Tebipenem *In vitro* Activity against a Collection of Pathogens Responsible for Urinary Tract Infections in the US

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Introduction

- *Enterobacterales*—especially *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*—are widely implicated in urinary tract infection (UTI).
- Many oral agents are used to manage UTIs, but their clinical usefulness has been compromised by the increased prevalence of extended-spectrum β-lactamases (ESBL) and presence of co-resistance to trimethoprim-sulfamethoxazole (TMP-SMX) and quinolones.
- Tebipenem is an oral, bioavailable carbapenem in clinical development for treating complicated UTIs and acute pyelonephritis.
- This study assessed the *in vitro* activity of tebipenem and comparator agents against *Enterobacterales* responsible for UTI in the US during 2019–2020.

Materials and Methods

Bacterial organisms

- A total of 3,576 *Enterobacterales* collected from 52 medical centers in 9 US Census Divisions were recovered from urine samples during the 2019–2020 STEWARD Surveillance Program and included in the study.
- Bacterial identification was confirmed by standard algorithms supported by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany).

Susceptibility testing

- Isolates were tested for susceptibility by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) M07 (2018) guidelines.
- Frozen-form broth microdilution panels were manufactured by JMI Laboratories (North Liberty, IA, USA) and contained cation-adjusted Mueller-Hinton broth. *E. coli*, *K. pneumoniae*, and *P. mirabilis* displaying MIC results of ≥2 µg/mL for ceftazidime, aztreonam, and/or ceftriaxone were analyzed separately, and presumptively characterized here as ESBL producers.
- Quality assurance was performed by sterility checks, colony counts, and testing CLSI-recommended quality control reference strains.

Results

- *E. coli* comprised 65.4% of all *Enterobacterales* pathogens included in the study and associated with UTI, followed by *K. pneumoniae* (14.3%) and *P. mirabilis* (6.6%) (Table 1).
  - Other pathogens comprised 25 species or species groups (13.7%).
- In general, tebipenem (MIC_{90}, 0.015–0.06 µg/mL) and ertapenem (MIC_{90}, 0.03 µg/mL) showed similar MIC_{90} results against all *Enterobacterales*, *E. coli*, and *K. pneumoniae* (Table 1).
- The oral agents, amoxicillin-clavulanate, cefazolin, levofloxacin, and TMP-SMX, showed non-susceptibility rates against *E. coli* within US Census regions between 11% and 53% (Figure 1A).
  - The highest non-susceptibility rates (30%–53%) for these oral agents were observed against *E. coli* clinical isolates from the Middle Atlantic.
- Non-susceptibility rates for amoxicillin-clavulanate and cefazolin were not observed among *K. pneumoniae* isolates from the Pacific region, whereas non-susceptibility rates for amoxicillin-clavulanate, cefazolin, levofloxacin, and TMP-SMX were between 5% and 32% in other regions (Figure 1B).
  - The highest non-susceptibility rates (23%–32%) for these agents were observed among *K. pneumoniae* from the Middle Atlantic (Figure 1B).
- Overall, *P. mirabilis* were susceptible (>92%) to amoxicillin-clavulanate, except for those isolates from the Mountain and Pacific regions (Figure 1C).
  - Oral cephalosporins (cefazolin as a surrogate) showed susceptibility rates >90% only against *P. mirabilis* isolates from East North Central, West North Central, East South Central, West South Central, and South Atlantic (Figure 1C).
  - Other oral agents, such as levofloxacin and TMP-SMX, had non-susceptibility rates between 14% and 57% (Figure 1C).
- In general, 15.0% of *E. coli*, 15.9% of *K. pneumoniae*, and 4.3% of *P. mirabilis* displayed MIC results of ≥2 µg/mL for ceftazidime, aztreonam, and/or ceftriaxone, as a presumptive production of β-lactamases (Table 1).
  - The distribution of *E. coli* displaying this phenotype across the US Census regions is shown in Figure 2, and rates between 7.2% and 20.5% were noted. The exception was for those isolates from Middle Atlantic, where almost half of isolates (47.5%) exhibited this phenotype.
  - Rates among *K. pneumoniae* were between 7.9% and 18.5%, with a higher rate (32.0%) also among isolates from Middle Atlantic.
- Tebipenem ($MIC_{50/90}$, 0.015/0.03 µg/mL) and meropenem ($MIC_{50/90}$, 0.03/0.03 µg/mL) showed similar MIC results against *E. coli* isolates with presumptive production of ESBL (Table 2).
  - Ertapenem, imipenem, nitrofurantoin, and piperacillin-tazobactam were also active (90.6%–99.7% susceptible) against this *E. coli* subset.
- The small subset of ESBL *K. pneumoniae* had highest susceptibility rates for imipenem (86.4% susceptible) and meropenem (86.4% susceptible) (Table 2).

Conclusions

- Tebipenem displayed potent activity against *Enterobacterales* pathogens causing UTI among patients in the US. The *in vitro* potency of oral tebipenem was similar to that of the intravenous ertapenem.
- In general, these data showed compromised activity of oral agents used for treating UTI. These data support the development of tebipenem as an oral option for management of UTI in the US.

Acknowledgements

This research was supported by a contract by Spero Therapeutics, Inc. and funded in whole or in part with Federal funds from the Department of Health and Human Services; Office of the Assistant Secretary for Preparedness and Response; Biomedical Advanced Research and Development Authority, under Contract No. HHSO100201800015C.

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Table 1. Antimicrobial activity of tebipenem and ertapenem tested against the main organisms and organism groups

Organism/organism group (no. of isolates)		No. and cumulative % of isolates inhibited at MIC (µg/mL) of:													MIC_{50}	MIC_{90}
		≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8		
All[a] (3,576)	Tebipenem	4 (0.1)	606 (17.1)	2,060 (74.7)	429 (86.7)	207 (92.4)	193 (97.8)	50 (99.2)	9 (99.5)	0 (99.5)	3 (99.6)	2 (99.6)	5 (99.8)	8 100.0	0.015	0.06
	Ertapenem		2,111 (63.0)	668 (83.0)	249 (90.4)	132 (94.3)	56 (96.0)	46 (97.4)	37 (98.5)	26 (99.3)	7 (99.5)			18 100.0[c]	≤0.008	0.03
E. coli (2,339)	Tebipenem	4 (0.2)	578 (24.9)	1,578 (92.3)	134 (98.1)	29 (99.3)	10 (99.7)	4 (99.9)	1 (>99.9)	0 (>99.9)	0 (>99.9)	1 (100.0)			0.015	0.015
	Ertapenem		1,644 (74.6)	320 (89.2)	118 (94.5)	69 (97.6)	26 (98.8)	11 (99.3)	6 (99.6)	7 (99.9)	2 (100.0)				≤0.008	0.03
ESBL[b] (351)	Tebipenem		22 (6.3)	241 (74.9)	62 (92.6)	15 (96.9)	6 (98.6)	3 (99.4)	1 (99.7)	0 (99.7)	0 (99.7)	1 (100.0)			0.015	0.03
	Ertapenem		33 (9.6)	104 (40.1)	99 (69.0)	57 (85.7)	24 (92.7)	10 (95.6)	6 (97.4)	7 (99.4)	2 (100.0)				0.03	0.12
K. pneumoniae (511)	Tebipenem		3 (0.6)	296 (58.5)	176 (93.0)	18 (96.5)	3 (97.1)	2 (97.5)	1 (97.7)	0 (97.7)	1 (97.8)	1 (98.0)	4 (98.8)	6 100.0[c]	0.015	0.03
	Ertapenem		250 (51.7)	151 (82.9)	36 (90.3)	18 (94.0)	5 (95.0)	5 (96.1)	1 (96.3)	5 (97.3)	0 (97.3)			13 100.0[c]	≤0.008	0.03
ESBL (81)	Tebipenem			28 (34.6)	32 (74.1)	4 (79.0)	2 (81.5)	2 (84.0)	1 (85.2)	0 (85.2)	1 (86.4)	1 (87.7)	4 (92.6)	6 100.0	0.03	8
	Ertapenem		2 (2.5)	7 (11.1)	26 (43.2)	17 (64.2)	5 (70.4)	5 (76.5)	1 (77.8)	5 (84.0)	0 (84.0)			13 100.0[c]	0.06	>2
P. mirabilis (235)	Tebipenem		1 (0.4)	6 (3.0)	23 (12.8)	63 (39.6)	120 (90.6)	22 (100.0)							0.12	0.12
	Ertapenem		96 (45.3)	112 (98.1)	4 (100.0)										0.015	0.015
ESBL (10)	Tebipenem				1 (10.0)	3 (40.0)	5 (90.0)	1 (100.0)							0.12	0.12
	Ertapenem		1 (10.0)	8 (90.0)	1 (100.0)										0.015	0.015

[a] Includes *Citrobacter amalonaticus/farmeri* (4), *C. freundii* species complex (57), *C. koseri* (40), *Enterobacter asburiae* (1), *E. cloacae* species complex (143), *E. hormaechei* (1), *Escherichia coli* (2,339), *E. marmotae* (1), *Hafnia alvei* (2), *Klebsiella aerogenes* (58), *K. ornithinolytica* (1), *K. oxytoca* (87), *K. pneumoniae* (511), *K. variicola* (5), *Morganella morganii* (21), *Proteus hauseri* (1), *P. mirabilis* (235), *P. penneri* (2), *P. vulgaris* group (13), *Providencia rettgeri* (6), *P. stuartii* (4), *Raoultella ornithinolytica* (1), *R. planticola* (2), *Serratia fonticola* (1), *S. liquefaciens* (1), *S. marcescens* (36), *Citrobacter* spp. (1), and *Raoultella* spp. (2).
[b] Defined here as isolates displaying MIC results of ≥2 µg/mL for ceftazidime, aztreonam, and/or ceftriaxone, and presumptively characterized here as ESBL producers.
[c] Represents an MIC >2 µg/mL.

Table 2. Antimicrobial activity of tebipenem and comparator agents tested against *E. coli* and *K. pneumoniae* showing MIC results of ≥2 µg/mL for ceftazidime, aztreonam, and/or ceftriaxone

Antimicrobial agent	MIC (µg/mL)			CLSI[a]		
	50%	90%	Range	%S	%I	%R
E. coli (351)						
Tebipenem	0.015	0.03	0.008 to 4	NA	NA	NA
Amoxicillin-clavulanic acid	16	32	2 to >32	47.6	29.9	22.5
Aztreonam	16	>16	0.12 to >16	18.8	17.4	63.8
Cefazolin	>32	>32	8 to >32	0.6 [b] 0.6 [c]	— —	99.4 99.4
Ceftazidime	16	>32	0.25 to >32	28.8	17.1	54.1
Ceftriaxone	>8	>8	0.12 to >8	6.3	1.4	92.3
Cefuroxime	>64	>64	8 to >64	0.0 [b] 1.7 [c]	4.3 2.6	95.7 95.7
Ertapenem	0.03	0.12	≤0.008 to 2	97.4	2.0	0.6
Imipenem	≤0.12	0.25	≤0.12 to 4	99.4	0.3	0.3
Levofloxacin	8	32	≤0.015 to >32	26.2	2.6	71.2
Meropenem	0.03	0.03	≤0.015 to 2	99.7	0.3	0.0
Nitrofurantoin	16	32	≤4 to >64	90.6	3.5	5.8
Piperacillin-tazobactam	4	16	≤0.06 to >128	93.7	4.3	2.0
Trimethoprim-sulfamethoxazole	>4	>4	≤0.12 to >4	35.6	—	64.4
K. pneumoniae (81)						
Tebipenem	0.03	8	0.015 to >8	NA	NA	NA
Amoxicillin-clavulanic acid	16	>32	2 to >32	28.4	46.9	24.7
Aztreonam	>16	>16	0.12 to >16	9.9	4.9	85.2
Cefazolin	>32	>32	32 to >32	0.0 [b] 0.0 [c]	— —	100.0 100.0
Ceftazidime	32	>32	2 to >32	12.3	9.9	77.8
Ceftriaxone	>8	>8	0.25 to >8	7.4	0.0	92.6
Cefuroxime	>64	>64	4 to >64	2.5 [b] 4.9 [c]	3.7 1.2	93.8 93.8
Ertapenem	0.06	>2	≤0.008 to >2	77.8	6.2	16.0
Imipenem	≤0.12	4	≤0.12 to >8	86.4	0.0	13.6
Levofloxacin	1	16	0.03 to >32	41.8	16.5	41.8
Meropenem	0.03	2	≤0.015 to >32	86.4	4.9	8.6
Nitrofurantoin	>64	>64	8 to >64	14.8	25.9	59.3
Piperacillin-tazobactam	16	>128	1 to >128	59.3	14.8	25.9
Trimethoprim-sulfamethoxazole	>4	>4	≤0.12 to >4	24.7	—	75.3

[a] Criteria as published by CLSI (2021); NA, not applicable; "—", not available.
[b] Using oral breakpoints.
[c] Using parenteral breakpoints.

Figure 1. Rates of non-susceptibility for amoxicillin-clavulanate, cefazolin (predicts nonsusceptibility to oral cephalosporins), levofloxacin, and trimethoprim-sulfamethoxazole (TMP-SMX) against *E. coli* (Figure 1A), *K. pneumoniae* (Figure 1B), and *P. mirabilis* (Figure 1C). Criteria as published by CLSI (2021).

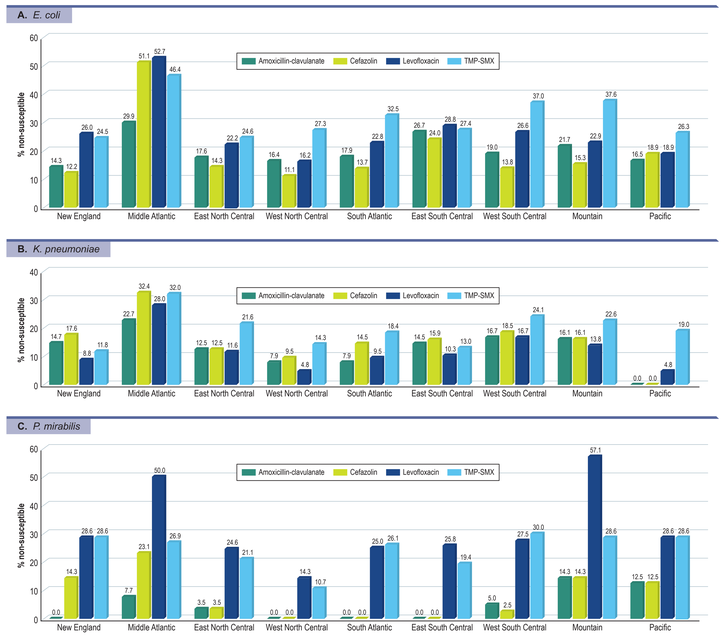

Figure 2. Distribution by US Census region of *E. coli* and *K. pneumoniae* clinical isolates with MIC results of ≥2 µg/mL for ceftazidime, aztreonam, and/or ceftriaxone, and presumptively characterized here as ESBL producers