Antimicrobial Spectrum and Potency of Ceftaroline-Avibactam when Tested against Bacterial Isolates from Complicated Urinary Tract Infections in the United States

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HS SADER, M CASTANHEIRA, RN JONES
JMI Laboratories, North Liberty, Iowa, USA

Helio S. Sader, M.D., Ph.D.
JMI Laboratories
www.jmilabs.com
ph. 319.665.3370, fax 319.665.3371
helio-sader@jmilabs.com

Abstract

Objective: To evaluate the activity of ceftaroline combined with avibactam (at fixed 4 mg/L) against isolates from complicated urinary tract infections (cUTI) collected in USA medical centres. Ceftaroline is a broad-spectrum cephalosporin and avibactam is a novel non-β-lactam β-lactamase (BL) inhibitor that inhibits Ambler class A, C, and some D enzymes.

Methods: Ceftaroline-avibactam and comparators were tested for susceptibility by CLSI broth microdilution methods against 1131 strains, including *Escherichia coli* (348; 8.0% ESBL-phenotype), *Klebsiella* spp. (326; 8.6% ESBL-phenotype and 1.5% meropenem-resistant), group B streptococci (GBS; 176), *Enterococcus faecalis* (78), coagulase-negative staphylococci (CoNS; 77; 57.1% oxacillin-resistant), *Proteus mirabilis* (61) and *Morganella morganii* (34). Non-fermentative bacilli were not included. Isolates were collected in 2009-2010 from 65 medical centres located in all nine USA Census Regions.

Results: Overall, 98.4% of strains were inhibited at ≤2 mg/L of ceftaroline-avibactam and all 18 isolates with ceftaroline-avibactam MIC at ≥4 (4-16) mg/L were *E. faecalis*. *E. coli* and *Klebsiella* spp. were very susceptible to ceftaroline-avibactam with $MIC_{50/90}$ of ≤0.03/0.06 and 0.06/0.12 mg/L, respectively. Ceftriaxone and ciprofloxacin were active against 92.0% and 73.9% of *E. coli* and 92.3% and 94.2% of *Klebsiella* spp., respectively; and 1.5% of *Klebsiella* spp. were resistant to meropenem. Among *P. mirabilis* and *M. morganii*, the highest ceftaroline-avibactam MIC values were only 0.5 and 0.25 mg/L, and resistance rates to ciprofloxacin were 29.5% and 35.3%, respectively. The highest ceftaroline-avibactam MIC value among *Enterobacter* spp. was only 0.5 mg/L ($MIC_{50/90}$, 0.06/0.5 mg/L). All GBS were inhibited at ceftaroline-avibactam MIC of ≤0.06 mg/L. Ceftaroline-avibactam showed activity against *E. faecalis* ($MIC_{50/90}$, 2/8 mg/L) and was very active against CoNS ($MIC_{50/90}$, 0.25/0.5 mg/L; 57.1% oxacillin-resistant).

Conclusions: Ceftaroline-avibactam exhibited potent activity against a large collection of Enterobacteriaceae and Gram-positive organisms from patients with cUTI. Avibactam can effectively lower ceftaroline MIC values for Enterobacteriaceae that produced the most clinically significant BLs occurring in USA hospitals.

Introduction

Urinary tract infection (UTI) is one of the most common nosocomial infections and a main source of bacteremia in hospitalized patients. Ceftaroline, the active component of ceftaroline fosamil, is a broad-spectrum cephalosporin with potent activity against Gram-positive organisms (including methicillin-resistant *Staphylococcus aureus* [MRSA]) and most Enterobacteriaceae species but, like all cephalosporins, has limited activity against organisms that produce extended-spectrum β-lactamase (ESBL), derepressed AmpC and carbapenemases.

Avibactam (also known as NXL104) is a new non-β-lactam inhibitor of β-lactamases currently in clinical development that displays a broad-spectrum inhibition profile against both class A and class C enzymes, and a variable level of activity against class D enzymes. Avibactam efficiently protects β-lactams from hydrolysis by a variety of strains producing enzymes, including ESBL, AmpC, and KPC types. In this study, we report the activity of ceftaroline combined with avibactam (fixed 4 mg/L) against isolates from complicated UTI (cUTI), including ESBL- and KPC-producers, recovered in USA medical centres in 2009 and 2010.

Materials and Methods

Bacterial isolates. A total of 1131 strains were collected, including *E. coli* (348), *Klebsiella* spp. (326), *P. mirabilis* (61), *M. morganii* (34), *Enterobacter* spp. (17), *Citrobacter* spp. (8), *Serratia marcescens* (6), group B streptococci (GBS; 176), *Enterococcus faecalis* (78) and CoNS (77; 57.1% oxacillin-R). Non-fermentative bacilli were not included. Isolates were collected in 2009-2010 from 65 medical centres located in all nine USA Census Regions. Species identification was confirmed by standard biochemical tests, the Vitek System (bioMerieux, Hazelwood, Missouri, USA) or 16S rRNA sequencing, when necessary.

Antimicrobial susceptibility testing. All isolates were tested for antimicrobial susceptibility using the broth microdilution method (BMD) as described by the Clinical and Laboratory Standards Institute (CLSI; M07-A8, 2009). Cation-adjusted Mueller-Hinton broth was used in validated BMD panels. Ceftaroline-avibactam was tested in a fixed 4 mg/L concentration of avibactam. Susceptibility percentages and validation of quality control (QC) results were based on the CLSI guidelines (M100-S22) and susceptibility breakpoints were used to determine susceptibility/resistance rates (CLSI and EUCAST). No interpretive criteria for ceftaroline-avibactam susceptibility have been established by CLSI or EUCAST. QC was performed using *E. coli* ATCC 25922, *S. aureus* ATCC 29213 and *P. aeruginosa* ATCC 45853. *E. coli* and *Klebsiella* spp. isolates for which ceftriaxone or ceftazidime or aztreonam MICs were ≥2 mg/L, were considered to be phenotypic-positive for ESBL production (CLSI, 2012).

Results

- Overall, 98.4% of strains were inhibited at ≤2 mg/L of ceftaroline-avibactam and all 18 isolates with ceftaroline-avibactam MIC at ≥4 (4-16) mg/L were *E. faecalis* (Table 1)
- *E. coli* and *Klebsiella* spp. were very susceptible to ceftaroline-avibactam with $MIC_{50/90}$ of ≤0.03/0.06 and 0.06/0.12 mg/L, respectively. Ceftriaxone and ciprofloxacin were active against 92.0 and 73.9% of *E. coli* and 92.3 and 94.2% of *Klebsiella* spp., respectively; and 1.5% of *Klebsiella* spp. were resistant to meropenem (Table 2)
- An ESBL phenotype was observed in 8.0% of *E. coli* and 8.6% of *Klebsiella* spp. strains; and these ESBL-phenotype strains were very susceptible to ceftaroline-avibactam (highest MIC of only 1 mg/L). Ceftaroline-avibactam was also active against meropenem-resistant *Klebsiella* spp. (highest MIC of 1 mg/L; Table 1)
- Among *P. mirabilis* and *M. morganii*, the highest ceftaroline-avibactam MIC values were only 0.5 and 0.25 mg/L, and resistance rates to ciprofloxacin were 29.5 and 35.3%, respectively (Tables 1 and 2)
- The highest ceftaroline-avibactam MIC values among *Enterobacter* spp. ($MIC_{50/90}$, 0.06/0.5 mg/L), *Citrobacter* spp. (MIC_{50}, 0.12 mg/L) and *S. marcescens* (MIC_{50}, 0.5 mg/L) were 0.5, 0.5, and 1 mg/L, respectively (Table 1)
- All group B streptococci (*S. agalactiae*) were inhibited at ceftaroline-avibactam MIC of ≤0.06 mg/L. These organisms exhibited high susceptibility rates to most antimicrobial agents tested, except tetracycline (11.4% susceptible), erythromycin (50.6%) and clindamycin (73.3%; Table 2)
- Ceftaroline-avibactam showed modest activity against *E. faecalis* ($MIC_{50/90}$, 2/8 mg/L). All *E. faecalis* strains were susceptible to ampicillin ($MIC_{50/90}$, ≤1/2 mg/L) and daptomycin ($MIC_{50/90}$, 1/2 mg/L), whereas susceptibility rates for vancomycin and linezolid were 97.4 and 98.7%, respectively ($MIC_{50/90}$, 1/2 mg/L for both compounds; Table 2)
- CoNS strains, including those resistant to oxacillin (57.1%), were very susceptible to ceftaroline-avibactam ($MIC_{50/90}$, 0.25/0.5 mg/L) with MIC values ranging up to 2 mg/L (Table 2).

Conclusions

- Ceftaroline-avibactam exhibited potent activity against a large collection of Enterobacteriaceae and Gram-positive organisms isolated in USA medical centres from patients with cUTI
- Enterobacteriaceae strains resistant to broad-spectrum cephalosporins (ceftriaxone and ceftazidime), β-lactam/β-lactamase inhibitor combinations (piperacillin/tazobactam and ampicillin/sulbactam), and carbapenems (meropenem) exhibited low ceftaroline-avibactam MIC values (≤1 mg/L)
- Ceftaroline combined with avibactam represents a potential therapeutic option for the treatment of multidrug-resistant organisms causing UTIs.

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Table 1. Summary of ceftaroline-avibactam activity tested against organisms collected from patients with urinary tract infections in USA medical centers (2009 - 2010)

Organism (no. tested)	No. of isolates (cumulative %) inhibited at ceftaroline-avibactam MIC (mg/L) of [a]:									
	≤0.03	0.1	0.1	0.3	0.5	1	2	4	8	16
E. coli (348)	205 (58.9)	1115 (92.0)	24 (98.9)	3 (99.7)	1 (100.0)	-	-	-	-	-
ESBL-phenotype (28)	6 (21.40)	10 (57.1)	9 (89.3)	2 (96.4)	1 (100.0)	-	-	-	-	-
Klebsiella spp. (326)	72 (22.1)	173 (75.2)	50 (90.5)	22 (97.2)	7 (99.4)	2 (100.0)	-	-	-	-
ESBL-phenotype (28)	3 (10.7)	7 (35.7)	5 (53.6)	7 (78.6)	4 (92.9)	2 (100.0)	-	-	-	-
Meropenem-resistant (5)	1 (20.0)	1 (40.0)	0 (40.0)	0 (40.0)	2 (80.0)	1 (100.0)	-	-	-	-
P. mirabilis (61)	2 (3.3)	16 (29.5)	34 (85.3)	7 (96.7)	2 (100.0)	-	-	-	-	-
M. morganii (34)	12 (35.3)	15 (79.4)	5 (94.1)	2 (100.0)	-	-	-	-	-	-
Enterobacter spp. (17)	2 (11.8)	7 (52.9)	3 (70.6)	3 (88.2)	2 (100.0)	-	-	-	-	-
Citrobacter spp. (8)	0 (0.0)	3 (37.5)	3 (75.0)	1 (87.5)	1 (100.0)	-	-	-	-	-
S. marcescens (6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	2 (50.0)	3 (100.0)	-	-	-	-
Group B strep. (176)	174 (98.9)	2 (100.0)	-	-	-	-	-	-	-	-
E. faecalis (78)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	10 (14.1)	49 (76.9)	8 (87.2)	5 (93.6)	5 (100.0)
CoNS (77)	2 (2.6)	15 (22.1)	21 (49.4)	21 (76.6)	15 (96.1)	2 (98.7)	1 (100.0)	-	-	-

a. Concentrations reported in the table for ceftaroline-avibactam refer to the concentration of ceftaroline tested with fixed 4 mg/L avibactam concentration.

Table 2. Antimicrobial activity of ceftaroline-avibactam and comparator agents tested against bacterial isolates from urinary tract infections

Antimicrobial agent (no. of isolates)	MIC_{50}	MIC_{90}	Range	% Susc. / % Resistant[a]	
				CLSI	EUCAST
Escherichia coli (348)					
Ceftaroline-avibactam	≤0.03	0.06	≤0.03 – 0.5	- / -	- / -
Ceftriaxone	≤0.25	≤0.25	≤0.25 – >8	92.0 / 8.0	92.0 / 8.0
Ceftazidime	≤1	≤1	≤1 – >16	95.1 / 3.4	92.8 / 4.9
Ampicillin/sulbactam	8	>16	≤2 – >16	56.4 / 21.8	- / 43.6
Piperacillin/tazobactam	2	8	≤0.5 – >64	95.7 / 1.7	93.1 / 4.3
Ciprofloxacin	≤0.5	>4	≤0.5 – >4	73.9 / 26.1	73.4 / 26.1
Levofloxacin	≤0.5	>4	≤0.5 – >4	73.9 / 25.8	73.9 / 26.1
Gentamicin	≤2	8	≤2 – >8	89.7 / 9.7	89.1 / 10.3
Tigecycline[b]	0.12	0.25	0.06 – 2	100.0 / 0.0	99.4 / 0.0
Meropenem	≤0.12	≤0.12	≤0.12 – 0.25	100.0 / 0.0	100.0 / 0.0
Klebsiella spp.[c] (326)					
Ceftaroline-avibactam	0.06	0.12	≤0.03 – 1	- / -	- / -
Ceftriaxone	≤0.25	≤0.25	≤0.25 – >8	92.3 / 6.7	92.3 / 6.7
Ceftazidime	≤1	≤1	≤1 – >16	94.8 / 5.2	92.3 / 5.2
Ampicillin/sulbactam	4	>16	≤2 – >16	79.8 / 10.7	- / 20.2
Piperacillin/tazobactam	2	8	≤0.5 – >64	94.5 / 4.3	90.5 / 5.5
Ciprofloxacin	≤0.5	≤0.5	≤0.5 – >4	92.9 / 5.5	92.3 / 7.1
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	94.2 / 4.9	93.6 / 5.8
Gentamicin	≤2	≤2	≤2 – >8	96.9 / 2.1	96.0 / 3.1
Tigecycline[b]	0.25	0.5	0.06 – 4	99.1 / 0.0	97.9 / 0.9
Meropenem	≤0.12	≤0.12	≤0.12 – >8	98.5 / 1.5	98.5 / 0.9
Proteus mirabilis (61)					
Ceftaroline-avibactam	0.12	0.25	≤0.03 – 0.5	- / -	- / -
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 4	96.7 / 1.6	96.7 / 1.6
Ceftazidime	0.06	0.12	0.03 – 8	98.4 / 0.0	98.4 / 1.6
Ampicillin/sulbactam	≤2	16	≤2 – >16	82.0 / 4.9	- / 18.0
Piperacillin/tazobactam	≤0.5	1	≤0.5 – 2	100.0 / 0.0	100.0 / 0.0
Ciprofloxacin	≤0.5	>4	≤0.5 – >4	65.6 / 29.5	62.3 / 34.4
Levofloxacin	≤0.5	>4	≤0.5 – >4	68.9 / 26.2	65.6 / 31.1
Gentamicin	≤2	>8	≤2 – >8	82.0 / 14.8	70.5 / 18.0
Tigecycline[b]	2	4	0.25 – >4	75.4 / 1.6	44.3 / 24.6
Meropenem	≤0.12	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0
Morganella morganii (34)					
Ceftaroline-avibactam	0.06	0.12	≤0.03 – 0.25	- / -	- / -
Ceftriaxone	≤0.25	4	≤0.25 – >8	76.5 / 11.8	76.5 / 11.8
Ceftazidime	0.12	32	0.06 – >32	73.5 / 17.6	70.6 / 26.5
Ampicillin/sulbactam	32	32	8 – >32	14.7 / 55.9	- / 85.3
Piperacillin/tazobactam	≤0.5	4	≤0.5 – >64	91.2 / 2.9	91.2 / 8.8
Ciprofloxacin	≤0.03	>4	≤0.03 – >4	64.7 / 35.3	52.9 / 35.3
Levofloxacin	≤0.5	>4	≤0.5 – >4	64.7 / 29.4	61.8 / 35.3
Gentamicin	≤1	>8	≤1 – >8	85.3 / 14.7	82.4 / 14.7
Tigecycline[b]	0.5	1	0.12 – 2	100.0 / 0.0	97.1 / 0.0
Meropenem	≤0.12	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0

Antimicrobial agent (no. of isolates)	MIC_{50}	MIC_{90}	Range	% Susc. / % Resistant[a]	
				CLSI	EUCAST
Enterobacter spp.[d] (17)					
Ceftaroline-avibactam	0.06	0.5	≤0.03 – 0.5	- / -	- / -
Ceftriaxone	≤0.25	4	≤0.25 – >32	88.2 / 11.8	88.2 / 11.8
Ceftazidime	0.25	8	0.06 – >16	88.2 / 5.9	88.2 / 11.8
Ampicillin/sulbactam	8	>16	≤2 – >16	52.9 / 23.5	- / 47.1
Piperacillin/tazobactam	4	16	1 – >64	94.1 / 5.9	88.2 / 5.9
Ciprofloxacin	≤0.5	≤0.5	≤0.5	100.0 / 0.0	100.0 / 0.0
Levofloxacin	≤0.5	≤0.5	≤0.5 – 1	100.0 / 0.0	100.0 / 0.0
Gentamicin	≤2	≤2	≤2 – 4	100.0 / 0.0	94.1 / 0.0
Tigecycline[b]	0.25	0.5	0.25 – 0.5	100.0 / 0.0	100.0 / 0.0
Meropenem	≤0.12	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0
Group B *Streptococcus* (176)					
Ceftaroline-avibactam	≤0.03	≤0.03	≤0.03 – 0.06	- / -	- / -
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0 / -	100.0 / 0.0
Penicillin	0.06	0.06	≤0.03 – 0.12	100.0 / -	100.0 / 0.0
Erythromycin	≤0.25	>2	≤0.25 – >2	50.6 / 48.3	50.6 / 48.3
Clindamycin	≤0.25	>2	≤0.25 – >2	73.3 / 26.7	73.3 / 26.7
Levofloxacin	≤0.5	1	≤0.5 – >4	98.3 / 1.7	97.2 / 1.7
Linezolid	1	1	0.5 – 2	100.0 / -	100.0 / 0.0
Tetracycline	>8	>8	≤2 – >8	11.4 / 88.6	11.4 / 88.6
Tigecycline[b]	≤0.03	0.06	≤0.03 – 0.12	100.0 / -	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2	- / -	100.0 / 0.0
Vancomycin	0.5	0.5	≤0.12 – 1	100.0 / -	100.0 / 0.0
Daptomycin	0.25	0.25	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
Enterococcus faecalis (78)					
Ceftaroline-avibactam	2	8	0.5 – 16	- / -	- / -
Ceftriaxone	>8	>8	2 – >8	- / -	- / -
Ampicillin	≤1	2	≤1 – 2	100.0 / 0.0	100.0 / 0.0
Levofloxacin	1	>4	≤0.5 – >4	66.7 / 32.1	- / -
Linezolid	1	2	0.5 – >8	98.7 / 1.3	98.7 / 1.3
Tigecycline[b]	0.06	0.25	≤0.03 – 0.25	100.0 / -	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2 – >8	97.4 / 2.6	96.2 / 3.8
Vancomycin	1	2	0.5 – >16	97.4 / 2.6	97.4 / 2.6
Daptomycin	1	2	≤0.06 – 4	100.0 / -	- / -
Coagulase-negative staphylococci[e] (77)					
Ceftaroline-avibactam	0.25	0.5	≤0.03 – 2	- / -	- / -
Ceftriaxone[f]	4	>8	0.5 – >8	42.9 / 57.1	42.9 / 57.1
Oxacillin	1	>2	≤0.25 – >2	42.9 / 57.1	42.9 / 57.1
Clindamycin	≤0.25	>2	≤0.25 – >2	80.5 / 14.3	80.5 / 19.5
Levofloxacin	≤0.5	>4	≤0.5 – >4	57.1 / 42.9	57.1 / 42.9
Linezolid	0.5	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Tigecycline[b]	0.12	0.25	≤0.03 – 0.5	- / -	100.0 / 0.0
Teicoplanin	≤2	4	≤2 – 8	100.0 / 0.0	97.4 / 2.6
Vancomycin	1	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0

a. Criteria as published by the CLSI [2012] and EUCAST [2012], β-lactam susceptibility should be directed by the oxacillin test results.
b. USA-FDA breakpoints were applied when available [Tygacil® Product Insert, 2010].
c. Includes: *Klebsiella oxytoca* (73), *K. pneumoniae* (230), and unspeciated *Klebsiella* (23).
d. Includes: *Enterobacter aerogenes* (6) and *E. cloacae* (11).
e. Includes: *Staphylococcus auricularis* (1), *S. capitis* (2), *S. epidermidis* (20), *S. haemolyticus* (2), *S. saprophyticus* (5), and unspeciated coagulase-negative staphylococci (47).
f. USA-FDA breakpoints were applied when available [Rocephin® Product Insert, 2010].