Antimicrobial Activity of Ceftazidime-Avibactam, Ceftolozane-Tazobactam and Comparators Tested against *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* Isolates Collected from US Medical Centers in 2016–2018

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HS Sader, CG Carvalhaes, JM Streit, TB Doyle, M Castanheira
JMI Laboratories, North Liberty, IA, USA

Helio S. Sader, MD/PhD
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, Iowa 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: helio-sader@jmilabs.com

INTRODUCTION

- Very few agents remain active against *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* in some geographic regions; rapidly introducing appropriate antimicrobial therapy is crucial to reduce morbidity and mortality of patients with infections caused by these organisms in these areas.
- Ceftazidime-avibactam is approved by the European Medicines Agency (EMA) and by the United States Food and Drug Administration (US FDA) to treat hospital-acquired bacterial pneumonia, including ventilator-associated bacterial pneumonia (HABP/VABP), complicated intra-abdominal infections (cIAIs) in combination with metronidazole, and complicated urinary tract infections (UTIs), including pyelonephritis.
- We evaluated the *in vitro* activity of ceftazidime-avibactam, ceftolozane-tazobactam, and many comparator agents against a large collection of contemporary *P. aeruginosa* and *K. pneumoniae* isolates from United States (US) medical centers.

MATERIALS AND METHODS

Bacterial isolates

- A total of 6,210 *P. aeruginosa* and 6,041 *K. pneumoniae* isolates were consecutively collected from 85 US medical centers (37 states) in 2016-2018.
- Only isolates determined to be significant by local criteria as the reported probable cause of infection were included in the program.
- Multidrug-resistant (MDR) was defined as nonsusceptibility (NS; CLSI breakpoints) to at least 1 drug in 3 classes.

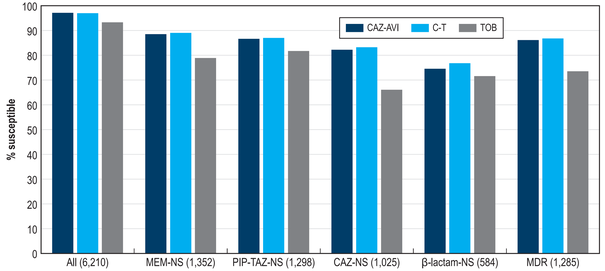
Susceptibility testing and screening for β-lactamase-encoding genes

- Broth microdilution testing was conducted according to CLSI reference method.
- *Enterobacteriaceae* isolates displaying MIC values ≥2 mg/L for at least 2 of the following β-lactams: ceftazidime, ceftriaxone, aztreonam, or cefepime and all carbapenem-resistant *Enterobacteriaceae* isolates (CRE, defined as MIC values at ≥4 mg/L for imipenem [except *Proteeae*], meropenem, and/or doripenem) were tested for β-lactamase-encoding genes using next-generation sequencing.
- Libraries were normalized using the bead-based normalization procedure (Illumina) and sequenced on MiSeq. FASTQ files were assembled using SPAdes Assembler and subjected to a proprietary software (JMI Laboratories) for screening of β-lactamase genes.

RESULTS

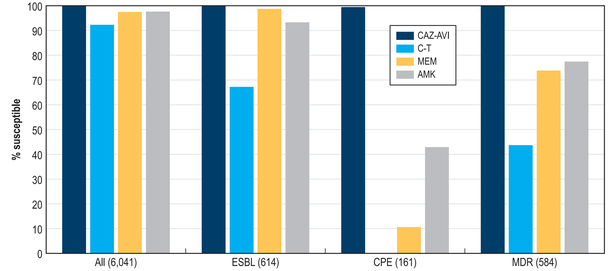
- Ceftazidime-avibactam (97.1% susceptible [S]) and ceftolozane-tazobactam (97.0%S) were the most active compounds against *P. aeruginosa* after colistin (99.7%S), and retained activity against meropenem-nonsusceptible (88.5-89.0%S), piperacillin-tazobactam-nonsusceptible (86.6-87.0%S), and ceftazidime-nonsusceptible (82.2-83.2%) isolates (Tables 1 and 2 and Figure 1).
- Among *P. aeruginosa*, 40.7% of ceftolozane-tazobactam-nonsusceptible isolates were susceptible to ceftazidime-avibactam and 44.2% of ceftazidime-avibactam-nonsusceptible isolates were susceptible to ceftolozane-tazobactam (Table 2).
- The most active agents against *K. pneumoniae* were ceftazidime-avibactam (>99.9%S), colistin (98.3%S), amikacin (97.6%S), and meropenem (97.5%S; Table 1).
- Ceftolozane-tazobactam was active against 92.3% of *K. pneumoniae* isolates overall and showed limited activity against ESBL-producers (67.2%S) and carbapenemase (CPE)-producers (0.0%S; Figure 2).
- Among *K. pneumoniae*, 10.2% were ESBL-producers (excluding CPE co-producers) and 2.7% were CPE-producers (Figure 3).
- The most common ESBLs were CTX-M-15 (75.9%) and OXA-1/OXA-30 (52.4%); 54.4% produced >1 ESBL, mainly CTX-M-15+OXA-1/OXA-30 (50.2% of ESBL-producers; Figure 3).
- The most common CPE among KPN were KPC-3 (57.8% of CPE-producers) and KPC-2 (39.8%). Only one OXA-48-producing and one metallo-beta-lactamase-producing isolate (NDM-1) were observed (Figure 3).
- The most active agents against ESBL-producing *K. pneumoniae* were ceftazidime-avibactam (100.0%S), the carbapenems meropenem and imipenem (98.7-100.0%S), colistin (96.2%S), and amikacin (95.6%S; Figure 2).
- Only ceftazidime-avibactam (99.4%S; Figure 2) and colistin (82.4%S) were active against >45% of CPE-producers.

Figure 1. Antimicrobial activity of ceftazidime-avibactam (CAZ-AVI), ceftolozane-tazobactam (C-T), and tobramycin (TOB) tested against *P. aeruginosa* resistant subsets from United States medical centers (2016–2018)



Abbreviations: MEM, meropenem; NS, nonsusceptible; PIP-TAZ, piperacillin-tazobactam; CAZ, ceftazidime; β-lactam-NS, isolates not susceptible to meropenem, piperacillin-tazobactam and ceftazidime; and MDR, multidrug-resistant.

Figure 2. Antimicrobial activity of ceftazidime-avibactam (CAZ-AVI), ceftolozane-tazobactam (C-T), meropenem (MEM), and amikacin (AMK) tested against *K. pneumoniae* resistant subsets from United States medical centers (2016–2018)



Abbreviations: ESBL, extended-spectrum β-lactamase producers; CPE, carbapenemase producers; and MDR, multidrug-resistant.

Figure 3. Frequency of ESBLs and carbapenemases among *K. pneumoniae* isolates from United States medical centers (2016–2018)

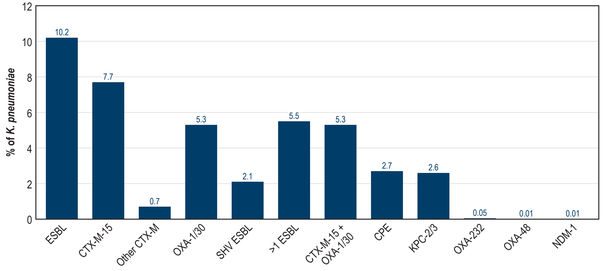


Table 1. Antimicrobial activity of ceftazidime-avibactam, ceftolozane-tazobactam and comparator agents tested against *P. aeruginosa* and *K. pneumoniae* from United States medical centers (2016–2018)

Antimicrobial agent	MIC (mg/L)		CLSI[a]		EUCAST[a]	
	50%	90%	%S	%R	%S	%R
P. aeruginosa (6,210)						
Ceftazidime-avibactam	2	4	97.1	2.9	97.1	2.9
Ceftolozane-tazobactam	0.5	2	97.0	1.8	97.0	3.0
Piperacillin-tazobactam	4	>64	79.1	10.8	79.1	20.9
Meropenem	0.5	8	78.2	15.5	78.2	9.8
Imipenem	1	>8	77.2	18.9	81.1	18.9
Ceftazidime	2	32	83.5	11.9	83.5	16.5
Cefepime	2	16	83.7	5.6	83.7	16.3
Ciprofloxacin	0.25	>4	71.8	21.4	71.8	28.2
Levofloxacin	0.5	>4	63.5	26.4	63.5	36.5
Gentamicin	2	8	83.9	8.6	83.9	16.1
Amikacin	4	16	95.3	2.4	88.8	4.7
Tobramycin	0.5	2	93.3	5.3	93.3	6.7
Colistin	0.5	1	99.7	0.3	99.7	0.3
K. pneumoniae (6,041)						
Ceftazidime-avibactam	0.12	0.25	>99.9	<0.1	>99.9	<0.1
Ceftolozane-tazobactam	0.25	1	95.3	3.7	92.3	7.7
Piperacillin-tazobactam	4	16	91.9	5.5	85.5	8.1
Meropenem	0.03	0.03	97.1	2.5	97.5	1.7
Imipenem	≤0.12	0.25	97.2	2.6	97.4	2.2
Ceftazidime	0.25	16	86.8	12.0	84.8	13.2
Cefepime	≤0.12	16	87.8	10.7	87.2	11.4
Ceftriaxone	≤0.06	>8	86.4	13.2	86.4	13.2
Ciprofloxacin	≤0.03	2	82.2	13.8	82.2	13.8
Levofloxacin	0.06	1	85.9	9.8	85.9	9.8
Gentamicin	0.25	1	92.4	6.6	91.9	7.6
Amikacin	1	2	98.4	0.5	97.6	1.6
Colistin	0.12	0.25			98.3	1.7

[a] Criteria as published by CLSI [2019] and EUCAST [2019].

Table 2. Cross-resistance among β-lactams and β-lactamase inhibitor combinations when tested against *P. aeruginosa* isolates from United States medical centers (2016–2018)

Antimicrobial	% Susceptible by resistant subset (no. of isolates)				
	CAZ-NS (1,025)	MEM-NS (1,352)	PIP-TAZ-NS (1,298)	C-T-NS (113)	CAZ-AVI-NS (183)
CAZ	0.0	54.5	25.9	3.5	4.9
MEM	40.0	0.0	39.9	15.9	15.3
PIP-TAZ	6.1	42.3	0.0	6.2	4.9
C-T	83.2	89.0	87.0	0.0	44.2
CAZ-AVI	82.2	88.5	86.6	40.7	0.0

Abbreviations: CAZ, ceftazidime; MEM, meropenem; PIP-TAZ, piperacillin-tazobactam; C-T, ceftolozane-tazobactam; AVI, avibactam; NS, not susceptible.

CONCLUSIONS

- Ceftazidime-avibactam and ceftolozane-tazobactam showed similar coverage (%S) against *P. aeruginosa* (97.0-97.1%S), including against isolates resistant to other antipseudomonal agents.
- Among *P. aeruginosa*, 40.7% of isolates were susceptible to ceftazidime-avibactam and resistant to ceftolozone-tazobactam and 44.2% were susceptible to ceftolozone-tazobactam and resistant to ceftazidime-avibactam.
- Ceftazidime-avibactam was active against 100.0% of ESBL-producing and 99.4% of CPE-producing *K. pneumoniae*, whereas ceftolozane-tazobactam showed very limited activity against these organisms.
- Ceftazidime-avibactam represents a valuable treatment option for infections caused by *P. aeruginosa* and *K. pneumoniae* in US medical centers, including those caused by MDR organisms.

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This poster was originally intended for presentation at ECCMID 2020, which was canceled due to the COVID-19 pandemic. The corresponding accepted abstract can be found in the 30th ECCMID abstract book under abstract 473.

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