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In Vitro Activity of Ceftaroline-Avibactam against Gram-Negative and Gram-Positive Pathogens Isolated from Patients in Canadian Hospitals from 2010 to 2012: Results from the CANWARD Surveillance Study

James A. Karlowsky,[a,b] Heather J. Adam,[a,b] Melanie R. Baxter,[b] Philippe R. S. Lagacé-Wiens,[a,b] Andrew J. Walkty,[a,b,c] Daryl J. Hoban,[a,b] George G. Zhanel[b]

Diagnostic Services Manitoba,[a] Department of Medical Microbiology and Infectious Diseases, Faculty of Medicine, University of Manitoba,[b] and Department of Medicine, Health Sciences Centre,[c] Winnipeg, Manitoba, Canada

The *in vitro* activities of ceftaroline-avibactam, ceftaroline, and comparative agents were determined for a collection of bacterial pathogens frequently isolated from patients seeking care at 15 Canadian hospitals from January 2010 to December 2012. In total, 9,758 isolates were tested by using the Clinical and Laboratory Standards Institute (CLSI) broth microdilution method (document M07-A9, 2012), with MICs interpreted by using CLSI breakpoints (document M100-S23, 2013). Ceftaroline-avibactam demonstrated potent activity (MIC_{90}, ≤0.5 μg/ml) against *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Proteus mirabilis*, *Enterobacter cloacae*, *Enterobacter aerogenes*, *Serratia marcescens*, *Morganella morganii*, *Citrobacter freundii*, and *Haemophilus influenzae*; >99% of isolates of *E. coli*, *K. pneumoniae*, *K. oxytoca*, *P. mirabilis*, *M. morganii*, *C. freundii*, and *H. influenzae* were susceptible to ceftaroline-avibactam according to CLSI MIC interpretative criteria for ceftaroline. Ceftaroline was less active than ceftaroline-avibactam against all species of *Enterobacteriaceae* tested, with rates of susceptibility ranging from 93.9% (*P. mirabilis*) to 54.0% (*S. marcescens*). All isolates of methicillin-susceptible *Staphylococcus aureus* (MIC_{90}, 0.25 μg/ml) and 99.6% of methicillin-resistant *S. aureus* isolates (MIC_{90}, 1 μg/ml) were susceptible to ceftaroline; the addition of avibactam to ceftaroline did not alter its activity against staphylococci or streptococci. All isolates of *Streptococcus pneumoniae* (MIC_{90}, 0.03 μg/ml), *Streptococcus pyogenes* (MIC_{90}, ≤0.03 μg/ml), and *Streptococcus agalactiae* (MIC_{90}, 0.015 μg/ml) tested were susceptible to ceftaroline. We conclude that combining avibactam with ceftaroline expanded its spectrum of activity to include most isolates of *Enterobacteriaceae* resistant to third-generation cephalosporins, including extended-spectrum β-lactamase (ESBL)- and AmpC-producing *E. coli* and ESBL-producing *K. pneumoniae*, while maintaining potent activity against staphylococci and streptococci.

Antimicrobial-resistant bacteria contribute significantly to patient morbidity and mortality as well as rising health care costs. New agents are needed to treat infections caused by antimicrobial-resistant bacterial pathogens, particularly multidrug-resistant Gram-negative bacilli. Ceftaroline, the active component of the prodrug ceftaroline fosamil, is approved in the United States for the treatment of adults with acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia and by the European Medicines Agency for the treatment of patients with complicated skin and soft tissue infections and community-acquired pneumonia. Ceftaroline is a parenteral, broad-spectrum cephalosporin with *in vitro* activity against resistant Gram-positive pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and *Streptococcus pneumoniae* as well as *Enterobacteriaceae*, excluding isolates harboring extended-spectrum β-lactamases (ESBLs), cephalosporinases, and carbapenemases (1–6). Ceftaroline also demonstrates potent *in vitro* activity against Gram-positive and Gram-negative anaerobic bacteria, excluding *Bacteroides fragilis* (7, 8), but lacks activity against enterococci, *Pseudomonas aeruginosa*, and other nonfermentative Gram-negative bacilli (1, 2, 4, 6). Unlike many other oxyimino-cephalosporins, ceftaroline demonstrates some lability to classical TEM and SHV β-lactamases, is resistant to *Klebsiella oxytoca* hyperproducing the K1 enzyme, and produces high MICs, relative to those of other oxyimino-cephalosporins, for isolates harboring CTX-M enzymes (9).

Avibactam, previously known as NXL104 and AVE1330A, is a novel non-β-lactam β-lactamase inhibitor that, when combined with ceftaroline or ceftazidime, has been demonstrated to broaden the spectra of activity of these two cephalosporins to include Gram-negative bacteria that produce one or more Ambler class A (e.g., ESBL and KPC) and/or class C (e.g., AmpC) and some class D (e.g., OXA-like) enzymes (4, 8, 10–14). Avibactam inactivates susceptible β-lactamases by covalent acylation (15); however, avibactam's binding also appears reversible, as deacylation slowly follows initial acylation with recyclization (and not hydrolysis) of avibactam's 5-membered urea ring, which restores its activity (15, 16). Avibactam possesses a unique mechanism of inhibition among known β-lactamase inhibitors, as current, clinically used β-lactamase inhibitors form irreversible acyl-enzyme intermediates that decompose through hydrolysis (15, 16). *In vitro*, avibactam at a concentration of 4 μg/ml protects ceftaroline from hydrolysis by all currently relevant β-lactamases except metalloenzymes and *Acinetobacter* OXA carbapenemases (11, 12).

The intent of the current study was to evaluate the *in vitro*

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Address correspondence to James A. Karlowsky, jkarlowsky@dsmanitoba.ca.

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activities of the ceftaroline-avibactam combination, ceftaroline alone, and a collection of relevant comparator agents against a recent Canadian collection of common Gram-negative and Gram-positive bacteria isolated from patients with skin and skin structure, respiratory, urinary tract, and bacteremic infections. The isolates tested in this study were collected and tested as a part of the ongoing CANWARD surveillance study. CANWARD, initiated in 2007, is a national, annual, Health Canada-endorsed, population-based surveillance study intended to assess changing patterns of antimicrobial susceptibility among pathogens recovered from patients in medical/surgical wards, emergency rooms, and intensive care units in Canadian hospitals (http://www.can-r.ca/).

MATERIALS AND METHODS

Bacterial isolates. From January 2010 to December 2012, 15 sentinel Canadian hospital laboratories were asked to submit consecutive bacterial pathogens (1 per patient) isolated from blood ($n = 165$), respiratory ($n = 100$), urine ($n = 50$), and wound ($n = 50$) infections. All isolates collected were deemed clinically significant by the participating site. Isolate inclusion was independent of patient age. Primary isolate identification was performed by the submitting site. Isolates were reidentified by the coordinating laboratory using morphological characteristics and spot tests. If an isolate identification made by the coordinating laboratory was not consistent with that provided by the submitting site, the isolate was removed from the study. In total, 11,233 isolates (4,868 in 2010, 3,557 in 2011, and 2,808 in 2012) were submitted, and 9,758 isolates (4,296 in 2010, 3,107 in 2011, and 2,355 in 2012) were tested for antimicrobial susceptibilities. Yeasts, coagulase-negative staphylococci not identified to the species level, viridans group streptococci, *Moraxella catarrhalis*, and species with <10 isolates were not tested for antimicrobial susceptibilities. Of the 9,758 isolates tested, 4,084 (41.9%) were from blood, 3,173 (32.5%) were from respiratory sources, 1,317 (13.5%) were from urine, and 1,184 (12.1%) were from wounds. Bacterial isolates tested included 4,413 Gram-positive (45.2%) and 5,345 Gram-negative (54.8%) isolates. The 15 sentinel hospital laboratory sites were geographically distributed across Canada in a population-based fashion (British Columbia [1 site], Alberta [1 site], Saskatchewan [1 site], Manitoba [1 site], Ontario [5 sites], Quebec [4 sites], New Brunswick [1 site], and Nova Scotia [1 site]).

Antimicrobial susceptibility testing. Isolates were tested for antimicrobial susceptibilities by using in-house-prepared 96-well broth microdilution panels according to Clinical and Laboratory Standards Institute (CLSI) guidelines (17, 18). The antimicrobial agents tested were obtained as laboratory-grade powders from their respective manufacturers. Ceftaroline was supplied by Forest Laboratories, Inc. (New York, NY). Avibactam was supplied by AstraZeneca (Wilmington, DE). Avibactam was tested at a fixed concentration of 4 μg/ml in combination with ceftaroline (ceftaroline-avibactam). Stock solutions and dilutions were prepared as described in CLSI document M07-A9, in cation-adjusted Mueller-Hinton broth (MHB), MHB with 5% laked horse blood (LHB), and *Haemophilus* test medium (HTM) (17). Quality control was performed according to CLSI recommendations, and MICs were interpreted by using CLSI document M100-S23 breakpoints (18), except for tigecycline, where U.S. FDA-approved MIC breakpoints were used. Ceftaroline-avibactam MICs were interpreted by using ceftaroline MIC breakpoints (18).

ESBL and AmpC confirmation. CLSI criteria were used to screen for potential extended-spectrum-β-lactamase (ESBL)-producing isolates of *E. coli* and *K. pneumoniae* (18). Confirmatory testing was done by using the disk diffusion method according to CLSI guidelines (18), using disks containing ceftazidime (30 μg), ceftazidime-clavulanic acid (30 μg and 10 μg, respectively), cefotaxime (30 μg), and cefotaxime-clavulanic acid (30 μg and 10 μg, respectively), supplied by Mast Diagnostics (United Kingdom). PCR and sequence analysis were used to identify bla_{SHV}, bla_{TEM}, and $bla_{CTX\text{-}M}$ among ESBL-producing isolates (19–21). Any putative ESBL-producing *E. coli* isolate that was negative by the ESBL confirmatory test and resistant to cefoxitin (MICs of ≥32 μg/ml) was identified as a putative AmpC producer. Putative AmpC producers were screened for acquired *ampC* genes and for mutations within the chromosomal *ampC* promoter and/or attenuator region by PCR and sequencing, as previously described (22, 23).

Methicillin-resistant *S. aureus* confirmation. Potential methicillin resistance in *S. aureus* isolates was confirmed by using the cefoxitin disk test according to CLSI guidelines (18) and by PCR amplification of the *mecA* gene (24). Other molecular methods, including Panton-Valentine leukocidin (PVL) analysis (24) and staphylococcal protein A (*spa*) typing (25), were used to assign isolates to community-associated (resembling USA300 and USA400) or health care-associated (resembling USA100/800, USA200, USA500, and USA600) groups. A high degree of concordance between *spa* types and Canadian epidemic clones has been documented (25).

RESULTS

The *in vitro* activities of ceftaroline-avibactam, ceftaroline, and comparative agents against Gram-negative pathogens are summarized in Table 1. Ceftaroline-avibactam demonstrated potent activity (MIC_{90}, ≤0.5 μg/ml) against *E. coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Proteus mirabilis*, *Enterobacter cloacae*, *Enterobacter aerogenes*, *Serratia marcescens*, *Morganella morganii*, *Citrobacter freundii*, and *Haemophilus influenzae*; >99% of isolates of *E. coli*, *K. pneumoniae*, *K. oxytoca*, *P. mirabilis*, *M. morganii*, *C. freundii*, and *H. influenzae* were susceptible to ceftaroline-avibactam according to CLSI MIC interpretative criteria for ceftaroline (18). Ceftaroline-avibactam exhibited limited activity (MIC_{90}, ≥8 μg/ml) against *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, and *Acinetobacter baumannii*. Ceftaroline was less active than ceftaroline-avibactam against all species of *Enterobacteriaceae* tested, with rates of susceptibility ranging from 93.9% (*P. mirabilis*) to 54.0% (*S. marcescens*).

Ceftaroline-avibactam is equally active against ESBL-producing and non-ESBL-, non-AmpC-producing isolates of *E. coli*; only 1 of 57 isolates of AmpC-producing *E. coli* had a MIC of 1 μg/ml (Table 2). Ceftaroline was inactive against ESBL-producing *E. coli*, and only 35.1% of AmpC-producing *E. coli* isolates were susceptible to ceftaroline. Of the 114 phenotypically confirmed ESBL-producing *E. coli* isolates identified, 76 were positive for CTX-M-15, 16 were positive for CTX-M-14, 13 were positive for CTX-M-27, 2 were positive for CTX-M15 and SHV-12, 1 was positive for CTX-M-3, 1 was positive for CTX-M-24, and 5 had no ESBL identified genetically; the *in vitro* activity of ceftaroline-avibactam was consistent against the isolates harboring each of these enzymes. Of the 57 phenotypically confirmed AmpC-producing *E. coli* isolates identified, 30 were positive for CMY-2, and 27 were promoter mutants; the *in vitro* activity of ceftaroline-avibactam was consistent against the isolates in each of these groups. Ceftaroline-avibactam demonstrated a similar activity against ESBL-positive isolates of *K. pneumoniae* (MIC_{90}, 0.5 μg/ml; MIC range, ≤0.03 to 1 μg/ml) compared to that of non-ESBL-producing/non-AmpC-producing isolates (MIC_{90}, 0.12 μg/ml; MIC range, ≤0.03 to 2 μg/ml). Ceftaroline was also inactive against ESBL-producing *K. pneumoniae*. Of the 25 phenotypically confirmed ESBL-producing *K. pneumoniae* isolates identified, 7 were positive for CTX-M-15, 4 were positive for SHV-12, 3 were positive for CTX-M-15 and SHV-11, 2 were positive for SHV-2a, 1 was positive for CTX-M-14, 1 was positive for SHV-2, 1 was positive for CTX-M-3 and SHV-108, 1 was positive for CTX-M-14 and SHV-11, 1 was positive for CTX-M-15 and SHV-28, 1 was

TABLE 1 *In vitro* activities of ceftaroline-avibactam, ceftaroline, and comparators against Gram-negative pathogens

Organism (no. of isolates tested) and drug	MIC (μg/ml)			% of isolates[d]		
	50%	90%	Range	Susceptible	Intermediate	Resistant
Escherichia coli (2,162)						
Ceftaroline-avibactam[a]	≤0.03	0.06	≤0.03–1	99.9	0.1	0
Ceftaroline	0.12	1	≤0.03–>16	89.7	1.8	8.5
Cefepime[b]	≤0.25	≤0.25	≤0.25–>64	97.2	1.7	1.1
Ceftriaxone	≤0.25	≤0.25	≤0.25–>64	92.6	0.2	7.3
Ceftazidime	≤0.25	1	≤0.25–>32	94.3	0.7	5.0
Cefoxitin	4	8	≤0.06–>32	91.5	5.0	3.5
Cefazolin	2	32	≤0.5–>128	72.3	11.0	16.7
Meropenem	≤0.03	≤0.03	≤0.03–1	100	0	0
Ertapenem	≤0.03	≤0.03	≤0.03–8	99.7	0.1	0.2
Piperacillin-tazobactam	2	4	≤1–>512	97.5	0.9	1.6
Amoxicillin-clavulanate	4	16	0.25–>32	79.2	13.7	7.1
Ciprofloxacin	≤0.06	>16	≤0.06–>16	76.2	0.1	23.7
Tigecycline[c]	0.25	0.5	0.12–2	100	0	0
Trimethoprim-sulfamethoxazole	≤0.12	>8	≤0.12–>8	72.6	0	27.4
Amikacin	2	4	≤1–>64	99.5	0.4	0.1
Gentamicin	≤0.5	4	≤0.5–>32	90.2	0.4	9.4
Klebsiella pneumoniae (702)						
Ceftaroline-avibactam	0.06	0.12	≤0.03–2	99.7	0.1	0.1
Ceftaroline	0.12	0.5	≤0.03–>16	93.7	1.3	5.0
Cefepime	≤0.25	≤0.25	≤0.25–64	99.0	0.3	0.8
Ceftriaxone	≤0.25	≤0.25	≤0.25–>64	95.7	0.6	3.7
Ceftazidime	≤0.25	1	≤0.25–>32	96.2	0.1	3.7
Cefoxitin	2	8	0.25–>32	91.7	4.4	3.8
Cefazolin	1	4	≤0.5–>128	87.9	4.1	8.0
Meropenem	≤0.03	≤0.03	≤0.03–8	99.9	0	0.1
Ertapenem	≤0.03	≤0.03	≤0.03–16	99.3	0.6	0.1
Piperacillin-tazobactam	2	8	≤1–>512	97.6	0.9	1.6
Amoxicillin-clavulanate	2	8	0.5–>32	93.0	2.9	4.1
Ciprofloxacin	≤0.06	0.5	≤0.06–>16	94.2	1.1	4.7
Tigecycline	1	1	0.06–16	94.9	4.3	0.9
Trimethoprim-sulfamethoxazole	≤0.12	2	≤0.12–>8	90.9		9.1
Amikacin	≤1	≤1	≤1–>64	99.9	0	0.1
Gentamicin	≤0.5	≤0.5	≤0.5–>32	97.6	0	2.4
Enterobacter cloacae (283)						
Ceftaroline-avibactam	0.12	0.5	≤0.03–8	97.2	2.1	0.7
Ceftaroline	0.25	>16	≤0.03–>16	71.4	1.8	26.9
Cefepime	≤0.25	2	≤0.25–32	98.8	0.6	0.6
Ceftriaxone	≤0.25	>64	≤0.25 > 64	71.7	1.8	26.5
Ceftazidime	0.5	>32	≤0.25–>32	74.6	0.7	24.7
Cefoxitin	>32	>32	2–>32	4.6	3.2	92.2
Cefazolin	>128	>128	2–>128	1.1	1.8	97.2
Meropenem	≤0.03	0.12	≤0.03–2	99.3	0.7	0
Ertapenem	0.06	1	≤0.03–32	87.3	6.7	6.0
Piperacillin-tazobactam	2	64	≤1–256	82.3	7.8	9.9
Amoxicillin-clavulanate	>32	>32	4–>32	2.8	3.2	94.0
Ciprofloxacin	≤0.06	0.25	≤0.06–>16	93.6	2.5	3.9
Tigecycline	0.5	1	0.25–8	95.4	3.5	1.1
Trimethoprim-sulfamethoxazole	≤0.12	1	≤0.12–>8	91.5		8.5
Amikacin	≤1	2	≤1–16	100	0	0
Gentamicin	≤0.5	≤0.5	≤0.5–>32	96.8	0	3.2
Serratia marcescens (198)						
Ceftaroline-avibactam	0.25	0.5	0.12–2	91.4	6.1	2.5
Ceftaroline	0.5	2	0.25–>16	54.0	29.8	16.2
Cefepime	≤0.25	≤0.25	≤0.25–0.5	100	0	0
Ceftriaxone	≤0.25	1	≤0.25–8	92.4	2.0	5.6
Ceftazidime	≤0.25	1	≤0.25–4	100	0	0

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TABLE 1 (Continued)

Organism (no. of isolates tested) and drug	MIC (μg/ml)			% of isolates[d]		
	50%	90%	Range	Susceptible	Intermediate	Resistant
Cefoxitin	16	>32	4–>32	22.3	48.2	29.4
Cefazolin	>128	>128	2–>128	1.0	0	99.0
Meropenem	0.06	0.06	≤0.03–0.5	100	0	0
Ertapenem	≤0.03	0.12	≤0.03–2	99.0	0.5	0.5
Piperacillin-tazobactam	≤1	4	≤1–256	95.5	3.5	1.0
Amoxicillin-clavulanate	>32	>32	≤0.06–>32	3.6	2.5	93.9
Ciprofloxacin	≤0.06	2	≤0.06–>16	88.9	5.1	6.1
Tigecycline	2	2	1–8	92.4	7.1	0.5
Trimethoprim-sulfamethoxazole	0.5	1	≤0.12–>8	95.9		4.1
Amikacin	2	2	≤1–16	100	0	0
Gentamicin	≤0.5	1	≤0.5–>32	98.5	0.5	1.0
Klebsiella oxytoca (188)						
Ceftaroline-avibactam	≤0.03	0.12	≤0.03–2	99.5	0	0.5
Ceftaroline	0.12	8	≤0.03–>16	85.6	2.1	12.2
Cefepime	≤0.25	≤0.25	≤0.25–2	100	0	0
Ceftriaxone	≤0.25	0.5	≤0.25–>64	93.6	1.1	5.3
Ceftazidime	≤0.25	0.5	≤0.25–>32	98.9	0	1.1
Cefoxitin	2	8	0.5–>32	97.9	0.5	1.6
Cefazolin	4	>128	1–>128	29.8	28.7	41.5
Meropenem	≤0.03	≤0.03	≤0.03–1	100	0	0
Ertapenem	≤0.03	≤0.03	≤0.03–2	99.5	0	0.5
Piperacillin-tazobactam	2	128	≤1–>512	88.8	1.1	10.1
Amoxicillin-clavulanate	2	16	1–>32	87.2	5.3	7.4
Ciprofloxacin	≤0.06	≤0.06	≤0.06–>16	96.8	1.1	2.1
Tigecycline	0.5	1	0.06–2	100	0	0
Trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12–>8	96.8		3.2
Amikacin	≤1	2	≤1–4	100	0	0
Gentamicin	≤0.5	≤0.5	≤0.5–16	99.5	0	0.5
Proteus mirabilis (165)						
Ceftaroline-avibactam	0.06	0.12	≤0.03–0.5	100	0	0
Ceftaroline	0.12	0.25	≤0.03–>16	93.9	1.8	4.2
Cefepime	≤0.25	≤0.25	≤0.25–1	100	0	0
Ceftriaxone	≤0.25	≤0.25	≤0.25–16	97.0	2.4	0.6
Ceftazidime	≤0.25	≤0.25	≤0.25–32	99.4	0	0.6
Cefoxitin	4	4	1–>32	95.8	2.4	1.8
Cefazolin	4	8	1–>128	4.2	63.6	32.1
Meropenem	0.06	0.12	≤0.03–0.25	100	0	0
Ertapenem	≤0.03	≤0.03	≤0.03–0.12	100	0	0
Piperacillin-tazobactam	≤1	≤1	≤1–8	100	0	0
Amoxicillin-clavulanate	1	8	0.5–>32	93.9	1.8	4.2
Ciprofloxacin	≤0.06	2	≤0.06–>16	89.1	3.6	7.3
Tigecycline	4	8	1–16	14.5	47.9	37.6
Trimethoprim-sulfamethoxazole	≤0.12	>8	≤0.12–>8	80.6		19.4
Amikacin	2	4	≤1–16	100	0	0
Gentamicin	≤0.5	1	≤0.5–>32	94.5	1.2	4.2
Enterobacter aerogenes (97)						
Ceftaroline-avibactam	0.06	0.12	≤0.03–2	96.9	1.0	2.1
Ceftaroline	0.12	8	≤0.03–>16	73.2	6.2	20.6
Cefepime	≤0.25	≤0.25	≤0.25–4	100	0	0
Ceftriaxone	≤0.25	16	≤0.25–>64	72.2	2.1	25.8
Ceftazidime	0.5	32	≤0.25–>32	77.3	4.1	18.6
Cefoxitin	>32	>32	0.25–>32	9.3	1.0	89.7
Cefazolin	32	>128	1–>128	10.3	6.2	83.5
Meropenem	≤0.03	0.12	≤0.03–2	99.0	1.0	0
Ertapenem	0.12	0.5	≤0.03–16	90.7	6.2	3.1
Piperacillin-tazobactam	4	16	≤1–128	90.6	7.3	2.1
Amoxicillin-clavulanate	>32	>32	2–>32	8.3	3.1	88.5

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TABLE 1 (Continued)

Organism (no. of isolates tested) and drug	MIC (μg/ml)			% of isolates[d]		
	50%	90%	Range	Susceptible	Intermediate	Resistant
Ciprofloxacin	≤0.06	0.5	≤0.06–8	94.8	0	5.2
Tigecycline	1	1	0.25–8	94.8	4.2	1.0
Trimethoprim-sulfamethoxazole	≤0.12	0.5	≤0.12–8	99.0		1.0
Amikacin	≤1	2	≤1–8	100	0	0
Gentamicin	≤0.5	≤0.5	≤0.5–1	100	0	0
Citrobacter freundii (49)						
Ceftaroline-avibactam	0.06	0.12	≤0.03–0.5	100	0	0
Ceftaroline	0.12	8	≤0.03–>16	81.6	2.0	16.3
Cefepime	≤0.25	≤0.25	≤0.25–0.5	100	0	0
Ceftriaxone	≤0.25	16	≤0.25–>64	85.7	2.0	12.2
Ceftazidime	0.5	32	≤0.25–>32	85.7	0	14.3
Cefoxitin	>32	>32	2–>32	10.2	6.1	83.7
Cefazolin	32	>128	2–>128	4.1	4.1	91.8
Meropenem	≤0.03	0.06	≤0.03–0.5	100	0	0
Ertapenem	≤0.03	0.06	≤0.03–2	98.0	0	2.0
Piperacillin-tazobactam	2	16	≤1–256	91.8	6.1	2.0
Amoxicillin-clavulanate	>32	>32	0.5–>32	10.2	14.3	75.5
Ciprofloxacin	≤0.06	0.5	≤0.06–>16	91.8	2.0	6.1
Tigecycline	0.5	1	0.25–8	95.9	2.0	2.0
Trimethoprim-sulfamethoxazole	≤0.12	>8	≤0.12–>8	79.6		20.4
Amikacin	≤1	2	≤1–8	100	0	0
Gentamicin	≤0.5	32	≤0.5–>32	83.7	0	16.3
Morganella morganii (35)						
Ceftaroline-avibactam	≤0.03	0.12	≤0.03–0.25	100	0	0
Ceftaroline	0.06	2	≤0.03–16	80.0	8.6	11.4
Cefepime	≤0.25	≤0.25	≤0.25	100	0	0
Ceftriaxone	≤0.25	≤0.25	≤0.25–1	100	0	0
Ceftazidime	≤0.25	4	≤0.25–16	91.4	5.7	2.9
Cefoxitin	8	16	2–>32	77.1	20.0	2.9
Cefazolin	128	>128	64–>128	0	0	100
Meropenem	0.06	0.12	≤0.03–0.25	100	0	0
Ertapenem	≤0.03	≤0.03	≤0.03–1	97.1	2.9	0
Piperacillin-tazobactam	≤1	≤1	≤1	100	0	0
Amoxicillin-clavulanate	>32	>32	>32	0	0	100
Ciprofloxacin	≤0.06	1	≤0.06–8	91.4	0	8.6
Tigecycline	2	4	1–4	80.0	20.0	0
Trimethoprim-sulfamethoxazole	≤0.12	>8	≤0.12–>8	77.1		22.9
Amikacin	2	4	≤1–4	100	0	0
Gentamicin	≤0.5	16	≤0.5–>32	88.8	0	11.4
Pseudomonas aeruginosa (969)						
Ceftaroline-avibactam	4	16	≤0.03–>16	NA	NA	NA
Ceftaroline	16	>16	0.12–>16	NA	NA	NA
Cefepime	4	16	≤0.25–>64	87.9	9.6	2.5
Ceftazidime	4	32	≤0.25–>32	83.1	5.9	11.0
Meropenem	0.5	8	≤0.03–>32	81.8	7.8	10.3
Piperacillin-tazobactam	4	32	≤1–>512	84.7	9.5	5.8
Ciprofloxacin	0.25	4	≤0.06–>16	77.8	8.4	13.8
Amikacin	4	16	≤1–>64	92.9	3.5	3.6
Gentamicin	2	8	≤0.5–>32	83.8	6.7	9.5
Colistin	1	2	0.25–>16	96.2	2.2	1.7
Stenotrophomonas maltophilia (174)						
Ceftaroline-avibactam	>16	>16	0.12–>16	NA	NA	NA
Ceftaroline	>16	>16	0.12–>16	NA	NA	NA
Ceftazidime	>32	>32	1–>32	23.6	7.5	69.0
Trimethoprim-sulfamethoxazole	0.5	8	≤0.12–>8	84.5		15.5

(Continued on following page)

TABLE 1 (Continued)

Organism (no. of isolates tested) and drug	MIC (μg/ml)			% of isolates[d]		
	50%	90%	Range	Susceptible	Intermediate	Resistant
Acinetobacter baumannii (54)						
Ceftaroline-avibactam	2	8	0.5–>16	NA	NA	NA
Ceftaroline	2	8	0.5–>16	NA	NA	NA
Cefepime	2	16	0.5–64	88.5	3.8	7.7
Ceftriaxone	8	32	4–>64	53.7	38.9	7.4
Ceftazidime	8	32	1–>32	81.5	5.6	13.0
Meropenem	0.5	1	0.12–>32	98.1	0	1.9
Piperacillin-tazobactam	≤1	32	≤1–512	87.0	5.6	7.4
Ciprofloxacin	0.12	1	≤0.06–>16	92.6	1.9	5.6
Trimethoprim-sulfamethoxazole	0.25	2	≤0.12–>8	92.6		7.4
Amikacin	2	4	≤1–>64	96.3	0	3.7
Gentamicin	≤0.5	2	≤0.5–>32	94.4	1.9	3.7
Colistin	1	1	0.25–4	98.2		1.9
Haemophilus influenzae (252)[e]						
Ceftaroline-avibactam	≤0.03	≤0.03	≤0.03–0.06	100		
Ceftaroline	≤0.03	≤0.03	≤0.03–4	99.6		0.4
Ceftriaxone	≤0.06	≤0.06	≤0.06–0.25	100		
Cefuroxime	≤0.25	2	≤0.25–16	99.2	0.4	0.4
Meropenem	≤0.06	≤0.06	≤0.06–0.25	100		
Ertapenem	≤0.03	0.06	≤0.03–0.5	100		
Piperacillin-tazobactam	≤1	≤1	≤1–2	99.6		0.4
Amoxicillin-clavulanate	0.5	1	≤0.06–4	100		0
Ampicillin	≤0.25	8	≤0.25–>128	78.2	2.4	19.4
Ciprofloxacin	≤0.015	≤0.015	≤0.015–0.06	100		
Clarithromycin	8	16	≤0.03–32	75.0	22.2	2.8
Trimethoprim-sulfamethoxazole	≤0.12	4	≤0.12–>8	86.5	3.2	10.3

[a] Ceftaroline-avibactam MICs were interpreted by using ceftaroline MIC breakpoints (18).
[b] Isolates were tested against cefepime in 2011 and 2012 only (1,146 *E. coli*, 593 *P. aeruginosa*, 395 *K. pneumoniae*, 173 *K. oxytoca*, 113 *E. cloacae*, 109 *S. marcescens*, 85 *P. mirabilis*, 55 *E. aerogenes*, 26 *A. baumannii*, 24 *C. freundii*, and 21 *M. morganii* isolates).
[c] Tigecycline MICs were interpreted by using breakpoints defined by the FDA.
[d] NA, MIC breakpoints not available in CLSI document M100-S23 (18).
[e] Isolates of *H. influenzae* tested were from 2010 and 2011 only.

positive for CTX-M-15 and SHV-168, 1 was positive for CTX-M-27 and SHV-11, and 2 had no ESBL identified genetically; the *in vitro* activity of ceftaroline-avibactam was consistent against the isolates harboring each of these enzymes.

The *in vitro* activities of ceftaroline-avibactam, ceftaroline, and comparative agents tested against Gram-positive pathogens are summarized in Table 3. The addition of avibactam to ceftaroline did not impact the activity of ceftaroline against any of the Gram-positive organisms tested. Ceftaroline-avibactam and ceftaroline inhibited all methicillin-susceptible *S. aureus* and methicillin-susceptible *S. epidermidis* isolates at a concentration of 0.5 μg/ml; all isolates of methicillin-resistant *S. epidermidis* had MICs of ceftaroline and ceftaroline-avibactam of ≤1 μg/ml. One isolate of methicillin-resistant *S. aureus* (0.2% of isolates) had a ceftaroline-avibactam MIC of 2 μg/ml; two isolates (0.4% of isolates) had a ceftaroline MIC of 2 μg/ml.

Against streptococci including *S. pneumoniae*, ceftaroline-avibactam and ceftaroline MICs (MIC_{90}, ≤0.03 μg/ml) were lower than those of penicillin and meropenem (Table 3). All isolates of *S. pyogenes* and *S. agalactiae* were inhibited by ceftaroline and ceftaroline-avibactam at concentrations of ≤0.03 μg/ml.

DISCUSSION

The effectiveness of β-lactams against Gram-negative bacteria has declined over time because of the emergence and spread of β-lactamase enzymes, some of which are not affected by currently marketed β-lactam/β-lactamase inhibitor combinations. Current marketed β-lactamase inhibitors (clavulanic acid, tazobactam, and sulbactam) inactivate only class A β-lactamases and are clinically ineffective against class C and class D β-lactamases (16, 26). Ceftaroline-avibactam was substantially more potent than ceftaroline against all species of *Enterobacteriaceae* tested, with the exception of *P. mirabilis*, for which equivalent activity was observed (Table 1). Ceftaroline-avibactam demonstrated potent *in vitro* activity against ESBL-positive and AmpC-positive isolates of *E. coli* and ESBL-positive isolates of *K. pneumoniae*. If the ceftaroline FDA susceptibility breakpoint for *Enterobacteriaceae* (susceptible, ≤0.5 μg/ml) was used for ceftaroline-avibactam, the susceptibility rate was >99% (3,846/3,879 isolates) for all *Enterobacteriaceae* tested. Ceftaroline is known to be hydrolyzed by ESBL, AmpC, KPC, and metallo-β-lactamases, and its *in vitro* activity is reflected by the prevalence of these enzymes in isolate collections (9, 27, 28, 29). Isolates of *Enterobacteriaceae* collected by the CANWARD surveillance study in 2009 (2) demonstrated levels of susceptibility to ceftaroline similar to those reported in the current study from 2010 to 2012 (Table 1).

Mushtaq and colleagues reported that ceftaroline is a weak inducer of AmpC β-lactamases at or below their MIC, similar to other oxyimino-cephalosporins, and suggested that the addition

TABLE 2 *In vitro* activities of ceftaroline-avibactam, ceftaroline, and comparators against ESBL- and AmpC-producing *E. coli* and *K. pneumoniae* isolates

Organism (no. of isolates tested) and drug	MIC (μg/ml)			% of isolates		
	50%	90%	Range	Susceptible	Intermediate	Resistant
ESBL-producing *E. coli* (114)						
Ceftaroline-avibactam[a]	≤0.03	0.06	≤0.03–0.12	100	0	0
Ceftaroline	>16	>16	2–>16	0	0	100
Cefepime[b]	8	32	≤0.25–>64	63.1	21.4	15.5
Ceftriaxone	>64	>64	4–>64	0	0	100
Ceftazidime	16	>32	1–>32	30.7	7.0	62.3
Cefoxitin	8	16	1–>32	81.6	13.2	5.3
Cefazolin	>128	>128	32–>128	0	0	100
Meropenem	≤0.03	≤0.03	≤0.03–0.12	100	0	0
Ertapenem	0.06	0.25	≤0.03–2	97.4	0.9	1.8
Piperacillin-tazobactam	4	16	≤1–256	93.9	4.4	1.8
Amoxicillin-clavulanate	16	32	1–>32	34.2	51.8	14.0
Ciprofloxacin	>16	>16	≤0.06–>16	7.0	0.9	92.1
Tigecycline[c]	0.5	1	0.12–2	100	0	0
Trimethoprim-sulfamethoxazole	>8	>8	≤0.12–>8	38.6		61.4
Amikacin	2	8	≤1–32	96.5	3.5	0
Gentamicin	1	>32	≤0.5–>32	57.9	0	42.1
AmpC-producing *E. coli* (57)						
Ceftaroline-avibactam	0.06	0.12	≤0.03–1	98.3	1.8	0
Ceftaroline	4	16	0.12–>16	35.1	3.5	61.4
Cefepime	≤0.25	0.5	≤0.25–2	100	0	0
Ceftriaxone	8	32	≤0.25–>64	40.4	5.3	54.4
Ceftazidime	16	>32	1–>32	35.1	10.5	54.4
Cefoxitin	>32	>32	32–>32	0	0	100
Cefazolin	>128	>128	4–>128	0	3.5	96.5
Meropenem	≤0.03	≤0.03	≤0.03–0.12	100	0	0
Ertapenem	0.06	0.25	≤0.03–1	98.3	1.8	0
Piperacillin-tazobactam	4	16	≤1–>512	94.7	1.8	3.5
Amoxicillin-clavulanate	>32	>32	8–>32	5.3	10.5	84.2
Ciprofloxacin	≤0.06	>16	≤0.06–>16	73.7	0	26.3
Tigecycline	0.5	1	0.12–2	100	0	0
Trimethoprim-sulfamethoxazole	≤0.12	>8	≤0.12–>8	70.2		29.8
Amikacin	2	4	≤1–>64	98.2	0	1.8
Gentamicin	≤0.5	32	≤0.5–>32	87.7	0	12.3
Non-ESBL-, non-AmpC-producing *E. coli* (1,991)						
Ceftaroline-avibactam	≤0.03	0.06	≤0.03–1	99.9	0.1	0
Ceftaroline	0.06	0.25	≤0.03–>16	96.4	1.9	1.7
Cefepime	≤0.25	≤0.25	≤0.25–16	99.9	0.1	0
Ceftriaxone	≤0.25	≤0.25	≤0.25–64	99.4	0.1	0.6
Ceftazidime	≤0.25	0.5	≤0.25–>32	99.6	0.1	0.3
Cefoxitin	4	8	≤0.06–>32	94.7	4.7	0.6
Cefazolin	2	4	≤0.5–>128	78.5	11.9	9.6
Meropenem	≤0.03	≤0.03	≤0.03–1	100	0	0
Ertapenem	≤0.03	≤0.03	≤0.03–8	99.9	0	0.1
Piperacillin-tazobactam	≤1	4	≤1–>512	97.8	0.7	1.5
Amoxicillin-clavulanate	4	16	0.25–>32	84.0	11.6	4.4
Ciprofloxacin	≤0.06	>16	≤0.06–>16	80.2	0.1	19.7
Tigecycline	0.25	0.5	0.12–2	100	0	0
Trimethoprim-sulfamethoxazole	≤0.12	>8	≤0.12–>8	74.6		25.4
Amikacin	2	4	≤1–32	99.7	0.3	0
Gentamicin	≤0.5	2	≤0.5–>32	92.1	0.5	7.4
ESBL-producing *K. pneumoniae* (25)						
Ceftaroline-avibactam	0.06	0.5	≤0.03–1	96.0	4.0	0
Ceftaroline	>16	>16	0.5–>16	4.0	4.0	92.0
Cefepime	4	32	≤0.25–32	80.0	6.7	13.3
Ceftriaxone	64	>64	≤0.25–>64	8.0	8.0	84.0

(Continued on following page)

TABLE 2 (Continued)

Organism (no. of isolates tested) and drug	MIC (μg/ml)			% of isolates		
	50%	90%	Range	Susceptible	Intermediate	Resistant
Ceftazidime	32	>32	0.25–>32	20.0	4.0	76.0
Cefoxitin	4	>32	2–>32	80.0	4.0	16.0
Cefazolin	>128	>128	8–>128	0	0	100
Meropenem	≤0.03	0.06	≤0.03–0.12	100	0	0
Ertapenem	0.06	0.5	≤0.03–1	96.0	4.0	0
Piperacillin-tazobactam	8	128	2–512	72.0	16.0	12.0
Amoxicillin-clavulanate	16	32	4–>32	32.0	36.0	32.0
Ciprofloxacin	2	>16	≤0.06–>16	40.0	12.0	48.0
Tigecycline	1	4	0.5–16	88.0	4.0	8.0
Trimethoprim-sulfamethoxazole	>8	>8	0.25–>8	24.0		76.0
Amikacin	≤1	16	≤1–>64	96.0	0	4.0
Gentamicin	≤0.5	>32	≤0.5–>32	56.0	0	44.0
Non-ESBL-producing *K. pneumoniae* (677)						
Ceftaroline-avibactam	0.06	0.12	≤0.03–2	99.8	0	0.2
Ceftaroline	0.12	0.25	≤0.03–>16	97.0	1.2	1.8
Cefepime	≤0.25	≤0.25	≤0.25–64	99.7	0	0.3
Ceftriaxone	≤0.25	≤0.25	≤0.25–>64	99.0	0.3	0.7
Ceftazidime	≤0.25	0.5	≤0.25–>32	99.0	0	1.0
Cefoxitin	2	8	0.25–>32	92.2	4.4	3.4
Cefazolin	1	2	≤0.5–>128	91.1	4.3	4.6
Meropenem	≤0.03	≤0.03	≤0.03–8	99.9	0	0.1
Ertapenem	≤0.03	≤0.03	≤0.03–16	99.4	0.4	0.2
Piperacillin-tazobactam	2	8	≤1–>512	98.5	0.3	1.2
Amoxicillin-clavulanate	2	8	0.5–>32	95.3	1.6	3.1
Ciprofloxacin	≤0.06	0.25	≤0.06–>16	96.2	0.7	3.1
Tigecycline	1	1	0.06–8	95.1	4.3	0.6
Trimethoprim-sulfamethoxazole	≤0.12	1	≤0.12–>8	93.3		6.7
Amikacin	≤1	≤1	≤1–8	100	0	0
Gentamicin	≤0.5	≤0.5	≤0.5–>32	99.1	0	0.9

[a] Ceftaroline-avibactam MICs were interpreted by using ceftaroline MIC breakpoints (18).
[b] Isolates were tested against cefepime in 2011 and 2012 only (1,031 non-ESBL-producing *E. coli*, 84 ESBL-producing *E. coli*, 30 AmpC-producing *E. coli*, 380 non-ESBL-producing *K. pneumoniae*, and 15 ESBL-producing *K. pneumoniae* isolates).
[c] Tigecycline MICs were interpreted by using breakpoints defined by the FDA.

of avibactam to ceftaroline is best suited for indications where AmpC-inducible *Enterobacteriaceae* are likely, such as nosocomial pneumonia, because avibactam inhibits hydrolysis by AmpC and many other β-lactamases, excluding metallo-β-lactamases (12, 30). A previous mutational study demonstrated that stable resistant mutants were difficult to select for with ceftaroline-avibactam (11).

Ceftaroline-avibactam and ceftaroline demonstrated equivalent *in vitro* activities against the Gram-positive pathogens tested (*S. aureus*, *S. epidermidis*, *S. pneumoniae*, and *S. pyogenes*). All isolates of methicillin-sensitive *S. aureus* (MSSA), *S. pneumoniae*, *S. pyogenes*, and *S. agalactiae* were susceptible to ceftaroline. Ceftaroline's enhanced potency, compared with those of other broad-spectrum cephalosporins and penicillins, is due to its enhanced affinity for target penicillin-binding proteins, PBP2a in MRSA and PBP2X in penicillin-nonsusceptible *S. pneumoniae* (31). Ceftaroline demonstrates potent activity against health care-associated and community-associated MRSA genotypes as well as bactericidal activity against vancomycin-intermediate *S. aureus* (VISA), heteroresistant VISA (hVISA), vancomycin-resistant *S. aureus* (VRSA), and daptomycin-nonsusceptible *S. aureus* (MIC_{90}s, 0.5 to 1 μg/ml; MIC ranges, 0.12 to 1 μg/ml) (5). Ceftaroline also retains its potency against coagulase-negative staphylococci with reduced susceptibility to linezolid, daptomycin, and vancomycin (32). The current study found >99% of isolates of MRSA, including both health care-associated and community-associated isolates of MRSA, to be susceptible to ceftaroline-avibactam and ceftaroline, similar to results reported by other investigators (5, 27–29). Isolates of MRSA collected by the CANWARD surveillance study in 2009 (2) demonstrated an MIC_{90} (1 μg/ml) identical to the one reported by the current study for isolates tested from 2010 to 2012. Mushtaq and colleagues reported that they were unable to select higher-level resistance to ceftaroline in MSSA, MRSA, and VISA isolates by using an *in vitro* multistep procedure at four times the MIC (9).

Ceftaroline demonstrated 2- to 4-fold more potent activity than ceftriaxone against isolates of *S. pneumoniae* (Table 3). Previously, ceftaroline was reported to demonstrate 4- to 16-fold more activity than ceftriaxone against multidrug-resistant isolates of *S. pneumoniae*. All isolates of *S. pneumoniae* tested were susceptible to ceftaroline (MIC, ≤0.25 μg/ml).

Ceftaroline fosamil-avibactam is currently in phase 1 and phase 2 clinical trials in the United States (http://clinicaltrials.gov/). A murine thigh infection model (33) and an *in vitro* hollow-fiber

TABLE 3 *In vitro* activities of ceftaroline-avibactam, ceftaroline, and comparators against Gram-positive pathogens

Organism (no. of isolates tested) and drug	MIC (μg/ml)			% of isolates[c]		
	50%	90%	Range	Susceptible	Intermediate	Resistant
Methicillin-susceptible *Staphylococcus aureus* (2,037)						
Ceftaroline-avibactam[a]	0.25	0.25	≤0.03–0.5	100	0	0
Ceftaroline	0.25	0.25	≤0.03–0.5	100	0	0
Cefepime[b]	2	4	≤0.25–16	NA	NA	NA
Ceftriaxone	4	4	≤0.25–64	NA	NA	NA
Cefazolin	≤0.5	≤0.5	≤0.5–32	NA	NA	NA
Meropenem	0.12	0.25	≤0.03–4	NA	NA	NA
Piperacillin-tazobactam	≤1	≤1	≤1–32	NA	NA	NA
Vancomycin	1	1	≤0.12–2	100	0	0
Daptomycin	0.25	0.25	≤0.03–1	100		
Linezolid	2	4	≤0.12–4	100		0
Clindamycin	≤0.12	≤0.12	≤0.12–>8	94.1	0.1	5.8
Doxycycline[d]	≤0.12	0.25	≤0.12–16	98.9	0.7	0.4
Tigecycline[e]	0.12	0.25	0.06–1	100	0	0
Trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12–>8	99.6		0.4
Methicillin-resistant *Staphylococcus aureus* (502)[f]						
Ceftaroline-avibactam	0.5	1	0.25–2	99.8	0.2	0
Ceftaroline	0.5	1	0.25–2	99.6	0.4	0
Cefepime	64	>64	4–>64	NA	NA	NA
Ceftriaxone	>64	>64	4–>64	NA	NA	NA
Cefazolin	32	>128	1–>128	NA	NA	NA
Meropenem	4	32	0.12–>32	NA	NA	NA
Piperacillin-tazobactam	32	128	2–256	NA	NA	NA
Vancomycin	1	1	0.5–2	100	0	0
Daptomycin	0.25	0.5	0.06–2	99.8		0.2
Linezolid	2	4	≤0.12–4	100		0
Clindamycin	≤0.12	>8	≤0.12–>8	61.0	0	39.0
Doxycycline	≤0.12	0.5	≤0.12–16	98.9	0.7	0.4
Tigecycline	0.12	0.5	0.06–1	98.8	0	1.2
Trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12–>8	96.4		3.6
Methicillin-susceptible *Staphylococcus epidermidis* (265)						
Ceftaroline-avibactam	0.25	0.25	≤0.03–0.5	NA	NA	NA
Ceftaroline	0.25	0.5	≤0.03–0.5	NA	NA	NA
Cefepime	4	16	≤0.25–>64	NA	NA	NA
Ceftriaxone	8	32	≤0.25–>64	NA	NA	NA
Cefazolin	1	4	≤0.5–8	NA	NA	NA
Meropenem	1	16	≤0.03–32	NA	NA	NA
Piperacillin-tazobactam	≤1	4	≤1–64	NA	NA	NA
Vancomycin	1	2	≤0.12–2	100	0	0
Daptomycin	0.12	0.25	≤0.03–0.5	100		
Linezolid	0.5	1	≤0.12–4	100		0
Clindamycin	≤0.12	>8	≤0.12–>8	62.1	1.5	36.4
Doxycycline	0.25	1	≤0.12–32	95.9	3.3	0.8
Tigecycline	0.12	0.5	≤0.03–1	98.1	0	1.9
Trimethoprim-sulfamethoxazole	≤0.12	8	≤0.12–>8	66.8		33.2
Methicillin-resistant *Staphylococcus epidermidis* (52)						
Ceftaroline-avibactam	0.5	0.5	0.25–1	NA	NA	NA
Ceftaroline	0.5	0.5	0.25–1	NA	NA	NA
Cefepime	>64	>64	16–>64	NA	NA	NA
Ceftriaxone	>64	>64	16–>64	NA	NA	NA
Cefazolin	128	128	32–>128	NA	NA	NA
Meropenem	32	32	4–>32	NA	NA	NA
Piperacillin-tazobactam	32	64	≤1–128	NA	NA	NA
Vancomycin	1	2	≤0.12–2	100	0	0
Daptomycin	0.12	0.25	≤0.03–0.25	100		
Linezolid	1	1	≤0.12–2	100		0

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TABLE 3 (Continued)

Organism (no. of isolates tested) and drug	MIC (μg/ml)			% of isolates[c]		
	50%	90%	Range	Susceptible	Intermediate	Resistant
Clindamycin	>8	>8	≤0.12–>8	19.2	0	80.8
Doxycycline	0.5	1	≤0.12–1	100	0	0
Tigecycline	0.12	0.25	0.06–0.5	100	0	0
Trimethoprim-sulfamethoxazole	4	8	≤0.12–>8	15.4		84.6
Streptococcus pneumoniae (540)						
Ceftaroline-avibactam	≤0.03	0.03	≤0.03–0.25	100		
Ceftaroline	≤0.03	0.03	≤0.03–0.25	100		
Ceftriaxone	≤0.12	≤0.12	≤0.12–4	99.1	0.7	0.2
Cefuroxime	≤0.25	≤0.25	≤0.25–16	92.2	1.7	6.1
Penicillin[g]	≤0.03	0.25	≤0.03–8	84.7	10.7	4.6
Meropenem	≤0.06	0.12	≤0.06–1	93.3	3.3	3.3
Vancomycin	0.25	0.5	≤0.12–1	100		
Linezolid	1	1	≤0.12–2	100		
Trimethoprim-sulfamethoxazole	0.25	2	≤0.12–>8	83.9	6.5	9.6
Streptococcus pyogenes (154)						
Ceftaroline-avibactam	≤0.03	≤0.03	≤0.03	100		
Ceftaroline	≤0.03	≤0.03	≤0.03	100		
Ceftriaxone	≤0.12	≤0.12	≤0.12–0.25	100		
Penicillin	≤0.03	≤0.03	≤0.03–0.06	100		
Meropenem	≤0.06	≤0.06	≤0.06–0.12	100		
Vancomycin	0.5	0.5	0.25–1	100		
Daptomycin	0.06	0.12	≤0.03–0.12	100		
Linezolid	1	1	0.25–2	100		
Clarithromycin	≤0.03	1	≤0.03–>32	86.4	1.9	11.7
Tigecycline	0.03	0.06	≤0.015–0.25	100		
Streptococcus agalactiae (93)[h]						
Ceftaroline-avibactam	≤0.008	0.015	≤0.008–0.015	100		
Ceftaroline	≤0.015	≤0.015	≤0.008–0.03	100		
Ceftriaxone	≤0.12	≤0.12	≤0.12	100		
Penicillin	0.06	0.06	≤0.03–0.12	100		
Meropenem	≤0.06	≤0.06	≤0.06	100		
Vancomycin	0.5	0.5	0.25–0.5	100		
Daptomycin	0.25	0.25	≤0.03–0.5	100		
Linezolid	1	2	0.25–2	100		
Clarithromycin	≤0.03	32	≤0.03–>32	67.7	5.4	26.9
Tigecycline	0.06	0.06	≤0.015–0.12	100		

[a] Ceftaroline-avibactam MICs were interpreted by using ceftaroline MIC breakpoints (18).
[b] Isolates were tested against cefepime in 2011 and 2012 only.
[c] NA, MIC breakpoints not available in CLSI document M100-S23 (18).
[d] Isolates of staphylococci were tested against doxycycline in 2011 and 2012 only (1,206 methicillin-susceptible *S. aureus*, 279 methicillin-resistant *S. aureus*, 121 methicillin-susceptible *S. epidermidis*, and 21 methicillin-susceptible *S. epidermidis* isolates).
[e] Tigecycline MICs were interpreted by using breakpoints defined by the FDA. Isolates of *S. aureus* testing as nonsusceptible to tigecycline were reported as resistant.
[f] The 502 MRSA (*mecA*-positive) isolates included 189 community-associated isolates (CMRSA7 [USA400] and CMRSA10 [USA300]), 291 genotypically defined health care-associated isolates (various genotypes), and 22 *mecA*-positive isolates with unique staphylococcal protein A (*spa*) types.
[g] Penicillin MICs interpreted by using oral penicillin V breakpoints in CLSI document M100-S23 (18).
[h] Isolates of *S. agalactiae* tested were from 2011 and 2012 only.

infection model (34) have both demonstrated the efficacy of ceftaroline-avibactam against infections established by ESBL-, KPC-, and AmpC-producing *Enterobacteriaceae* when dosed every 8 h.

In conclusion, ceftaroline-avibactam demonstrated potent *in vitro* activity against a recent collection of frequently isolated *Enterobacteriaceae*, including ESBL- and AmpC-producing *E. coli* and ESBL-producing *K. pneumoniae*, *H. influenzae*, and Gram-positive bacterial pathogens (MRSA, *S. pneumoniae*, *S. pyogenes*, and *S. agalactiae*), from patients seeking treatment at hospitals across Canada.

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