Comparison of Ceftazidime-Avibactam, Ceftolozane-Tazobactam, Piperacillin-Tazobactam, and Meropenem Activities when Tested against Gram-Negative Organisms Isolated from Complicated Urinary Tract Infections

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INTRODUCTION

- 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 (cUTIs), including pyelonephritis
- We evaluated the antimicrobial susceptibility of gram-negative bacilli causing complicated urinary tract infection (cUTI) in US medical centers, focusing on the β-lactamase inhibitor combinations ceftazidime-avibactam, ceftolozane-tazobactam, and piperacillin-tazobactam and the carbapenem meropenem

MATERIALS AND METHODS

Bacterial isolates

- A total of 4,371 gram-negative bacilli, including 4,120 *Enterobacterales*, 230 *P. aeruginosa*, and 21 *Acinetobacter* spp. isolates, were consecutively collected (1/patient) from patients with cUTI in 65 US medical centers in 2018
- Carbapenem-resistant *Enterobacterales* (CRE) isolates were defined as displaying imipenem, meropenem, and/or doripenem MIC values at ≥4 mg/L (Clinical and Laboratory Standards Institute [CLSI], 2019)
 - Imipenem was not applied to *Proteus mirabilis* or indole-positive Proteeae due to the intrinsically elevated MIC values

Susceptibility testing

- All isolates were tested for susceptibility by reference broth microdilution test method according to CLSI as part of the INFORM program
- 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

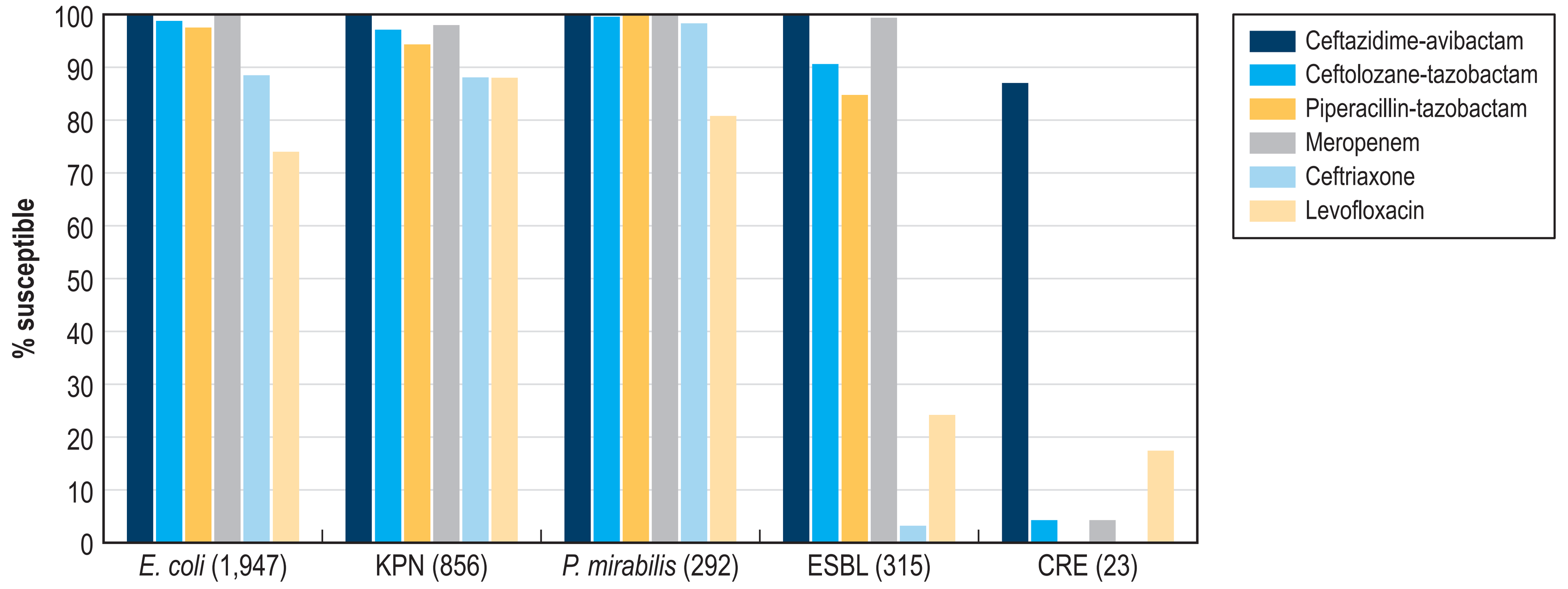
RESULTS

- The most common gram-negative organisms were *Escherichia coli* (44.5%), *Klebsiella pneumoniae* (19.6%), *P. mirabilis* (6.7%), and *P. aeruginosa* (5.3%; data not shown)
- The most active agents against *Enterobacterales* were ceftazidime-avibactam (99.9% susceptible [S]), amikacin (99.7%S), and meropenem (99.4%S), whereas ceftolozane-tazobactam and piperacillin-tazobactam were active against 96.7% and 95.0% of isolates at the respective susceptible breakpoint (Table 1)
- Extended-spectrum β-lactamase (ESBL) genes were identified in 315 *Enterobacterales* (7.6%; excluding carbapenemase co-producers), including CTX-M-15 (63% of ESBL producers), other CTX-M types (25%), OXA-1/OXA-30 (41%), and SHV-type ESBLs (8%); approximately 40% of ESBL producers had ≥2 ESBL genes, mainly a CTX-M-type and an OXA-type (37% of isolates; data not shown)
- The most active agents against ESBL producers were ceftazidime-avibactam (100.0%S), amikacin (99.7%S), and meropenem (99.4%S), while ceftolozane-tazobactam and piperacillin-tazobactam were active against 90.6% and 84.8% of ESBL producers, respectively (Figure 1)
- Only ceftazidime-avibactam (87.0%S; Figure 1), colistin (87.0%S per EUCAST), and tigecycline (95.7%S) exhibited good activity against CRE
- Only 3 *Enterobacterales* isolates (0.07%) were ceftazidime-avibactam resistant and all had a metallo-β-lactamase gene (2 VIM-1 and 1 NDM-1; data not shown)
- Ceftazidime-avibactam (97.0%S; Table 1 and Figure 2) and ceftolozane-tazobactam (99.1%S) were the most active β-lactams tested against *P. aeruginosa*; other compounds with >90%S for *P. aeruginosa* were colistin (99.6%), amikacin (97.8%), tobramycin (93.5%), and ceftazidime (90.4%; Table 1)
- *Acinetobacter* spp. represented only 0.5% of the isolates collected from patients with cUTI, and the most active agents tested against these organisms were colistin (100.0%S), followed by the carbapenems imipenem and meropenem and the aminoglycosides amikacin and tobramycin, all 4 compounds with 95.2%S (data not shown)

CONCLUSIONS

- Ceftazidime-avibactam demonstrated potent activity against contemporary *Enterobacterales* isolates (n=4,120) from patients with cUTI in US hospitals, including ESBL producers and CRE
- Ceftolozane-tazobactam, piperacillin-tazobactam, and meropenem exhibited good activity against the overall *Enterobacterales* (≥95%S) collection, but ceftolozane-tazobactam and piperacillin-tazobactam displayed limited activity against ESBL producers and all 3 compounds were inactive against CRE
- Ceftazidime-avibactam and ceftolozane-tazobactam showed similar coverage (%S) against *P. aeruginosa* (97.0%S vs. 99.1%S, respectively)
- Ceftazidime-avibactam exhibited the best overall coverage (*Enterobacterales* + *P. aeruginosa*) among antimicrobial agents tested against gram-negative bacilli from patients with cUTI in US hospitals during 2018

Figure 1 Antimicrobial susceptibility of *Enterobacterales* isolated from patients with complicated urinary tract infections in US medical centers (INFORM program, 2018)


% susceptible
0
10
20
30
40
50
60
70
80
90
100
E. coli (1,947)
KPN (856)
P. mirabilis (292)
ESBL (315)
CRE (23)
Ceftazidime-avibactam
Ceftolozane-tazobactam
Piperacillin-tazobactam
Meropenem
Ceftriaxone
Levofloxacin

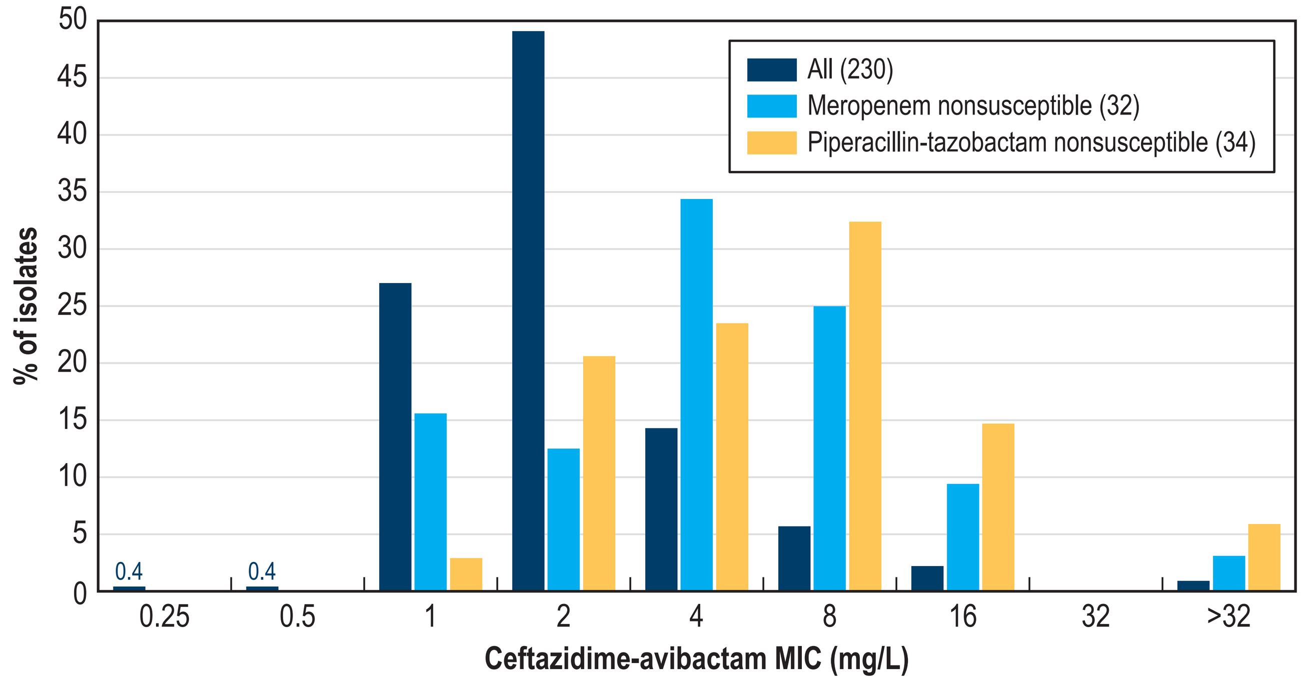
KPN, *K. pneumoniae*; ESBL, extended-spectrum β-lactamases (excluding carbapenemase producing strains); CRE, carbapenem-resistant *Enterobacterales*.

Table 1 Antimicrobial activity of ceftazidime-avibactam and comparator agents tested against *Enterobacterales* and *P. aeruginosa* isolated from patients with complicated urinary tract infections in US medical centers (2018)

Organism/organism group (no. of isolates) Antimicrobial agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	CLSI[a]	
			%S	%R
Enterobacterales (4,120)				
Ceftazidime-avibactam	0.12	0.25	99.9	0.1
Ceftolozane-tazobactam	0.25	1	96.7	2.4
Piperacillin-tazobactam	2	8	95.0	2.3
Ceftriaxone	≤0.06	>8	86.8	12.6
Meropenem	0.03	0.06	99.4	0.4
Levofloxacin	0.06	8	80.9	16.7
Amikacin	2	4	99.7	0.2
Colistin	0.12	>8	85.2[b]	14.8[b]
Pseudomonas aeruginosa (230)				
Ceftazidime-avibactam	2	4	97.0	3.0
Ceftolozane-tazobactam	1	2	99.1	0.9
Piperacillin-tazobactam	4	32	85.2	5.7
Ceftazidime	2	8	90.4	6.1
Meropenem	0.5	4	86.1	9.1
Levofloxacin	0.5	32	65.5	25.3
Tobramycin	0.5	2	93.5	6.5
Colistin	0.5	1	99.6	0.4

[a] Criteria as published by CLSI 2019.
[b] Per EUCAST 2019 criteria.

Figure 2 Ceftazidime-avibactam susceptibility of *P. aeruginosa* isolated from patients with complicated urinary tract infections in US medical centers (INFORM program, 2018)


% of isolates
0
5
10
15
20
25
30
35
40
45
50
0.4
0.4
0.25
0.5
1
2
4
8
16
32
>32
Ceftazidime-avibactam MIC (mg/L)
All (230)
Meropenem nonsusceptible (32)
Piperacillin-tazobactam nonsusceptible (34)

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