In vitro Activity of Gepotidacin and Comparator Agents Against a Collection of *Klebsiella pneumoniae* Urine Isolates Collected from the United States during 2019–2022

[1] S. J. Ryan Arends, [2] R. Kapoor, [3] D. Torumkuney, [1] R.E. Mendes

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

Gepotidacin demonstrated *in vitro* activity against contemporary *K. pneumoniae* isolates, including ESBL-producing and MDR isolates.

Digital poster

Introduction

Gepotidacin is a novel, bactericidal, first-in-class triazaacenaphthylene antibiotic that inhibits bacterial DNA replication by a unique mechanism of action, distinct binding site, and for most pathogens provides a well-balanced inhibition of two different Type II topoisomerase enzymes (1-3).

Gepotidacin is currently under development for the treatment of uncomplicated urinary tract infections (uUTIs) and gonorrhea (4-5).

This study reports on the *in vitro* activity of gepotidacin and other oral antibiotics tested against contemporary *Klebsiella pneumoniae* clinical isolates collected from patients with UTI in the United States as part of a gepotidacin uropathogen global surveillance study.

Study design

A total of 2,001 *K. pneumoniae* isolates were collected between 2019-2022.

- These isolates came from 73 USA medical centers located in 36 states.
- Most isolates (65%) were cultured from urine specimens collected from patients seen in ambulatory, emergency, family practice, and outpatient medical services.
- Bacterial identifications were confirmed by MALDI-TOF MS.

Isolates were tested for susceptibility by CLSI methods (6) at a central laboratory (JMI Laboratories / Element Iowa City).

- Susceptibility to mecillinam was determined by agar dilution.

MIC results for comparator agents were interpreted per CLSI (7) guidelines to determine % of susceptible (S), intermediate (I), and resistant (R) isolates.

- Extended-spectrum β-lactamase (ESBL) phenotype in *K. pneumoniae* was characterized as isolates displaying aztreonam, ceftazidime, or ceftriaxone MIC values ≥ 2 µg/mL.
- The MDR phenotype was defined for *K. pneumoniae* as described by Magiorakos et al. (8) as having a CLSI-not susceptible phenotype to 3 or more drug classes from the following: extended-spectrum cephalosporins (ceftriaxone or ceftazidime); carbapenems (meropenem); antipseudomonal penicillins + β-lactamase inhibitors (piperacillin-tazobactam); fluoroquinolones (ciprofloxacin or levofloxacin); and aminoglycosides (gentamicin or amikacin).
- Data was not reported for all drugs utilized in the SENTRY program MDR classification.

Results

Gepotidacin displayed activity against 2,001 *K. pneumoniae* isolates (Table 1).

- An $MIC_{50/90}$ of 4/16 µg/mL was observed.
- 94.9% of all observed gepotidacin MICs were ≤16 µg/mL.

Susceptibility rates for all oral comparators tested were at or below 90% (Table 1).

- Amoxicillin-clavulanic acid (90.0%; $MIC_{50/90}$, 2/8 µg/mL)
- Ciprofloxacin (86.3%; $MIC_{50/90}$, 0.015/0.5 µg/mL)
- Levofloxacin (88.3%; $MIC_{50/90}$, 0.06/1 µg/mL)
- Nitrofurantoin (34.0%, $MIC_{50/90}$, 64/>128 µg/mL)
- Trimethoprim-sulfamethoxazole (84.7%; $MIC_{50/90}$, ≤0.12/>4 µg/mL)

Most gepotidacin MIC_{50} (ranging from 4 – 16 µg/mL) and MIC_{90} values (ranging from 16 – 32 µg/mL) for drug-resistant subsets were within 2-fold of the overall $MIC_{50/90}$ values (Table 2).

The MIC_{50} value for fluoroquinolone-NS isolates was 4-fold higher (MIC_{50}, 16 µg/mL) compared to the overall isolate set (MIC_{50}, 4 µg/mL)

Gepotidacin remained active against the 11.0% and 6.8%of *K. pneumoniae* isolates that displayed an ESBL or MDR phenotype, respectively, with observed $MIC_{50/90}$ values of 8/32 µg/mL for both (Table 2).

Table 1 Activity of gepotidacin and other oral agents tested against *K. pneumoniae* UTI isolates collected from medical centers in the United States during 2019–2022

Organism (No. isolates) / Antimicrobial agent	µg/mL MIC_{50}	µg/mL MIC_{90}	µg/mL MIC range	CLSI [a] %S	CLSI [a] %I	CLSI [a] %R
K. pneumoniae (2,001)						
Gepotidacin	4	16	0.12 to >64	[b]		
Amoxicillin-clavulanic acid [c]	2	8	≤0.25 to >32	90	6.9	3.1
Ciprofloxacin	0.015	0.5	≤0.002 to >4	86.3	4.7	9
Levofloxacin	0.06	1	≤0.015 to >32	88.3	5.1	6.6
Nitrofurantoin [d]	64	>128	≤2 to >128	34	30.9	35.1
Trimethoprim-sulfamethoxazole	≤0.12	>4	≤0.12 to >4	84.7	-	15.3

[a] Interpretations per CLSI (2024) guidelines.
[b] Breakpoints not established.
[c] Tested at 2:1 ratio.
[d] Using UTI only breakpoints.

Table 2 Frequency distribution of gepotidacin MIC values for *K. pneumoniae* isolate subsets from the United States with resistance to oral agents in 2019–2022

Organism (No. isolates) / Phenotypic subset [a]	No. and cumulative % of isolates inhibited at gepotidacin MIC (µg/mL) of: 0.5	1	2	4	8	16	32	64	> 64	Gepotidacin MIC_{50}	Gepotidacin MIC_{90}
K. pneumoniae (2,001)	7	27	187	1,112	430	136	80	21	1	4	16
	0.3%	1.7%	11.0%	66.6%	88.1%	94.9%	98.9%	99.9%	100%		
Amoxicillin-clavulanate-NS [b] (199)	0	2	16	53	61	44	13	10		8	32
	0.0%	1.0%	9.0%	35.7%	66.3%	88.4%	95.0%	100%			
Fluoroquinolone-NS [c] (291)	1	8	15	32	69	76	70	19	1	16	32
	0.3%	3.1%	8.2%	19.2%	43.0%	69.1%	93.1%	99.7%	100%		
Nitrofurantoin-NS [d] (1,321)	4	11	95	729	286	100	75	20	1	4	16
	0.3%	1.1%	8.3%	63.5%	85.2%	92.7%	98.4%	99.9%	100%		
Trimethoprim-sulfamethoxazole-R (307)	0	6	17	93	87	59	28	16	1	8	32
	0.0%	2.0%	7.5%	37.8%	66.1%	85.3%	94.5%	99.7%	100%		
ESBL (220)	0	3	17	45	68	56	20	11		8	32
	0.0%	1.4%	9.1%	29.5%	60.5%	85.9%	95.0%	100%			
MDR (137)	0	2	12	23	48	32	9	10	1	8	32
	0.0%	1.5%	10.2%	27.0%	62.0%	85.4%	92.0%	99.3%	100%		

NS, not susceptible; R, resistant; ESBL, extended-spectrum β-lactamase; MDR, multidrug resistant.
[a] Interpreted by CLSI breakpoints.
[b] Tested at 2:1 ratio.
[c] Indications other than meningitidis.
[d] Using UTI only breakpoints.

Conclusions

Gepotidacin demonstrated *in vitro* activity against contemporary *K. pneumoniae* UTI isolates from the United States.

This activity remained mostly unaffected by resistance to other oral standard-of-care antibiotics with $MIC_{50/90}$ values in general within 2-fold of those described for the overall population.

Almost all oral comparator agents reported against US *K. pneumoniae* UTI isolates had susceptibility rates between 80.0 and 90.0%; while nitrofurantoin had a lower susceptibility percentage of 34.0%.

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