P-1214

In Vitro Antibacterial Spectrum and Activity of Tebipenem Against Enterobacterales Clinical Isolates Causing Urinary Tract and Bloodstream Infections in the United States and United Kingdom in 2023-2024

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Tebipenem demonstrated potent *in vitro* activity against contemporary Enterobacterales isolates recovered from UTI and BSI, including ESBL-producing and MDR isolates.

Digital poster

Audio recording

Introduction

- Many oral agents are used to manage urinary tract infections (UTIs), but their clinical usefulness has been compromised by the increased prevalence of extended-spectrum β-lactamases (ESBLs) and the presence of co-resistance to trimethoprim-sulfamethoxazole (TMP/SMX) and quinolones[1].
- Tebipenem is a broad-spectrum carbapenem antibiotic currently in development[2-3] and is orally administered as the prodrug tebipenem-pivoxil.
- A phase 3 clinical trial (PIVOT-PO) evaluating the safety and efficacy of tebipenem for the treatment of complicated urinary tract infection (cUTI) and acute pyelonephritis (AP) was recently completed[4].
- This study assessed the *in vitro* activity of tebipenem and comparator agents against Enterobacterales isolates responsible for UTIs and bloodstream infections (BSIs) in the US and UK during 2023–2024.

Methods

Bacterial isolates

- A total of 7,694 Enterobacterales clinical isolates collected from 72 medical centers in the US (n= 7,437) and UK (n=257) were included in the Tebipenem Surveillance Program for 2023 - 2024.
- UTIs accounted for 73.5% of isolates collected (5,654), of which 54.8% (3,101) were from outpatient settings.
- Isolates recovered from BSIs accounted for 26.5% of the isolates (2,040), of which 22.4% (456) were from outpatient settings.

Susceptibility testing and interpretation

- Isolates were tested for susceptibility by broth microdilution and results were interpreted following Clinical and Laboratory Standards Institute guidelines[5,6].
- *Escherichia coli*, *Klebsiella pneumoniae* isolates with aztreonam, ceftazidime, or ceftriaxone MICs of ≥2 µg/mL), and *Proteus mirabilis* isolates with cefpodoxime or ceftazidime MICs of ≥2 µg/mL were categorized as ESBL phenotype .
- Enterobacterales displaying imipenem and/or meropenem MIC values ≥2 mg/mL, or ertapenem MIC values ≥1 mg/mL were categorized as carbapenem-not susceptible (CNSE). Only meropenem was used for the categorization of *Morganellaceae* due to their intrinsic decreased susceptibility to imipenem.
- The MDR phenotype was defined as described by Magiorakos et al.[7] as having a CLSI-not susceptible phenotype to 3 or more drug classes.

Table 1 Activity of tebipenem and comparator agents against Enterobacterales isolates from the United States and United Kingdom collected during 2023-2024 from urinary tract and bloodstream infections

	MIC_{50}/MIC_{90} in µg/mL (% susceptible by CLSI)								
Phenotype (No. tested)	TBP	IMI	MER	ERT	LEV	CRO	FEP*	SXT	TZP
All (7,694)	0.015/0.06 (-)	≤0.12/1 (92.9)	0.03/0.06 (99.4)	≤0.008/0.06 (98.3)	0.06/8 (81.5)	≤0.06/>8 (82.7)	0.06/8 (88.3)	≤0.12/>4 (75.2)	2/8 (91.3)
United States (7,437)	0.015/0.06 (-)	≤0.12/1 (93.0)	0.03/0.06 (99.4)	≤0.008/0.06 (98.3)	0.06/8 (81.4)	≤0.06/>8 (82.5)	0.06/8 (88.2)	≤0.12/>4 (75.2)	2/8 (91.3)
United Kingdom (257)	0.015/0.12 (-)	≤0.12/1 (90.3)	≤0.15/0.06 (100)	≤0.008/0.03 (98.4)	0.03/2 (85.2)	≤0.06/>8 (87.9)	0.06/2 (90.7)	≤0.12/>4 (73.5)	2/8 (91.1)
CSE (7,617)	0.015/0.06 (-)	≤0.12/1 (93.8)	0.03/0.06 (100)	≤0.008/0.06 (99.0)	0.06/8 (81.9)	≤0.06/>8 (83.3)	0.06/4 (88.9)	≤0.12/>4 (75.5)	2/8 (91.9)
Non-ESBL (5,344)	0.015/0.03 (-)	≤0.12/0.5 (93.5)	≤0.015/0.03 (100)	≤0.008/0.015 (99.9)	0.03/4 (87.6)	≤0.06/0.12 (100)	≤0.03/0.12 (99.9)	≤0.12/>4 (80.6)	4/8 (97.4)
ESBL (1,113)	0.015/0.06 (-)	≤0.12/0.5 (95.2)	0.03/0.06 (96.8)	0.03/0.25 (93.9)	4/16 (41.5)	>8/>8 (7.9)	16/>32 (25.2)	>4/>4 (35.5)	4/64 (73.0)
ESBL, CSE (1,074)	0.015/0.06 (-)	≤0.12/0.5 (98.1)	0.03/0.06 (100)	0.03/0.25 (97.3)	2/16 (42.2)	>8/>8 (8.2)	16/>32 (26.2)	>4/>4 (36.1)	4/32 (75.7)
CNSE (77)	4/>8 (-)	4/>8 (7.8)	4/>32 (40.3)	>2/>2 (29.9)	1/32 (45.5)	>8/>8 (24.7)	16/>32 (33.8)	>4/>4 (41.6)	>128/>128 (24.7)
MDR (1,656)	0.015/0.12 (-)	≤0.12/1 (95.4)	0.03/0.06 (97.2)	0.03/0.5 (92.1)	1/16 (44.9)	>8/>8 (36.9)	2/>32 (56.0)	>4/>4 (26.3)	4/128 (64.0)
LEV-NS (1,422)	0.015/0.12 (-)	≤0.12/2 (89.5)	0.03/0.06 (97.4)	0.015/0.25 (95.1)	8/32 (0.0)	0.5/>8 (51.8)	0.25/>32 (59.8)	>4/>4 (40.7)	4/32 (78.5)
SXT-R (1,910)	0.015/0.12 (-)	≤0.12/1 (92.3)	0.03/0.06 (98.0)	0.015/0.12 (96.2)	0.5/16 (55.9)	0.12/>8 (59.5)	0.12/>32 (67.4)	>4/>4 (0.0)	2/32 (83.9)
UTI (5,654)	0.015/0.06 (-)	≤0.12/1 (92.9)	≤0.015/0.06 (99.5)	≤0.008/0.06 (98.5)	0.06/8 (82.2)	≤0.06/>8 (83.9)	0.06/4 (89.0)	≤0.12/>4 (75.1)	2/8 (92.1)
BSI (2,040)	0.015/0.12 (-)	≤0.12/1 (93.0)	0.03/0.06 (99.3)	≤0.008/0.06 (97.8)	0.06/8 (79.5)	≤0.06/>8 (79.4)	0.06/16 (86.3)	≤0.12/>4 (75.4)	16/8 (89.1)

CSE, carbapenem-susceptible Enterobacterales; ESBL, extended-spectrum-β-lactamase; CNSE, carbapenem not susceptible Enterobacterales; MDR, multidrug-resistant (resistant to ≥3 classes of drugs); NS, not susceptible; R, resistant; TBP, tebipenem; IMI, imipenem, MER, meropenem; ERT, ertapenem; LEV, levofloxacin; CRO, ceftriaxone; FEP, cefepime; SXT, trimethoprim-sulfamethoxazole; TZP, piperacillin-tazobactam; CLSI breakpoints applied for comparator agents; "-" breakpoints not available.

[a] Susceptibility breakpoints for all agents are same for CLSI and EUCAST, except for meropenem and imipenem.

[b] Intermediate is interpreted as susceptible-dose dependent

Table 2 Frequency distribution of tebipenem MIC values against Enterobacterales isolates from the United States and United Kingdom collected during 2023-2024 from urinary tract and bloodstream infections

Phenotype/genotype (No. tested)	No. and cumulative % of isolates inhibited at a gepotidacin MIC (mg/L) of:													Tebipenem	
	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8	MIC_{50}	MIC_{90}
All (7,694)	22 0.3%	1551 20.4%	3935 71.6%	982 84.4%	484 90.6%	488 97%	126 98.6%	37 99.1%	20 99.4%	10 99.5%	4 99.5%	4 99.6%	31 100%	0.015	0.06
United States (7,437)	21 0.3%	1482 20.2%	3813 71.5%	962 84.4%	465 90.7%	471 97.0%	117 98.6%	37 99.1%	20 99.3%	10 99.5%	4 99.5%	4 99.6%	31 100.0%	0.015	0.06
United Kingdom (257)	1 0.4%	69 27.2%	122 74.7%	20 82.5%	19 89.9%	17 96.5%	9 100.0%							0.015	0.12
CSE (7,617)	22 0.3%	1551 20.7%	3931 72.3%	978 85.1%	478 91.4%	486 97.8%	122 99.4%	33 99.8%	12 99.9%	4 100%				0.015	0.06
Non-ESBL (5,344)	19 0.4%	1409 26.7%	2950 81.9%	476 90.8%	181 94.2%	244 98.8%	61 99.9%	3 99.9%	1 100%					0.015	0.03
ESBL (1,113)	2 0.2%	69 6.4%	643 64.2%	225 84.4%	71 90.7%	38 94.2%	11 95.1%	9 96%	9 96.8%	7 97.4%	3 97.7%	1 97.8%	25 100%	0.015	0.06
ESBL, CSE (1,074)	2 0.2%	69 6.6%	643 66.5%	225 87.4%	71 94%	38 97.6%	11 98.6%	9 99.4%	4 99.8%	2 100%				0.015	0.06
CNSE (77)		0 0%	4 5.2%	4 10.4%	6 18.2%	2 20.8%	4 26%	4 31.2%	8 41.6%	6 49.4%	4 54.5%	4 59.7%	31 100%	4	>8
MDR (1,656)	2 0.1%	189 11.5%	849 62.8%	261 78.6%	157 88%	78 92.8%	24 94.2%	31 96.1%	17 97.1%	9 97.6%	4 97.9%	4 98.1%	31 100%	0.015	0.12
LEV-NS (1,422)	3 0.2%	220 15.7%	713 65.8%	184 78.8%	93 85.3%	98 92.2%	43 95.2%	19 96.6%	11 97.3%	7 97.8%	2 98%	3 98.2%	26 100%	0.015	0.12
SXT-R (1,910)	6 0.3%	349 18.6%	1037 72.9%	233 85.1%	85 89.5%	99 94.7%	35 96.5%	14 97.3%	12 97.9%	8 98.3%	4 98.5%	4 98.7%	24 100%	0.015	0.12
UTI (5,654)	16 0.3%	1227 22%	2931 73.8%	667 85.6%	322 91.3%	327 97.1%	89 98.7%	28 99.2%	14 99.4%	6 99.5%	4 99.6%	2 99.6%	21 100%	0.015	0.06
BSI (2,040)	6 0.3%	324 16.2%	1004 65.4%	315 80.8%	162 88.8%	161 96.7%	37 98.5%	9 98.9%	6 99.2%	4 99.4%	0 99.4%	2 99.5%	10 100%	0.015	0.12

CSE, carbapenem-susceptible Enterobacterales; ESBL, extended-spectrum-β-lactamase; CNSE, carbapenem not susceptible Enterobacterales; MDR, multidrug-resistant (resistant to ≥3 classes of drugs); NS, not susceptible; R, resistant; LEV, levofloxacin; SXT, trimethoprim-sulfamethoxazole.

Results

- *E. coli* comprised 57.0% of all Enterobacterales pathogens included in the study, followed by *K. pneumoniae* (17.5%) and *P. mirabilis* (6.5%).
  - Other pathogens comprised 37 species or species groups (19.0%).
- Tebipenem and comparator agents displayed similar susceptibility profiles among US and UK isolate subsets (Tables 1 and 2)
- $MIC_{50/90}$ values against all Enterobacterales were: tebipenem 0.015/0.06 mg/mL, ertapenem ≤0.008/0.06 mg/mL, imipenem ≤0.12/1 mg/mL, and meropenem 0.03/0.06 mg/mL, with similar results for UTI and BSI isolates (Table 1).
- Susceptibility to other comparator agents ranged from 75.2% – 91.3% (Table 1).
- The proportions of isolates displaying ESBL, MDR, and CNSE phenotypes among Enterobacterales were 14.5%, 21.5%, and 1.0%, respectively.
- Tebipenem $MIC_{50/90}$ values among drug resistant subsets, including ESBL and MDR phenotypes, were similar to those for all isolates (Table 2)
  - $MIC_{50/90}$ values for intravenous (IV)carbapenems were also similar to those for all isolates
  - Susceptibility to the other comparator agents ranged from 0% to 83.9%
- Against CNSE, tebipenem $MIC_{50/90}$ values were 4/>8 ug/mL, and these isolates also displayed higher MICs for IV carbapenems as well as other antibacterial agents tested.

Conclusions

- Tebipenem demonstrated potent *in vitro* activity against Enterobacterales pathogens recovered from UTIs or BSIs in the US and UK.
- The *in vitro* $MIC_{50/90}$ values for tebipenem, which can be administered orally, were similar to those of the IV drugs ertapenem, imipenem and meropenem .
- Tebipenem activity remained consistent against drug-resistant isolates, including those with ESBL and MDR phenotypes, with the exception of carbapenem-not susceptible isolates.
- These data support the further clinical development of tebipenem as a treatment for cUTI and AP infections caused by Enterobacterales, including for infections caused by common drug-resistant isolates where other oral treatment options are limited.

Abbreviations

AP, acute pyelonephritis; BSI, Bloodstream Infection; CLSI, Clinical and Laboratory Standards Institute; CNSE, carbapenem not susceptible; CPE, carbapenemase-producing Enterobacterales; cUTI, complicated urinary tract infection; ESBL, extended-spectrum b-lactamase; US, United States; UTI, Urinary Tract Infection

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Acknowledgments

This study at Element (JMI Laboratories) was supported by GSK. Element received compensation fees for services in relation to preparing the abstract and poster.

Disclosures

This study was funded by GSK. Element Iowa City received compensation fees for services in relation to preparing the poster. RK and DT are employees of the GSK group of companies..

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IDWeek 2025 | October 19–22, 2025 | Atlanta, GA, USA

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