to 0.25/4.8	100.0/0.0
Tigecycline	0.25	0.25	0.12 to 0.5	100.0/0.0
Piperacillin-tazobactam	1/4	2/4	0.5/4 to 4/4	100.0/0.0
Cefepime	2	4	1/4	100.0/0.0
Ceftazidime-avibactam	8/4	16/4	8/4 to 16/4	100.0/0.0

^aS, susceptible; R, resistant.^b—, not applicable.

A total of 521 unique patient isolates (497 GNB and 24 methicillin-susceptible *Staphylococcus aureus*) recovered between 2010 and 2014 were tested. The majority of isolates (>90%) were from blood cultures, and the remaining isolates (10%) were recovered from respiratory tract infections. Only the first isolate per unique patient was collected to avoid duplication. We performed CLSI-recommended broth microdilution tests (13) using validated MIC panels from Thermo Fisher Scientific, Inc. (Oakwood, OH, USA). Ceftazidime-avibactam breakpoints approved by the U.S. FDA and CLSI ($\leq 8/4$ μg/ml for susceptibility and ≥ 16 μg/ml for resistance) were used for all *Enterobacteriaceae* and for *Pseudomonas aeruginosa* (14). The susceptibility interpretations for comparator agents were those found in the CLSI document M100-S26 (15) or in the

TABLE 2 Resistances to ceftazidime-avibactam and comparator agents among *Enterobacteriaceae* and *Pseudomonas aeruginosa*

Antimicrobial agent	No. (%) of resistant <i>Enterobacteriaceae</i>		No. (%) of resistant <i>P. aeruginosa</i>	
	Non-CRE (<i>n</i> = 288)	CRE (<i>n</i> = 33)	Non-MDR (<i>n</i> = 70)	Non-MDR (<i>n</i> = 51)
Ceftazidime	88 (30.6)	33 (100.0)	8 (11.4)	15 (29.4)
Cefepime	67 (23.3)	33 (100.0)	5 (7.1)	15 (29.4)
Meropenem	0 (0.0)	33 (100.0)	5 (7.1)	32 (62.7)
Piperacillin-tazobactam	44 (15.3)	33 (100.0)	5 (7.1)	25 (49.0)
Tigecycline	10 (3.5)	10 (30.3)	— ^a	—
Trimethoprim-sulfamethoxazole	131 (45.5)	33 (30.3)	—	—
Ceftazidime-avibactam	1 (0.3)	6 (18.2)	1 (1.4)	9 (17.6)

^a—, not applicable.

manufacturer's package insert. *Escherichia coli* ATCC 25922, *P. aeruginosa* ATCC 27853, and *Klebsiella pneumoniae* ATCC 700603 were used as quality control strains to ensure the validity of our results.

Ceftazidime-avibactam inhibited 97.8% of all *Enterobacteriaceae* (*n* = 321), including all ESBL[−] *E. coli* isolates (MIC₉₀, 0.25/4 μg/ml), all *Citrobacter* spp. (*n* = 4), all ESBL[−] *Klebsiella* spp. (*n* = 33; MIC₉₀, 0.12/4 μg/ml), all ESBL⁺ *Klebsiella* spp. (*n* = 34; MIC₉₀, 1.0/4 μg/ml), and all *Serratia marcescens* isolates (*n* = 30; MIC₉₀, 1.0/4 μg/ml) (Table 1). Ceftazidime-avibactam also inhibited 98% of ESBL⁺ *E. coli* isolates (one of 50 isolates was nonsusceptible) with an MIC₉₀ of 1.0/4 μg/ml. Additionally, 82.1% of carbapenem-resistant *Klebsiella* species (CRE; *n* = 28) were susceptible to ceftazidime-avibactam. The 6 nonsusceptible CRE isolates were not tested for the production of metallo-β-lactamases. Ceftazidime-avibactam and meropenem inhibited 97.6% of the *Enterobacter* spp. tested at their respective susceptibility breakpoints. Regarding other agents, 95.2% were susceptible to cefepime, 88.1% to trimethoprim-sulfamethoxazole, 85.7% to tigecycline, and 71.4% each to ceftazidime and piperacillin-tazobactam. Overall, ceftazidime-avibactam had the most potent activity against *Enterobacteriaceae*. Ceftazidime-avibactam also had potent *in vitro* activity against *P. aeruginosa*. It inhibited 98.6% of *P. aeruginosa* isolates that were not considered multidrug resistant (MDR; *n* = 70) at or below the susceptibility breakpoint, with only one of 70 such isolates being nonsusceptible. Regarding comparator agents, 91.4% of *P. aeruginosa* isolates were susceptible to meropenem, 87.1% to ceftazidime alone, 88.6% to cefepime, and 85.7% to piperacillin-tazobactam. Additionally, 42 of 51 (82.4%) MDR *P. aeruginosa* isolates were susceptible to ceftazidime-avibactam. In comparison, only 21.6% of these isolates were susceptible to meropenem, 35.3% were susceptible to piperacillin-tazobactam, and 37.3% were susceptible to cefepime. Most of the agents tested, including ceftazidime-avibactam, had moderate to poor activity against *Stenotrophomonas maltophilia* and *Acinetobacter* species. All 24 methicillin-susceptible *Staphylococcus aureus* (MSSA) isolates were susceptible to each of the agents tested.

The proportion of *Enterobacteriaceae* and *P. aeruginosa* isolates resistant to ceftazidime-avibactam and comparator agents is depicted in Table 2. Overall, ceftazidime-avibactam was associated with the lowest level of resistance. Among non-CRE *Enterobacteriaceae*, only 1 isolate (0.3%) was resistant to ceftazidime-avibactam, and 10 (3.5%) were resistant to tigecycline, 44 (15.3%) to piperacillin-tazobactam, 67 (23.3%) to cefepime, 88 (30.6%) to ceftazidime, and 131 (45.5%) to trimethoprim-sulfamethoxazole. By definition, each of these isolates was susceptible to meropenem. Six CRE isolates (18.2%) were resistant to ceftazidime-avibactam. Among the comparators, resistance rates ranged from 30.3% for tigecycline and trimethoprim-sulfamethoxazole to 100% for meropenem, piperacillin-tazobactam, cefepime, and ceftazidime. Lower levels of resistance were seen among non-MDR *P. aeruginosa* isolates (ranging from 1.4% for ceftazidime-avibactam to 11.4% for ceftazidime) than among MDR[−] *P. aeruginosa* isolates (17.6% for ceftazidime-avibactam, and ranging from 29.4% to 62.7% for com-

TABLE 3 Comparative *in vitro* activities of ceftazidime-avibactam and comparator agents against bacterial isolates from cancer patients

Isolate type and antimicrobial agent	No. of isolates at MIC ($\mu\text{g ml}^{-1}$) of:																
	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	>256
<i>E. coli</i> ESBL ⁻ (n = 100)																	
Meropenem	10	74	5	3	1	0	2	0	3	2	0	0	0	— ^a	—	—	—
Ceftazidime	0	0	0	2	24	47	9	2	2	1	0	0	2	2	9 (>64)	—	—
Trimethoprim-sulfamethoxazole	0	0	0	11	13	8	1	4	2	0	1	0	1	59 (>32/608)	—	—	—
Tigecycline	0	0	0	0	0	20	55	19	3	2	1	0	0	—	—	—	—
Piperacillin-tazobactam	0	0	0	0	0	0	0	8	38	25	6	5	3	2	3	0	10 (>256/4)
Cefepime	0	2	23	40	11	5	5	0	1	3	1	0	0	1	8 (>64)	—	—
Ceftazidime-avibactam	0	11	13	37	27	2	2	2	1	3	2	0	0	—	—	—	—
<i>E. coli</i> ESBL ⁺ (n = 50)																	
Meropenem	2	25	10	5	2	0	0	1	4	0	1	0	0	—	—	—	—
Ceftazidime	—	—	0	0	2	2	1	1	2	3	4	7	5	13	10 (>64)	—	—
Trimethoprim-sulfamethoxazole	—	—	—	7	7	2	1	1	0	1	0	0	0	31 (>32/608)	—	—	—
Tigecycline	—	0	0	0	0	14	29	7	0	0	0	0	0	—	—	—	—
Piperacillin-tazobactam	—	—	—	—	0	0	0	0	10	5	9	8	6	3	1	1	7 (>256/4)
Cefepime	0	0	1	1	0	0	2	0	3	4	2	5	3	9	20 (>64)	—	—
Ceftazidime-avibactam	—	3	5	10	12	13	1	4	1	0	0	1	0	—	—	—	—
<i>Klebsiella</i> spp. ESBL ⁻ (n = 33)																	
Meropenem	0	18	12	1	0	0	1	0	1	0	0	0	0	0	0	0	—
Ceftazidime	0	0	2	5	12	4	7	0	0	0	0	0	0	1	2 (>64)	—	—
Trimethoprim-sulfamethoxazole	0	0	0	2	3	16	4	1	1	0	0	0	1	5 (>32/608)	—	—	—
Tigecycline	0	0	0	0	0	0	17	10	5	1	0	0	0	—	—	—	—
Piperacillin-tazobactam	0	0	0	0	0	0	2	1	12	6	4	4	1	0	2	1	—
Cefepime	1	4	13	7	4	1	0	0	0	1	0	0	0	0	2 (>64)	—	—
Ceftazidime-avibactam	—	2	1	21	6	1	1	1	0	0	0	0	0	—	—	—	—
<i>Klebsiella</i> spp. ESBL ⁺ (n = 34)																	
Meropenem	0	6	16	6	1	1	1	2	1	0	0	0	0	—	—	—	—
Ceftazidime	0	0	0	0	1	0	3	0	0	1	2	2	4	3	18 (>64)	—	—
Trimethoprim-sulfamethoxazole	0	0	0	1	3	1	3	0	1	1	0	0	1	23 (>32/608)	—	—	—
Tigecycline	0	0	0	0	0	1	4	8	9	8	4	0	0	—	—	—	—
Piperacillin-tazobactam	0	0	0	0	0	0	0	0	2	3	4	3	4	3	3	7	5 (>256/4)
Cefepime	0	0	0	0	1	2	1	0	6	1	2	1	4	3	13 (>64)	—	—
Ceftazidime-avibactam	0	0	1	4	8	14	3	3	1	0	0	0	0	—	—	—	—
<i>Klebsiella</i> spp. CRE (n = 28)																	
Meropenem	0	0	0	0	0	0	0	0	0	1	4	2	5	16 (>32)	—	—	—
Ceftazidime	0	0	0	0	0	0	0	0	0	0	0	0	0	0	28 (>64)	—	—
Trimethoprim-sulfamethoxazole	0	0	0	0	0	0	0	0	0	0	0	0	0	28 (>32/608)	—	—	—
Tigecycline	0	0	0	0	0	0	0	1	3	14	9	0	1	—	—	—	—
Piperacillin-tazobactam	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	28 (>256/4)
Cefepime	0	0	0	0	0	0	0	0	0	0	0	0	0	0	28 (>64)	—	—
Ceftazidime-avibactam	0	0	0	0	0	0	7	8	6	2	0	3	0	2 (>32)	—	—	—
<i>Enterobacter</i> spp. (n = 42)																	
Meropenem	0	6	25	7	2	0	1	0	0	0	0	0	0	1 (>32)	—	—	—
Ceftazidime	0	0	0	2	3	17	5	1	1	1	0	1	1	5	5 (>64)	—	—
Trimethoprim-sulfamethoxazole	0	0	0	4	13	7	9	3	1	1	0	0	0	4 (>32/608)	—	—	—
Tigecycline	0	0	0	0	0	2	9	20	5	3	3	0	0	—	—	—	—
Piperacillin-tazobactam	0	0	0	0	0	0	0	4	11	8	4	3	1	4	5	1	1 (>256/4)
Cefepime	0	5	6	14	4	1	3	1	6	0	0	0	0	1	1 (>64)	—	—
Ceftazidime-avibactam	0	1	2	2	11	14	7	3	1	0	0	0	0	1 (>32/4)	—	—	—
<i>Citrobacter</i> spp. (n = 4)																	
Meropenem	0	1	2	0	0	0	0	0	0	0	0	0	1	—	—	—	—
Ceftazidime	0	0	0	0	0	1	0	1	0	0	0	0	0	0	2 (>64)	—	—
Trimethoprim-sulfamethoxazole	0	0	0	1	1	0	0	0	0	0	0	0	0	2 (>32/608)	—	—	—
Tigecycline	0	0	0	0	0	0	1	0	2	1	0	0	0	—	—	—	—
Piperacillin-tazobactam	0	0	0	0	0	0	0	0	0	1	1	0	0	1	—	—	1 (>256/4)
Cefepime	0	0	0	1	0	1	1	0	0	0	0	0	0	0	1 (>64)	—	—
Ceftazidime-avibactam	0	0	0	1	0	2	1	0	0	0	0	0	0	—	—	—	—
<i>Serratia marcescens</i> (n = 30)																	
Meropenem	0	0	9	3	1	5	11	1	0	0	0	0	0	—	—	—	—
Ceftazidime	0	0	0	0	4	7	6	11	0	0	0	1	1	—	—	—	—
Trimethoprim-sulfamethoxazole	0	0	0	0	2	10	9	4	0	1	2	0	0	2 (>32)	—	—	—
Tigecycline	0	0	0	0	0	0	0	2	23	3	2	0	0	—	—	—	—
Piperacillin-tazobactam	0	0	0	0	0	0	0	4	10	7	6	0	1	1	0	0	1 (>256/4)
Cefepime	0	0	0	4	5	3	8	6	1	1	2	0	0	0	—	—	—
Ceftazidime-avibactam	0	0	0	0	4	6	8	12	0	0	0	0	0	—	—	—	—

(Continued on following page)

TABLE 3 (Continued)

Isolate type and antimicrobial agent	No. of isolates at MIC ($\mu\text{g ml}^{-1}$) of:																
	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	>256
<i>Pseudomonas aeruginosa</i> , sensitive (n = 70)																	
Meropenem	0	0	1	4	6	21	16	11	5	1	4	0	0	1 (>32)	—	—	—
Ceftazidime	0	0	0	0	0	0	1	9	32	12	7	1	2	4	2 (>64)	—	—
Trimethoprim-sulfamethoxazole	0	0	0	0	0	0	0	0	2	7	24	14	16	7 (>32/608)	—	—	—
Tigecycline	0	0	0	0	0	0	0	0	1	3	32	28	5	1 (>32)	—	—	—
Piperacillin-tazobactam	0	0	0	0	0	1	0	1	6	27	16	9	2	3	1	0	4 (>265/4)
Cefepime	0	0	0	0	0	1	1	4	32	14	10	3	4	1	—	—	—
Ceftazidime-avibactam	0	0	0	0	0	0	2	15	42	5	5	0	0	1 (>32/4)	—	—	—
<i>Pseudomonas aeruginosa</i> MDR (n = 51)																	
Meropenem	0	0	0	0	1	0	1	3	6	8	12	10	3	7 (>32)	—	—	—
Ceftazidime	0	0	0	0	0	0	0	1	6	16	9	4	2	8	5 (>64)	—	—
Trimethoprim-sulfamethoxazole	0	0	0	0	0	0	0	0	2	1	4	5	10	29 (>32/608)	—	—	—
Tigecycline	0	0	0	0	0	0	0	0	0	1	7	22	15	6 (>32)	—	—	—
Piperacillin-tazobactam	0	0	0	0	0	0	0	0	0	3	3	12	4	4	4	6	15 (>256/4)
Cefepime	0	0	0	0	0	0	0	2	2	3	12	17	9	2	4 (>64)	—	—
Ceftazidime-avibactam	0	0	0	0	0	0	0	4	10	17	11	3	0	6 (>32/4)	—	—	—
<i>Stenotrophomonas maltophilia</i> (n = 41)																	
Meropenem	0	0	0	0	0	0	0	1	0	1	3	0	4	32 (>32)	—	—	—
Ceftazidime	0	0	0	0	0	0	0	2	6	0	2	3	5	9	14 (>64)	—	—
Trimethoprim-sulfamethoxazole	0	0	0	1	2	0	5	3	3	4	2	0	2	19 (>32/608)	—	—	—
Tigecycline	0	0	0	0	1	0	1	2	9	17	8	3	0	—	—	—	—
Piperacillin-tazobactam	0	0	0	0	0	0	0	0	0	0	0	2	2	6	1	2	28 (>256/4)
Cefepime	0	0	0	0	0	0	0	0	3	0	0	6	11	14	7 (>64)	—	—
Ceftazidime-avibactam	0	0	0	0	0	0	1	3	8	2	0	6	6	15 (>32/4)	—	—	—
<i>Acinetobacter</i> spp. (n = 14)																	
Meropenem	0	1	3	0	0	3	0	1	1	1	0	0	1	3 (>32)	—	—	—
Ceftazidime	0	0	0	1	0	0	1	1	0	2	1	1	2	1	4 (>64)	—	—
Trimethoprim-sulfamethoxazole	0	0	0	1	0	4	2	3	1	0	0	0	0	3 (>32/208)	—	—	—
Tigecycline	0	0	0	0	0	1	0	3	5	3	1	1	0	—	—	—	—
Piperacillin-tazobactam	0	0	0	0	1	1	1	0	1	0	1	1	0	1	0	1	6 (>256/4)
Cefepime	0	0	0	1	0	0	1	0	2	0	3	0	0	2	5 (>64)	—	—
Ceftazidime-avibactam	0	0	0	0	2	0	0	0	1	2	1	1	2	5 (>32/4)	—	—	—
Methicillin-susceptible <i>S. aureus</i> (n = 24)																	
Meropenem	0	0	0	15	7	2	0	0	0	0	0	0	0	—	—	—	—
Ceftazidime	0	0	0	0	0	0	0	0	0	0	18	6	0	0	—	—	—
Trimethoprim-sulfamethoxazole	0	0	0	22	1	1	0	0	0	0	0	0	0	—	—	—	—
Tigecycline	0	0	0	0	5	17	2	0	0	0	0	0	0	—	—	—	—
Piperacillin-tazobactam	0	0	0	0	0	0	5	13	4	2	0	0	0	0	0	0	—
Cefepime	0	0	0	0	0	0	0	1	14	9	0	0	0	—	—	—	—
Ceftazidime-avibactam	0	0	0	0	0	0	0	0	0	0	19	5	0	—	—	—	—

a—, not applicable.

parators). The MIC distributions for individual organisms and antimicrobial agents are presented in Table 3. Distributions for ceftazidime-avibactam trended toward lower MICs for resistant organisms than with standard of care antimicrobial agents.

To our knowledge, ours is the only study evaluating the *in vitro* activity of ceftazidime-avibactam against common Gram-negative pathogens isolated from cancer patients. We have also shown that ceftazidime-avibactam is active against MSSA, a very common pathogen isolated in our cancer patient population. Our data demonstrate that ceftazidime-avibactam has the most potent *in vitro* activity among all the agents tested, including activity against many isolates that are resistant to comparator agents commonly used in cancer patients. Although our data are from a single institution and may not represent national or global trends, they are similar to data from other large studies that have tested isolates from multiple centers, different patient populations, and various sites of infection, including the bloodstream, the urinary tract, the respiratory tract, and skin/skin structure sites (16, 17). Another potential limitation of our study is that the CRE isolates were not tested for metallo- β -lactamase production. Since the completion of this *in vitro* study, a diverse group of

metallo- β -lactamase-producing *Enterobacteriaceae* have been isolated from blood-stream infections in patients treated at our institution (18). These do not appear to be related to an ongoing outbreak and are of great concern. The higher rate of resistance to ceftazidime-avibactam reported in the Aitken study might be related to the emergence of resistance to ceftazidime-avibactam in the tested isolates that were obtained from a later period (2015) than the isolates tested in this current study (2010 to 2014). Nevertheless, based on our data, we conclude that the *in vitro* activity of ceftazidime-avibactam is potent and sufficiently broad to warrant its evaluation for treating various infections in cancer patients, including empirical therapy of febrile episodes in patients with neutropenia.

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