Gepotidacin activity against *Escherichia coli* and *Klebsiella pneumoniae*, including molecularly characterized ESBL- and carbapenemase-positive subsets causing urinary tract infections in United States Medical Centers (2023)

R. E. Mendes[1], Z. Kockler[1], G. M. Morgan[1], R. Kapoor[2], N. Scangarella-Oman[2], S.J.R. Arends[1]

[1]Element Iowa City (JMI Laboratories), North Liberty, Iowa, USA, [2]GSK, Collegeville, PA, USA

Gepotidacin demonstrated activity against *E. coli* and *K. pneumoniae* carrying β-lactamase genes, including genes encoding extended-spectrum enzymes and carbapenemases.

Digital poster

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Introduction

- Gepotidacin is a novel, bactericidal, first-in-class triazaacenaphthylene antibacterial that inhibits bacterial DNA replication by a unique mechanism of action, possesses a distinct binding site [1, 2], and provides well-balanced inhibition of two different type II topoisomerase enzymes in most pathogens causing uncomplicated urinary tract infections (uUTI) and *Neisseria gonorrhoeae*.[3, 4]
- Gepotidacin was approved earlier this year for the treatment of uUTI caused by the following susceptible microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter freundii* complex, *Staphylococcus saprophyticus*, and *Enterococcus faecalis*.[5]
- This study reports the *in vitro* activity of gepotidacin and other oral antibiotics tested against *E. coli* and *K. pneumoniae*, including molecularly characterized isolates carrying extended-spectrum β-lactamase (ESBL), plasmid-mediated AmpC (pAmpC), and/or carbapenemase-encoding genes collected from UTI patients in the United States.

Methods

Bacterial Isolates

- A total of 1,011 *E. coli* and 398 *K. pneumoniae* isolates responsible for UTI in patients seen in 58 sites in the USA, as part of the SENTRY Antimicrobial Surveillance Program for 2023 were included in this study.

Antimicrobial Susceptibility Testing

- Isolates were tested for susceptibility by broth microdilution following Clinical and Laboratory Standards Institute (CLSI) M07 (2024) guidelines.[6] Gepotidacin MIC values were interpreted based on the FDA susceptible breakpoint (≤16 µg/mL), whereas CLSI breakpoints were applied for comparator agents.[5, 7]

Screening of FQ Resistance Determinants

- *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.[7]
- Isolates were subjected to genome sequencing, and screening of ESBL, pAmpC, and/or carbapenemase genes.

Table 1 Frequency distribution of gepotidacin MIC values against *E. coli* and *K. pneumoniae*, and respective resistant subsets from the United States

Organism (No. tested)	Number and cumulative % of isolates inhibited at a gepotidacin MIC (mg/L) of:									Gepotidacin	
Phenotype/genotype [a]	≤0.5	1	2	4	8	16	32	64	>64	MIC_{50}	MIC_{90}
E. coli (1011)	93 9.2	373 46.1	438 89.4	82 97.5	17 99.2	8 100				2	4
MIC screen-negative (864)	73 8.4	331 46.8	381 90.9	65 98.4	8 99.3	6 100				2	2
MIC screen-positive[a] (147)	20 13.6	42 42.2	57 81.0	17 92.5	9 98.6	2 100				2	4
ESBL/pAmpC[b] (135)	17 12.6	41 43.0	52 81.5	15 92.6	9 99.3	1 100				2	4
K. pneumoniae (398)		1 0.3	10 2.8	190 50.5	129 82.9	38 92.5	21 97.7	5 99.0	4 100	4	16
MIC screen-negative (331)		1 0.3	10 3.3	178 57.1	108 89.7	23 96.7	8 99.1	3 100		4	16
MIC screen-positive[a] (67)				12 17.9	21 49.3	15 71.6	13 91.0	2 94.0	4 100	16	32
ESBL/pAmpC[c] (59)				9 15.3	19 47.5	14 71.2	12 91.5	2 94.9	3 100	16	32
Carbapenemase[d] (6)				1 16.7	2 50.0	1 66.7	1 83.3	0 83.3	1 100	-	-

ESBL, extended spectrum-β-lactamase; pAmpC, plasmid-mediated AmpC; "-", $MIC_{50/90}$ values not calculated due to small number of isolates.

[a] Includes isolates with aztreonam, ceftazidime, ceftriaxone or meropenem MICs of ≥2 µg/mL.

[b] The following β-lactamase alleles with extended-spectrum were detected: 10 bla_{CMY-2}, 1 bla_{CMY-16} and $bla_{CTX-M-15}$, 1 $bla_{CTX-M-115}$, 10 $bla_{CTX-M-14}$, 64 $bla_{CTX-M-15}$, 1 bla_{CMY-2} and $bla_{CTX-M-15}$, 1 bla_{CMY-2} and $bla_{CTX-M-27}$, 1 $bla_{CTX-M-3}$ and $bla_{CTX-M-27}$, 1 $bla_{CTX-M-174}$, 34 $bla_{CTX-M-27}$, 1 $bla_{CTX-M-32}$, 6 $bla_{CTX-M-55}$, 1 $bla_{CTX-M-65}$, 2 bla_{DHA-1}, and 1 bla_{SHV-12}.

[c] The following β-lactamase alleles with extended-spectrum were detected: 2 $bla_{CTX-M-14}$, 1 bla_{DHA-1} and $bla_{CTX-M-14}$, 44 $bla_{CTX-M-15}$, 6 $bla_{CTX-M-15}$ and bla_{SHV-27}, 1 $bla_{CTX-M-27}$, 1 $bla_{CTX-M-55}$, 1 bla_{DHA-1}, 1 bla_{SHV-2}, 1 bla_{SHV-12}, and 1 bla_{SHV-27}.

[d] The following carbapenemases were detected: 2 bla_{KPC-2}, 1 bla_{KPC-3}, 1 bla_{NDM-1}, 1 bla_{NDM-7}, and 1 bla_{OXA-48}.

Results

E. coli

- A total of 14.5% (147/1,011) of *E. coli* met the MIC criteria for screening of β-lactamases and were defined as presumptive ESBL, pAmpC, and/or carbapenemase producers (Table 1).
  - Most *E. coli* isolates (91.8%; 135/147) selected for screening of β-lactamase genes carried ESBL and/or pAmpC genes.
  - ESBL, pAmpC or carbapenemase genes were not detected in 8.9% (12/147) isolates selected for screening of β-lactamase genes.
- Gepotidacin had both MIC_{50} and MIC_{90} values of 2 µg/mL against isolates that did not meet the MIC criteria for screening of β-lactamase genes (Table 1).
- Gepotidacin MIC_{50} and MIC_{90} values were 2 µg/mL and 4 µg/mL, respectively, against isolates that met the MIC criteria for screening of β-lactamases and defined as ESBL, pAmpC, and/or carbapenemase producers (Table 1).
  - Gepotidacin had MIC_{50} and MIC_{90} values of 2 µg/mL and 4 µg/mL, respectively, against characterized ESBL and/or pAmpC-carrying *E. coli* (Table 1)
  - In addition, gepotidacin inhibited all *E. coli* at the FDA susceptible breakpoint of ≤16 µg/mL, regardless of resistance phenotype or genotype.
- Among oral comparators, nitrofurantoin (91.1–91.8% susceptible) showed activity against these resistant *E. coli* subsets (Table 2).

K. pneumoniae

- A total of 16.8% (67/398) *K. pneumoniae* met the MIC criteria for screening of β-lactamases and were defined as presumptive pAmpC, ESBL and/or carbapenemase producers (Table 1).
  - Among the *K. pneumoniae* selected for screening of β-lactamase genes, 88.1% (59/67) carried ESBL and/or pAmpC genes, whereas 9.0% (6/67) carried carbapenemases (Tables 1 & 2).
  - The carbapenemase genes detected were as follows: bla_{KPC-2} (2), bla_{KPC-3} (1), bla_{NDM-1} (1), bla_{NDM-7} (1), and bla_{OXA-48} (1).
- Gepotidacin ($MIC_{50/90}$, 4/16 µg/mL) inhibited 92.5% of all *K. pneumoniae* at the FDA susceptible breakpoint of ≤16 µg/mL (Tables 1 & 2).
- Gepotidacin also inhibited at the susceptible breakpoint, 96.7% of the *K. pneumoniae* from the subset that did not meet the MIC criteria for β-lactamase screening.
  - Oral comparators also showed activity (94.3–99.4% susceptible) against *K. pneumoniae* that were presumptively negative for the presence of ESBL, pAmpC, and/or carbapenemase genes, except for nitrofurantoin (31.1% susceptible).
- At the FDA susceptible breakpoint, gepotidacin inhibited 71.2% of *K. pneumoniae* carrying ESBL/pAmpC (Tables 1 & 2).
  - All but 2 carbapenemase isolates (KPC-2 and KPC-3) were inhibited by gepotidacin at ≤16 µg/mL.
  - Comparator agents had limited activity (<56% susceptible) when tested against *K. pneumoniae* isolates carrying ESBL/pAmpC and carbapenemase genes (Table 2).

Table 2 Activity of gepotidacin and comparator agents against *E. coli* and *K. pneumoniae*, and respective resistant subsets from the United States

Organism (No. tested)	MIC_{50}/MIC_{90} in µg/mL (% susceptible by CLSI)					
Phenotype/genotype	GEP	AMC	CFZ	CIP	NIT	SXT
E. coli (1011)	2/4 (100)	4/16 (88.1)	2/>32 (85.0)	0.015/>4 (80.3)	16/32 (97.4)	≤0.12/>4 (71.5)
MIC screen-negative (864)	2/2 (100)	4/8 (91.6)	1/4 (98.7)	0.008/>4 (87.2)	16/32 (98.4)	≤0.12/>4 (78.2)
MIC screen-positive[a] (147)	2/4 (100)	8/32 (68.0)	>32/>32 (4.1)	4/>4 (40.1)	16/32 (91.8)	>4/>4 (31.5)
ESBL/pAmpC[b] (135)	2/4 (100)	8/32 (73.3)	>32/>32 (0.7)	>4/>4 (36.3)	16/32 (91.1)	>4/>4 (26.7)
K. pneumoniae (398)	4/16 (92.5)	2/8 (90.4)	1/>32 (82.9)	0.015/1 (82.4)	64/>128 (28.4)	≤0.12/>4 (81.4)
MIC screen-negative (331)	4/16 (96.7)	2/4 (98.5)	1/2 (99.4)	0.015/0.12 (94.3)	64/>128 (31.1)	≤0.12/0.5 (94.6)
MIC screen-positive[a] (67)	16/32 (71.6)	8/>32 (50.7)	>32/>32 (1.5)	1/>4 (23.9)	128/>128 (14.9)	>4/>4 (16.4)
ESBL/pAmpC[c] (59)	16/32 (71.2)	8/32 (55.9)	>32/>32 (1.7)	0.5/>4 (23.7)	128/>128 (15.3)	>4/>4 (13.6)
Carbapenemase[d] (6)	-/- (66.7)	-/- (0.0)	-/- (0.0)	-/- (16.7)	-/- (16.7)	-/- (33.3)

ESBL, extended spectrum-β-lactamase; GEP, gepotidacin; AMC, amoxicillin-clavulanate; CFZ, cefazolin; CIP, ciprofloxacin; NIT, nitrofurantoin; SXT, trimethoprim-sulfamethoxazole; Gepotidacin FDA susceptible breakpoint (≤16 µg/mL) applied; CLSI breakpoints applied for comparator agents; "-", $MIC_{50/90}$ values not calculated due to small number of isolates.

[a] Includes isolates with aztreonam, ceftazidime, ceftriaxone or meropenem MICs of ≥2 µg/mL.

[b] The following β-lactamase alleles with extended-spectrum were detected: 10 bla_{CMY-2}, 1 bla_{CMY-16} and $bla_{CTX-M-15}$, 1 $bla_{CTX-M-115}$, 10 $bla_{CTX-M-14}$, 64 $bla_{CTX-M-15}$, 1 bla_{CMY-2} and $bla_{CTX-M-15}$, 1 bla_{CMY-2} and $bla_{CTX-M-27}$, 1 $bla_{CTX-M-3}$ and $bla_{CTX-M-27}$, 1 $bla_{CTX-M-174}$, 34 $bla_{CTX-M-27}$, 1 $bla_{CTX-M-32}$, 6 $bla_{CTX-M-55}$, 1 $bla_{CTX-M-65}$, 2 bla_{DHA-1}, and 1 bla_{SHV-12}.

[c] The following β-lactamase alleles with extended-spectrum were detected: 2 $bla_{CTX-M-14}$, 1 bla_{DHA-1} and $bla_{CTX-M-14}$, 44 $bla_{CTX-M-15}$, 6 $bla_{CTX-M-15}$ and bla_{SHV-27}, 1 $bla_{CTX-M-27}$, 1 $bla_{CTX-M-55}$, 1 bla_{DHA-1}, 1 bla_{SHV-2}, 1 bla_{SHV-12}, and 1 bla_{SHV-27}.

[d] The following carbapenemases were detected: 2 bla_{KPC-2}, 1 bla_{KPC-3}, 1 bla_{NDM-1}, 1 bla_{NDM-7}, and 1 bla_{OXA-48}.

Conclusions

- In general, gepotidacin showed susceptibility higher than oral comparator agents when tested against *E. coli* and *K. pneumoniae* clinical isolates causing UTI in patients in the US, including those carrying β-lactamase genes.
- These data benchmark gepotidacin against *E. coli* and *K. pneumoniae* for subsequent monitoring following its FDA approval for the treatment of uUTIs.

Abbreviations

CLSI, Clinical and Laboratory Standards Institute; ESBL, extended-spectrum β-lactamase; FDA, Food and Drug Administration; I, Susceptible, increased exposure; MDR, multidrug resistance; MIC, Minimal inhibitory concentration; NS, not susceptible; pAmpC, plasmid AmpC; S, susceptible; R, resistant; UTI, urinary tract infection.

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Presenting author: Rodrigo Mendes, rodrigo-mendes@element.com

Disclosures

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