Activity of Gepotidacin Against *Escherichia coli* Isolates from Community-acquired Urinary Tract Infections Collected Between 2019-2021 in the United States

[1] S.J. Ryan Arends, [2] D. Butler, [2] N. Scangarella-Oman, [1] L. Tholen, [1] J. Streit, [1] **R.E. Mendes**

[1]JMI Laboratories, North Liberty, Iowa, USA

[2]GlaxoSmithKline, Collegeville, Pennsylvania, USA

Introduction

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

Gepotidacin (GSK2140944) is in Phase 3 clinical development for the treatment of gonorrhea and uncomplicated urinary tract infections (UTIs).

This study reports on results of the in vitro activity of gepotidacin and comparator agents when tested against contemporary *E. coli* and *S. saprophyticus* clinical isolates collected from patients with UTIs for a gepotidacin global surveillance study as part of the SENTRY Antimicrobial Surveillance Program.

Materials and Methods

A total of 1,978 *E. coli* isolates were collected between 2019-2021.

- These isolates came from 47 medical centers in the United States.
- All isolates were cultured from urine specimens collected from patients seen in emergency and outpatient medical services representative of community-acquired infections.
- Bacterial identifications were confirmed by MALDI-TOF.

Isolates were tested for susceptibility by CLSI methods 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.

- 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. 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

This study at JMI Laboratories was supported by GlaxoSmithKline. JMI Laboratories received compensation fees for services in relation to preparing the poster.

This project has been funded in whole or in part with Federal funds from the Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority, under Contract No. HHSO100201300011C.

Gepotidacin demonstrated potent *in vitro* activity against contemporary community-acquired *E. coli* urine isolates.

This 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 94.7% of ESBL phenotype and 95.9% of MDR isolates at concentrations ≤4 mg/L.

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

Organism (No. of isolates) Drug-resistant subset	MIC$_{50}$/MIC$_{90}$ in mg/L (% susceptible; CLSI)							
	Gepotidacin	Ciprofloxacin	Amoxicillin-clavulanate	Ampicillin	Trimethoprim-sulfamethoxazole[a]	Nitrofurantoin[a]	Fosfomycin[b]	Mecillinam[b]
E. coli (n=1,978)	2/4	0.015/>4 (79.1)	4/16 (83.7)	8/>64 (50.9)	≤0.12/>4 (71.3)	16/32 (98.2)	0.5/1 (99.7)	0.5/4 (94.2)
Fluoroquinolone - R (n=369)	1/4	>4/>4 (0.0)	8/16 (63.6)	>64/>64 (18.4)	>4/>4 (47.6)	16/32 (95.1)	0.5/2 (99.2)	1/8 (92.1)
Amoxicillin-clavulanate - R (n=90)	2/4	0.25/>4 (56.7)	32/>32 (0.0)	>64/>64 (0.0)	0.25/>4 (57.8)	16/32 (92.2)	0.5/2 (100.0)	2/32 (81.1)
Ampicillin - R (n=961)	2/4	0.06/>4 (65.5)	8/16 (66.7)	>64/>64 (0.0)	>4/>4 (49.2)	16/32 (97.0)	0.5/1 (99.6)	2/16 (89.8)
Trimethoprim-sulfamethoxazole - R (n=567)	2/4	0.12/>4 (60.6)	8/16 (70.0)	>64/>64 (13.6)	>4/>4 (0.0)	16/32 (96.5)	0.5/1 (99.3)	1/16 (89.4)
Nitrofurantoin - R (n=20)	2/4	>4/>4 (40.0)	8/>32 (60.0)	>64/>64 (20.0)	>4/>4 (35.0)	128/128 (0.0)	0.5/2 (100.0)	1/8 (90.0)
Mecillinam - R (n=82)	2/4	0.015/>4 (65.9)	16/32 (31.7)	>64/>64 (19.5)	0.5/>4 (50.0)	16/32 (93.9)	0.5/2 (100.0)	>32/>32 (0.0)
ESBL phenotype (n=246)	2/4	>4/>4 (26.4)	16/32 (48.6)	>64/>64 (0.4)	>4/>4 (38.2)	16/32 (93.1)	0.5/2 (98.4)	1/8 (92.7)
MDR phenotype (n=98)	2/4	>4/>4 (0.0)	16/>32 (26.5)	>64/>64 (0.0)	>4/>4 (29.6)	16/64 (88.8)	0.5/2 (96.9)	1/16 (88.8)

R, resistant per CLSI M100 2022; 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*.

IDWEEK 2022
October 19-23, 2022, Washington, DC

SCAN ME

Results

Gepotidacin (MIC$_{50/90}$, 2/4 mg/L) displayed good activity against 1,978 *E. coli* isolates from UTI infections, with 98.3% of all observed gepotidacin MICs ≤4 mg/L (Tables 1 and 2).

Susceptibility (S) to comparators amoxicillin-clavulanate (83.7%S), ampicillin (50.9%S), ciprofloxacin (79.1%S), fosfomycin (99.7%S), mecillinam (94.2%S), nitrofurantoin (98.2%S), and trimethoprim-sulfamethoxazole (71.3%S) was observed (Table 1).

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

Most comparator agents displayed reduced susceptibility against drug-specific resistant subsets while others retained activity (Table 1).

- Ciprofloxacin (40.0–65.9%S), amoxicillin-clavulanate (31.7–70.0%S), trimethoprim-sulfamethoxazole (35.0–57.8%S), and ampicillin (0.0–20.0%)
- Nitrofurantoin (92.2–97.0%S), fosfomycin (99.2–100.0%S), and mecillinam (81.1–92.7%).

ESBL and MDR phenotypes were observed in 12.4% and 5.0%, respectively, of *E. coli* isolates from community-acquired infections.

- For ESBL and MDR isolates, the percentage of susceptible isolates to ciprofloxacin, amoxicillin-clavulanate, and trimethoprim-sulfamethoxazole was <50% while nitrofurantoin, fosfomycin, and mecillinam displayed percent susceptibilities ≥88.8%.

Gepotidacin was active against ESBL and MDR isolates, inhibiting 94.7% and 95.9%, respectively, at ≤4 mg/L (Table 2).

Table 2 Distribution of MIC values for gepotidacin against community-acquired UTI isolate subsets with resistance to oral agents

Organism (No. of isolates) Drug-resistant subset	No. and cumulative % of isolates inhibited at a gepotidacin MIC (mg/L) of:								Gepotidacin	
	0.25	0.5	1	2	4	8	16	32	MIC$_{50}$	MIC$_{90}$
E. coli (1,978)	21 (1.1%)	94 (5.8%)	614 (36.9%)	1043 (89.6%)	173 (98.3%)	25 (99.6%)	7 (99.9%)	1 (100%)	2	4
Fluoroquinolone - R (369)	12 (3.3%)	44 (15.2%)	133 (51.2%)	127 (85.6%)	41 (96.7%)	9 (99.2%)	2 (99.7%)	1 (100%)	1	4
Amoxicillin-clavulanate - R (90)	0 (0.0%)	2 (2.2%)	20 (24.4%)	46 (75.6%)	17 (94.4%)	4 (98.9%)	1 (100%)		2	4
Ampicillin - R (961)	14 (1.5%)	62 (7.9%)	333 (42.6%)	442 (88.6%)	87 (97.6%)	16 (99.3%)	6 (99.9%)	1 (100%)	2	4
Trimethoprim-sulfamethoxazole - R (567)	8 (1.4%)	42 (8.8%)	202 (44.4%)	252 (88.9%)	46 (97%)	11 (98.9%)	5 (99.8%)	1 (100%)	2	4
Nitrofurantoin - R (20)		0 (0.0%)	3 (15.0%)	12 (75.0%)	3 (90.0%)	1 (95.0%)	1 (100%)		2	4
Fosfomycin - R (3)		0 (0.0%)	1 (33.3%)	0 (33.3%)	1 (66.7%)	1 (100%)			ND[a]	ND[a]
Mecillinam - R (82)	0 (0.0%)	3 (3.7%)	22 (30.5%)	44 (84.1%)	11 (97.6%)	2 (100%)			2	4
ESBL phenotype (246)	3 (1.2%)	22 (10.2%)	82 (43.5%)	94 (81.7%)	32 (94.7%)	9 (98.4%)	3 (99.6%)	1 (100%)	2	4
MDR phenotype (98)	1 (1.0%)	4 (5.1%)	37 (42.9%)	36 (79.6%)	16 (95.9%)	3 (99.0%)	0 (99.0%)	1 (100%)	2	4

R, resistant per CLSI M100 2022; ESBL, extended-spectrum β-lactamase; MDR, multidrug resistant.
[a] MIC$_{50/90}$ values were not determined due to small sample size.

References

CLSI. M07Ed11. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard: eleventh edition. Wayne, PA, Clinical and Laboratory Standards Institute, 2018.

CLSI. M100Ed32. Performance standards for antimicrobial susceptibility testing: 32st informational supplement. Wayne, PA, Clinical and Laboratory Standards Institute, 2022.

Magiorakos AP, et. al.(2012) Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin. Microbiol. Infect. 18: 268-281.10.1111/j.1469-0691.2011.03570.x

Contact

S. J. Ryan Arends, Ph,D,
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, Iowa 52317
Phone: (319) 665-3370
Fax: (319)665-3371
Email: ryan-arends@jmilabs.com