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SCAN ME

Analysis of Resistance to Oral Standard-of-Care Antibiotics for Urinary Tract Infections Caused By *Escherichia coli* and *Staphylococcus saprophyticus* Collected in Europe in 2022

Gepotidacin displays activity against *E. coli* and *S. saprophyticus* European urine isolates, including those isolates not susceptible to other oral antibiotics.

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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, distinct binding site, and for most pathogens provides a well-balanced inhibition of two different Type II topoisomerase enzymes.
- Gepotidacin is currently under development for the treatment of uncomplicated urinary tract infections (uUTIs) and gonorrhea.
- This study reports on a subset of data from a gepotidacin uropathogen global surveillance study to test in vitro activity of gepotidacin and other oral standard-of-care antibiotics against recent contemporary *Escherichia coli* and *Staphylococcus saprophyticus* clinical isolates collected from patients with UTIs

Methods

- A total of 524 *E. coli* and 65 *S. saprophyticus* isolates were collected during 2022 from 29 medical centers located in 13 European countries.
- All isolates were cultured from urine specimens collected from patients seen mostly (64%) in ambulatory, emergency, family practice, and outpatient medical services.
- Bacterial identifications were confirmed by MALDI-TOF.
- Isolates were tested for susceptibility by CLSI methods (CLSI, 2018).
- MIC results for antibiotics for the treatment of uncomplicated UTI and drug-resistant subsets were interpreted per CLSI and EUCAST guidelines (CLSI, 2023; EUCAST, 2024).
- Amoxicillin-clavulanate was tested at a 2:1 ratio and MICs were interpreted using CLSI breakpoints.
- The extended-spectrum β-lactamase (ESBL) phenotype in E. coli was characterized as isolates displaying aztreonam, ceftazidime, or ceftriaxone MIC values ≥ 2 mg/L.
- The MDR phenotype was defined for E. coli as described by Magiorakos et al. (2012) as having a EUCAST-not susceptible phenotype to 3 or more drug classes. Data was not reported for all drugs utilized in the SENTRY program MDR classification.

Results

- Gepotidacin displayed good activity against 524 *E. coli* isolates (Table 1).
  - An $MIC_{50/90}$ of 2/2 mg/L was observed.
  - 96.9% of all observed gepotidacin MICs were ≤4 mg/L.
- The percentage of *E. coli* isolates susceptible (S) to ampicillin, amoxicillin-clavulanate, cefadroxil, levofloxacin, and trimethoprim-sulfamethoxazole was below 90% (Table 1).
- Higher susceptibility (>96% S) was observed for fosfomycin, mecillinam, nitrofurantoin, and nitroxoline against all *E. coli* (Table 1).
- Gepotidacin maintained similar MIC_{50} values (ranging from 1 – 2 mg/L) and MIC_{90} values of 4 mg/L against drug-resistant E. coli subsets (Table 2).
- Gepotidacin maintained similar activity ($MIC_{50/90}$, 2/4 mg/L) against the 13% of *E. coli* isolates with an ESBL phenotype (Table 2).
- $MIC_{50/90}$ values of 2/8 mg/L were observed against the 3.7% of *E. coli* isolates with an MDR phenotype (Table 2).
- Gepotidacin inhibited 100% of *S. saprophyticus* isolates at ≤0.12 mg/L ($MIC_{50/90}$, 0.06/0.12 mg/L) (Table 1).
- *S. saprophyticus* isolates showed 100% S to all tested oral agents with applicable EUCAST breakpoints (Table 1).

Table 1: **Activity of gepotidacin and other oral agents tested against *E. coli* UTI isolates collected from medical centers in Europe during 2022**

Organism (No. isolates)	mg/L			EUCAST[a]			CLSI[a]		
Antimicrobial agent	MIC_{50}	MIC_{90}	MIC range	%S	%I	%R	%S	%I	%R
Escherichia coli (524)									
Gepotidacin	2	2	0.06 to 16	[b]			[b]		
Ampicillin	4	>64	≤1 to >64	55.0[h]		45.0	55.0	0.0	45.0
Amoxicillin-clavulanate [c]	4	16	1 to >32				84.2	9.9	5.9
Cefadroxil[d]	NA	NA	NA	86.6[e]		13.4	[b]		
Fosfomycin[f]	0.5	1	0.25 to >256	98.1[h]		1.9	99.0[g]	0.2	0.8
Levofloxacin	0.03	8	≤0.015 to >32	82.4	1.3	16.2	82.4	1.3	16.2
Mecillinam[f]	0.25	4	0.03 to >32	95.8[h]		4.2	95.8[g]	1.5	2.7
Nitrofurantoin	16	32	≤2 to >128	99.0[e]		1.0	97.7[g]	1.3	1.0
Nitroxoline[d]	NA	NA	NA	100.0[e]		0.0	[b]		
Trimethoprim-sulfamethoxazole	≤0.12	>4	≤0.12 to >4	73.7	1.7	24.6	73.7		26.3
Staphylococcus saprophyticus (65)									
Gepotidacin	0.06	0.12	0.06 to 0.12	[b]			[b]		
Ciprofloxacin	0.25	0.5	0.25 to 0.5		100.0[i]	0.0	100.0	0.0	0.0
Levofloxacin	0.5	0.5	0.5 to 1		100.0[i]	0.0	100.0	0.0	0.0
Nitrofurantoin	16	16	16 to 16	100.0[e]		0.0	100.0[g]	0.0	0.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 to ≤0.5	100.0	0.0	0.0	100.0		0.0

NA, not applicable
[a] Criteria as published by CLSI (2023) and EUCAST (2023).
[b] Breakpoints not established
[c] Tested in CLSI recommended 2:1 ratio; only CLSI breakpoints applied.
[d] Tested by disk diffusion.
[e] Using uncomplicated urinary tract infection breakpoints.
[f] Tested by agar dilution.
[g] For infections originating from the urinary tract.
[h] Using oral, uncomplicated urinary tract infection breakpoints.
[i] Intermediate interpreted as susceptible-increased exposure.

Table 2: **Frequency distribution of gepotidacin MIC values for *E. coli* isolate subsets from Europe with resistance to oral agents in 2022**

Organism (No. isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of:							Gepotidacin	
Not suceptible subset [a]	≤0.25	0.5	1	2	4	8	16	MIC_{50}	MIC_{90}
E. coli (524)	7 1.3%	33 7.6%	172 40.5%	260 90.1%	36 96.9%	12 99.2%	4 100%	2	2
Ampicillin-NS[b] (234)	2 0.9%	21 9.8%	77 42.7%	102 86.3%	17 93.6%	11 98.3%	4 100%	2	4
Amoxicillin-clavulanate-NS[c] (83)	0 0.0%	5 6.0%	19 28.9%	45 83.1%	9 94.0%	4 98.8%	1 100%	2	4
Cefadroxil-NS[e] (70)	0 0.0%	12 17.1%	11 32.9%	32 78.6%	9 91.4%	5 98.6%	1 100%	2	4
Fosfomycin-NS[b,d] (10)	1 10.0%	1 20.0%	2 40.0%	4 80.0%	1 90.0%	1 100.0%		2	4
Fluoroquinolone-NS (92)	0 0.0%	17 18.5%	26 46.7%	29 78.3%	15 94.6%	5 100%		2	4
Mecillinam-NS[b,d] (22)	0 0.0%	1 4.5%	10 50.0%	8 86.4%	2 95.5%	1 100%		1	4
Nitrofurantoin-NS[e] (5)	0 0.0%	1 20.0%	1 40.0%	2 80.0%	0 80.0%	1 100%		ND	ND
Trimethoprim-sulfamethoxazole-NS (138)	2 1.4%	12 10.1%	48 44.9%	57 86.2%	8 92%	9 98.6%	2 100%	2	4
ESBL (67)	0 0.0%	12 17.9%	10 32.8%	30 77.6%	9 91.0%	5 98.5%	1 100%	2	4
MDR (19)	0 0.0%	3 15.8%	1 21.1%	9 68.4%	2 78.9%	3 94.7%	1 100%	2	8

ESBL, Extended-spectrum β-lactamases; MDR, multidrug resistance; ND, not determined if n<10; NS; not susceptible
[a] Interpreted by EUCAST breakpoints.
[b] Using oral, uncomplicated urinary tract infection breakpoints.
[c] Tested at 2:1 ratio and therefore interpreted by CLSI breakpoints.
[d] Tested by agar dilution.
[e] Using uncomplicated urinary tract infection breakpoints.

Abbreviations

CLSI, Clinical and Laboratory Standards Institute
ESBL, extended-spectrum β-lactamase
EUCAST, European Committee on Antimicrobial Susceptibility Testing
MDR, multidrug resistance
MIC, Minimal inhibitory concentration
NS, not susceptible
NA, not applicable
ND, not determined
S, susceptible
UTI, urinary tract infection

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Disclosures

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Conclusions

- Gepotidacin demonstrated *in vitro* activity against contemporary *E. coli* and *S. saprophyticus* UTI isolates from Europe.
- This activity remained more or less unaffected by resistance to other oral standard-of-care antibiotics.
- Gepotidacin maintained activity against the 13% and 4% of *E. coli* isolates with an ESBL phenotype or MDR phenotype, respectively.

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