



Amended Abstract

Background: Ceftazidime-avibactam (CAZ-AVI) consists of CAZ combined with the novel non- β -lactam β -lactamase (BL) inhibitor AVI, which inhibits Ambler class A (e.g., ESBL and KPC), C and some class D enzymes. We evaluated the activity of CAZ-AVI tested against contemporary isolates causing intraabdominal infections (IAI).

Methods: A total 1,541 isolates (one per patient) were collected in 57 United States (US) hospitals from patients with IAI in 2012-2014. Susceptibility (S) testing was performed by reference broth microdilution methods and Enterobacteriaceae (ENT) isolates with an ESBL phenotype were evaluated for the presence of genes encoding CTX-M, TEM, SHV, KPC, NDM and transferable AmpC enzymes by microarray-based assay.

Results: *Escherichia coli* was the most commonly isolated organism (40.7% of total) and they had an overall ESBL-phenotype rate of 15.8%. All *E. coli* isolates were S to CAZ-AVI (Table 1) and S rates for meropenem (MER), piperacillin/tazobactam (P/T) and gentamicin (GEN) were 99.8, 93.6 and 85.5%, respectively. Among *K. pneumoniae* (KPN; 2nd most common pathogen, 17.6%), the ESBL rate was 13.3% and the highest CAZ-AVI MIC value was only 2 μ g/ml (MIC_{50/90}, 0.12/0.25 μ g/ml, 100.0% S). KPN S rates to MER and GEN were 94.5 and 91.9%, respectively. CAZ-AVI was active against *E. cloacae* (MIC_{50/90}, 0.12/0.5 μ g/ml; 99.3%S), including CAZ-non-S strains (97.8% S). Only two ENT isolates (*P. mirabilis** and *E. cloacae*) were non-S to CAZ-AVI and both had negative results for all BLs tested. *P. aeruginosa* (PSA) was the 3rd most common pathogen (13.6%); CAZ-AVI (MIC_{50/90}, 2/4 μ g/ml; 97.1% S), amikacin (MIC_{50/90}, 2/8 μ g/ml; 99.0% S) and colistin (MIC_{50/90}, 1/2 μ g/ml; 98.6% S) were the most active compounds tested against this organism. CAZ-AVI retained activity against many MER-non-S (88.6% S) and CAZ-non-S (80.6% S) PSA.

Conclusions: CAZ-AVI demonstrated potent in vitro activity against aerobic Gram-negative organisms isolated from IAI in US hospitals. CAZ-AVI overall coverage (98.7% inhibited at \leq 8 μ g/ml) was greater than that observed for MER (95.7% S) and P/T (88.4% S).

* Further investigation performed after the submission of this abstract revealed that the *P. mirabilis* strain was mixed with a *Myrodes odoratimimus*, which is an environmental organism carrying an intrinsic metallo- β -lactamase. The *P. mirabilis* isolate is susceptible to CAZ-AVI and does not have an ESBL-phenotype.

Introduction

Intraabdominal infections (IAIs) are among the most serious bacterial infections in US hospitals with significant associated morbidity and mortality; IAIs generally require surgical intervention and early initiation of appropriate antimicrobial therapy to prevent associated morbidity and mortality. The most common etiologic pathogens of IAI are Enterobacteriaceae species and anaerobic organisms originating from the endogenous gut flora. Standard antimicrobial regimens for the treatment of IAIs often include a β -lactam (e.g. broad spectrum cephalosporin or carbapenem); however, the emergence and spread of β -lactamase producing Gram-negative organisms (including ESBL- or KPC- producing strains) presents a significant therapeutic challenge, leaving clinicians with limited options for infections caused by multidrug-resistant organisms.

Avibactam is a broad spectrum β -lactamase inhibitor with activity against common serine β -lactamase enzymes, including Ambler classes A (e.g., ESBL and KPC), class C (Amp C) and some class D (OXA-48) enzymes. The addition of avibactam to ceftazidime restores ceftazidime activity against common Gram-negative pathogens causing IAI, including most of those that are resistant to carbapenem agents (e.g. meropenem) due to the production of β -lactamase enzymes.

Ceftazidime-avibactam has recently been approved by the US Food and Drug Administration (FDA) for treatment of complicated IAI, in combination with metronidazole, and complicated urinary tract infections, including pyelonephritis, in patients with limited or no alternative treatment options. Ceftazidime-avibactam is also under clinical development for treatment of nosocomial pneumonia (<http://clinicaltrials.gov>; NCT01808092). We evaluated the activity of ceftazidime-avibactam against contemporary isolates causing IAI in US medical centers.

Methods

Bacterial isolates: A total 1,541 Gram-negative organisms, including 1,313 Enterobacteriaceae, 210 *Pseudomonas aeruginosa* and 18 *Acinetobacter* spp., were collected from 57 US hospitals from patients with IAI between January 2012 and December 2014 as part of the International Network for Optimal Resistance Monitoring (INFORM) program. Only clinically significant isolates were included in the study (one per patient episode). Species identification was confirmed when necessary by Matrix-Assisted Laser Desorption Ionization-Time Of Flight mass spectrometry (MALDI-TOF MS) using the Bruker Daltonics MALDI Biotyper (Billerica, Massachusetts, US) by following manufacturer instructions.

Antimicrobial susceptibility testing: All isolates were tested for susceptibility using the reference broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI). Ceftazidime was combined with avibactam at a fixed concentration of 4 μ g/ml. Ceftazidime-avibactam breakpoints approved by the US-FDA (\leq 8 μ g/ml for susceptible and \geq 16 μ g/ml for resistant) were applied for all Enterobacteriaceae species and *P. aeruginosa*. Susceptibility interpretations for all comparator agents were based on the CLSI (document M100-S25, 2015) and EUCAST (2015) breakpoints criteria. Quality control (QC) was performed using *Escherichia coli* ATCC 25922 and 35218, *Klebsiella pneumoniae* 700603 and *P. aeruginosa* ATCC 27853. All QC MIC results were within acceptable ranges as published in CLSI documents.

Results

- Overall, 99.9% of Enterobacteriaceae isolates (1,312/1,313) were susceptible to ceftazidime-avibactam (MIC_{50/90}, 0.12/0.25 μ g/ml; Tables 1 and 2). Only one Enterobacteriaceae isolate was non-susceptible to ceftazidime-avibactam, an *E. cloacae* from Indianapolis, IN, with a MIC of 16 μ g/ml.

- E. coli* was the most common organism (40.7%) and had an overall ESBL-phenotype rate of 15.8%. All *E. coli* isolates were susceptible to ceftazidime-avibactam (MIC_{50/90}, 0.06/0.12 μ g/ml; Table 1 and Figure 1).

- E. coli* susceptibility rates for meropenem (MIC_{50/90}, \leq 0.06/ \leq 0.06 μ g/ml), piperacillin/tazobactam (MIC_{50/90}, 2/8 μ g/ml) and gentamicin (MIC_{50/90}, \leq 1/ $>$ 8 μ g/ml) were 99.8, 93.6 and 85.5%, respectively (Figure 1).

- K. pneumoniae* was the second most common pathogen (17.6%) and 13.3% of isolates exhibited an ESBL-phenotype. The highest ceftazidime-avibactam MIC value was only 2 μ g/ml (MIC_{50/90}, 0.12/0.25 μ g/ml, 100.0% susceptible), and susceptibility rates to meropenem (MIC_{50/90}, \leq 0.06/ \leq 0.06 μ g/ml) and piperacillin/tazobactam (MIC_{50/90}, 4/32 μ g/ml) were 94.5 and 88.9%, respectively (Table 2 and Figure 1).

- Ceftazidime-avibactam was active against *E. cloacae* (MIC_{50/90}, 0.12/0.5 μ g/ml; 99.3% susceptible), including ceftazidime-non-susceptible strains (MIC_{50/90}, 0.12/0.5 μ g/ml; 97.8% susceptible; Table 1 and Figures 1 and 2).

- P. aeruginosa* was the third most common pathogen (13.6% of total) and 97.1% of strains were susceptible to ceftazidime-avibactam (MIC_{50/90}, 2/4 μ g/ml; Table 1 and Figure 1). Other compounds active against $>$ 90% of *P. aeruginosa* isolates were amikacin (MIC_{50/90}, 2/4 μ g/ml; 99.0% susceptible) and colistin (MIC_{50/90}, 1/2 μ g/ml; 98.6% susceptible; Table 2).

- Ceftazidime-avibactam retained activity against many meropenem-non-susceptible (MIC_{50/90}, 4/16 μ g/ml; 88.6% susceptible) and ceftazidime-non-susceptible (MIC_{50/90}, 4/16 μ g/ml; 80.6% susceptible) *P. aeruginosa* isolates (Table 1 and Figure 2).

Table 1. Summary of ceftazidime-avibactam activity tested against bacterial isolates from patients with intraabdominal infections (USA, 2012-2014).

Organism (no. tested)	No. of isolates (cumulative %) inhibited at ceftazidime-avibactam MIC (μ g/ml) of:											MIC (μ g/ml)	
	\leq 0.06	0.12	0.25	0.5	1	2	4	8	16	32	$>$ 32	50%	90%
Enterobacteriaceae (1,313)	593 (45.2)	478 (81.6)	145 (92.6)	69 (97.9)	21 (99.5)	5 (99.8)	1 ($>$ 99.9)	0 ($>$ 99.9)	1 (100.0)	--	--	0.12	0.25
<i>E. coli</i> (627)	344 (54.9)	227 (91.1)	37 (97.0)	15 (99.4)	3 (99.8)	0 (99.8)	1 (100.0)	--	--	--	--	0.06	0.12
<i>K. pneumoniae</i> (271)	103 (38.0)	118 (81.5)	32 (93.4)	9 (96.7)	5 (98.5)	4 (100.0)	--	--	--	--	--	0.12	0.25
ESBL-phenotype (36)	3 (8.3)	8 (30.6)	9 (55.6)	7 (75.0)	5 (88.9)	4 (100.0)	--	--	--	--	--	0.25	2
MER-NS (15)	3 (6.7)	1 (13.3)	3 (33.3)	5 (66.7)	3 (86.7)	2 (100.0)	--	--	--	--	--	0.5	2
<i>E. cloacae</i> (147)	9 (6.1)	66 (51.0)	32 (72.8)	28 (91.8)	10 (98.6)	1 (99.3)	0 (99.3)	0 (99.3)	1 (100.0)	--	--	0.12	0.5
CAZ-NS (46)	2 (4.3)	6 (17.4)	8 (34.8)	19 (76.1)	9 (95.7)	1 (97.8)	0 (97.8)	0 (97.8)	1 (100.0)	--	--	0.5	1
<i>P. aeruginosa</i> (210)	--	1 (0.5)	0 (0.5)	5 (2.9)	86 (43.8)	71 (77.6)	33 (93.3)	8 (97.1)	4 (99.0)	2 (100.0)	--	2	4
CAZ-NS (31)	--	--	--	--	1 (3.2)	9 (32.3)	10 (64.5)	5 (80.6)	4 (93.5)	2 (100.0)	--	4	16
MER-NS (35)	--	--	--	--	2 (5.7)	9 (31.4)	14 (71.4)	6 (88.6)	2 (94.3)	2 (100.0)	--	4	16
<i>Acinetobacter</i> spp. (18)	--	--	--	--	--	1 (5.6)	4 (27.8)	1 (33.3)	3 (50.0)	4 (72.2)	5 (100.0)	16	$>$ 32
All isolates (1541)	593 (38.5)	479 (69.6)	145 (79.0)	74 (83.8)	107 (90.8)	77 (95.8)	38 (98.2)	9 (98.8)	8 (99.3)	6 (99.7)	5 (100.0)	0.12	1

Abbreviations: ESBL = extended-spectrum β -lactamase; MER = meropenem; NS = non-susceptible; CAZ = ceftazidime.

Table 2. Activity of ceftazidime-avibactam and comparator antimicrobial agents when tested against bacterial isolates from intraabdominal infection (USA, 2012-2014).

Organism / Antimicrobial Agent	MIC ₅₀	MIC ₉₀	CLSI ^a			EUCAST ^a		
			%S	%I	%R	%S	%I	%R
Enterobacteriaceae (1,313) ^b								
Ceftazidime-avibactam	0.12	0.25	>99.9	-	<0.1 ^b	-	-	-
Ceftazidime	0.25	16	86.7	1.7	11.6	84.2	2.6	13.3
Ceftriaxone	≤0.06	>8	83.2	0.6	16.2	83.2	0.6	16.2
Piperacillin/tazobactam	2	32	89.9	3.4	6.8	86.7	3.2	10.1
Meropenem	≤0.06	≤0.06	98.3	0.4	1.3	98.7	0.5	0.8
Levofloxacin	≤0.12	>4	82.3	0.6	17.1	81.2	1.1	17.7
Gentamicin	≤1	8	89.8	0.7	9.5	88.8	1.0	10.2

Pseudomonas aeruginosa (210)

Ceftazidime-avibactam	2	4	97.1	-	2.9 ^a	-	-	-
Ceftazidime	2	32	85.2	2.9	11.9	85.2	-	14.8
Cefepime	2	16	85.7	8.1	6.2	85.7	-	14.3
Piperacillin/tazobactam	4	$>$ 64	83.3	6.2	10.5	83.3	-	16.7
Meropenem	0.5	8	83.3	5.3	11.5	83.3	13.4	3.3
Levofloxacin	0.5	$>$ 4	74.8	6.7	18.6	70.0	4.8	25.2
Gentamicin	\leq 1	4	92.9	1.4	5.7	92.9	-	7.1
Amikacin	2	8	99.0	0.5	0.5	97.6	1.4	1.0
Colistin	1	2	98.6	1.4	0.0	100.0	-	0.0

Acinetobacter baumannii (18)

Ceftazidime-avibactam	16	$>$ 32	-	-	-	-	-	-
Ceftazidime	8	$>$ 32	50.0	0.0	50.0	-	-	-
Cefepime	$>$ 16	$>$ 16	44.4	0.0	55.6	-	-	-
Ampicillin/sulbactam	4	$>$ 32	55.6	16.7	27.8	-	-	-
Piperacillin/tazobactam	$>$ 64	$>$ 64	35.3	5.9	58.8	-	-	-
Meropenem	$>$ 8	$>$ 8	38.9	0.0	61.1	38.9	0.0	61.1
Levofloxacin	$>$ 4	$>$ 4	38.9	0.0	61.1	38.9	0.0	61.1
Gentamicin	8	$>$ 8	44.4	16.7	38.9	44.4	-	55.6
Amikacin	8	$>$ 32	77.8	5.6	16.7	55.6	22.2	22.2
Colistin	1	2	100.0	-	0.0	100.0	-	0.0

a. Criteria as published by CLSI [2015] and EUCAST [2015]

b. Organisms include: *Citrobacter freundii* (41), *C. freundii* species complex (4), *C. koseri* (12), *Enterobacter aerogenes* (29), *Escherichia coli* (627), *E. cloacae* (147), *Klebsiella oxytoca* (81), *K. pneumoniae* (271), *Morganella morganii* (14), *Proteus mirabilis* (47), *P. vulgaris* (5), *Providencia rettgeri* (2), *P. stuartii* (3), *Serratia marcescens* (30).

Figure 1. Antimicrobial susceptibility of bacterial isolates collected from patients with intraabdominal infections (USA, 2012-2014).

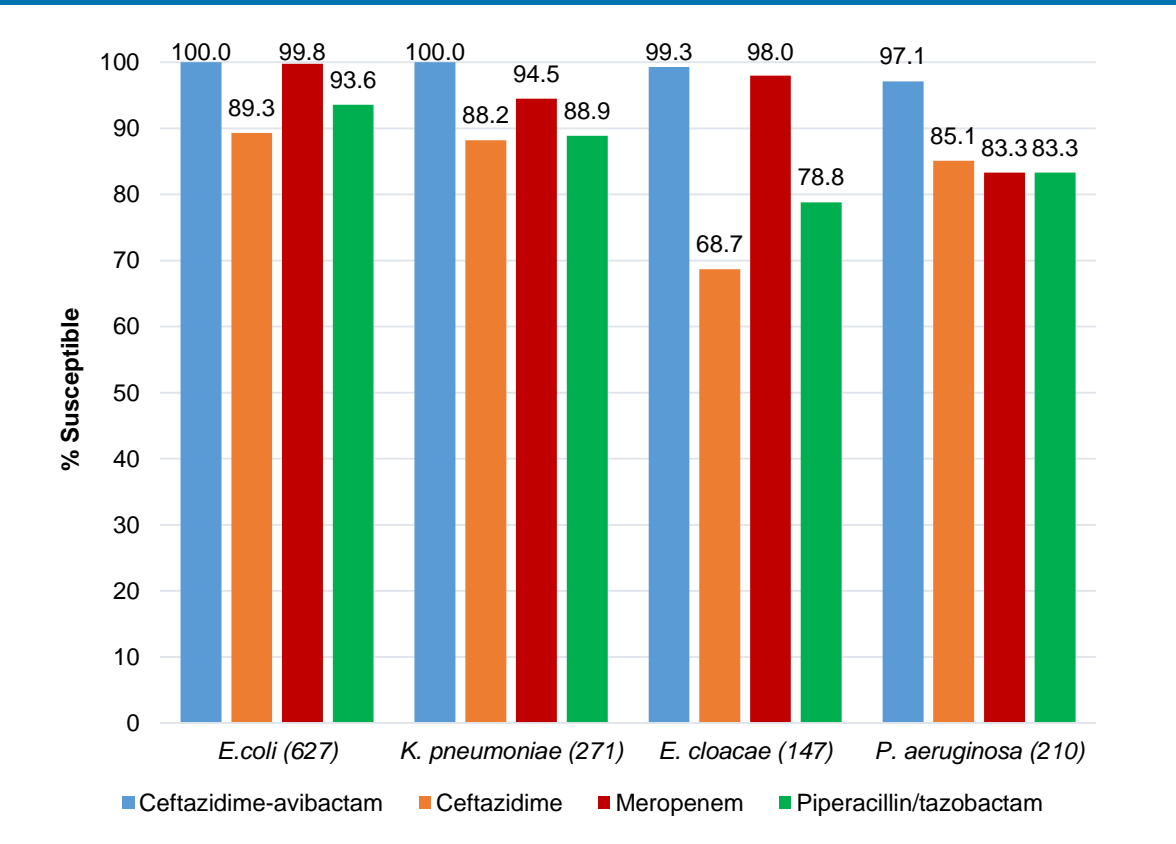
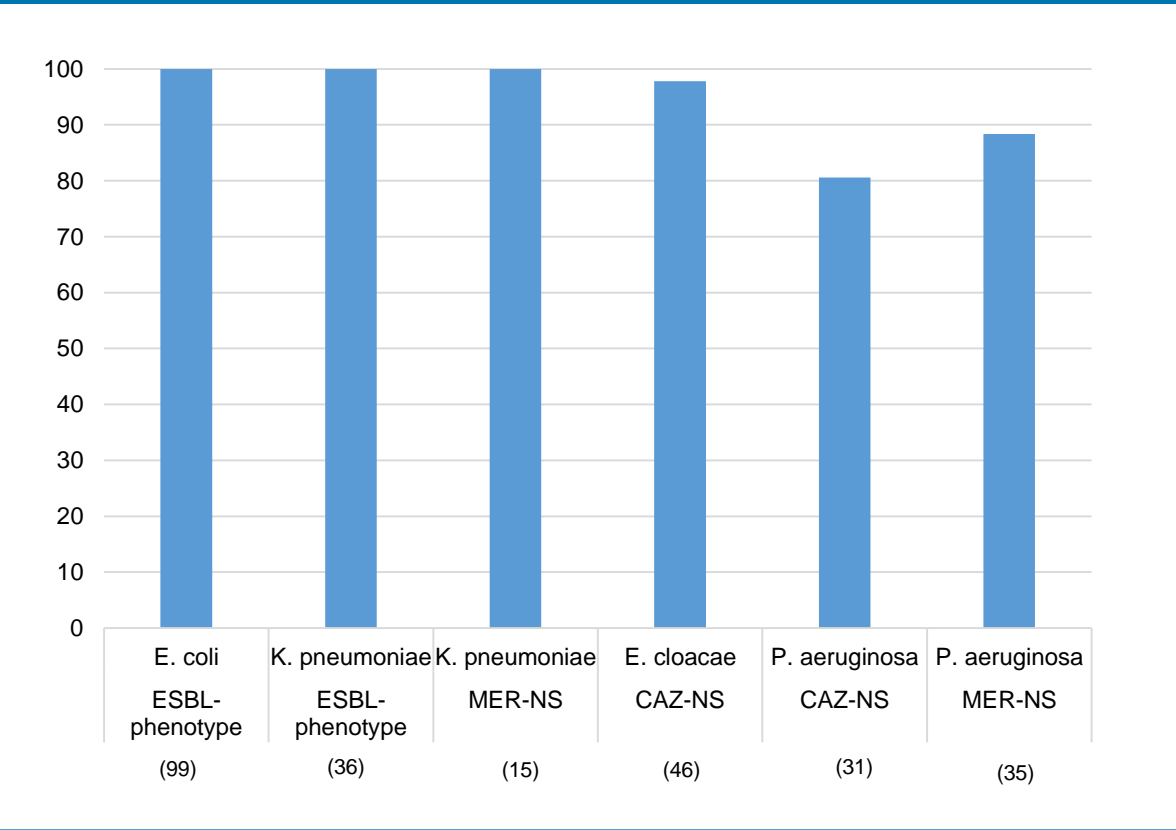


Figure 2. Antimicrobial activity of ceftazidime-avibactam tested against selected antimicrobial resistance subsets (USA, 2012-2014).



Conclusions

- Ceftazidime-avibactam demonstrated potent in vitro activity against aerobic Gram-negative organisms isolated from IAI in US hospitals.

- Ceftazidime-avibactam overall coverage (98.8% inhibited at \leq 8 μ g/ml) was greater than that observed for meropenem (95.7% susceptible) and piperacillin/tazobactam (88.4% susceptible).

- Ceftazidime-avibactam represents an important addition to the armamentarium of antimicrobial agents used for the treatment of IAI, especially those caused by multidrug-resistant organisms.

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