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Antimicrobial Activity of New β-lactam/β-lactamase Inhibitor Combinations against *Pseudomonas aeruginosa* and Enterobacterales from Patients with Pneumonia in Intensive Care Units

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CONCLUSIONS

The novel BL/BLIs represent valuable new therapeutic options for Gram-negative pneumonia, especially those caused by MDR *P. aeruginosa* and Enterobacterales for which limited treatment options were available.

Ceftazidime-avibactam demonstrated a more balanced coverage against *P. aeruginosa* and Enterobacterales and may represent a better option for empiric therapy compared to other BL/BLIs.

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References

1. Clinical and Laboratory Standards Institute (2018). *M07Ed11E. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard: eleventh edition.* Wayne, PA: CLSI.
2. Clinical and Laboratory Standards Institute (2022). *M100Ed32E. Performance standards for antimicrobial susceptibility testing: 32nd informational supplement.* Wayne, PA: CLSI.
3. Magiorakos AP, Srinivasan A, Carey RB, et al. (2012). Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 18: 268–281.
4. Sader HS, Castanheira M, Mendes RE, Flamm RK (2018). Frequency and antimicrobial susceptibility of Gram-negative bacteria isolated from patients with pneumonia hospitalized in ICUs of US medical centres (2015–17). *J Antimicrob Chemother* 73:3053-9.

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INTRODUCTION

- The initial antimicrobial therapy of patients with pneumonia is frequently empirical, and timely and effective antimicrobial therapy is critical to decrease complications and mortality.
- The most prominent group of new antimicrobial agents with broad spectrum activity are the β-lactam/β-lactamase inhibitor combinations (BL/BLIs) and 4 such combinations have been approved in recent years: ceftazidime-avibactam (CAZ-AVI), ceftolozane-tazobactam (C-T), meropenem-vaborbactam (MEM-VAB), and imipenem-relebactam (IMI-REL).
- We evaluated the *in vitro* activities of these 4 BL/BLIs against Enterobacterales and *Pseudomonas aeruginosa* isolates recovered from ICU and non-ICU patients with pneumonia in United States hospitals.

MATERIALS AND METHODS

- A total of 2,309 isolates, including 1,365 from ICU and 944 from non-ICU patients, were consecutively collected from the lower respiratory tract of patients with pneumonia in 25 US hospitals in 2020–2021.
- Only isolates determined to be significant by local criteria as the reported probable cause of infection were included in the program.
- Organisms were tested for susceptibility by reference broth microdilution methods in a central laboratory according to the current CLSI documents.
- Frozen-form MIC panels were manufactured at JMI Laboratories.
- Susceptibility percentages were based on US FDA and CLSI breakpoints.
- The MEM-VAB susceptible breakpoint of ≤4 mg/L for Enterobacterales was applied for comparison purposes to *P. aeruginosa.*

RESULTS

- CAZ-AVI, C-T, and IMI-REL were the most active β-lactams against *P. aeruginosa* (Table 1 and Figure 1).
- CAZ-AVI and MEM-VAB were the most active β-lactams against Enterobacterales (Table 1 and Figure 2).
- In general, the activities of the newer BL/BLIs were similar against ICU and non-ICU isolates, except for IMI-REL against Enterobacterales (Table 1 and Figures 1 and 2).
- MEM-VAB exhibited lower activity against *P. aeruginosa* compared to the other 3 new BL/BLIs, especially against resistant subsets (Table 1 and Figure 1).
- Against *P. aeruginosa*, susceptibility of ICU isolates to piperacillin-tazobactam and meropenem were slightly lower and susceptibility to tobramycin was slightly higher compared to non-ICU isolates (Figure 1).
- CAZ-AVI and MEM-VAB showed almost complete activity (≥99.8%) against Enterobacterales from ICU and non-ICU patients (Table 1 and Figure 2).
- IMI-REL exhibited limited activity against some *P. mirabilis* and indole-positive Proteeae isolates (data not shown).
- C-T showed limited activity against *E. cloacae* complex as well as against ESBL-producing, carbapenem-resistant (CRE), and multidrug-resistant (MDR) Enterobacterales (Table 1).
- Susceptibility of Enterobacterales to ceftriaxone, ceftazidime, levofloxacin, and gentamicin was slightly higher among ICU compared to non-ICU isolates (Figure 2).
- The occurrence of CRE and MDR phenotypes among Enterobacterales as well as MDR and XDR phenotypes among *P. aeruginosa* was lower among ICU compared to non-ICU isolates (Table 3).
- Rates of cross-resistance among the 4 new BL/BLIs against *P. aeruginosa* varied markedly (Table 2).
- CAZ-AVI remained active against 75.0%–80.2% of isolates resistant to IMI-REL or MEM-VAB (Table 2).
- Similarly, IMI-REL remained active against 60.0% and 76.9% of isolates nonsusceptible to C-T and CAZ-AVI, respectively (Table 2).

Table 1. Antimicrobial susceptibility of *P. aeruginosa* and Enterobacterales from ICU and non-ICU patients with pneumonia

Organism/subset no. (ICU / non-ICU)	% Susceptible per US FDA (ICU / non-ICU)				
	CAZ-AVI	C-T	MEM-VAB[a]	IMI-REL	PIP-TAZ
P. aeruginosa (433 / 406)	95.8 / 95.8	97.0 / 97.3	82.6 / 86.2[a]	95.1 / 97.4	77.1 / 80.0
PIP-TAZ-NS (99 / 81)	81.8 / 82.7	86.9 / 88.9	48.5 / 63.0[a]	87.8 / 95.5	0.0 / 0.0
MDR (76 / 82)	77.6 / 79.3	85.5 / 86.6	22.4 / 43.9[a]	75.9 / 86.4	13.2 / 25.6
Enterobacterales (932 / 538)	99.9 / 100.0	89.9 / 91.6	100.0 / 99.8	100.0 / 94.3	82.2 / 80.4
CRE (11 / 14)	100.0 / 100.0	9.1 / 14.3	100.0 / 92.9	100.0 / 100.0	0.0 / 7.1
MDR (65 / 57)	100.0 / 100.0	47.7 / 66.7	100.0 / 98.2	100.0 / 100.0	26.2 / 29.8
K. pneumoniae (175 / 142)	100.0 / 100.0	94.9 / 90.8	100.0 / 99.3	100.0 / 100.0	81.1 / 78.0
E. coli (176 / 93)	100.0 / 100.0	96.0 / 96.8	100.0 / 100.0	100.0 / 100.0	89.7 / 80.6
E. cloacae (127 / 52)	100.0 / 100.0	66.1 / 74.5	100.0 / 100.0	100.0 / 100.0	61.1 / 67.3
ESBL-producers (57 / 51)	100.0 / 100.0	78.9 / 76.5	100.0 / 98.0	100.0 / 98.0	66.7 / 66.0

[a] The MEM-VAB susceptible breakpoint of ≤4 mg/L for Enterobacterales was applied for comparison purposes to *P. aeruginosa*.
Abbreviations: CAZ-AVI, ceftazidime-avibactam; C-T, ceftolozane-tazobactam; MEM-VAB, meropenem-vaborbactam; IMI-REL, imipenem-relebactam; PIP-TAZ, piperacillin-tazobactam.

Table 2. Cross-resistance among β-lactams and β-lactamase inhibitor combinations tested against *P. aeruginosa* isolates (ICU and non-ICU combined; *n* = 839)

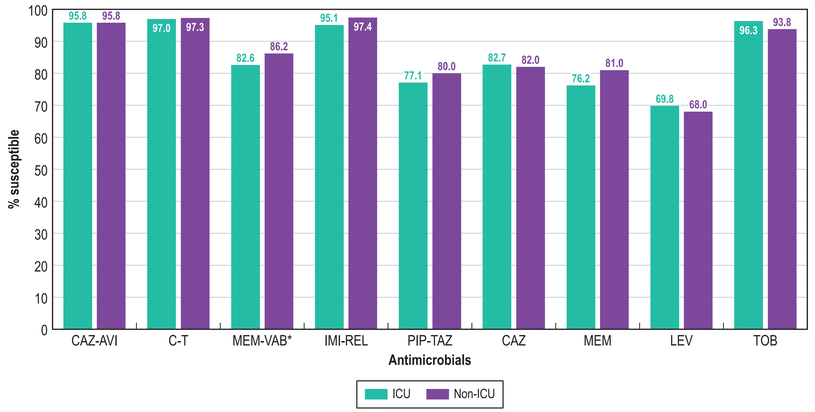
Antimicrobials	% Susceptible by resistant subset (no. of isolates)						
	CAZ-NS (148)	PIP-TAZ-NS (180)	MEM-NS (180)	MEM-VAB-NS (131)[a]	IMI-REL-NS (12)[b]	C-T-NS (24)	CAZ-AVI-NS (35)
CAZ	0.0	22.2	55.6	48.1	50.0	0.0	0.0
PIP-TAZ	5.4	0.0	44.4	32.8	50.0	8.3	8.6
MEM	45.9	44.4	0.0	0.0	0.0	12.5	14.3
MEM-VAB[a]	54.1	51.1	27.2	0.0	16.7	37.5	25.7
IMI-REL	89.5	90.5	79.7	74.4	0.0	60.0	76.9
C-T	83.8	87.8	88.3	88.5	66.7	0.0	51.4
CAZ-AVI	76.4	82.2	83.3	80.2	75.0	29.2	0.0

[a] The meropenem-vaborbactam susceptible breakpoint of ≤4 mg/L for Enterobacterales was applied for comparison purposes to *P. aeruginosa*.
[b] Only 299 isolates were tested against imipenem-relebactam.
Abbreviations: CAZ, ceftazidime; PIP-TAZ, piperacillin-tazobactam; MEM, meropenem; VAB, vaborbactam; IMI-REL, imipenem-relebactam; C-T, ceftolozane-tazobactam; AVI, avibactam; NS, nonsusceptible.

Table 3. Occurrence of resistance phenotypes among *P. aeruginosa* and Enterobacterales from ICU and non-ICU patients

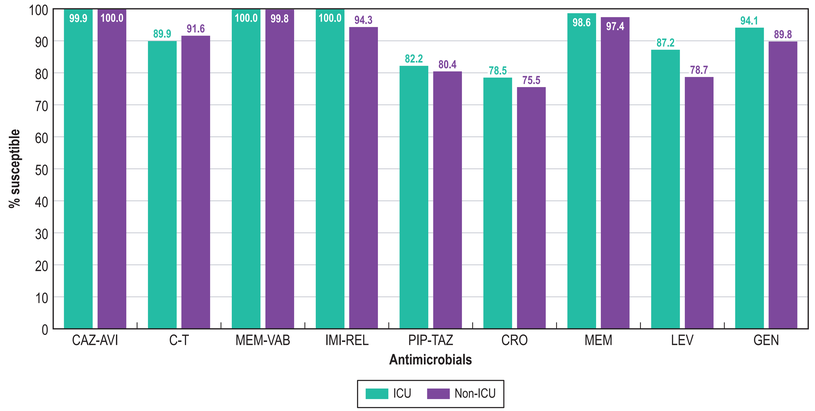
Resistance phenotype	Frequency	
	ICU	Non-ICU
P. aeruginosa		
MDR	17.6%	20.2%
XDR	9.9%	10.6%
Enterobacterales		
CRE	1.2%	2.6%
MDR	7.0%	10.6%

Figure 1. Antimicrobial susceptibility of *P. aeruginosa* isolates from ICU and non-ICU patients



* Based on Enterobacterales breakpoints (≤4 mg/L); not approved in the US for *P. aeruginosa*.
Abbreviations: CAZ-AVI, ceftazidime-avibactam; C-T, ceftolozane-tazobactam; MEM-VAB, meropenem-vaborbactam; IMI-REL, imipenem-relebactam; PIP-TAZ, piperacillin-tazobactam; CAZ, ceftazidime; LEV, levofloxacin; TOB, tobramycin.

Figure 2. Antimicrobial susceptibility of Enterobacterales isolates from ICU and non-ICU patients



Abbreviations: CAZ-AVI, ceftazidime-avibactam; C-T, ceftolozane-tazobactam; MEM-VAB, meropenem-vaborbactam; IMI-REL, imipenem-relebactam; PIP-TAZ, piperacillin-tazobactam; CRO, ceftriaxone; LEV, levofloxacin; GEN, gentamicin.