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

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Introduction

Gepotidacin is a novel, bactericidal, first-in-class triazaacenaphthylene antibiotic that inhibits bacterial DNA replication by a distinct mechanism of action [1,2] which confers activity against most strains of target pathogens, such as *Escherichia coli*, *Staphylococcus saprophyticus*, and *Neisseria gonorrhoeae*, including those resistant to current antibiotics [3].

Gepotidacin demonstrated efficacy for treatment of uncomplicated urinary tract infections (uUTIs) in two recently concluded phase 3 clinical trials [4] and is currently in phase 3 clinical development for the treatment of urogenital gonorrhea [5].

This study reports on the in vitro activity of gepotidacin and other oral antibiotics when tested against recent contemporary *E. coli* and *S. saprophyticus* clinical isolates collected from patients with UTIs for a gepotidacin uropathogen global surveillance study.

Materials and Methods

A total of 1,001 *E. coli* and 92 *S. saprophyticus* isolates were collected during 2022.

- These isolates came from 45 medical centers in the United States.
- Most isolates (77%) 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).

- Susceptibility to fosfomycin and mecillinam was determined by agar dilution.
- Fosfomycin testing was supplemented with glucose-6-phosphate (25 mg/L).

MIC results for oral antibiotics licensed for the treatment of uUTI, multidrug-resistant (MDR), and extended-spectrum β-lactamase (ESBL) subsets were interpreted per CLSI criteria [7].

- The ESBL phenotype was classified for *E. coli* when isolates displayed aztreonam, ceftazidime, or ceftriaxone MIC values ≥2 mg/L.
- The MDR phenotype was defined for *E. coli* 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.

Disclosures

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Gepotidacin demonstrated *in vitro* activity against contemporary *E. coli* and *S. saprophyticus* urine isolates from the US.

Gepotidacin activity was maintained among isolates demonstrating resistance to other oral standard-of-care antibiotics including amoxicillin-clavulanate, fluoroquinolones, fosfomycin, mecillinam, nitrofurantoin, and trimethoprim-sulfamethoxazole.

Gepotidacin inhibited 91.5% of ESBL positive and 97.2% of MDR isolates at concentrations ≤4 mg/L.

Table 1 Activity of gepotidacin and comparator antimicrobials against UTI isolate subsets with resistance to oral agents

Organism (No. of isolates)	MIC_{50}/MIC_{90} in mg/L (% susceptible; CLSI)							
Drug-resistant subset	Gepotidacin	Ciprofloxacin	Amoxicillin-clavulanate	Ampicillin	Trimethoprim-sulfamethoxazole[a]	Nitrofurantoin[a]	Fosfomycin[b]	Mecillinam[b]
E. coli (1,001)	2/4 - [c]	0.015/>4 (78.8%)	4/16 (85.2%)	4/>64 (55.6%)	≤0.12/>4 (73.3%)	16/16 (97.5%)	0.5/1 (99.3%)	0.25/4 (93.5%)
Fluoroquinolone - NS (213)	1/4 -	>4/>4 (0.5%)	8/16 (74.2%)	>64/>64 (25.9%)	4/>4 (49.3%)	16/32 (91.1%)	0.5/2 (98.6%)	0.5/4 (93.4%)
Amoxicillin-clavulanate - NS (148)	2/4 -	0.12/>4 (62.8%)	16/32 (0.0%)	>64/>64 (0.0%)	0.5/>4 (52.0%)	16/32 (93.9%)	0.5/1 (98.6%)	4/>32 (66.9%)
Ampicillin - NS (444)	2/4 -	0.12/>4 (64.9%)	8/16 (66.7%)	>64/>64 (0.0%)	>4/>4 (48.9%)	16/32 (96.4%)	0.5/1 (98.6%)	1/16 (87.2%)
Trimethoprim-sulfamethoxazole - NS (267)	2/4 -	0.12/>4 (59.6%)	8/16 (73.4%)	>64/>64 (14.7%)	>4/>4 (0.0%)	16/32 (94.8%)	0.5/1 (98.9%)	1/16 (88.8%)
Nitrofurantoin - NS (25)	1/2 -	>4/>4 (24.0%)	4/16 (64.0%)	>64/>64 (36.0%)	>4/>4 (44.0%)	128/>128 (0.0%)	0.5/2 (100.0%)	0.5/>32 (88.0%)
Fosfomycin - NS (7)	ND [d] -	ND (57.1%)	ND (71.4%)	ND (14.3%)	ND (57.1%)	ND (100.0%)	ND (0.0%)	ND (71.4%)
Mecillinam - NS (65)	2/4 -	0.015/>4 (78.5%)	16/16 (24.6%)	>64/>64 (12.3%)	0.25/>4 (53.8%)	16/32 (95.4%)	0.5/4 (96.9%)	32/>32 (0.0%)
ESBL phenotype (106)	2/4 -	>4/>4 (25.5%)	8/32 (52.8%)	>64/>64 (0.9%)	>4/>4 (39.6%)	16/64 (89.6%)	0.5/2 (97.2%)	0.5/4 (93.4%)
MDR phenotype (36)	2/2 -	>4/>4 (0.0%)	16/32 (22.2%)	>64/>64 (0.0%)	>4/>4 (38.9%)	16/64 (83.3%)	1/2 (94.4%)	1/4 (94.4%)
S. saprophyticus (92)	0.06/0.12 -	0.25/0.5 (100.0%)	0.5/4 (88.0%) [e]	≤1/4 - [c]	≤0.5/1 (94.6%)	16/16 (100.0%)	128/>256 - [c]	NT

NS, not susceptible per CLSI M100 2023; NT, not tested; ESBL, extended spectrum β-lactamase phenotype; MDR, multi-drug resistant.
[a] Used only or primarily for treating UTIs.
[b] Using oral breakpoints for urinary tract infection caused by *E. coli*.
[c] Breakpoints not established
[d] $MIC_{50/90}$ values were not determined due to small sample size.
[e] Based on surrogate testing of oxacillin/cefoxatin

Table 2 Distribution of MIC values for gepotidacin against *E. coli* UTI isolate subsets with resistance to oral agents

Organism (No. of isolates)	No. and cumulative % of isolates inhibited at a gepotidacin MIC (mg/L) of:								Gepotidacin	
Drug-resistant subset	≤0.25	0.5	1	2	4	8	16	32	MIC_{50}	MIC_{90}
E. coli (1,001)	8 (0.8%)	46 (5.4%)	298 (35.2%)	527 (87.8%)	110 (98.8%)	5 (99.3%)	5 (99.8%)	2 (100%)	2	4
Fluoroquinolone - NS (213)	5 (2.3%)	25 (14.1%)	85 (54%)	64 (84%)	24 (95.3%)	4 (97.2%)	4 (99.1%)	2 (100%)	1	4
Amoxicillin-clavulanate - NS (148)	1 (0.7%)	10 (7.4%)	44 (37.2%)	75 (87.8%)	16 (98.6%)	0 (98.6%)	2 (100%)		2	4
Ampicillin - NS (444)	6 (1.4%)	23 (6.5%)	156 (41.7%)	210 (89%)	40 (98%)	4 (98.9%)	4 (99.8%)	1 (100%)	2	4
Trimethoprim-sulfamethoxazole - NS (267)	4 (1.5%)	16 (7.5%)	110 (48.7%)	108 (89.1%)	23 (97.8%)	2 (98.5%)	3 (99.6%)	1 (100%)	2	4
Nitrofurantoin - NS (25)		2 (8.0%)	11 (52.0%)	11 (96.0%)	1 (100%)				1	2
Fosfomycin - NS (7)			1 (14.3%)	4 (71.4%)	1 (85.7%)	1 (100%)			ND[a]	ND[a]
Mecillinam - NS (65)	1 (1.5%)	5 (9.2%)	21 (41.5%)	30 (87.7%)	7 (98.5%)	0 (98.5%)	1 (100%)		2	4
ESBL phenotype (106)		5 (4.7%)	39 (41.5%)	41 (80.2%)	12 (91.5%)	4 (95.3%)	4 (99.1%)	1 (100%)	2	4
MDR phenotype (36)		1 (2.8%)	14 (41.7%)	18 (91.7%)	2 (97.2%)	0 (97.2%)	1 (100%)		2	2

NS, not susceptible per CLSI M100 2023; ESBL, extended-spectrum β-lactamase; MDR, multidrug resistant.
[a] $MIC_{50/90}$ values were not determined due to small sample size.

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Results

Gepotidacin ($MIC_{50/90}$, 2/4 mg/L) displayed good activity against 1,001 *E. coli* isolates from UTI infections, with 98.8% of all observed gepotidacin MICs ≤4 mg/L (Tables 1 and 2).

Susceptibility (S) to comparators amoxicillin-clavulanate (85.2% S), ampicillin (55.6% S), ciprofloxacin (78.8% S), fosfomycin (99.3% S), mecillinam (93.5% S), nitrofurantoin (97.5% S), and trimethoprim-sulfamethoxazole (73.3% S) was observed (Table 1).

Gepotidacin maintained similar $MIC_{50/90}$ values (1-2/2-4 mg/L) against drug-resistant subsets (Table 2).

Most comparator agents displayed reduced susceptibility against drug-specific not susceptible subsets while others retained activity (Table 1). The susceptibility rates were:

- Ciprofloxacin (24.0–78.5%), amoxicillin-clavulanate (24.6–74.2%), trimethoprim-sulfamethoxazole (44.0–53.8%), and ampicillin (0.0–36.0%).
- Nitrofurantoin (91.1–100.0%), fosfomycin (96.9–100.0%), and mecillinam (66.9–93.4%).

ESBL and MDR phenotypes were observed in 10.6% and 3.6%, respectively, of *E. coli* isolates.

Gepotidacin was active against ESBL-positive and MDR isolates, inhibiting 91.5% and 97.2%, respectively, at ≤4 mg/L (Table 2).

The susceptibility rates of comparator agents against ESBL-positive and MDR isolates were:

- Ciprofloxacin (25.5% and 0%), amoxicillin-clavulanate (52.8% and 22.2%), and trimethoprim-sulfamethoxazole (39.6 and 38.8%) respectively.
- Nitrofurantoin (89.6% and 83.3%), fosfomycin (97.2% and 94.4%), and mecillinam (93.4% and 94.4%), respectively.

Gepotidacin inhibited 100% of *S. saprophyticus* isolates at ≤0.12 mg/L, with $MIC_{50/90}$ values of 0.06/0.12 mg/L.

Most oral agents showed >94% susceptibility against *S. saprophyticus* isolates, except for amoxicillin-clavulanate (88.0% S).

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