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Activity of gepotidacin against molecularly characterized β-lactamase-producing *E. coli* and *K. pneumoniae* isolates from patients with urinary tract infections in Europe and adjacent regions (2023)

Gepotidacin demonstrated activity against *E. coli* and *K. pneumoniae* carrying β-lactamase genes, including serine carbapenemases, including bla_{KPC} and bla_{OXA-48} variants, and metallo-β-lactamase genes.

Digital poster
Supplemental data

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Introduction

- Gepotidacin is a novel, bactericidal, first-in-class triazaacenaphthylene antibacterial that inhibits bacterial DNA replication by a distinct binding site [1, 2], a unique mechanism of action, and for most pathogens provides well-balanced inhibition of two different type II topoisomerase enzymes.[3]
- Gepotidacin was recently approved by the United States Food and Drug Administration for the treatment of uncomplicated urinary tract infections (uUTI).[4]
- This study reports the *in vitro* activity of gepotidacin and other oral antibiotics against *Escherichia coli* and *Klebsiella pneumoniae*, including extended-spectrum β-lactamase (ESBL), plasmid-mediated AmpC (pAmpC), and/or carbapenemase-carrying isolates collected from UTI patients in European countries, Israel and Turkiye.

Methods

Bacterial Isolates

- A total of 310 *E. coli* and 154 *K. pneumoniae* isolates from 32 sites in 16 European countries, Israel, and Turkiye were included in this study, as part of the SENTRY Antimicrobial Surveillance Program for 2023.
- Bacterial identification was confirmed by standard algorithms supported by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (Bruker Daltonics, Bremen, Germany).

Antimicrobial Susceptibility Testing

- Isolates were tested for susceptibility by broth microdilution and agar dilution (i.e. mecillinam) following Clinical and Laboratory Standards Institute (CLSI) M07 (2024) guidelines.[5]

Screening of β-lactamase Genes

- *E. coli* and *K. pneumoniae* with MIC of ≥2 µg/mL for aztreonam, ceftazidime, ceftriaxone, or meropenem were defined as presumptive ESBL, pAmpC, and/or carbapenemase producers and selected for screening of β-lactamase genes.[6]
- Isolates were subjected to genome sequencing, and screening of ESBL, pAmpC, and/or carbapenemase genes.

Results

E. coli

- A total of 18.7% (58/310) of *E. coli* isolates met the MIC criteria for screening of β-lactamases and defined as presumptive pAmpC, ESBL, and/or carbapenemase producers (Table 1).
  - Most isolates (93.1%; 54/58) carried ESBL and/or pAmpC genes, except for 1 *E. coli* with a bla_{NDM-1}.
  - Three 3 isolates carried only narrow-spectrum β-lactamases.
- Gepotidacin ($MIC_{50/90}$, 1/4 mg/L) inhibited 99.7% of all 310 *E. coli* isolates at MIC of ≤16 mg/L (Table 1).
- Gepotidacin had $MIC_{50/90}$ values of 1/4 mg/L against isolates that did not meet the MIC criteria for screening of β-lactamase genes (Table 1).
- Gepotidacin had $MIC_{50/90}$ values of 2/8 mg/L against isolates that met the MIC criteria for screening of β-lactamase genes (Table 1).
  - Among oral comparators, only mecillinam showed activity (93.1–94.4% susceptible) against both subsets. (Table 2).

K. pneumoniae

- A total of 35.7% (55/154) *K. pneumoniae* isolates met the MIC criteria for screening of β-lactamases and defined as presumptive pAmpC, ESBL and/or carbapenemase producers (Tables 1 and 2).
  - Among these isolates, 72.7% (40/55) carried ESBL and/or pAmpC genes, whereas 21.8% (12/55) carried carbapenemases.
  - The carbapenemase genes detected were as follows: 4 bla_{KPC-3}, 2 bla_{NDM-1}, 1 bla_{NDM-5}, 1 bla_{NDM-5} and $bla_{OXA-232}$, 1 $bla_{OXA-232}$, 1 bla_{OXA-48}, 1 bla_{VIM-1}, and 1 bla_{VIM-4}.
- Gepotidacin ($MIC_{50/90}$, 4/16 mg/L) inhibited 92.9% of all 154 *K. pneumoniae* isolates at MIC of ≤16 mg/L (Table 1).
- Gepotidacin $MIC_{50/90}$ values were 4/16 mg/L against *K. pneumoniae* that did not meet the MIC criteria for screening of β-lactamase genes (Tables 1 and 2).
- Gepotidacin had $MIC_{50/90}$ values of 8/32 mg/L against *K. pneumoniae* that met the MIC criteria for screening of β-lactamase genes (Tables 1 and 2).
  - Gepotidacin had similar MIC_{50} (8 mg/L) and MIC_{90} (16-32 mg/L) values against isolates carrying ESBL and/or pAmpC, and those carrying carbapenemase genes.
- Oral comparators showed activity (86.9–96.0% susceptible) only against *K. pneumoniae* that were presumptively not pAmpC, ESBL and/or carbapenemase producers, except for mecillinam (92.5% susceptible) against ESBL or pAmpC producers (Table 2).

Table 1: **Frequency distribution of gepotidacin MIC values against molecularly characterized *E. coli* and *K. pneumoniae***

Phenotype/genotype (No. tested)	No. and cumulative % of isolates inhibited at MIC (mg/L) of:								MIC (mg/L)	
	≤0.5	1	2	4	8	16	32	64	MIC_{50}	MIC_{90}
***E. coli* (310)**	32 10.3	126 51	110 86.5	30 96.1	4 97.4	7 99.7	1 100		1	4
MIC screen-negative (252)	30 11.9	101 52	90 87.7	26 98	1 98.4	3 99.6	1 100		1	4
MIC screen-positive[a] (58)	2 3.4	25 46.6	20 81	4 87.9	3 93.1	4 100			2	8
ESBL and/or AmpC (55)	2 3.7	23 45.5	19 80	4 87.3	3 92.7	4 100			2	8
***K. pneumoniae* (154)**			6 3.9	76 53.2	38 77.9	23 92.9	8 98.1	3 100	4	16
MIC screen-negative (99)			1 1	63 64.6	24 88.9	6 94.9	2 97	3 100	4	16
MIC screen-positive[b] (55)			5 9.1	13 32.7	14 58.2	17 89.1	6 100		8	32
ESBL or AmpC[c] (40)			3 7.5	9 30	11 57.5	13 90	4 100		8	16
Carbapenemase[d] (12)			2 16.7	3 41.7	2 58.3	3 83.3	2 100		8	32

[a] Includes isolates with aztreonam, ceftazidime, ceftriaxone or meropenem MICs of ≥2 mg/L, where the following alleles were detected: 4 bla_{CMY-2}, 1 bla_{CMY-4} and bla_{DHA-1}, 1 $bla_{CTX-M-14}$ and bla_{DHA-1}, 33 $bla_{CTX-M-15}$, 7 $bla_{CTX-M-27}$, 1 $bla_{CTX-M-32}$, 2 $bla_{CTX-M-55}$, 2 bla_{DHA-1}, 1 bla_{NDM-1}, 3 bla_{SHV-12}, and 3 isolates negative for ESBL, pAMPC or carbapenemase genes.
[b] Includes isolates with aztreonam, ceftazidime, ceftriaxone or meropenem MICs of ≥2 mg/L, where the following alleles were detected: 1 $bla_{CTX-M-1}$, 1 $bla_{CTX-M-100}$, 1 $bla_{CTX-M-14}$, 1 $bla_{CTX-M-14}$ and bla_{SHV-27}, 31 $bla_{CTX-M-15}$, 1 $bla_{CTX-M-15}$ and bla_{SHV-27}, 1 $bla_{CTX-M-3}$, 1 $bla_{CTX-M-55}$, 2 bla_{DHA-1}, 4 bla_{KPC-3}, 2 bla_{NDM-1}, 1 bla_{NDM-5}, 1 bla_{NDM-5} and $bla_{OXA-232}$, 1 $bla_{OXA-232}$, 1 bla_{OXA-48}, 1 bla_{VIM-1}, 1 bla_{VIM-4}, and 3 isolates negative for ESBL, pAMPC or carbapenemase genes.
[c] Includes isolates where the following alleles were detected: 1 $bla_{CTX-M-1}$, 1 $bla_{CTX-M-100}$, 1 $bla_{CTX-M-14}$, 1 $bla_{CTX-M-14}$ and bla_{SHV-27}, 31 $bla_{CTX-M-15}$, 1 $bla_{CTX-M-15}$ and bla_{SHV-27}, 1 $bla_{CTX-M-3}$, 1 $bla_{CTX-M-55}$, and 2 bla_{DHA-1}.
[d] Includes isolates where the following alleles were detected: 4 bla_{KPC-3}, 2 bla_{NDM-1}, 1 bla_{NDM-5}, 1 bla_{NDM-5} and $bla_{OXA-232}$, 1 $bla_{OXA-232}$, 1 bla_{OXA-48}, 1 bla_{VIM-1}, and 1 bla_{VIM-4}.

Table 2: **Activity of gepotidacin and comparator agents against molecularly characterized *E. coli* and *K. pneumoniae***

Phenotype/genotype (No)	MIC_{50}/MIC_{90} in mg/L (% susceptible by EUCAST)*						
	GEP	AMC	CFZ	CIP	MEC	SXT	NIT
***E. coli* (310)**	1/4 (-)	4/16 (81.3)	2/>32 (74.8)	0.015/>4 (73.9)	0.25/4 (93.5)	≤0.12/>4 (70.6)	16/32 (98.4)
MIC screen-negative (252)	1/4 (-)	4/16 (89.3)	1/4 (92.1)	0.008/>4 (83.7)	0.25/4 (93.7)	≤0.12/>4 (74.6)	16/32 (99.2)
MIC screen-positive[a] (58)	2/8 (-)	16/32 (46.6)	>32/>32 (0.0)	>4/>4 (31.0)	0.5/2 (93.1)	1/>4 (53.4)	16/32 (94.8)
ESBL and/or AmpC (55)	2/8 (-)	16/32 (49.1)	>32/>32 (0.0)	>4/>4 (29.1)	0.5/2 (94.6)	2/>4 (50.9)	16/32 (94.6)
***K. pneumoniae* (154)**	4/16 (-)	4/32 (67.3)	2/>32 (61.7)	0.03/>4 (66.9)	0.5/32 (86.4)	0.25/>4 (63.6)	64/>128 (-)
MIC screen-negative (99)	4/16 (-)	2/8 (93.9)	1/4 (96.0)	0.015/0.5 (90.0)	0.5/2 (96.0)	≤0.12/>4 (86.9)	64/>128 (-)
MIC screen-positive[b] (55)	8/32 (-)	16/>32 (20.0)	>32/>32 (0.0)	2/>4 (25.5)	4/>32 (69.1)	>4/>4 (21.8)	128/>128 (-)
ESBL or AmpC[c] (40)	8/16 (-)	16/32 (27.5)	>32/>32 (0.0)	2/>4 (25.0)	2/8 (92.5)	>4/>4 (15.0)	64/>128 (-)
Carbapenemase[d] (12)	8/32 (-)	>32/>32 (0.0)	>32/>32 (0.0)	>4/>4 (16.7)	>32/>32 (8.3)	>4/>4 (25.0)	>128/>128 (-)

GEP, gepotidacin; AMC, amoxicillin-clavulanate; CFZ, cefazolin; CIP, ciprofloxacin; MEC, mecillinam; SXT, trimethoprim-sulfamethoxazole; NIT, nitrofurantoin; EUCAST breakpoints and interpretive criteria applied, except for amoxicillin-clavulanate, which was tested at 2/1 ratio and interpreted per CLSI guidelines; "-" breakpoints not available.
[a] Includes isolates with aztreonam, ceftazidime, ceftriaxone or meropenem MICs of ≥2 mg/L, where the following alleles were detected: 4 bla_{CMY-2}, 1 bla_{CMY-4} and bla_{DHA-1}, 1 $bla_{CTX-M-14}$ and bla_{DHA-1}, 33 $bla_{CTX-M-15}$, 7 $bla_{CTX-M-27}$, 1 $bla_{CTX-M-32}$, 2 $bla_{CTX-M-55}$, 2 bla_{DHA-1}, 1 bla_{NDM-1}, 3 bla_{SHV-12}, and 3 isolates negative for ESBL, pAMPC or carbapenemase genes.
[b] Includes isolates with aztreonam, ceftazidime, ceftriaxone or meropenem MICs of ≥2 mg/L, where the following alleles were detected: 1 $bla_{CTX-M-1}$, 1 $bla_{CTX-M-100}$, 1 $bla_{CTX-M-14}$, 1 $bla_{CTX-M-14}$ and bla_{SHV-27}, 31 $bla_{CTX-M-15}$, 1 $bla_{CTX-M-15}$ and bla_{SHV-27}, 1 $bla_{CTX-M-3}$, 1 $bla_{CTX-M-55}$, 2 bla_{DHA-1}, 4 bla_{KPC-3}, 2 bla_{NDM-1}, 1 bla_{NDM-5}, 1 bla_{NDM-5} and $bla_{OXA-232}$, 1 $bla_{OXA-232}$, 1 bla_{OXA-48}, 1 bla_{VIM-1}, 1 bla_{VIM-4}, and 3 isolates negative for ESBL, pAMPC or carbapenemase genes.
[c] Includes isolates where the following alleles were detected: 1 $bla_{CTX-M-1}$, 1 $bla_{CTX-M-100}$, 1 $bla_{CTX-M-14}$, 1 $bla_{CTX-M-14}$ and bla_{SHV-27}, 31 $bla_{CTX-M-15}$, 1 $bla_{CTX-M-15}$ and bla_{SHV-27}, 1 $bla_{CTX-M-3}$, 1 $bla_{CTX-M-55}$, and 2 bla_{DHA-1}.
[d] Includes isolates where the following alleles were detected: 4 bla_{KPC-3}, 2 bla_{NDM-1}, 1 bla_{NDM-5}, 1 bla_{NDM-5} and $bla_{OXA-232}$, 1 $bla_{OXA-232}$, 1 bla_{OXA-48}, 1 bla_{VIM-1}, and 1 bla_{VIM-4}.

Conclusions

- Gepotidacin showed activity against *E. coli* and *K. pneumoniae* causing UTI in patients in European countries, Israel and Turkiye, including isolates carrying ESBL, pAmpC and/or carbapenemase genes.
- These data support the development of gepotidacin for the treatment of uUTI caused by *E. coli* and *K. pneumoniae* in Europe, Israel and Turkiye.

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References

[1] Bax BD *et al* (2010). "Type IIA topoisomerase inhibition by a new class of antibacterial agents." Nature. 466: 935-40.

[2] Gibson EG *et al* (2019). Mechanistic and structural basis for the actions of the antibacterial gepotidacin against *Staphylococcus aureus* gyrase. ACS infectious diseases. 5: 570-581.

[3] Oviatt AA *et al* (2024). Interactions between gepotidacin and *Escherichia coli* gyrase and topoisomerase IV: Genetic and biochemical evidence for well-balanced dual targeting. ACS Infectious Diseases 10: 1137-1151.

[4] GSK (2025). BLUJEPA (gepotidacin) [package insert]. U.S. Food and Drug Administration website: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/218230s000lbl.pdf. Revised March 2025. Accessed March 26, 2025.

[5] Clinical and Laboratory Standards Institute (2024). Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. CLSI Standard M07 12th Edition. Wayne, PA, USA.

[6] Clinical and Laboratory Standards Institute (2024). Performance standards for antimicrobial susceptibility testing. CLSI Standard M100 34th Edition. Wayne, PA, USA.

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