Activity of gepotidacin against molecularly characterized *Klebsiella pneumoniae* isolates from patients with urinary tract infections in Europe and adjacent regions (2019–2022)

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

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Introduction

- Gepotidacin is a novel, bactericidal, first-in-class triazaacenaphthylene antibiotic that inhibits bacterial DNA replication by a unique mechanism of action and distinct binding site, providing a well-balanced inhibition of two different Type II topoisomerase enzymes.
- Gepotidacin has shown *in vitro* activity against most strains of target pathogens, such as *Escherichia coli*, *Staphylococcus saprophyticus*, and *Neisseria gonorrhoeae*, including those resistant to current antibiotics.
- Results from two phase 3 clinical trials demonstrated the efficacy of gepotidacin for the treatment of uncomplicated urinary tract infections (uUTIs). More recently, gepotidacin met its primary efficacy endpoint of non-inferiority in a phase 3 trial comparing gepotidacin with intramuscular ceftriaxone plus oral azithromycin combination for the treatment of urogenital gonorrhea.
- This study reports on the *in vitro* activity of gepotidacin and other oral antibiotics against molecularly characterized *Klebsiella pneumoniae* collected from patients with UTI in Europe.

Materials and Methods

Bacterial organisms

- A total of 807 *K. pneumoniae* causing UTI during 2019–2022 in 38 sites in 17 European countries, Israel and Turkiye were included as part of the gepotidacin uropathogen global surveillance 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 and agar dilution following Clinical and Laboratory Standards Institute (CLSI) M07 guidelines.
- Interpretation of MIC results was performed using the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria, except for amoxicillin-clavulanate MIC values that were interpreted using CLSI breakpoints.

Materials and Methods, *continued*

Screening of resistance determinants

- *K. pneumoniae* with MIC results ≥2 mg/L for aztreonam and/or ceftazidime and/or ceftriaxone were defined as presumptive ESBL producers and subjected to genome sequencing followed by β-lactamase gene screening.
- Selected isolates had total genomic DNA extracted by the fully automated Thermo Scientific™ KingFisher™ Flex Magnetic Particle Processor (Cleveland, OH, USA), which was used to generate input material for library construction.
- DNA libraries were prepared using the Nextera™ library or Illumina DNA Prep construction protocol (Illumina, San Diego, CA, USA) following the manufacturer's instructions and were sequenced on MiSeq or NextSeq Sequencer platforms at JMI Laboratories.
- FASTQ format sequencing files for each sample set were assembled independently using the *de novo* assembler SPAdes 3.11.0. An in-house software was applied to align the assembled sequences against a comprehensive in-house database containing known β-lactamase genes.

Results

- Gepotidacin had MIC_{50} and MIC_{90} values of 4 mg/L and 8 mg/L, respectively, against isolates that did not meet the MIC criteria for screening of β-lactamases (Table 1).
  - Other oral comparator agents showed susceptibility rates of 88.9–95.6% against the group of isolates that did not meet the MIC criteria for screening of β-lactamases.
- A total of 40.3% (323/801) *K. pneumoniae* were selected for screening of β-lactamases.
- The majority of these isolates carried bla_{CTX-M} alone (64.7%; 209/323) and a small number carried pAmpC alone (3.1%; 10/323) or other ESBL genes or combinations (6.2%; 20/239).
  - Among β-lactamase screened isolates, 22.6% (73/323) carried carbapenemases, and these isolates originated mostly from Greece (11/73, 15.1%), Italy (9/73, 12.3%), Spain (9/73, 12.3%) and Turkiye (17/73, 23.3%) (data not shown).
- Gepotidacin had an MIC_{90} of 32 mg/L against strains that meet the MIC criteria for screening of β-lactamases, regardless of β-lactamase gene detected, including carbapenemases.
  - Other oral agents had limited activity (0–60% susceptible) against strains carrying β-lactamase genes, except for mecillinam with susceptibility rates of 88.0–95.0%.

Table 1. Activity of gepotidacin and comparator agents tested against *K. pneumoniae* subsets from Europe and adjacent regions (2019–2022)

Phenotype/genotype (No. isolates)	MIC_{50}/MIC_{90} in mg/L (% susceptible by EUCAST criteria)					
	GEP	A/C	CFZ	CIP	MEC	SXT
Not-screened (478)	4/8 (—)	2/8 (91.6)	1/4 (91.4)	0.015/0.5 (88.9)	0.25/2 (95.6)	≤0.12/4 (89.5)
Screened[a] (323)	8/32 (—)	16/>32 (22.3)	>32/>32 (0.3)	>4/>4 (18.0)	4/>32 (75.2)	>4/>4 (19.2)
ESBL/pAmpC (239)	8/32 (—)	16/32 (29.7)	>32/>32 (0.8)	4/>4 (18.0)	2/16 (88.7)	>4/>4 (14.6)
CTX-M[b] (209)	8/32 (—)	16/32 (30.6)	>32/>32 (1.0)	>4/>4 (15.8)	2/16 (88.0)	>4/>4 (11.5)
pAmpC[c] (10)	8/32 (—)	32/>32 (0.0)	>32/>32 (0.0)	0.5/>4 (20.0)	0.5/4 (90.0)	≤0.12/>4 (60.0)
Other[d] (20)	16/32 (—)	16/>32 (35.0)	>32/>32 (0.0)	0.5/>4 (40.0)	4/8 (95.0)	>4/>4 (25.0)
Carbapenemase[e] (74)	8/32 (—)	>32/>32 (1.4)	>32/>32 (0.0)	>4/>4 (8.2)	>32/>32 (37.0)	>4/>4 (21.9)
Negative[f] (11)	8/32 (—)	16/32 (9.1)	>32/>32 (9.1)	0.03/0.5 (81.8)	16/>32 (36.4)	≤0.12/0.5 (100)

ESBL, extended-spectrum β-lactamase; GEP, gepotidacin; A/C, amoxicillin-clavulanate; CFZ, cefazolin; CIP, ciprofloxacin; MEC, mecillinam; SXT, trimethoprim-sulfamethoxazole; EUCAST breakpoints and interpretive criteria applied, except for amoxicillin-clavulanate (tested at 2/1 ratio and interpreted per CLSI guidelines); "—" breakpoint not available.
[a] Includes isolates with aztreonam, ceftazidime, ceftriaxone or meropenem MICs of ≥2 mg/L.
[b] Includes 4 $bla_{CTX-M-1}$, 3 $bla_{CTX-M-3}$, 5 $bla_{CTX-M-14}$, 192 $bla_{CTX-M-15}$, 1 $bla_{CTX-M-55}$, 1 $bla_{CTX-M-237}$, 1 $bla_{CTX-M-3}$ and $bla_{CTX-M-15}$, 2 $bla_{CTX-M-9}$ and $bla_{CTX-M-15}$.
[c] Includes plasmidic AmpC: 9 bla_{DHA-1} and 1 bla_{CMY-16}.
[d] Includes 4 bla_{SHV-2}, 1 $bla_{CTX-M-15}$ and bla_{CMY-4}, 3 $bla_{CTX-M-15}$ and bla_{DHA-1}, 1 bla_{SHV-27} and bla_{DHA-1}, 1 bla_{SHV-27} and bla_{DHA-6}, 10 bla_{CTX-M} and bla_{SHV} (ESBL SHV variant).
[e] Includes 28 $bla_{OXA-48-like}$, 25 bla_{KPC}, 15 metallo-β-lactamases and 6 isolates carrying 2 carbapenemase genes (2 bla_{KPC-2} plus bla_{NDM-1} and 4 bla_{NDM-1} plus bla_{OXA-48}).
[f] Includes isolates where pAmpC, ESBL or carbapenemase genes were not detected.

Conclusions

- Gepotidacin demonstrated activity against *K. pneumoniae* causing UTI in European countries and adjacent regions, including isolates carrying ESBL, pAmpC and/or carbapenemase genes.
- These data support further clinical development of gepotidacin as a potential treatment option for uUTI caused by *K. pneumoniae* including when other oral treatment options showed limited activity due to drug resistance.

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