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Antimicrobial Activity of Ceftazidime-Avibactam Tested Against *Pseudomonas aeruginosa* Isolates from USA Hospitals Stratified by Site of Infection: Results from the INFORM Surveillance Program, 2013-2015

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Abstract

Background: Ceftazidime (CAZ)-avibactam (AVI) was approved by the United States Food and Drug Administration (US-FDA) for treatment of complicated intra-abdominal and urinary tract infections in 2015 and is under clinical development for treatment of hospital-acquired pneumonia.

Methods: 5,486 *P. aeruginosa* (PSA) isolates (one per patient) were consecutively collected in 2013-2015 from 77 USA medical centers (37 states from all 9 Census regions) by the INFORM Surveillance Program. CAZ-AVI (AVI at fixed 4 µg/mL) and comparators were tested for susceptibility (S) by CLSI broth microdilution methods and results were stratified by infection type.

Results: Isolates were mostly from pneumonia (n=2,903; 52.9%), skin/soft tissue (SSSI; 1,286; 23.4%), bloodstream (BSI; 436; 7.9%), urinary tract (UTI; 417; 7.6%) and intra-abdominal infections (IAI; 199; 3.6%). Overall, CAZ-AVI was active against 97.0% of isolates at the US-FDA S breakpoint of ≤8 µg/mL, while S rates for meropenem (MEM), piperacillin-tazobactam (PT) and amikacin (AMK) were 82.0%, 81.3% and 96.8%, respectively (Table). When stratified by infection type, CAZ-AVI S rates varied from 95.6% (BSI) to 98.2% (SSSI), whereas S rates for MEM varied from 78.9% (pneumonia) to 87.1% (SSSI). The occurrences of multidrug-resistance (MDR) and extensively drug-resistance (XDR) were highest among isolates from pneumonia (18.2 and 10.7%, respectively) and UTI (14.9 and 9.6%, respectively), and CAZ-AVI was active against 81.9 and 74.6% of MDR and XDR isolates, respectively. In contrast, S rates for MEM and PT were only 20.5 and 17.8% among MDR and 7.0 and 6.4% among XDR isolates, respectively. High rates of cross-resistance were observed among MEM, PT and CAZ; while CAZ-AVI retained good *in vitro* activity against PSA isolates that were not S to MEM, PT and CAZ, inhibiting 69.9% at ≤8 µg/mL.

Conclusions: CAZ-AVI exhibited potent *in vitro* activity and spectrum when tested against a large collection (n=5,486) of recent PSA clinical isolates. CAZ-AVI was consistently active against PSA isolates from all infection types and retained activity against isolates not S to other anti-PSA β-lactams, as well as MDR and XDR strains.

Infection type/ resistant subset (no.)	MIC_{50}/MIC_{90} (% susceptible [CLSI/US-FDA])					
	CAZ-AVI	MEM	PT	Levofloxacin	Gentamicin	AMK
All (5,486)	2 / 4 (97.0)	0.5 / 8 (82.0)	4 / 64 (81.3)	0.5 / >4 (74.8)	≤1 / 8 (88.1)	2 / 8 (96.8)
BSI (436)	2 / 4 (95.6)	0.5 / 8 (81.4)	4 / 64 (83.4)	0.5 / >4 (81.0)	≤1 / 4 (91.1)	2 / 8 (97.5)
Pneumonia (2,903)	2 / 4 (96.6)	0.5 / 8 (78.9)	4 / >64 (78.6)	0.5 / >4 (72.1)	2 / >8 (84.3)	4 / 16 (95.0)
SSSI (1,286)	2 / 4 (98.2)	0.5 / 4 (87.1)	4 / 32 (85.0)	0.5 / >4 (78.8)	≤1 / 4 (94.1)	2 / 8 (99.0)
UTI (417)	2 / 4 (97.8)	0.5 / 8 (82.9)	4 / 32 (84.9)	0.5 / >4 (70.3)	≤1 / 8 (89.0)	2 / 8 (99.3)
IAI (199)	2 / 4 (97.5)	0.5 / 8 (82.8)	4 / 64 (83.9)	0.5 / >4 (77.9)	≤1 / 4 (94.0)	2 / 8 (100.0)
MDR (842)	4 / 16 (81.9)	8 / >8 (20.5)	64 / >64 (17.8)	>4 / >4 (14.7)	4 / >8 (51.0)	8 / 32 (86.1)
XDR (500)	8 / 32 (74.6)	8 / >8 (7.0)	>64 / >64 (6.4)	>4 / >4 (3.8)	>8 / >8 (39.2)	8 / >32 (81.6)
Non S to CAZ, MEM and PT (432)	8 / 32 (69.9)	8 / >8 (0.0)	>64 / >64 (0.0)	>4 / >4 (20.1)	4 / >8 (56.7)	4 / >32 (83.8)

Introduction

Pseudomonas aeruginosa represents a major cause of nosocomial infections worldwide, including sepsis, hospital-acquired pneumonia, ventilator-associated pneumonia (VAP), skin and skin structure infections (SSSI) and urinary tract infections (UTI). *P. aeruginosa* carries an inducible AmpC cephalosporinase which is similar to the chromosomally encoded AmpC found in Enterobacteriaceae, and when AmpC production is significantly increased, *P. aeruginosa* expresses resistance to all β-lactams currently available for clinical use, with the exception of the carbapenems. Furthermore, up-regulation of MexA-MexB-OprM and loss of OprD are considered the most prevalent mechanisms of carbapenem resistance in *P. aeruginosa*, and these mechanisms are usually associated with AmpC hyperproduction.

Ceftazidime-avibactam is a combination agent consisting of the non-β-lactam β-lactamase inhibitor avibactam and the broad-spectrum cephalosporin, ceftazidime. Avibactam is a member of the diazabicyclooctanes (DBOs), a novel class of non-β-lactam β-lactamase inhibitors which has a different mechanism of action when compared with currently available inhibitors for clinical use. Avibactam effectively inactivates class A (including KPC), class C (AmpC), and some D (OXA) β-lactamases, with low IC_{50} (concentration resulting in 50% inhibition) values and low turnover numbers.

The ceftazidime-avibactam combination was approved by the United States Food and Drug Administration (US-FDA) for treatment of complicated intra-abdominal infections (IAI) and complicated UTI, including pyelonephritis, in patients with limited or no alternative treatment options in 2015, and is under clinical development for treatment of hospital-acquired pneumonia. In the present study, we evaluated the activity of ceftazidime combined with avibactam when tested against a large collection of contemporary *P. aeruginosa* clinical isolates recovered in United States (USA) medical centers in 2013-2015.

Methods

Bacterial isolates: A total 5,486 *P. aeruginosa* isolates (one per patient episode) were consecutively collected from 77 USA medical centers (37 states from all 9 Census regions) between January 2013 and December 2015 as part of the International Network for Optimal Resistance Monitoring (INFORM) program. Only bacterial isolates determined to be significant by local criteria as the reported probable cause of an infection were included in this investigation and the results were stratified by infection type. 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, USA) by following manufacturer instructions.

Isolates were categorized as multidrug-resistant (MDR), extensively drug-resistant (XDR) and pan drug-resistant (PDR) according to criteria published by Magiorakos *et al.* (2012); i.e. MDR = non-susceptible (NS) to ≥1 agent in ≥3 antimicrobial classes, XDR = NS to ≥1 agent in all but ≤2 antimicrobial classes, and PDR = NS to all antimicrobial classes tested.

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 µg/mL. Ceftazidime-avibactam breakpoints approved by the US-FDA (≤8/4 µg/mL for susceptible and ≥16/4 µg/mL for resistant) when testing *P. aeruginosa* were applied. Susceptibility interpretations for comparator agents were those found in CLSI document M100-S26 and/or US-FDA package insert. Quality control (QC) was performed using *Escherichia coli* ATCC 25922 and 35218, *Klebsiella pneumoniae* ATCC 700603 and BAA 1705, and *P. aeruginosa* ATCC 27853.

Results

- Isolates were mostly from pneumonia (n=2,903; 52.9%), skin and skin structure (SSSI; 1,286; 23.4%), bloodstream (BSI; 436; 7.9%), urinary tract (UTI; 417; 7.6%) and intra-abdominal infections (IAI; 199; 3.6%).
- Overall, ceftazidime-avibactam ($MIC_{50/90}$, 2/4 µg/mL) was active against 97.0% of isolates at the US-FDA susceptible breakpoint of ≤8 µg/mL, while susceptibility rates for ceftazidime ($MIC_{50/90}$, 2/32 µg/mL), meropenem ($MIC_{50/90}$, 0.5/8 µg/mL), and piperacillin-tazobactam ($MIC_{50/90}$, 4/64 µg/mL) were 84.7%, 82.0% and 81.3%, respectively (Table 1 and Figure 1).
- Ceftazidime-avibactam retained activity against 81.9 and 74.6% of MDR and XDR isolates, respectively. In contrast, susceptibility rates for meropenem and piperacillin-tazobactam were only 20.5 and 17.8% among MDR and 7.0 and 6.4% among XDR isolates, respectively (Table 1).
- Ceftazidime-avibactam was highly active against *P. aeruginosa* from all infection types, with susceptibility rates varying from 95.6% (BSI) to 98.2% (SSSI; Table 2 and Figure 2).
- Susceptibility rates varied from 78.9% (pneumonia) to 87.1% (SSSI) for meropenem, and from 78.6 (pneumonia) to 85.0% (SSSI) for piperacillin-tazobactam (Table 2 and Figure 2)
- The occurrences of MDR and XDR were highest among isolates from pneumonia (18.2 and 10.7%, respectively) and UTI (14.9 and 9.6%, respectively; Table 2).
- High rates of cross-resistance were observed among meropenem, piperacillin-tazobactam and ceftazidime; while ceftazidime-avibactam retained good *in vitro* activity against *P. aeruginosa* isolates that were non-susceptible to either one of these β-lactams (Table 3).
- Ceftazidime-avibactam inhibited 69.9% of isolates non-susceptible to ceftazidime, meropenem and piperacillin-tazobactam at ≤8 µg/mL (Table 1).

Figure 1. Antimicrobial susceptibility of 5,486 *P. aeruginosa* isolates from USA hospitals (all infection types combined; 2013-2015).

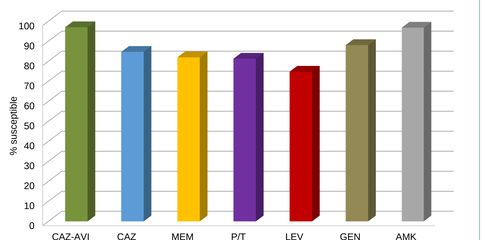


Table 1. Activity of ceftazidime-avibactam and comparator antimicrobial agents when tested against *Pseudomonas aeruginosa* from USA hospitals (2013-2015).

Antimicrobial Agent	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	CLSI[a] %S	CLSI[a] %I	CLSI[a] %R
All isolates (5,486)					
Ceftazidime-avibactam[b]	2	4	97.0	-	3.0
Ceftazidime	2	32	84.7	4.1	11.2
Meropenem	0.5	8	82.0	6.0	12.0
Piperacillin-tazobactam	4	64	81.3	9.2	9.5
Levofloxacin	0.5	>4	74.8	6.6	18.6
Gentamicin	≤1	8	88.1	3.8	8.1
Amikacin	2	8	96.8	1.2	2.0
Colistin	1	2	99.7	0.3	0.1
MDR (842)					
Ceftazidime-avibactam[b]	4	16	81.9	-	18.1
Ceftazidime	32	>32	29.5	15.9	54.6
Meropenem	8	>8	20.5	19.6	59.9
Piperacillin-tazobactam	64	>64	17.8	35.6	46.6
Levofloxacin	>4	>4	14.7	15.3	70.0
Gentamicin	4	>8	51.0	10.1	39.0
Amikacin	8	32	86.1	4.9	9.0
Colistin	1	2	99.4	0.4	0.2
XDR (500)					
Ceftazidime-avibactam[b]	8	32	74.6	-	25.4
Ceftazidime	32	>32	19.6	15.6	64.8
Meropenem	8	>8	7.0	18.8	74.2
Piperacillin-tazobactam	>64	>64	6.4	36.8	56.8
Levofloxacin	>4	>4	3.8	15.4	80.8
Gentamicin	>8	>8	39.2	10.4	50.4
Amikacin	8	>32	81.6	6.2	12.2
Colistin	1	2	99.6	0.2	0.2
Non-susceptible to CAZ, MEM and P/T (432)					
Ceftazidime-avibactam[b]	8	32	69.9	-	30.1
Ceftazidime	32	>32	0.0	19.4	80.6
Piperacillin-tazobactam	>64	>64	0.0	32.9	67.1
Meropenem	8	>8	0.0	21.1	78.9
Levofloxacin	>4	>4	20.1	12.3	67.6
Gentamicin	4	>8	56.7	5.8	37.5
Amikacin	4	>32	83.8	5.6	10.6
Colistin	1	2	99.5	0.2	0.2

a. Criteria as published by CLSI [2016] and EUCAST [2016]
b. Breakpoints from FDA Package Insert
Abbreviations: MDR = multidrug-resistant; XDR = extensively-drug resistant; CAZ = ceftazidime; MEM = meropenem; and P/T = piperacillin-tazobactam.

Table 2. Susceptibility by infection type.

Infection Type (no.)	% susceptible to CAZ-AVI	CAZ	MEM	P/T	MDR rate (%)	XDR rate (%)
BSI (436)	95.6	85.8	81.4	83.4	13.3	9.2
Pneumonia (2,903)	96.6	82.4	78.9	78.6	18.2	10.7
SSSI (1,286)	98.2	88.2	87.1	85.0	10.6	5.9
UTI (417)	97.8	88.0	82.9	84.9	14.9	9.6
IAI (199)	97.5	86.4	82.8	83.9	13.6	7.5
Others (245)	96.3	84.9	89.4	82.8	12.7	6.9

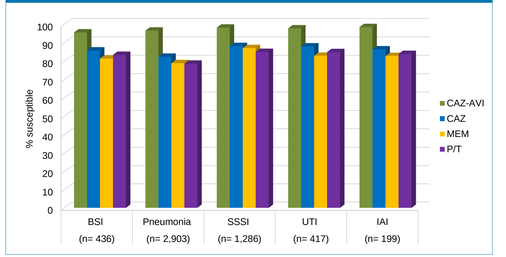
Abbreviations: BSI = bloodstream infection; SSSI = skin and skin structure infection, UTI = urinary tract infection; IAI = intraabdominal infection.

Table 3. Cross-resistance between β-lactams and their activity against multidrug and extensively-drug resistant *P. aeruginosa*.

Organism subset (n)	% Susceptible CAZ-AVI	CAZ	MEM	P/T
CAZ-NS (838)	80.5	--	43.8	9.5
MEM-NS (988)	85.8	52.4	--	42.7
P/T-NS (1,023)	85.2	25.9	44.6	--
CAZ-AVI-NS (164)	--	0.0	14.6	7.9
MDR (842)	81.9	29.5	20.5	17.8
XDR (500)	74.6	19.6	7.0	6.4

Abbreviations: CAZ = ceftazidime; CAZ-AVI = ceftazidime-avibactam; MDR = multidrug-resistant; MEM = meropenem; NS = non-susceptible; P/T = piperacillin-tazobactam; and XDR = extensively-drug resistant.

Figure 2. Antimicrobial activity of ceftazidime-avibactam, ceftazidime, meropenem, and piperacillin-tazobactam when tested against *P. aeruginosa* and stratified by site of infection.



Conclusions

- Ceftazidime-avibactam exhibited potent *in vitro* activity and spectrum when tested against a large collection (n=5,486) of recent *P. aeruginosa* clinical isolates.
- Ceftazidime-avibactam was consistently active against *P. aeruginosa* isolates from all infection types and retained activity against isolates non-susceptible to other anti- *P. aeruginosa* β-lactams, as well as MDR and XDR strains.

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