Frequency of Occurrence and Antimicrobial Susceptibility of Bacteria Isolated from Patients Hospitalized with Bloodstream Infections in United States Medical Centers (2015–2017)

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INTRODUCTION

- Despite impressive achievements reached in the fields of microbiological diagnosis and antimicrobial therapy, bloodstream infections (BSIs) still account for significant morbidity and mortality
- The etiology of BSI may vary significantly according to the type of patient and source of infection, and studies evaluating large series of BSIs with non-selected types of patients or specific pathogens are scarce
- Ceftazidime-avibactam is approved by the United States Food and Drug Administration (US FDA) and by the European Medicine Agency (EMA) 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, including pyelonephritis
- Ceftazidime-avibactam is not licensed for treating BSI, but is potentially important in treating infections due to highly resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa*
- We evaluated the frequency and antimicrobial susceptibility of gram-negative bacteria isolated from patients with BSIs in US medical centers, and assessed the activity and spectrum of 2 recently approved β-lactamase inhibitor combinations, ceftazidime-avibactam and ceftolozane-tazobactam, and many other antimicrobial agents currently used to treat BSIs

MATERIALS AND METHODS

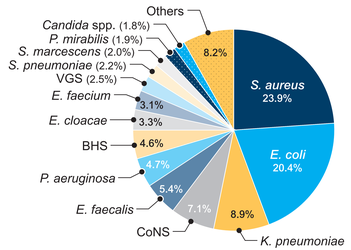
Bacterial isolates

- A total of 9,210 bacterial isolates were consecutively collected (1/patient) from patients with BSIs in 33 US medical centers in 2015-2017
- Only isolates determined to be significant by local criteria as the reported probable cause of infection were included in the program
- Carbapenem-resistant *Enterobacteriaceae* (CRE) isolates were defined as displaying imipenem, meropenem, and/or doripenem MIC values at ≥4 mg/L (CLSI, 2018)
  - Imipenem was not applied to *Proteus mirabilis* and indole-positive Proteeae due to the intrinsically elevated MIC values

Susceptibility testing

- Broth microdilution test method was conducted 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

Figure 1. Frequency of organisms isolated from patients with BSIs from US medical centers (INFORM Program, 2017)



Abbreviations: CoNS, coagulase-negative staphylococci; BHS, β-hemolytic streptococci; VGS, viridans group streptococci.

Table 1. Antimicrobial susceptibility of 2,240 *S. aureus* isolates collected from patients with BSIs (USA, 2015–2017)

Antimicrobial agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	CLSI[a]	
			%S	%R
Ceftaroline	0.25	1	97.6	0.0
Dalbavancin	0.03	0.03	100.0	
Daptomycin	0.25	0.5	>99.9	
Doxycycline	≤0.06	0.25	99.1	0.2
Erythromycin	8	>8	43.8	50.2
Levofloxacin	0.25	>4	61.9	37.3
Linezolid	1	2	100.0	0.0
Minocycline	≤0.06	0.12	99.1	0.2
Oxacillin	0.5	>2	57.8	42.2
Tigecycline	0.06	0.12	100.0[b]	
TMP-SMX[c]	≤0.5	≤0.5	97.6	2.4
Vancomycin	0.5	1	100.0	0.0

[a] Criteria as published by CLSI 2018.
[b] US FDA breakpoints published 2017-DEC-13.
[c] TMP-SMX, trimethoprim-sulfamethoxazole.

- 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)

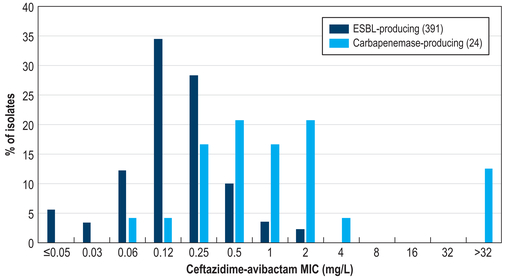
Screening for β-lactamase-encoding genes

- *Enterobacteriaceae* 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
- 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

- The most common organisms were *Staphylococcus aureus* (24.3%), *Escherichia coli* (20.8%), *Klebsiella pneumoniae* (9.1%), coagulase-negative staphylococci (7.3%), *Enterobacter faecalis* (5.5%), *P. aeruginosa* (4.7%), and β-hemolytic streptococci (4.7%; Figure 1)

Figure 2. Ceftazidime-avibactam MIC distributions when testing ESBL-producing (excluding carbapenemases) and carbapenemase-producing *Enterobacteriaceae* isolates (USA, 2015–2017)



Abbreviation: ESBL, extended-spectrum β-lactamase

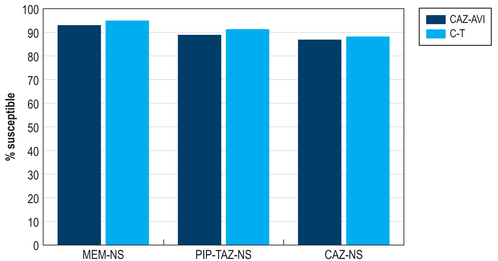
Table 2. Antimicrobial activity of ceftazidime-avibactam tested against the main gram-negative organisms and organism groups

Organism/ organism group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of:														MIC_{50}	MIC_{90}
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32			
Enterobacteriaceae (3,746)	161	333	1,081	1,400	561	146	33	23	4	1	0	0	3[a]		0.12	0.25
	4.3	13.2	42.0	79.4	94.4	98.3	99.2	99.8	99.9	99.9	99.9	99.9	100.0			
Escherichia coli (1,902)	138	181	618	707	207	31	10	8	0	0	0	0	2	100.0	0.12	0.25
	7.3	16.8	49.3	86.4	97.3	98.9	99.5	99.9	99.9	99.9	99.9	99.9	100.0			
Klebsiella pneumoniae (832)	8	27	259	366	122	36	3	6	4	0	0	0	1	100.0	0.12	0.25
	1.0	4.2	35.3	79.3	94.0	98.3	98.7	99.4	99.9	99.9	99.9	99.9	100.0			
Enterobacter cloacae species complex (297)	6	5	20	115	92	40	11	8							0.25	0.5
	2.0	3.7	10.4	49.2	80.1	93.6	97.3	100.0								
Serratia marcescens (188)	0	1	1	78	81	23	4								0.25	0.5
	0.0	0.5	1.1	42.6	85.6	97.9	100.0									
Proteus mirabilis (174)	3	93	72	4	2										0.03	0.06
	1.7	55.2	96.6	98.9	100.0											
Pseudomonas aeruginosa (433)				0	1	5	165	166	65	23	3	3	2		2	4
				0.0	0.2	1.4	39.5	77.8	92.8	98.2	98.8	99.5	100.0			

[a] *E. coli* and 1 *K. pneumoniae*; all NDM producers (2 NDM-1 and 1 NDM-9) from a single hospital in Texas

- Overall, 50.0% of isolates were gram-negative bacilli and 41.4% were *Enterobacteriaceae* (Figure 1)
- All *S. aureus* isolates were susceptible (S) to dalbavancin (MIC_{50} and MIC_{90}, 0.03 mg/L), linezolid ($MIC_{50/90}$, 1/2 mg/L), tigecycline ($MIC_{50/90}$, 0.06/0.12 mg/L), and vancomycin ($MIC_{50/90}$, 0.5/1 mg/L); >99.9%S to daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L), 97.6%S to ceftaroline ($MIC_{50/90}$, 0.25/1 mg/L), and 57.8%S to oxacillin (Table 1)
- The most active agents against *Enterobacteriaceae* were ceftazidime-avibactam (99.9%S), amikacin (99.7%S), and the carbapenems meropenem and doripenem (99.1%S; Tables 2 and 3)
- CRE represented only 0.7% of *Enterobacteriaceae* isolates (n=28) and were observed in 12 of 33 (36.4%) medical centers surveyed (Tables 3 and 4)
- Ceftazidime-avibactam demonstrated potent activity against extended-spectrum β-lactamase (ESBL)-producing (n=391; $MIC_{50/90}$, 0.12/0.5 mg/L; 100.0%S) and carbapenemase-producing (n=24; $MIC_{50/90}$, 1/>32 mg/L; 87.5%S) *Enterobacteriaceae* (Table 3, Figure 2)
- Only 3 *Enterobacteriaceae* isolates (0.1%) were ceftazidime-avibactam-resistant, 2 *E. coli* and 1 *K. pneumoniae*; all 3 were NDM-like producers (2 NDM-1 and 1 NDM-9) from a single hospital in Texas (Tables 3 and 4)

Figure 3. Antimicrobial susceptibility of *P. aeruginosa* isolated from patients with BSIs in US medical centers (2015–2017)



Abbreviations: CAZ-AVI, ceftazidime-avibactam; C-T, ceftolozane-tazobactam; MEM-NS, meropenem-nonsusceptible; PIP-TAZ-NS, piperacillin-tazobactam-nonsusceptible; CAZ-NS, ceftazidime-nonsusceptible

Table 3. Antimicrobial activity of ceftazidime-avibactam and comparator agents tested against *Enterobacteriaceae* and *P. aeruginosa* isolated from patients with BSIs (INFORM Program; 2015–2017)

Organism/ antimicrobial agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	CLSI[a] %S	%R
Enterobacteriaceae (3,746)				
Ceftazidime-avibactam	0.12	0.25	99.9	0.1
Ceftolozane-tazobactam[b]	0.25	0.5	96.9	2.5
Ceftriaxone	≤0.06	>8	83.8	15.6
Ceftazidime	0.25	16	87.1	11.6
Cefepime	≤0.12	8	88.8	9.3
Piperacillin-tazobactam	2	8	93.4	3.3
Meropenem	0.03	0.06	99.1	0.7
Doripenem	≤0.06	0.12	99.1	0.7
Levofloxacin	0.06	>4	78.9	19.5
Gentamicin	0.5	8	89.6	9.8
Amikacin	2	4	99.7	0.1
Tigecycline	0.25	1	97.3	0.3[c]
Colistin	0.12	>8	86.2[d]	
ESBL-producing *Enterobacteriaceae* (391)[e]				
Ceftazidime-avibactam	0.12	0.5	100.0	0.0
Ceftolozane-tazobactam[b]	0.5	4	88.8	9.1
Piperacillin-tazobactam	4	64	81.6	8.7
Meropenem	0.03	0.06	99.0	0.8
Doripenem	≤0.06	0.12	99.0	0.8
Levofloxacin	>4	>4	22.8	73.1
Gentamicin	2	>8	51.9	45.8
Amikacin	4	8	98.7	0.3
Tigecycline	0.25	1	98.0	0.0[c]
Colistin	0.12	0.25	97.9[d]	
Carbapenem-resistant *Enterobacteriaceae* (28)[f]				
Ceftazidime-avibactam	1	>32	89.3	10.7
Ceftolozane- tazobactam[b]	>16	>16	0.0	83.3
Piperacillin-tazobactam	>64	>64	0.0	89.3
Meropenem	8	>32	0.0	92.9
Doripenem	8	>8	0.0	92.9
Levofloxacin	>4	>4	14.3	82.1
Gentamicin	2	>8	53.6	39.3
Amikacin	8	>32	78.6	10.7
Tigecycline	0.5	2	96.4	0.0[c]
Colistin	0.12	>8	85.2	
Pseudomonas aeruginosa (433)				
Ceftazidime-avibactam	2	4	98.2	1.8
Ceftolozane- tazobactam[b]	0.5	1	98.7	0.7
Ceftazidime	2	16	87.8	9.5
Cefepime	2	16	87.8	4.2
Piperacillin-tazobactam	4	64	85.5	7.2
Meropenem	0.5	8	80.1	12.9
Doripenem	0.5	8	84.0	10.2
Levofloxacin	0.5	>4	78.5	16.6
Gentamicin	2	8	88.7	5.8
Amikacin	4	8	97.9	1.4
Tobramycin	0.5	2	95.6	4.1
Colistin	1	1	100.0	0.0

Abbreviation: ESBL, extended-spectrum β-lactamase

[a] Criteria as published by CLSI 2018.
[b] Tested only in 2017 against 1,311 *Enterobacteriaceae*, including 131 ESBL-producing and 6 carbapenemase-resistant isolates, and 149 *P. aeruginosa* isolates.
[c] FDA breakpoints published 2017-DEC-13.
[d] Percentage of wild type based on epidemiological cutoff value. CLSI M100 (2018).
[e] Organisms include: *Enterobacter aerogenes* (1), *E. cloacae* species complex (15), *Escherichia coli* (277), *Klebsiella oxytoca* (4), *K. pneumoniae* (90), *Proteus mirabilis* (4).
[f] Organisms include: *Enterobacter cloacae* species complex (3), *Escherichia coli* (5), *Klebsiella oxytoca* (2), *K. pneumoniae* (16), *Serratia marcescens* (2).

- Ceftolozane-tazobactam (tested in 2017 only) was active against 96.9% of *Enterobacteriaceae* overall and 88.8% of ESBL-producing (excluding carbapenemase) isolates (Table 3)
- Among 28 CRE, 21 produced a KPC-like, 1 an NDM-1, 1 an NDM-9, and 1 a KPC-17 and an NDM-1 (Table 4)
- Ceftazidime-avibactam was highly active against *P. aeruginosa* ($MIC_{50/90}$, 2/4 mg/L; 98.2%S; Tables 2 and 3)
- Colistin (100.0%S), ceftolozane-tazobactam (98.7%S), ceftazidime-avibactam (98.2%S), amikacin (97.9%S), and tobramycin (95.6%S) were the most active agents against *P. aeruginosa* (Table 3)
- Ceftazidime-avibactam and ceftolozane-tazobactam remained active against most *P. aeruginosa* isolates nonsusceptible to meropenem (93.0 and 95.0%S, respectively), piperacillin-tazobactam (88.9 and 91.3%S), and/or ceftazidime (86.9 and 88.2%S; Figure 3)

CONCLUSIONS

- Gram-negative bacilli represented 50.0% of bacteria isolated from patients with BSIs
- Ceftazidime-avibactam demonstrated potent activity against a large US collection of contemporary *Enterobacteriaceae* and *P. aeruginosa* isolates from patients with BSIs, including organisms resistant to most currently available agents, such as CRE and meropenem-nonsusceptible *P. aeruginosa*
- Ceftazidime-avibactam and ceftolozane-tazobactam showed similar coverage (%S) against *P. aeruginosa* (98.2%S vs. 98.7%S)
- Ceftolozane-tazobactam was less active than ceftazidime-avibactam against *Enterobacteriaceae* in general and exhibited limited activity against ESBL-producing isolates

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Table 4. Carbapenemases produced by carbapenem-resistant *Enterobacteriaceae* isolates

Organism / carbapenemase	No. of isolates
K. pneumoniae	**16**
KPC-2	6
KPC-3	5
KPC-17	1
KPC-17 plus NDM-1	1
Negative[a]	3
E. coli	**5**
KPC-2	2
NDM-1	1
NDM-9	1
Negative[a]	1
E. cloacae	**3**
KPC-3	3
K. oxytoca	**2**
KPC-2	2
S. marcescens	**2**
KPC-2	1
KPC-3	1
Total	28

[a] No carbapenemase gene found.

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