Antimicrobial Activity of Ceftazidime-Avibactam and Comparator Agents Tested against Gram-Negative Organisms Isolated from Patients with Bloodstream Infections in United States Medical Centers (2017–2018)

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INTRODUCTION

- The etiology of bloodstream infections (BSIs) has changed substantially in the last 2 decades due to an increase of gram-negative pathogens outnumbering gram-positive pathogens
- Recently, the most significant changes have been the antimicrobial resistance patterns, especially among gram-negative organisms recovered from BSIs
- The emergence and spread of multidrug-resistant (MDR) gram-negative organisms triggered the development of a series of β-lactamase inhibitor combinations
- Ceftazidime-avibactam is approved by the United States Food and Drug Administration (US FDA) to treat hospital-acquired bacterial pneumonia, including ventilator-associated bacterial pneumonia, complicated intra-abdominal infections in combination with metronidazole, and complicated urinary tract infections, including pyelonephritis
- Herein, we evaluated the antimicrobial susceptibility of *Enterobacterales* and *Pseudomonas aeruginosa* causing BSI in United States (US) medical centers, focusing on the new β-lactamase inhibitor combinations ceftazidime-avibactam and ceftolozane-tazobactam

MATERIALS AND METHODS

Bacterial isolates

- A total of 3,317 *Enterobacterales* and 331 *P. aeruginosa* isolates were consecutively collected (1/patient) from patients with BSI in 68 US medical centers in 2017-2018
- 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, meropenem, and/or doripenem MIC values at ≥4 mg/L (CLSI, 2019)
  - Imipenem was not applied to *Proteus mirabilis* or indole-positive Proteeae due to the intrinsically elevated MIC values
- Multidrug-resistant (MDR) *Enterobacterales* strains were classified according to recommended guidelines (Magiorakos et al., 2012) as follows:
  - MDR = nonsusceptible (CLSI breakpoints) to at least 3 antimicrobial classes

Susceptibility testing

- All isolates were tested for susceptibility as part of the INFORM program by broth microdilution method according to CLSI
- Avibactam was provided by Allergan (Irvine, California, USA) and combined with ceftazidime (avibactam at fixed concentration of 4 mg/L) for susceptibility testing
- Ceftolozane stock solution was obtained from ThermoFisher Scientific (Cleveland, Ohio, USA) and combined with tazobactam (acquired from United States Pharmacopeia [USP]) at fixed concentration of 4 mg/L for susceptibility testing
- All other compounds were obtained from USP or Sigma-Aldrich (St. Louis, Missouri, USA)

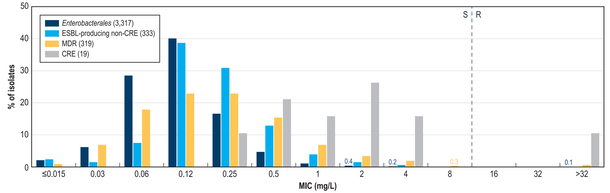
Screening for β-lactamase-encoding genes

- *Enterobacterales* isolates displaying MIC values ≥2 mg/L for at least 2 β-lactams (ie, ceftazidime, ceftriaxone, aztreonam, or cefepime) and all CRE isolates were tested for β-lactamase-encoding genes using next-generation sequencing

RESULTS

- The most common *Enterobacterales* species isolated from BSI were *Escherichia coli* (41.9% of all *Enterobacterales*), *Klebsiella pneumoniae* (24.4%), and *Enterobacter cloacae* species complex (8.7%)
- Ceftazidime-avibactam MIC distributions against *Enterobacterales* and resistant subsets are presented in Figure 1
- The most active agents against *Enterobacterales* were ceftazidime-avibactam (99.9% susceptible), amikacin (99.6% susceptible), and meropenem (99.3% susceptible; Table 1)
- Ceftazidime-avibactam was active against all *E. coli* and *K. pneumoniae* isolates (100.0% susceptible; Figure 2)
- Among *Enterobacterales*, only 2 *E. cloacae* species complex isolates (0.06%) were ceftazidime-avibactam resistant, which were both NDM-1-p isolated from patients in the New York City area from different medical centers
- Ceftolozane-tazobactam and piperacillin-tazobactam showed good activity against *E. coli* and *K. pneumoniae* (92.2–98.9% susceptible; Figure 2), with limited activity against *E. cloacae* species complex (81.9–83.7% susceptible)
- The most common extended-spectrum β-lactamase (ESBL) genes were CTX-M-type, which was observed in 93% of ESBL producers (mainly CTX-M-15 [64% of ESBL producers] and CTX-M-27 [13%]), and OXA-1/OXA-30 (42%; Figure 3)
- Isolates displaying ≥2 ESBL genes were observed in 42% of ESBL producers (n=333, excluding carbapenemase producers); mainly CTX-M-15 and OXA-1/OXA-30 (40% of ESBL producers)
- The most active agents against ESBL producers were ceftazidime-avibactam (100.0% susceptible), colistin (99.1% susceptible), tigecycline (97.9% susceptible), meropenem (97.6% susceptible), and amikacin (97.6% susceptible; Table 1)
- Only ceftazidime-avibactam (99.4% susceptible), amikacin (96.2% susceptible), and meropenem (92.8% susceptible) were active against >90% of MDR *Enterobacterales* (Table 1)
- Among 19 CRE (0.6% of *Enterobacterales*), 11 produced a KPC-like, 2 an NDM-1, and 2 an NMC-A; carbapenemase genes were not found in 4 CRE isolates (Table 2)
- Colistin (100.0% susceptible), ceftazidime-avibactam (98.5% susceptible), amikacin (98.5% susceptible), ceftolozane-tazobactam (98.1% susceptible), and tobramycin (97.0% susceptible) were very active against *P. aeruginosa* (Table 1 and Figure 2)

Figure 1. Ceftazidime-avibactam MIC distribution of *Enterobacterales* isolated from bloodstream infection in US medical centers (INFORM program, 2017–2018)



Abbreviations: ESBL, extended-spectrum β-lactamases (excluding carbapenemase producing strains); MDR, multidrug-resistant; CRE, carbapenem-resistant *Enterobacterales*; S, susceptible; R, resistant.

Breakpoint criteria as published by CLSI, 2019.

Figure 2. Antimicrobial susceptibility of *P. aeruginosa* and *Enterobacterales* isolated from bloodstream infections in US medical centers (INFORM Program, 2017)

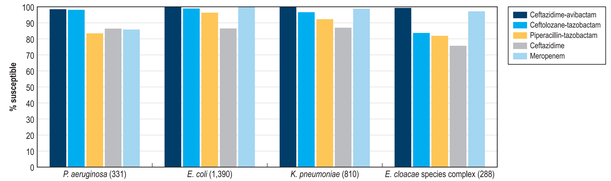


Table 1. Antimicrobial activity of ceftazidime-avibactam and comparator agents tested against *Enterobacterales* and *P. aeruginosa* isolated from bloodstream infection (INFORM program, 2017–2018)

Organism/organism group (no. of isolates) Antimicrobial agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	CLSI[a] %S	CLSI[a] %R
Enterobacterales (3,317)				
Ceftazidime-avibactam	0.12	0.25	99.9	0.1
Ceftolozane-tazobactam	0.25	1	96.2	3.0
Piperacillin-tazobactam	2	8	93.5	3.4
Ceftazidime	0.25	16	87.2	11.3
Ceftriaxone	≤0.06	>8	83.7	15.4
Cefepime	≤0.12	4	89.2	8.7
Meropenem	0.03	0.06	99.3	0.5
Levofloxacin	0.06	16	77.5	20.5
Gentamicin	0.5	4	90.1	9.1
Amikacin	2	4	99.6	0.1
Tigecycline[b]	0.25	1	95.4	0.6
Colistin[c]	0.12	>8	84.2[c]	
ESBL-producing non-CRE isolates (333)[d]				
Ceftazidime-avibactam	0.12	0.5	100.0	0.0
Ceftolozane-tazobactam	0.5	2	90.6	6.8
Piperacillin-tazobactam	4	64	80.2	8.4
Ceftriaxone	>8	>8	0.3	99.4
Ceftazidime	16	>32	18.3	70.6
Cefepime	>16	>16	6.6	79.6
Meropenem	0.03	0.06	97.6	1.2
Levofloxacin	8	>16	19.5	76.0
Gentamicin	1	>16	55.3	42.6
Amikacin	4	8	97.6	0.9
Tigecycline[b]	0.25	1	97.9	0.0
Colistin[c]	0.12	0.25	99.1[c]	
MDR isolates (319)				
Ceftazidime-avibactam	0.25	1	99.4	0.6
Ceftolozane-tazobactam	0.5	>16	78.1	16.2
Piperacillin-tazobactam	8	>128	64.6	18.5
Ceftriaxone	>8	>8	24.5	72.1
Ceftazidime	16	>32	33.2	59.9
Cefepime	16	>16	37.9	55.8
Meropenem	0.06	0.25	92.8	5.3
Levofloxacin	8	>16	13.8	78.9
Gentamicin	>16	>16	37.6	56.1
Amikacin	4	8	96.2	1.3
Tigecycline[b]	0.5	4	75.9	4.7
Colistin[c]	0.25	>8	64.5[c]	
Pseudomonas aeruginosa (331)				
Ceftazidime-avibactam	2	4	98.5	1.5
Ceftolozane-tazobactam	0.5	2	98.1	0.9
Piperacillin-tazobactam	4	64	83.4	8.8
Ceftazidime	2	32	86.4	10.3
Cefepime	2	16	88.5	3.3
Meropenem	0.5	4	85.8	9.7
Levofloxacin	0.5	16	70.4	21.1
Gentamicin	2	4	90.9	4.2
Amikacin	4	8	98.5	0.6
Tobramycin	0.5	1	97.0	2.4
Colistin	0.5	1	100.0	0.0

ESBL, extended-spectrum β-lactamase; MDR, multidrug-resistant.
[a] Criteria as published by CLSI 2019.
[b] FDA breakpoints accessed February 2019.
[c] Percentage of wild type based on epidemiologic cutoff value. CLSI M100 (2019).
[d] Organisms include: *Citrobacter freundii* species complex (3), *Enterobacter cloacae* species complex (16), *E. coli* (214), *Klebsiella oxytoca* (2), *K. pneumoniae* (98).

Figure 3. Frequency of ESBL genes detected among ESBL-producing non-CRE isolates recovered from bloodstream infections in US medical centers (INFORM program, 2017–2018)

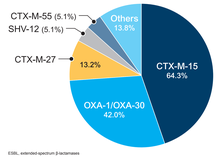


Table 2. Carbapenemase genes detected among *Enterobacterales* isolated from bloodstream infection in US medical centers (INFORM program, 2017–2018)

Organism Carbapenemase gene	No. of isolates
E. coli	
KPC-2	1
K. pneumoniae	
KPC-2	3
KPC-3	2
Enterobacter cloacae species complex	
KPC-2	1
KPC-3	1
KPC-4	1
KPC-6	1
NDM-1	2
NMC-A	2
Raoultella spp.	
KPC-2	1

CONCLUSIONS

- Ceftazidime-avibactam displayed potent activity against contemporary *Enterobacterales* (n = 3,317) and *P. aeruginosa* (n = 331) isolates from patients with bloodstream infections in US hospitals
- Ceftolozane-tazobactam was less active than ceftazidime-avibactam against *Enterobacterales* in general and exhibited limited activity against MDR isolates
- Ceftazidime-avibactam and ceftolozane-tazobactam showed similar coverage (% susceptible) against *P. aeruginosa* (98.5% susceptible vs. 98.1% susceptible)
- Ceftazidime-avibactam is not licensed by the FDA for treating BSIs, but is potentially important in treating infections due to highly resistant *Enterobacterales* and *P. aeruginosa*

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