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Antimicrobial Activity of Ceftaroline-Avibactam Tested against Clinical Isolates Collected from U.S. Medical Centers in 2010-2011

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Ceftaroline-avibactam and comparator agents were tested by the broth microdilution method against 20,089 isolates consecutively collected in 2010 and 2011 from 75 U.S. medical centers. Ceftaroline-avibactam was active against *Enterobacteriaceae* (4,908 strains; MIC_{90}, 0.25 μg/ml; highest MIC, 4 μg/ml), including meropenem-nonsusceptible *Klebsiella* spp. and ceftazidime-nonsusceptible *Enterobacter cloacae* strains (MIC_{90}, 1 μg/ml for both). Ceftaroline-avibactam was also active against ceftriaxone-nonsusceptible *Streptococcus pneumoniae* (MIC_{90}, 0.25 μg/ml) and methicillin-resistant *Staphylococcus aureus* (MIC_{90}, 1 μg/ml).

Ceftaroline fosamil, the prodrug form of the active metabolite ceftaroline, is a cephalosporin with notable *in vitro* bactericidal activity against organisms commonly responsible for community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin-structure infections (ABSSSIs), including multidrug-resistant (MDR) *Streptococcus pneumoniae* and methicillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA) (1, 2). Ceftaroline is also active against common *Enterobacteriaceae* species but, like many cephalosporins, has limited potencies against isolates producing extended-spectrum β-lactamases (ESBLs), cephalosporinases, and carbapenemases (2). However, the spectrum of activity of ceftaroline can be expanded when it is combined with avibactam, a β-lactamase inhibitor (3). Ceftaroline fosamil was approved by the U.S. Food and Drug Administration (FDA) in late 2010 for the treatment of ABSSSIs and CABP and more recently by the European Medicines Agency (EMA) for the treatment of complicated skin and soft tissue infections and community-acquired pneumonia (4).

Avibactam (formerly NXL104) is a non-β-lactam β-lactamase inhibitor currently in clinical development with ceftazidime and ceftaroline. Avibactam has very limited intrinsic antibacterial activity but efficiently protects β-lactams from hydrolysis by a variety of strains producing Ambler class A, C, and some D enzymes, including ESBLs and *Klebsiella pneumoniae* carbapenemase (KPC) β-lactamases (5). Thus, the addition of avibactam restores ceftaroline activity against *Enterobacteriaceae* strains that are resistant to broad-spectrum β-lactams due to the production of these hydrolytic enzymes (3). We report the *in vitro* activity of ceftaroline combined with avibactam (fixed concentration of 4 μg/ml) tested against bacterial organisms isolated in U.S. medical centers during 2010 and 2011 as part of a worldwide resistance surveillance program.

A total of 20,089 bacterial isolates were collected from 75 medical centers distributed across all U.S. census regions (4 to 10 medical centers per region) for this surveillance program in 2010 and 2011. Organisms were consecutively collected from patients with clinical infections, as defined by local clinical criteria, and target numbers of strains for each of the requested bacterial species/genera were predetermined by study protocol. Species identification was performed at the participant medical center and confirmed at the monitor laboratory (JMI Laboratories, North Liberty, IA) using the Vitek system (bioMérieux, St. Louis, MO) or matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry (Bruker Daltonics, Bremen, Germany) when necessary. Only one strain per patient infection episode was included in the surveillance study. The isolates were from respiratory tract infections (34.4%), bloodstream infections (28.3%), skin and skin structure infections (24.3%), urinary tract infections (7.1%), and infections of other sites (5.9%).

Isolates were tested for susceptibility to ceftaroline-avibactam and multiple comparator agents at a central (monitor) laboratory (JMI Laboratories, North Liberty, IA) by reference broth microdilution methods as described by the Clinical and Laboratory Standards Institute (CLSI) M07-A9 (2012) document (6). Ceftaroline and comparator agents' MIC results were interpreted according to CLSI criteria in M100-S23 (7) and M45-A (8), as well as EUCAST breakpoint tables (version 3.0, January 2013) (9). FDA breakpoint criteria were also applied for ceftaroline and tigecycline (10, 11). Ceftaroline was combined with avibactam at a fixed concentration of 4 μg/ml. *Escherichia coli* and *Klebsiella* isolates were grouped as ESBL-phenotype and non-ESBL-phenotype strains based on the CLSI screening criteria for ESBL production (7). Those isolates with positive ESBL screening tests, i.e., MICs of ≥2 μg/ml for ceftazidime, ceftriaxone, or aztreonam, were categorized as ESBL-phenotype strains for the purpose of analysis of susceptibility testing results. Although an ESBL confirmation test was not performed and other β-lactamases, such as AmpC and *K. pneumoniae* carbapenemases (KPCs), may also produce an ESBL phenotype, these strains were grouped together because they usually demonstrate resistance to various broad-spectrum β-lactam compounds.

Using the FDA, CLSI, and EUCAST breakpoints for ceftaroline (≤0.5 μg/ml for susceptibility by all three criteria), ceftaroline-avibactam was among the most active agents tested against *Enterobacteriaceae*, with 98.5% susceptibility. Only 10 of 4,908 (0.2%)

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strains had a ceftaroline-avibactam MIC of ≥2 μg/ml, which is the resistance breakpoint established by the CLSI and the FDA for ceftaroline (Tables 1 and 2) (7).

All *E. coli* isolates were inhibited at ceftaroline-avibactam MICs of ≤0.5 μg/ml ($MIC_{50/90}$, ≤0.03/0.06 μg/ml). Among non-ESBL-phenotype strains, 97.7% of strains were inhibited at ceftaroline-avibactam MICs of ≤0.06 μg/ml (highest MIC, 0.25 μg/ml) (Table 2). ESBL-phenotype strains also were susceptible to ceftaroline-avibactam ($MIC_{50/90}$, 0.06/0.12 μg/ml) but showed low susceptibility to ceftriaxone (5.7%), ceftazidime (31.0% by CLSI criteria), levofloxacin (15.8%) and gentamicin (70.3% by CLSI criteria) (Table 2).

Ceftaroline-avibactam was active against *Klebsiella* strains ($MIC_{50/90}$ of 0.06/0.12 μg/ml), including strains with an ESBL phenotype ($MIC_{50/90}$ of 0.12/0.5 μg/ml; 90.9 and 98.6% of strains inhibited at ≤0.5 and ≤1 μg/ml, respectively) (Table 1). Rates of resistance to other broad-spectrum cephalosporins were high among ESBL-phenotype *Klebsiella* spp. (88.7 and 68.0% resistance to ceftriaxone and ceftazidime, respectively, according to CLSI breakpoints) (Table 2). Decreased susceptibility to meropenem (MIC, ≥2 μg/ml) was observed in 26.2% of ESBL-phenotype *Klebsiella* strains (Table 2), whereas 68.1 and 95.8% of carbapenem-nonsusceptible *K. pneumoniae* strains were inhibited at ceftaroline-avibactam MIC values of ≤0.5 and ≤1 μg/ml, respectively ($MIC_{50/90}$ of 0.5/1 μg/ml) (Table 1).

When tested against *Enterobacter cloacae*, ceftaroline-avibactam ($MIC_{50/90}$, 0.12/0.25 μg/ml) inhibited 96.3% of isolates at MICs of 0.5 μg/ml or less, and the highest MIC value was 2 μg/ml (Table 1). Moreover, only 78.9% of *E. cloacae* strains were susceptible to ceftazidime according to the CLSI breakpoint (MIC, ≤4 μg/ml), and ceftaroline-avibactam was active against both ceftazidime-susceptible ($MIC_{50/90}$, 0.12/0.25 μg/ml) and ceftazidime-nonsusceptible ($MIC_{50/90}$, 0.25/1 μg/ml, highest MIC at 2 μg/ml) strains. Among ceftazidime-nonsusceptible *E. cloacae* isolates, 83.8 and 96.3% of strains were inhibited at ≤0.5 and ≤1 μg/ml of ceftaroline-avibactam, respectively (Table 1), and 7.5% of strains were nonsusceptible to meropenem (MIC, ≥2 μg/ml) (Table 2).

Ceftaroline-avibactam inhibited all strains of *Enterobacter aerogenes* ($MIC_{50/90}$, 0.06/0.12 μg/ml), *Morganella morganii* ($MIC_{50/90}$, ≤0.03/0.12 μg/ml), and *Proteus mirabilis* ($MIC_{50/90}$, 0.06/0.12 μg/ml) at ≤0.5 μg/ml, whereas against *Serratia marcescens* ($MIC_{50/90}$, 0.5/1 μg/ml), 89.0 and 98.3% of strains were inhibited at MICs of ≤0.5 and ≤1 μg/ml, respectively. *Citrobacter freundii* ($MIC_{50/90}$, 0.06/0.12 μg/ml) and *Citrobacter koseri* ($MIC_{50/90}$, 0.06/0.12 μg/ml) were also susceptible to ceftaroline-avibactam (Tables 1 and 2). Ceftaroline-avibactam ($MIC_{50/90}$, 4/16 μg/ml) showed limited activity against *Pseudomonas aeruginosa* (Table 1).

A total of 3,349 pneumococcal isolates were evaluated, and ceftaroline-avibactam ($MIC_{50/90}$, ≤0.03/0.12 μg/ml) showed *in vitro* activity very similar to that of ceftaroline alone ($MIC_{50/90}$, ≤0.015/0.12 μg/ml) (data not shown). The highest ceftaroline-avibactam MIC value observed against *S. pneumoniae* was 0.5 μg/ml (33 strains [1.0%]) (Table 1), and it was active against *S. pneumoniae* strains with penicillin MICs of ≥8 μg/ml ($n = 52$; $MIC_{50/90}$, 0.25/0.5 μg/ml) and ceftriaxone-nonsusceptible strains ($n = 372$; MIC_{50} and MIC_{90}, 0.25 μg/ml) (Table 1).

Ceftaroline-avibactam exhibited potent *in vitro* activity against *Haemophilus influenzae* (MIC_{50} and MIC_{90}, ≤0.03 μg/ml), and 100.0% of strains were inhibited at ceftaroline-avibactam MICs of ≤0.06 μg/ml (Table 1). Overall, 27.3% of strains were β-lactamase producers, and ceftaroline-avibactam activity was not adversely affected by β-lactamase production (Table 1). All strains of *Haemophilus parainfluenzae* were inhibited at ceftaroline-avibactam MICs of ≤0.12 μg/ml (MIC_{50} and MIC_{90}, ≤0.03 μg/ml), and ceftaroline-avibactam was also active against *Moraxella catarrhalis* (MIC_{50} and MIC_{90}, ≤0.03 μg/ml).

The addition of avibactam did not adversely affect ceftaroline activity against *S. aureus* (data not shown). Ceftaroline-avibactam was active against *S. aureus* (4,315 strains tested), including MRSA ($MIC_{50/90}$, 0.5/1 μg/ml). All *S. aureus* isolates were inhibited at a ceftaroline-avibactam MIC of ≤2 μg/ml, and 98.4% were inhibited at a ceftaroline-avibactam MIC of ≤1 μg/ml, which is the susceptibility breakpoint established by the CLSI, the FDA, and EUCAST for ceftaroline. Ceftaroline-avibactam was also active against coagulase-negative *Staphylococcus* spp. ($MIC_{50/90}$, 0.25/0.5 μg/ml), β-hemolytic streptococci ($n = 2,345$; $MIC_{50/90}$, ≤0.03/≤0.03 μg/ml), and viridans group streptococci (VGS; $MIC_{50/90}$, ≤0.03/0.12 μg/ml) (Table 1).

Antimicrobial resistance among Gram-negative organisms is particularly worrisome since some organisms have acquired sufficient resistance mechanisms to render them untreatable by virtually all clinically available antimicrobials (12, 13). The β-lactam class still represents the mainstay for treatment of Gram-negative infections, and the most common mechanism of resistance among these organisms has been the production of various β-lactamases capable of hydrolyzing the β-lactam ring. Avibactam is a diazabicyclooctane (DBO) inhibitor, and it is currently in phase 2 and 3 clinical trials combined with ceftaroline and ceftazidime (5). Avibactam was demonstrated to effectively inhibit Ambler class A (e.g., ESBL and KPC), C (AmpC), and some D (OXA-like) enzymes and consequently expands the spectrum of activity for ceftaroline to include most clinically significant MDR *Enterobacteriaceae* (3, 14).

In the present study, more than 20,000 contemporary bacterial isolates collected from U.S. medical centers during 2010 and 2011 were tested, including nearly 5,000 isolates of *Enterobacteriaceae*. The highest ceftaroline-avibactam MIC value observed among *Enterobacteriaceae* strains was only 4 μg/ml, and 98.5% of strains were inhibited at ≤0.5 μg/ml, which is the ceftaroline susceptibility breakpoint established by the FDA, the CLSI, and EUCAST for these organisms. *E. coli* and *Klebsiella* isolates with an ESBL phenotype were generally susceptible to ceftaroline-avibactam.

In conclusion, ceftaroline-avibactam demonstrated potent *in vitro* activity and broad antimicrobial coverage against a large collection of contemporary (2010-2011) strains from U.S. hospitals. Ceftaroline-avibactam exhibited greater activity than did other β-lactams currently available for clinical use against *Enterobacteriaceae*, including the carbapenems. Furthermore, ceftaroline-avibactam showed *in vitro* activity against staphylococci (including methicillin-resistant strains), *S. pneumoniae* (including ceftriaxone-nonsusceptible and MDR strains), and other streptococci of clinical importance. With its potent, broad-spectrum profile, ceftaroline-avibactam warrants further development among clinical indications where MDR Gram-positive or β-lactamase-producing *Enterobacteriaceae* may be a concern.

TABLE 1 Summary of ceftaroline-avibactam activity tested against 20,089 organisms from U.S. medical centers (2010-2011)

Organism (no. of isolates tested)[a]	No. of isolates (cumulative %) inhibited at MIC (μg/ml):											MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>16		
Enterobacteriaceae (4,908)	2,028 (41.3)	1,656 (75.0)	656 (88.4)	325 (95.0)	172 (98.5)	61 (99.8)	7 (>99.9)	3 (100.0)				0.06	0.25
Escherichia coli (1,375)	1,024 (74.5)	287 (95.3)	49 (98.9)	13 (99.9)	2 (100.0)							≤0.03	0.06
Non-ESBL phenotype (1,217)	961 (79.0)	228 (97.7)	24 (99.7)	4 (100.0)								≤0.03	0.06
ESBL phenotype (158)	63 (39.9)	59 (77.2)	25 (93.0)	9 (98.7)	2 (100.0)							0.06	0.12
Klebsiella spp. (1,964)	619 (31.5)	851 (74.8)	311 (90.6)	114 (96.4)	44 (98.7)	24 (99.8)	2 (100.0)					0.06	0.12
Non-ESBL phenotype (1,689)	590 (34.9)	801 (82.4)	232 (96.1)	56 (99.4)	10 (100.0)							0.06	0.12
ESBL phenotype (275)	29 (10.5)	50 (28.7)	79 (57.5)	58 (78.5)	34 (90.9)	23 (98.6)	2 (100.0)					0.12	0.5
Meropenem nonsusceptible (72)	3 (4.2)	2 (6.9)	11 (22.2)	13 (40.3)	20 (68.1)	21 (95.8)	2 (100.0)					0.5	1
Klebsiella pneumoniae (1,471)	390 (26.5)	674 (72.3)	262 (90.1)	84 (95.9)	38 (98.4)	21 (99.8)	2 (100.0)					0.06	0.12
Klebsiella oxytoca (493)	229 (46.5)	177 (82.4)	49 (92.3)	30 (98.4)	6 (99.6)	2 (100.0)						0.06	0.12
Proteus mirabilis (230)	39 (17.0)	142 (78.7)	41 (96.5)	7 (99.6)	1 (100.0)							0.06	0.12
Non-ESBL phenotype (222)	38 (17.1)	136 (78.4)	41 (96.8)	6 (99.5)	1 (100.0)							0.06	0.12
ESBL phenotype (8)	1 (12.5)	6 (87.5)	0 (87.5)	1 (100.0)								0.06	
Enterobacter cloacae (379)	29 (7.7)	101 (34.3)	143 (72.0)	70 (90.5)	22 (96.3)	11 (99.2)	3 (100.0)					0.12	0.25
Ceftazidime susceptible (299)	29 (9.7)	100 (43.1)	130 (86.6)	35 (98.3)	4 (99.7)	1 (100.0)						0.12	0.25
Ceftazidime nonsusceptible (80)		1 (1.3)	13 (17.5)	35 (61.3)	18 (83.8)	10 (96.3)	3 (100.0)					0.25	1
Enterobacter aerogenes (143)	66 (46.2)	60 (88.1)	10 (95.1)	5 (98.6)	2 (100.0)							0.06	0.12
Ceftazidime susceptible (123)	66 (53.7)	44 (89.4)	8 (95.9)	4 (99.2)	1 (100.0)							≤0.03	0.12
Ceftazidime nonsusceptible (20)		16 (80.0)	2 (90.0)	1 (95.0)	1 (100.0)							0.06	0.12
Morganella morganii (308)	165 (53.6)	94 (84.1)	30 (93.8)	13 (98.1)	6 (100.0)							≤0.03	0.12
Citrobacter koseri (115)	57 (49.6)	45 (88.7)	8 (95.7)	4 (99.1)	0 (99.1)	1 (100.0)						0.06	0.12
Citrobacter freundii (157)	29 (18.5)	75 (66.2)	39 (91.1)	8 (96.2)	1 (96.8)	4 (99.4)	1 (100.0)					0.06	0.12
Serratia marcescens (237)		1 (0.4)	25 (11.0)	91 (49.4)	94 (89.0)	22 (98.3)	1 (98.7)	3 (100.0)				0.5	1
Pseudomonas aeruginosa (213)					1 (0.5)	10 (5.2)	61 (33.8)	63 (63.4)	45 (84.5)	18 (93.0)	15 (100.0)	4	16
Streptococcus pneumoniae (3,349)	2,278 (68.0)	287 (76.6)	504 (91.6)	247 (99.0)	33 (100.0)							≤0.03	0.12
Penicillin MIC of ≥2 μg/ml (758)	1 (0.1)	32 (4.4)	446 (63.2)	246 (95.6)	33 (100.0)							0.12	0.25
Penicillin MIC of ≥8 μg/ml (52)		1 (1.9)	5 (11.5)	28 (65.4)	18 (100.0)							0.25	0.5
Ceftriaxone nonsusceptible (372)	1 (0.3)	2 (0.8)	134 (36.8)	202 (91.1)	33 (100.0)							0.25	0.5
Haemophilus influenzae (1,679)	1,675 (99.8)	4 (100.0)										≤0.03	≤0.03
β-Lactamase negative (1,220)	1,218 (99.8)	2 (100.0)										≤0.03	≤0.03
β-Lactamase positive (459)	457 (99.6)	2 (100.0)										≤0.03	≤0.03
Haemophilus parainfluenzae (190)	187 (98.4)	2 (99.5)	1 (100.0)									≤0.03	≤0.03
Moraxella catarrhalis (494)	491 (99.4)	2 (99.8)	1 (100.0)									≤0.03	≤0.03
Staphylococcus aureus (4,315)	2 (0.0)	15 (0.4)	363 (8.8)	1,790 (50.3)	1,495 (84.9)	582 (98.4)	68 (100.0)					0.25	1
MSSA (2,172)	2 (0.1)	15 (0.8)	361 (17.4)	1,723 (96.7)	71 (100.0)							0.25	0.25
MRSA (2,143)			2 (0.1)	67 (3.2)	1,424 (69.7)	582 (96.8)	68 (100.0)					0.5	1
CoNS (1,131)	63 (5.6)	217 (24.8)	204 (42.8)	373 (75.8)	246 (97.5)	22 (99.5)	6 (100.0)					0.25	0.5
MSCoNS (413)	56 (13.6)	203 (62.7)	130 (94.2)	24 (100.0)								0.06	0.12
MRCoNS (718)	7 (1.0)	14 (2.9)	74 (13.2)	349 (61.8)	246 (96.1)	22 (99.2)	6 (100.0)					0.25	0.5
Staphylococcus epidermidis (240)	15 (6.3)	40 (22.9)	37 (38.3)	86 (74.2)	59 (98.8)	3 (100.0)						0.25	0.5
Staphylococcus haemolyticus (20)			3 (15.0)	9 (60.0)	3 (75.0)	2 (85.0)	3 (100.0)					0.25	2
Staphylococcus hominis (27)		2 (7.4)	10 (44.4)	11 (85.2)	4 (100.0)							0.25	0.5
β-Hemolytic streptococci (2,345)	2,323 (99.1)	21 (100.0)	1 (100.0)									≤0.03	≤0.03
Group A *Streptococcus* (913)	909 (99.6)	3 (99.9)	1 (100.0)									≤0.03	≤0.03
Group B *Streptococcus* (1,137)	1,132 (99.6)	5 (100.0)										≤0.03	≤0.03
Group C *Streptococcus* (157)	152 (96.8)	5 (100.0)										≤0.03	≤0.03
Viridans group streptococci (1,051)	801 (76.2)	123 (87.9)	58 (93.4)	30 (96.3)	27 (98.9)	12 (100.0)						≤0.03	0.12
Streptococcus anginosus (90)	81 (90.0)	8 (98.9)	0 (98.9)	0 (98.9)	1 (100.0)							≤0.03	≤0.03
Enterococcus faecalis (414)				4 (1.0)	11 (3.6)	72 (21.0)	212 (72.2)	55 (85.5)	49 (97.3)	11 (100.0)		2	8

[a] Abbreviations: MSSA, methicillin-susceptible *S. aureus*; CoNS, coagulase-negative staphylococci; MSCoNS, methicillin-susceptible coagulase-negative staphylococci; MRCoNS, methicillin-resistant coagulase-negative staphylococci.

TABLE 2 Activities of ceftaroline-avibactam, ceftaroline, and selected comparator antimicrobial agents when tested against *Enterobacteriaceae* and *P. aeruginosa*

Organism and antimicrobial agent (no. of isolates tested)	MIC (μg/ml)			% S/% R[a]	
	MIC_{50}	MIC_{90}	Range	CLSI	EUCAST
Enterobacteriaceae (4,908)					
Ceftaroline-avibactam	0.06	0.25	≤0.03–4		
Ceftaroline	0.12	32	≤0.015–>32	80.6/15.2 (80.6/15.2)[b]	80.6/19.4
Ceftriaxone	≤0.06	8	≤0.06–>8	87.0/12.1	87.0/12.1
Ceftazidime	0.12	8	≤0.015–>32	89.6/9.2	87.3/10.4
Ampicillin-sulbactam	8	>32	≤0.25–>32	58.6/25.0	58.6/41.4
Piperacillin-tazobactam	2	16	≤0.5–>64	91.5/5.6	88.3/8.5
Meropenem	≤0.12	≤0.12	≤0.12–>8	98.3/1.5	98.5/1.1
Gentamicin	≤1	2	≤1–>8	92.0/6.8	91.1/8.0
Levofloxacin	≤0.5	>4	≤0.5–>4	84.3/14.3	82.9/15.7
Tigecycline[c]	0.25	1	≤0.03–>4	98.3/0.2	94.4/1.7
Escherichia coli					
Total (1,375)					
Ceftaroline-avibactam	≤0.03	0.06	≤0.03–0.5		
Ceftaroline	0.12	16	≤0.015–>32	83.8/13.6 (83.8/13.6)[b]	83.8/16.2
Ceftriaxone	≤0.06	8	≤0.06–>8	89.2/10.6	89.2/10.6
Ceftazidime	0.12	2	≤0.015–>32	92.1/6.3	89.3/7.9
Ampicillin-sulbactam	8	>32	≤0.25–>32	54.0/24.6	54.0/46.0
Piperacillin-tazobactam	2	8	≤0.5–>64	94.5/3.1	92.2/5.5
Meropenem	≤0.12	≤0.12	≤0.12–1	100.0/0.0	100.0/0.0
Gentamicin	≤1	>8	≤1–>8	88.2/11.3	87.6/11.8
Levofloxacin	≤0.5	>4	≤0.5–>4	70.1/29.5	70.0/29.9
Tigecycline[c]	0.12	0.25	≤0.03–1	100.0/0.0	100.0/0.0
Non-ESBL phenotype (1,217)					
Ceftaroline-avibactam	≤0.03	0.06	≤0.03–0.25		
Ceftaroline	0.06	0.5	≤0.015–32	94.3/2.9 (94.3/2.9)[b]	94.3/5.7
Ceftriaxone	≤0.06	0.12	≤0.06–1	100.0/0.0	100.0/0.0
Ceftazidime	0.12	0.25	≤0.015–1	100.0/0.0	100.0/0.0
Ampicillin-sulbactam	4	32	≤0.25–>32	59.3/18.8	59.3/40.7
Piperacillin-tazobactam	2	4	≤0.5–>64	97.2/1.8	96.3/2.8
Meropenem	≤0.12	≤0.12	≤0.12–0.25	100.0/0.0	100.0/0.0
Gentamicin	≤1	4	≤1–>8	90.6/8.9	90.0/9.4
Levofloxacin	≤0.5	>4	≤0.5–>4	77.2/22.5	77.0/22.8
Tigecycline[c]	0.12	0.25	≤0.03–1	100.0/0.0	100.0/0.0
ESBL phenotype (158)					
Ceftaroline-avibactam	0.06	0.12	≤0.03–0.5		
Ceftaroline	>32	>32	0.12–>32	2.5/96.2 (2.5/96.2)[b]	2.5/97.5
Ceftriaxone	>8	>8	0.12–>8	5.7/92.4	5.7/92.4
Ceftazidime	16	>32	0.25–>32	31.0/54.4	7.0/69.0
Ampicillin-sulbactam	32	>32	4–>32	13.3/69.0	13.3/86.7
Piperacillin-tazobactam	8	>64	1–>64	73.4/13.3	60.8/26.6
Meropenem	≤0.12	≤0.12	≤0.12–1	100.0/0.0	100.0/0.0
Gentamicin	≤1	>8	≤1–>8	70.3/29.7	69.0/29.7
Levofloxacin	>4	>4	≤0.5–>4	15.8/82.9	15.8/84.2
Tigecycline[c]	0.12	0.25	0.06–0.5	100.0/0.0	100.0/0.0
Klebsiella spp.[d]					
Total (1,964)					
Ceftaroline-avibactam	0.06	0.12	≤0.03–4		
Ceftaroline	0.12	>32	≤0.015–>32	83.6/14.2 (83.6/14.2)[b]	83.6/16.4
Ceftriaxone	≤0.06	>8	≤0.06–>8	87.0/12.5	87.0/12.5
Ceftazidime	0.12	8	≤0.015–>32	89.8/9.5	87.8/10.2
Ampicillin-sulbactam	8	>32	0.5–>32	72.9/16.3	72.9/27.1
Piperacillin-tazobactam	2	32	≤0.5–>64	89.5/8.8	84.5/10.5
Meropenem	≤0.12	≤0.12	≤0.12–>8	96.3/3.4	96.6/2.7
Gentamicin	≤1	≤1	≤1–>8	93.8/4.4	93.0/6.2
Levofloxacin	≤0.5	2	≤0.5–>4	90.1/8.9	88.7/9.9
Tigecycline[c]	0.25	1	0.06–>4	98.8/0.1	95.5/1.2

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TABLE 2 (Continued)

Organism and antimicrobial agent (no. of isolates tested)	MIC (μg/ml)			% S/% R[a]	
	MIC_{50}	MIC_{90}	Range	CLSI	EUCAST
Non-ESBL phenotype (1,689)					
Ceftaroline-avibactam	0.06	0.12	≤0.03–0.5		
Ceftaroline	0.12	0.5	≤0.015–8	97.0/0.7 (97.0/0.7)[b]	97.0/3.0
Ceftriaxone	≤0.06	0.12	≤0.06–1	100.0/0.0	100.0/0.0
Ceftazidime	0.12	0.25	≤0.015–1	100.0/0.0	100.0/0.0
Ampicillin-sulbactam	4	16	0.5–>32	84.1/4.9	84.1/15.9
Piperacillin-tazobactam	2	8	≤0.5–>64	98.9/0.7	94.9/1.1
Meropenem	≤0.12	≤0.12	≤0.12–0.25	100.0/0.0	100.0/0.0
Gentamicin	≤1	≤1	≤1–>8	99.1/0.8	99.1/0.9
Levofloxacin	≤0.5	≤0.5	≤0.5–>4	98.4/0.9	97.5/1.6
Tigecycline[c]	0.25	0.5	0.06–>4	99.2/0.1	96.6/0.8
ESBL phenotype (275)					
Ceftaroline-avibactam	0.12	0.5	≤0.03–4		
Ceftaroline	>32	>32	0.12–>32	1.5/96.7 (1.5/96.7)[b]	1.5/98.5
Ceftriaxone	>8	>8	0.12–>8	7.3/88.7	7.3/88.7
Ceftazidime	32	>32	0.12–>32	27.6/68.0	13.4/72.5
Ampicillin-sulbactam	>32	>32	2–>32	4.3/86.2	4.3/95.7
Piperacillin-tazobactam	>64	>64	1–>64	31.9/58.7	21.0/68.1
Meropenem	≤0.12	>8	≤0.12–>8	73.9/23.9	76.1/19.2
Gentamicin	2	>8	≤1–>8	62.0/26.8	55.8/38.0
Levofloxacin	>4	>4	≤0.5–>4	39.5/57.2	35.1/60.5
Tigecycline[c]	0.5	2	0.06–4	96.7/0.0	89.1/3.3
Proteus mirabilis (230)					
Ceftaroline-avibactam	0.06	0.12	0.03–0.5		
Ceftaroline	0.12	0.25	0.03–>32	93.0/3.9 (93.0/3.9)[b]	93.0/7.0
Ceftriaxone	≤0.06	≤0.06	≤0.06–>8	97.4/2.2	97.4/2.2
Ceftazidime	0.06	0.12	0.03–4	100.0/0.0	97.8/0.0
Ampicillin-sulbactam	1	8	≤0.25–32	90.4/2.6	90.4/9.6
Piperacillin-tazobactam	≤0.5	1	≤0.5–>64	99.6/0.4	99.6/0.4
Meropenem	≤0.06	≤0.06	≤0.06–0.5	100.0/0.0	100.0/0.0
Gentamicin	≤1	4	≤1–>8	90.0/6.5	87.8/10.0
Levofloxacin	≤0.12	>4	≤0.12–>4	76.0/19.2	73.4/24.0
Tigecycline[c]	2	4	0.12–>4	83.4/0.9	45.4/16.6
Enterobacter cloacae					
Total (379)					
Ceftaroline-avibactam	0.12	0.25	≤0.015–2		
Ceftaroline	0.25	>32	≤0.015–>32	72.8/23.7 (72.8/23.7)[b]	72.8/27.2
Ceftriaxone	0.25	>8	≤0.06–>8	75.7/22.7	75.7/22.7
Ceftazidime	0.25	>32	0.03–>32	78.9/19.8	76.5/21.1
Ampicillin-sulbactam	16	>32	1–>32	34.6/43.3	34.6/65.4
Piperacillin-tazobactam	2	64	≤0.5–>64	83.1/8.4	80.7/16.9
Meropenem	≤0.06	≤0.06	≤0.06–>8	98.4/1.3	98.7/0.3
Gentamicin	≤1	≤1	≤1–>8	94.4/5.0	94.2/5.6
Levofloxacin	≤0.12	0.5	≤0.12–>4	93.4/5.3	92.9/6.6
Tigecycline[c]	0.25	0.5	0.12–4	98.4/0.0	96.0/1.6
Ceftazidime susceptible (299)					
Ceftaroline-avibactam	0.12	0.25	≤0.015–1		
Ceftaroline	0.25	0.5	≤0.015–8	92.3/3.7 (92.3/3.7)[b]	92.3/7.7
Ceftriaxone	0.25	0.5	≤0.06–>8	96.0/2.7	96.0/2.7
Ceftazidime	0.25	0.5	0.03–4	100.0/0.0	97.0/0.0
Ampicillin-sulbactam	16	32	1–>32	43.8/28.4	43.8/56.2
Piperacillin-tazobactam	2	4	≤0.5–16	100.0/0.0	99.3/0.0
Meropenem	≤0.06	≤0.06	≤0.06–0.25	100.0/0.0	100.0/0.0
Gentamicin	≤1	≤1	≤1–>8	99.0/1.0	98.7/1.0
Levofloxacin	≤0.12	0.25	≤0.12–>4	98.0/1.0	97.7/2.0
Tigecycline[c]	0.25	0.5	0.12–4	99.0/0.0	98.0/1.0

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TABLE 2 (Continued)

Organism and antimicrobial agent (no. of isolates tested)	MIC (μg/ml)			% S/% R[a]	
	MIC_{50}	MIC_{90}	Range	CLSI	EUCAST
Ceftazidime nonsusceptible (80)					
Ceftaroline-avibactam	0.25	1	0.06–2		
Ceftaroline	>32	>32	1–>32	0.0/98.8 (0.0/98.8)[b]	0.0/100.0
Ceftriaxone	>8	>8	2–>8	0.0/97.5	0.0/97.5
Ceftazidime	>32	>32	8–>32	0.0/93.8	0.0/100.0
Ampicillin-sulbactam	>32	>32	16–>32	0.0/98.8	0.0/100.0
Piperacillin-tazobactam	64	>64	1–>64	20.0/40.0	11.3/80.0
Meropenem	≤0.06	0.5	≤0.06–>8	92.5/6.3	93.8/1.3
Gentamicin	≤1	>8	≤1–>8	77.5/20.0	77.5/22.5
Levofloxacin	≤0.12	>4	≤0.12–>4	76.3/21.3	75.0/23.8
Tigecycline[c]	0.25	2	0.12–4	96.3/0.0	88.8/3.8
Enterobacter aerogenes (143)					
Ceftaroline-avibactam	0.06	0.12	≤0.015–0.5		
Ceftaroline	0.12	32	≤0.015–>32	84.6/14.7 (84.6/14.7)[b]	84.6/15.3
Ceftriaxone	0.12	8	≤0.06–>8	85.3/14.0	85.3/14.0
Ceftazidime	0.25	16	0.03–>32	86.0/11.9	84.6/14.0
Ampicillin-sulbactam	16	>32	2–>32	45.5/28.0	45.5/54.5
Piperacillin-tazobactam	4	32	≤0.5–>64	88.1/2.1	83.9/11.9
Meropenem	≤0.06	≤0.06	≤0.06–8	98.6/0.7	99.3/0.0
Gentamicin	≤1	≤1	≤1–>8	99.3/0.7	99.3/0.7
Levofloxacin	≤0.12	0.25	≤0.12–>4	99.3/0.7	99.3/0.7
Tigecycline[c]	0.25	0.5	0.12–4	99.3/0.0	95.8/0.7
Morganella morganii (308)					
Ceftaroline-avibactam	≤0.03	0.12	≤0.03–0.5		
Ceftaroline	0.12	>32	≤0.015–>32	70.5/26.9 (70.5/26.9)[b]	70.5/29.5
Ceftriaxone	≤0.06	4	≤0.06–>8	82.1/11.4	82.1/11.4
Ceftazidime	0.12	16	0.03–>32	81.5/14.3	76.3/18.5
Ampicillin-sulbactam	16	32	1–>32	19.8/45.5	19.8/80.2
Piperacillin-tazobactam	≤0.5	2	≤0.5–>64	96.1/2.3	96.1/3.9
Meropenem	≤0.12	≤0.12	≤0.12–0.25	100.0/0.0	100.0/0.0
Gentamicin	≤1	>8	≤1–>8	84.7/13.0	81.8/15.3
Levofloxacin	≤0.5	>4	≤0.5–>4	79.5/15.3	73.1/20.5
Tigecycline[c]	0.5	1	0.12–>4	95.8/0.6	90.9/4.2
Citrobacter freundii (157)					
Ceftaroline-avibactam	0.06	0.12	≤0.015–2		
Ceftaroline	0.25	>32	0.12–>32	73.9/25.5 (73.9/25.5)[b]	73.9/26.1
Ceftriaxone	0.25	>8	≤0.06–>8	74.5/24.8	74.5/24.8
Ceftazidime	0.5	>32	0.12–>32	75.8/24.2	75.2/24.2
Ampicillin-sulbactam	8	>32	2–>32	63.7/28.7	63.7/36.3
Piperacillin-tazobactam	4	>64	≤0.5–>64	78.3/10.2	74.5/21.7
Meropenem	≤0.06	≤0.06	≤0.06–>8	97.4/1.9	98.1/0.6
Gentamicin	≤1	2	≤1–>8	92.4/7.0	90.4/7.6
Levofloxacin	≤0.12	2	≤0.12–>4	92.4/7.0	86.6/7.6
Tigecycline[c]	0.25	0.5	0.06–4	99.4/0.0	98.1/0.6
Citrobacter koseri (115)					
Ceftaroline-avibactam	0.06	0.12	≤0.015–1		
Ceftaroline	0.12	0.25	≤0.015–1	99.1/0.0 (99.1/0.0)[b]	99.1/0.9
Ceftriaxone	≤0.06	0.12	≤0.06–0.5	100.0/0.0	100.0/0.0
Ceftazidime	0.12	0.25	0.03–0.5	100.0/0.0	100.0/0.0
Ampicillin-sulbactam	2	8	≤0.25–32	96.5/0.9	96.5/3.5
Piperacillin-tazobactam	2	4	1–16	100.0/0.0	95.7/0.0
Meropenem	≤0.06	≤0.06	≤0.06	100.0/0.0	100.0/0.0
Gentamicin	≤1	≤1	≤1–2	100.0/0.0	100.0/0.0
Levofloxacin	≤0.12	≤0.12	≤0.12–0.5	100.0/0.0	100.0/0.0
Tigecycline[c]	0.12	0.25	0.06–0.5	100.0/0.0	100.0/0.0

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TABLE 2 (Continued)

Organism and antimicrobial agent (no. of isolates tested)	MIC (μg/ml)			% S/% R[a]	
	MIC_{50}	MIC_{90}	Range	CLSI	EUCAST
Serratia marcescens (237)					
Ceftaroline-avibactam	0.5	1	0.06–4		
Ceftaroline	1	4	0.25–>32	44.3/16.5 (44.3/16.5)[b]	44.3/55.7
Ceftriaxone	0.25	1	≤0.06–>8	91.1/8.0	91.1/8.0
Ceftazidime	0.25	0.5	0.03–>32	97.5/2.1	96.6/2.5
Ampicillin-sulbactam	32	>32	4–>32	11.4/72.2	11.4/88.6
Piperacillin-tazobactam	2	4	≤0.5–>64	96.6/0.8	95.8/3.4
Meropenem	≤0.06	≤0.06	≤0.06–2	99.6/0.0	100.0/0.0
Gentamicin	≤1	≤1	≤1–>8	98.3/1.7	98.3/1.7
Levofloxacin	≤0.12	0.5	≤0.12–>4	97.0/0.8	95.4/3.0
Tigecycline[c]	0.5	1	0.12–>4	98.7/0.8	96.2/1.3
Pseudomonas aeruginosa (213)					
Ceftaroline-avibactam	4	16	0.5–>32		
Ceftaroline	16	>32	1–>32		
Ceftazidime	2	32	0.5–>32	83.1/11.3	83.1/16.9
Piperacillin-tazobactam	8	>64	≤0.5–>64	76.1/11.7	76.1/23.9
Meropenem	0.5	8	≤0.06–>8	79.8/15.0	79.8/7.5
Gentamicin	≤1	4	≤1–>8	90.1/6.6	90.1/9.9
Levofloxacin	1	>4	≤0.12–>4	68.1/24.4	60.1/31.9

[a] Criteria as published by the CLSI (7) and EUCAST (9). S, susceptible; R, resistant.
[b] FDA breakpoints were applied (10).
[c] FDA breakpoints were applied (11).
[d] Includes *Klebsiella oxytoca* (493 strains) and *K. pneumoniae* (1,471 strains).

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REFERENCES

1. **File TM, Jr, Wilcox MH, Stein GE.** 2012. Summary of ceftaroline fosamil clinical trial studies and clinical safety Clin. Infect. Dis. **55**(Suppl 3):S173–S180.
2. **Flamm RK, Sader HS, Farrell DJ, Jones RN.** 2012. Summary of ceftaroline activity against pathogens in the United States, 2010: report from the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Surveillance Program. Antimicrob. Agents Chemother. **56**:2933–2940.
3. **Castanheira M, Sader HS, Farrell DJ, Mendes RE, Jones RN.** 2012. Activity of ceftaroline-avibactam tested against Gram-negative organism populations, including strains expressing one or more beta-lactamases and methicillin-resistant *Staphylococcus aureus* carrying various SCCmec types. Antimicrob. Agents Chemother. **56**:4779–4785.
4. **AstraZeneca AB.** 2012. Zinforo package insert. AstraZeneca AB, Södertälje, Sweden. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002252/WC500132586.pdf. Accessed December 2012.
5. **Ehmann DE, Jahic H, Ross PL, Gu RF, Hu J, Kern G, Walkup GK, Fisher SL.** 2012. Avibactam is a covalent, reversible, non-beta-lactam beta-lactamase inhibitor. Proc. Natl. Acad. Sci. U. S. A. **109**:11663–11668.
6. **Clinical and Laboratory Standards Institute.** 2012. M07-A9. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard: 9th ed. Clinical and Laboratory Standards Institute, Wayne, PA.
7. **Clinical and Laboratory Standards Institute.** 2013. M100-S23. Performance standards for antimicrobial susceptibility testing: 23rd informational supplement. Clinical and Laboratory Standards Institute, Wayne, PA.
8. **Clinical and Laboratory Standards Institute.** 2010. M45-A2. Methods for antimicrobial dilution and disk susceptibility testing of infrequently isolated or fastidious bacteria: 2nd ed. Clinical and Laboratory Standards Institute, Wayne, PA.
9. **EUCAST.** January 2013. Breakpoint tables for interpretation of MICs and zone diameters. Version 3.0. ESCMID, Basel, Switzerland. http://www.eucast.org/clinical_breakpoints/. Accessed 2 January 2013.
10. **Forest Pharmaceuticals, Inc.** 2012. Teflaro package insert. Forest Pharmaceuticals, Inc., St. Louis, MO. http://www.frx.com/pi/Teflaro_pi.pdf. Accessed September 2012.
11. **Pfizer.** 2011. Tygacil package insert. Pfizer, New York, NY. www.tygacil.com. Accessed September 2012.
12. **Kanj SS, Kanafani ZA.** 2011. Current concepts in antimicrobial therapy against resistant gram-negative organisms: extended-spectrum beta-lactamase-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, and multidrug-resistant *Pseudomonas aeruginosa*. Mayo Clin. Proc. **86**:250–259.
13. **Castanheira M, Mendes RE, Woosley LN, Jones RN.** 2011. Trends in carbapenemase-producing *Escherichia coli* and *Klebsiella* spp. from Europe and the Americas: report from the SENTRY Antimicrobial Surveillance Programme (2007-09). J. Antimicrob. Chemother. **66**:1409–1411.
14. **Mushtaq S, Warner M, Williams G, Critchley I, Livermore DM.** 2010. Activity of chequerboard combinations of ceftaroline and NXL104 versus beta-lactamase-producing Enterobacteriaceae. J. Antimicrob. Chemother. **65**:1428–1432.