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Frequency and Antimicrobial Susceptibility of Gram-negative Bacteria Isolated from Patients with Bloodstream Infections in United States (US) Medical Centers (2020–2021)

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CONCLUSIONS

- CAZ-AVI and MEM-VAB were the most active agents against Enterobacterales.
- CAZ-AVI, C-T, IMI-REL, and tobramycin were the most active agents against *P. aeruginosa*.
- The newer β-lactamase inhibitor combinations represent valuable treatment options for infections caused by MDR Enterobacterales and *P. aeruginosa*.
- CAZ-AVI exhibited a more balanced spectrum against Enterobacterales and *P. aeruginosa* when compared to other β-lactamase inhibitor combinations.

SCAN ME

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INTRODUCTION

- Antimicrobial resistance among Gram-negative bacteria (GNB) is a major problem in US hospitals.
- The development of various β-lactamase inhibitor combinations markedly increased the armamentarium to treat infections caused by GNB in recent years.
- We evaluated the frequency and antimicrobial susceptibility of GNB causing bloodstream infection (BSI) in US medical centers.

METHODS

- A total of 5,796 isolates were consecutively collected from patients with BSI in 31 US medical centers.
- Among those isolates, 2,893 (49.9%) were GNB and selected for evaluation, including 2,434 Enterobacterales and 296 *Pseudomonas aeruginosa* isolates.
- Only isolates determined to be significant by local criteria as the reported probable cause of infection were included in the program.
- Carbapenem-resistant Enterobacterales (CRE) isolates were defined as displaying imipenem and/or meropenem MIC ≥4 mg/L; imipenem was not applied to *Proteus mirabilis* and indole-positive Proteeae due to their intrinsically elevated MIC values.
- Multidrug resistance (MDR) was defined as nonsusceptible (CLSI breakpoints) to at least 3 antimicrobial classes (Magiorakos et al., 2012).
- Isolates were susceptibility tested by the CLSI broth microdilution test method.
- Enterobacterales with elevated MIC values for selected β-lactams (ceftazidime, ceftriaxone, aztreonam, and/or cefepime) were screened for β-lactamase genes by whole genome sequencing.

RESULTS

- The most common GNBs isolated from BSI were *E. coli* (41.9%), *K. pneumoniae* (16.1%), *P. aeruginosa* (10.2%), and *Enterobacter cloacae* complex (6.8%; Figure 1).
- Ceftazidime-avibactam (CAZ-AVI; 99.9% susceptible [S]) and meropenem-vaborbactam (MEM-VAB; 99.7% S) showed almost complete activity against Enterobacterales (Table 1 and Figure 2).
  - Imipenem-relebactam (IMI-REL; 96.2% S) exhibited potent activity against Enterobacterales, except *P. mirabilis* and indole-positive Proteeae isolates (Table 1 and Figure 2).
  - Ceftolozane-tazobactam (C-T; 95.4% S) showed limited activity against *E. cloacae* complex, ESBL-phenotype (84.7% S), and MDR isolates (75.2%; Table 1 and Figure 2).
- Ceftriaxone susceptibility rates were 80.1%, 82.9%, and 74.0% for *E. coli*, *K. pneumoniae*, and *E. cloacae* complex, respectively (data not shown).
- CAZ-AVI, MEM-VAB, and IMI-REL were active against 84.2%, 57.9%, and 52.6% of CRE isolates, respectively (Figure 2).
- CAZ-AVI (97.6% S), C-T (97.6% S), IMI-REL (99.0% S), and tobramycin (98.3% S) were the most active agents against *P. aeruginosa* and retained good activity against isolates nonsusceptible to piperacillin-tazobactam or meropenem and against MDR isolates (Table 2 and Figure 3).
- *P. aeruginosa* susceptibility to piperacillin-tazobactam, meropenem, and ceftazidime were 86.1%, 88.5%, and 88.5%, respectively (Table 2 and Figure 3).
- Frequency of β-lactamases found in Enterobacterales is shown in Table 3.

Figure 1. Frequency of Gram-negative bacteria isolated from patients with bloodstream infections in US medical centers (2020–2021)

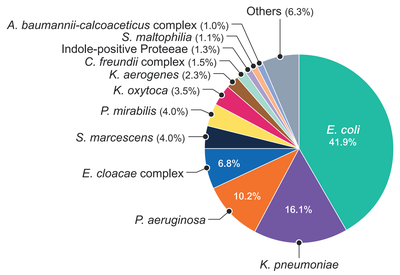
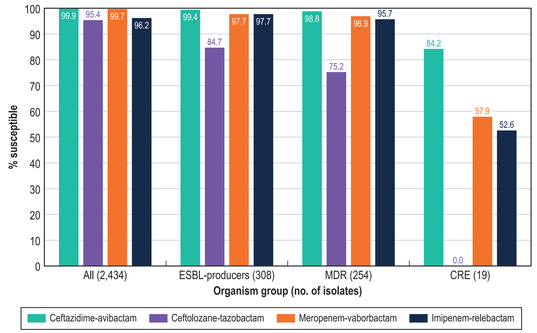
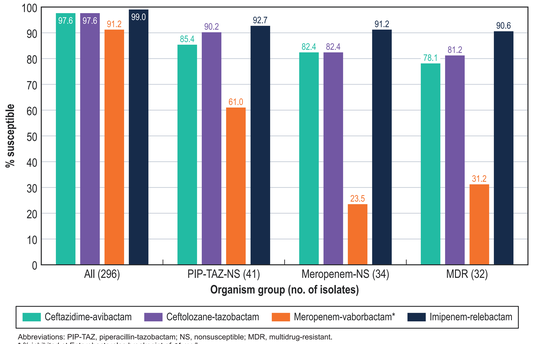


Figure 2. Ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, and imipenem-relebactam activities against Enterobacterales from patients with bloodstream infections



Abbreviations: ESBL, extended-spectrum β-lactamase; MDR, multidrug-resistant; CRE, carbapenem-resistant Enterobacterales.

Figure 3. Ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, and imipenem-relebactam activities against *P. aeruginosa* isolates from patients with bloodstream infections



Abbreviations: PIP-TAZ, piperacillin-tazobactam; NS, nonsusceptible; MDR, multidrug-resistant.
* % inhibited at Enterobacterales breakpoint of ≤4 mg/L.

Table 1. Antimicrobial susceptibility of Enterobacterales (*n*=2,434) isolated from patients with BSI in US medical centers (2020–2021)

Antimicrobial agent	MIC in mg/L		CLSI[a]		
	MIC_{50}	MIC_{90}	%S	%I	%R
Ceftazidime-avibactam	0.12	0.25	99.9		0.1
Ceftolozane-tazobactam	0.25	1	95.4	1.2	3.4
Meropenem-vaborbactam	0.03	0.06	99.7	0.0	0.3
Imipenem-relebactam	0.12	0.5	96.2[b]	3.0	0.8
Piperacillin-tazobactam	2	16	88.0	4.3	7.7
Ampicillin-sulbactam	16	64	49.4	15.2	35.4
Cefuroxime	4	>64	69.9[c]	4.1	26.0
Ceftriaxone	≤0.06	>8	80.7	0.7	18.5
Ceftazidime	0.25	32	84.1	2.1	13.8
Cefepime	0.06	32	86.0	2.0	12.0
Ertapenem	0.015	0.06	97.7	0.7	1.6
Imipenem	≤0.12	1	95.1	3.4	1.4
Meropenem	0.03	0.06	99.1	0.2	0.7
Ciprofloxacin	0.03	>4	74.9	3.1	22.0
Levofloxacin	0.06	16	77.1	3.2	19.7
Gentamicin	0.5	8	89.4	0.7	9.9
Amikacin	2	4	99.5	0.4	0.1

[a] Criteria as published by CLSI (2022).
[b] All Enterobacterales species were included in the analysis, but CLSI excludes *Morganella*, *Proteus*, and *Providencia* species.
[c] Using parenteral breakpoints.

Table 2. Antimicrobial susceptibility of 296 *P. aeruginosa* isolated from patients with BSI in US medical centers (2020–2021)

Antimicrobial agent	MIC in mg/L		CLSI[a]		
	MIC_{50}	MIC_{90}	%S	%I	%R
Ceftazidime-avibactam	2	4	97.6		2.4
Ceftolozane-tazobactam	0.5	2	97.6	1.4	1.0
Meropenem-vaborbactam	0.25	4	[91.2][b]	[4.4][b]	[4.4][b]
Imipenem-relebactam	0.25	1	99.0	0.3	0.7
Piperacillin-tazobactam	4	32	86.1	7.5	6.4
Ceftazidime	2	16	88.5	1.7	9.8
Cefepime	2	16	89.5	5.4	5.1
Imipenem	1	8	87.5	2.4	10.2
Meropenem	0.5	4	88.5	2.7	8.8
Ciprofloxacin	0.12	2	84.4	4.7	10.8
Levofloxacin	0.5	8	79.7	5.8	14.6
Tobramycin	0.5	1	98.3	0.0	1.7

[a] Criteria as published by CLSI (2022).
[b] Not approved to treat *P. aeruginosa* infections in the United States; Enterobacterales breakpoints of ≤4/8/≥16 mg/L (S/I/R) were applied for comparison.

Table 3. Frequency of extended-spectrum β-lactamases (ESBLs) and carbapenemases produced by Enterobacterales from BSI

β-Lactamase	No. of isolates	% of ESBL / carbapenemase producers
ESBL	308	
CTX-M type	289	93.8%
CTX-M-15	210	68.2%
CTX-M-27	37	12.0%
CTX-M-55	18	5.8%
CTX-M-14	17	5.5%
Other CTX-M enzymes	10	3.2%
2 CTX-M enzymes	3	1.0%
OXA type	136	44.2%
CTX-M + OXA-1/30	136	44.2%
SHV type	21	6.8%
≥2 ESBLs	139	45.1%
Carbapenemase	17	
KPC type	10	58.8%
OXA-48 type	6	35.3%
NDM type	2	11.8%
2 carbapenemases	1	5.9%