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Comparison of Ceftazidime-Avibactam, Ceftolozane-Tazobactam, and Meropenem-Vaborbactam *In Vitro* Activities against Gram-Negative Bacteria Isolated from Patients Hospitalized with Pneumonia in US Medical Centers in 2020

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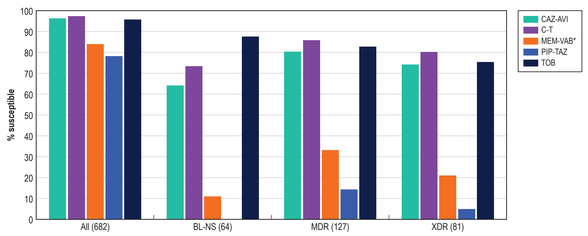
CONCLUSIONS

- Ceftazidime-avibactam demonstrated potent activity against a large US collection of contemporary (2020) *P. aeruginosa* (n=682) and *Enterobacterales* (n=1,388) isolates from patients with pneumonia, including organisms resistant to most currently available agents, such as meropenem-nonsusceptible *P. aeruginosa* and CRE.
- Ceftazidime-avibactam and ceftolozane-tazobactam showed similar coverage (%S) against *P. aeruginosa* (96.3% and 97.4% susceptibility, respectively).
- Ceftazidime-avibactam and meropenem-vaborbactam were the most active compounds against *Enterobacterales* (99.8% and 99.6% susceptibility, respectively) and retained activity against CRE (90.9% and 84.8% susceptibility, respectively).
- Ceftazidime-avibactam demonstrated a broad spectrum of activity against both *P. aeruginosa* and *Enterobacterales* and represents a valuable option for treating patients hospitalized with pneumonia caused by Gram-negative organisms in US medical centers.

RESULTS

- Ceftazidime-avibactam ($MIC_{50/90}$, 2/8 mg/L; 96.3% susceptible) and ceftolozane-tazobactam ($MIC_{50/90}$, 0.5/2 mg/L; 97.4% susceptible) were the most active β-lactams against *P. aeruginosa* (Table 1 and Figure 1).
- Meropenem-vaborbactam inhibited 83.9% of *P. aeruginosa* isolates at ≤4 mg/L, the susceptible breakpoint for *Enterobacterales* ($MIC_{50/90}$, 0.5/16 mg/L); piperacillin-tazobactam ($MIC_{50/90}$, 4/128 mg/L) was active against 78.2% of isolates (Table 1 and Figure 1).
- Ceftazidime-avibactam and ceftolozane-tazobactam retained activity against *P. aeruginosa* isolates nonsusceptible to piperacillin-tazobactam, meropenem, or ceftazidime; whereas meropenem-vaborbactam exhibited limited activity against these 3 resistant subsets (Table 2).
- When tested against *P. aeruginosa* isolates nonsusceptible to piperacillin-tazobactam, meropenem, and ceftazidime (n=64), susceptibility rates for ceftazidime-avibactam, ceftolozane-tazobactam, and meropenem-vaborbactam (at ≤4 mg/L) were 64.1%, 73.4%, and 10.9%, respectively (Table 1 and Figure 1).
- Ceftazidime-avibactam ($MIC_{50/90}$, 0.12/0.5 mg/L; 99.8% susceptible) and meropenem-vaborbactam ($MIC_{50/90}$, 0.03/0.06 mg/L; 99.6% susceptible) were the most active compounds against *Enterobacterales* (Table 3).
- Ceftazidime-avibactam and meropenem-vaborbactam retained potent activity against ceftriaxone-resistant *Enterobacterales* (99.1% and 98.5% susceptible, respectively), MDR *Enterobacterales* (98.2% and 97.1% susceptible, respectively), XDR *Enterobacterales* (88.0% and 80.0% susceptible, respectively), and CRE (90.9% and 84.8% susceptible, respectively; Table 3 and Figure 2).

Figure 1. Antimicrobial susceptibility of *P. aeruginosa* isolated from patients hospitalized with pneumonia in US medical centers (INFORM Program, 2020)



* The *Enterobacterales* susceptible breakpoint of ≤4 mg/L was applied for comparison.
Abbreviations: BL-NS, nonsusceptible to ceftazidime, meropenem, and piperacillin-tazobactam; MDR, multidrug-resistant; XDR, extensively drug-resistant.

- The most common *Enterobacterales* species were *Klebsiella pneumoniae* (24.8% of ENT), *Escherichia coli* (14.8%), *Serratia marcescens* (14.1%), and *Enterobacter cloacae* complex (12.4%).
- *Enterobacterales* susceptibility rates for ceftriaxone and ceftazidime were 74.7% and 79.1%, respectively (Table 3).

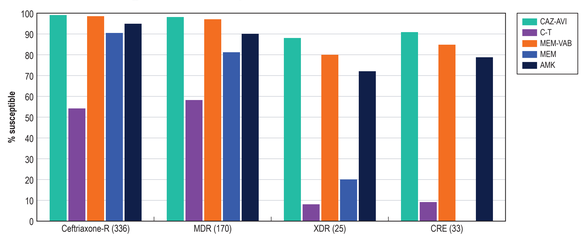
Table 1. Antimicrobial susceptibility of *P. aeruginosa* isolates from patients hospitalized with pneumonia in US medical centers (2020)

Antimicrobial agent	MIC in mg/L		CLSI[a]		
	MIC_{50}	MIC_{90}	%S	%I	%R
P. aeruginosa (682)					
Ceftazidime-avibactam	2	8	96.3		3.7
Ceftolozane-tazobactam	0.5	2	97.4	0.9	1.8
Meropenem-vaborbactam	0.5	16	83.9[b]		
Piperacillin-tazobactam	4	128	78.2	10.9	11.0
Meropenem	0.5	16	77.7	5.6	16.7
Ceftazidime	2	32	83.4	4.5	12.0
Cefepime	2	16	83.9	10.4	5.7
Ciprofloxacin	0.12	4	77.1	6.3	16.6
Levofloxacin	0.5	8	68.1	10.7	21.1
Tobramycin	0.5	2	95.7	1.2	3.1
β-lactam-nonsusceptible *P. aeruginosa* (64)[c]					
Ceftazidime-avibactam	8	>32	64.1		35.9
Ceftolozane-tazobactam	4	>16	73.4	9.4	17.2
Meropenem-vaborbactam	16	32	10.9[b]		
Levofloxacin	4	16	20.3	20.3	59.4
Tobramycin	1	8	87.5	4.7	7.8

[a] Criteria as published by CLSI (2021).
[b] For comparison, the *Enterobacterales* susceptible breakpoint of ≤4 mg/L was applied.
[c] β-lactam-nonsusceptible was defined as nonsusceptible to ceftazidime, meropenem, and piperacillin-tazobactam.

- Ceftolozane-tazobactam was active against 88.7% of *Enterobacterales* ($MIC_{50/90}$, 0.25/4 mg/L) and 91.6% of *K. pneumoniae* ($MIC_{50/90}$, 0.25/2 mg/L), but showed limited activity against ceftriaxone-resistant ($MIC_{50/90}$, 2/>16 mg/L; 54.2% susceptible), MDR ($MIC_{50/90}$, 2/>16 mg/L; 52.8% susceptible), XDR ($MIC_{50/90}$, >16/>16 mg/L; 8.0% susceptible), and CRE isolates ($MIC_{50/90}$, >16/>16 mg/L; 15.2% susceptible; Table 3 and Figure 2).
- Meropenem was active against 97.5% of *Enterobacterales* ($MIC_{50/90}$, 0.03/0.06 mg/L), 90.5% of ceftriaxone-resistant *Enterobacterales* ($MIC_{50/90}$, 0.06/1 mg/L), 81.2% of MDR *Enterobacterales* ($MIC_{50/90}$, 0.06/8 mg/L), and only 20.0% of XDR *Enterobacterales* ($MIC_{50/90}$, 8/>32 mg/L; Table 3 and Figure 2).

Figure 2. Antimicrobial susceptibility of *Enterobacterales* isolated from patients hospitalized with pneumonia in US medical centers (INFORM Program, 2020)



Abbreviations: R, resistant; MDR, multidrug-resistant; XDR, extensively drug-resistant; CRE, carbapenem-resistant *Enterobacterales*.

Table 2. Cross-resistance among β-lactams and β-lactamase inhibitor combinations tested against *P. aeruginosa* isolates from United States medical centers (2020)

Antimicrobial	% Susceptible by resistant subset (no. of isolates)					
	CAZ-NS (113)	PIP-TAZ-NS (149)	MEM-NS (152)	MEM-VAB-NS (110)[a]	C-T-NS (18)	CAZ-AVI-NS (25)
Ceftazidime	0.0	26.2	57.2	48.2	0.0	0.0
Piperacillin-tazobactam	2.7	0.0	40.8	26.4	6.2	4.0
Meropenem	42.5	39.6	0.0	0.0	0.0	4.0
Meropenem-vaborbactam	49.6	45.6	27.6	0.0	22.2	16.0
Ceftolozane-tazobactam	84.1	88.6	88.2	87.3	0.0	48.0
Ceftazidime-avibactam	77.9	83.9	84.2	80.9	27.8	0.0

[a] Isolates with a meropenem-vaborbactam MIC of ≥8 mg/L.
Abbreviations: CAZ, ceftazidime; MEM, meropenem; VAB, vaborbactam; PIP-TAZ, piperacillin-tazobactam; C-T, ceftolozane-tazobactam; AVI, avibactam; NS, nonsusceptible.

Table 3. Antimicrobial susceptibility of *Enterobacterales* isolates from patients hospitalized with pneumonia in US medical centers (2020)

Antimicrobial agent	mg/L		CLSI[a]		
	MIC_{50}	MIC_{90}	%S	%I	%R
Enterobacterales (1,388)					
Ceftazidime-avibactam	0.12	0.5	99.8		0.2
Ceftolozane-tazobactam	0.25	4	88.7	2.9	8.4
Meropenem-vaborbactam	0.03	0.06	99.6	0.1	0.3
Piperacillin-tazobactam	2	64	84.5	7.5	8.0
Meropenem	0.03	0.06	97.5	0.3	2.2
Ceftriaxone	0.12	>8	74.7	1.1	24.2
Ceftazidime	0.25	>32	79.1	2.2	18.7
Cefepime	0.06	16	84.6	4.4[b]	11.0
Levofloxacin	0.06	4	82.3	4.4	13.3
Gentamicin	0.5	2	91.5	1.6	6.9
Amikacin	2	4	98.6	0.9	0.5
Ceftriaxone-resistant *Enterobacterales* (336)					
Ceftazidime-avibactam	0.25	1	99.1		0.9
Ceftolozane-tazobactam	2	>16	54.2	11.1	34.7
Meropenem-vaborbactam	0.03	0.06	98.5	0.3	1.2
Piperacillin-tazobactam	32	>128	42.4	27.8	29.9
Meropenem	0.06	1	90.5	1.2	8.3
Ceftazidime	>32	>32	16.7	7.4	75.9
Cefepime	8	>32	37.5	17.9[b]	44.6
Levofloxacin	0.5	16	54.2	9.6	36.2
Gentamicin	0.5	>16	74.6	3.6	21.8
Amikacin	2	16	94.9	3.6	1.5
CRE (33)					
Ceftazidime-avibactam	1	8	90.9		9.1
Ceftolozane-tazobactam	>16	>16	15.2	0.0	84.8
Meropenem-vaborbactam	0.03	>32	84.8	3.0	12.1
Levofloxacin	2	32	27.3	12.1	60.6
Gentamicin	2	>16	60.6	9.1	30.3
Amikacin	4	32	78.8	12.1	9.1
K. pneumoniae (344)					
Ceftazidime-avibactam	0.12	0.5	99.7		0.3
Ceftolozane-tazobactam	0.25	2	91.6	2.0	6.4
Meropenem-vaborbactam	0.03	0.03	99.1	0.3	0.6
Piperacillin-tazobactam	4	32	87.5	5.5	7.0
Meropenem	0.03	0.06	95.1	0.6	4.4
Ceftriaxone	≤0.06	>8	75.9	0.9	23.3
Ceftazidime	0.25	>32	76.5	2.9	20.6
Cefepime	0.06	>32	77.3	1.5[b]	21.2
Levofloxacin	0.06	4	77.9	7.8	14.2
Gentamicin	0.25	>16	86.0	2.3	11.6
Amikacin	1	4	97.7	1.5	0.9

[a] Criteria as published by CLSI (2021).
[b] Intermediate is interpreted as susceptible-dose dependent.

INTRODUCTION

- Rapidly introducing appropriate antimicrobial therapy for patients hospitalized with pneumonia (PHP) is crucial to reduce morbidity and mortality.
- Antimicrobial treatment is determined mostly by understanding the causative pathogens.
- We compared the activities of ceftazidime-avibactam (CAZ-AVI), ceftolozane-tazobactam (C-T), meropenem-vaborbactam (MEM-VAB), and other comparators against Gram-negative bacteria causing pneumonia in United States (US) medical centers in 2020.

METHODS

Bacterial isolates

- The isolate number was updated since the submission of the abstract as additional isolates were tested.
- A total of 1,388 *Enterobacterales* and 682 *P. aeruginosa* isolates were consecutively collected from patients hospitalized with pneumonia (1/patient) in 60 US medical centers in 2020.
- Only isolates determined to be significant by local criteria as the reported probable cause of infection were included in the program.

Resistant subsets

- Carbapenem-resistant *Enterobacterales* (CRE) isolates were defined as displaying imipenem and/or meropenem MIC values at ≥4 mg/L (CLSI, 2021).
  - Imipenem was not applied to *Proteus mirabilis* and indole-positive Proteeae due to their intrinsically elevated MIC values.
- Multidrug-resistant (MDR) and extensively drug-resistant (XDR) *Enterobacterales* and *P. aeruginosa* strains were classified according to recommended guidelines (Magiorakos et al., 2012) as follows:
  - MDR = nonsusceptible (NS; CLSI breakpoints) to at least 3 antimicrobial classes.
  - XDR = susceptible (S) to 2 or fewer antimicrobial classes.
- Ceftriaxone-resistant *Enterobacterales* isolates were defined as displaying ceftriaxone MIC values of ≥4 mg/L (CLSI, 2021).

Susceptibility testing

- Organisms were tested for susceptibility by reference broth microdilution methods in a central laboratory according to the current Clinical and Laboratory Standards Institute (CLSI) documents.
- Frozen-form MIC panels were manufactured at JMI Laboratories.
- Susceptibility percentages were based on CLSI and/or US Food and Drug Administration (FDA) guidelines.
- The meropenem-vaborbactam susceptible breakpoint of ≤4 mg/L for *Entrobacterales* was applied for comparison purposes to *P. aeruginosa*.

DISCLOSURES

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