Analysis of Resistance to Oral Standard of Care Antibiotics for Urinary Tract Infections Caused by *Escherichia coli* and *Staphylococcus saprophyticus* Collected Worldwide between 2019–2020

S. J. Ryan Arends[1], D Butler[2], N Scangarella-Oman[2], L Paustian[1], JM Streit[1], RE Mendes[1]

[1] JMI Laboratories, North Liberty, Iowa, USA; [2] GlaxoSmithKline, Collegeville, PA

Introduction

- Gepotidacin (GSK2140944) is a novel triazaacenaphthylene bacterial type II topoisomerase inhibitor with a unique mechanism of action against bacterial DNA gyrase and topoisomerase IV.
- Gepotidacin is in Phase 3 clinical development for the treatment of uncomplicated urinary tract infections (uUTI) and gonorrhea.
- This study reports on the *in vitro* activity of gepotidacin and other oral antibiotics when tested against contemporary *Escherichia coli* and *Staphylococcus saprophyticus* clinical isolates collected from patients with UTIs for a gepotidacin uUTI global surveillance study as a part of the SENTRY Antimicrobial Surveillance Program.

Materials and Methods

- A total of 3,561 *E. coli* and 344 *S. saprophyticus* isolates were collected between 2019 and 2020 from 92 medical centers located in 4 regions and 25 countries, including:
  - North America (45 centers in the USA), Europe (34 centers in 17 countries), Asia-Pacific region (4 centers in Japan), and Latin America (9 centers in 6 countries).
- Most isolates (68%) tested were cultured from urine specimens collected from patients seen in ambulatory, emergency, family practice, or outpatient medical services.
- Bacterial identifications were confirmed by MALDI-TOF.
- Isolates were tested for susceptibility by CLSI reference methods at a central laboratory (JMI Laboratories).
- Susceptibility to mecillinam and fosfomycin was determined by agar dilution.
  - Fosfomycin testing included glucose-6-phosphate (25 µg/mL).
- MIC results were interpreted per CLSI guidelines.
- Extended-spectrum β-lactamase (ESBL) phenotype in *E. coli* was characterized by isolates displaying aztreonam, ceftazidime, or ceftriaxone MIC values ≥2 µg/mL.
- Multidrug resistant (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, ceftazidime, or cefepime); carbapenems (imipenem or meropenem); antipseudomonal penicillins + β-lactamase inhibitors (piperacillin-tazobactam); fluoroquinolones (ciprofloxacin or levofloxacin); aminoglycosides (gentamicin, tobramycin, or amikacin); glycylcyclines (tigecycline); and polymyxins ≥2 mg/L (colistin). Data not reported for all drugs utilized for MDR determination, however they are included as part of the SENTRY surveillance program.

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

This activity was largely unaffected among isolates demonstrating drug resistance to other oral standard of care antibiotics.

Gepotidacin also inhibited 94.3% of ESBL and 96.7% of MDR isolates at concentrations ≤4 mg/L.

Table 1 Distribution of MIC values for gepotidacin against isolate subsets with resistance to oral standard of care agents

Organism (No. 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 (3,561)	47	190	1217	1780	255	48	19	5	2	2
	1.3	6.7	40.8	90.8	98.0	99.3	99.9	100.0		
AMX-CLA-R (202)	3	12	50	95	31	4	5	2	2	4
	1.5	7.4	32.2	79.2	94.6	96.5	99.0	100.0		
AMP-R (1,914)	29	135	682	852	160	33	18	5	2	4
	1.5	8.6	44.2	88.7	97.1	98.8	99.7	100.0		
FQ-R (902)	34	100	311	338	92	16	8	3	2	4
	3.8	14.9	49.3	86.8	97.0	98.8	99.7	100.0		
FOS-R (25)	0	3	7	7	4	3	1		2	8
	0.0	12.0	40.0	68.0	84.0	96.0	100.0			
MEC-R (151)	4	8	39	78	17	3	2		2	4
	2.6	7.9	33.8	85.4	96.7	98.7	100.0			
NIT-R (46)	1	1	11	24	7	1	0	1	2	4
	2.2	4.3	28.3	80.4	95.7	97.8	97.8	100.0		
TMP-SMX-R (1,129)	19	87	420	468	91	31	9	4	2	4
	1.7	9.4	46.6	88.0	96.1	98.8	99.6	100.0		
ESBL (617)	11	49	201	246	75	20	11	4	2	4
	1.8	9.7	42.3	82.2	94.3	97.6	99.4	100.0		
MDR (209)	6	13	76	77	30	4	1	2	2	4
	2.9	9.1	45.5	82.3	96.7	98.6	99.0	100.0		

Abbreviations: R, resistant per CLSI M100 (2021); AMX-CLA, amoxicillin-clavulanate; AMP, ampicillin; FQ, fluoroquinolones; FOS, fosfomycin; MEC, mecillinam; NIT, nitrofurantoin; TMP-SMX, trimethoprim-sulfamethoxazole; ESBL, extended-spectrum β-lactamase; MDR, multidrug resistant.

Table 2 Activity of gepotidacin and comparator antimicrobial agents tested against 3,561 *Escherichia coli* isolates

Antimicrobial agent	No. of isolates[d]	mg/L			CLSI[a]		
		MIC_{50}	MIC_{90}	MIC Range	%S	%I	%R
Gepotidacin	3,561	2	2	≤0.03 to 32			
Ampicillin	3,558	>64	>64	≤1 to >64	45.6	0.6	53.8
Amoxicillin-clavulanic acid	3,556	8	16	0.5 to >32	79.6	14.8	5.7
Ciprofloxacin	3,554	0.015	>4	≤0.002 to >4	72.5	2.2	25.3
Levofloxacin	3,552	0.03	16	≤0.015 to >32	73.5	1.4	25.1
Nitrofurantoin	3,560	16	32	≤2 to >128	97.3[b]	1.4	1.3
Trimethoprim-sulfamethoxazole	3,555	≤0.12	>4	≤0.12 to >4	68.2[b]		31.8
Fosfomycin	3,560	0.5	1	≤0.12 to >256	99.0[c]	0.3	0.7
Mecillinam	3,561	0.5	4	0.03 to >32	94.1[c]	1.6	4.2

[a] Criteria as published by CLSI M100 (2021).
[b] Used only or primarily for treating UTIs.
[c] Using oral breakpoints for urinary tract infection caused by *E. coli*
[d] Not all isolates were tested against all drugs at time of publication and represents interim data

Table 3 Activity of antimicrobial agents tested against 344 *Staphylococcus saprophyticus* isolates

Antimicrobial agent	No. of isolates	mg/L			CLSI[a]		
		MIC_{50}	MIC_{90}	MIC Range	%S	%I	%R
Gepotidacin	344	0.06	0.12	≤0.03 to 0.25			
Ciprofloxacin	344	0.25	0.5	0.25 to >4	99.4	0.3	0.3
Levofloxacin	344	0.5	0.5	0.12 to >4	99.7	0.0	0.3
Nitrofurantoin	344	16	16	4 to 32	100.0	0.0	0.0
Trimethoprim-sulfamethoxazole	344	≤0.5	≤0.5	≤0.5 to >16	97.1		2.9
Penicillin	344	0.25	0.5	0.12 to >2	3.5		96.5

[a] Criteria as published by CLSI M100 (2021).

IDWEEK 2021, September 29–October 3, 2021

Results

- Gepotidacin ($MIC_{50/90}$, 2/2 mg/L) displayed good activity against 3,561 *E. coli* isolates, with 98.0% of all observed gepotidacin MICs ≤4 mg/L (Table 1).
- Susceptibility (S) rates for the other oral agents tested against these isolates were: amoxicillin-clavulanate (79.6% S), ampicillin (45.6% S), ciprofloxacin (72.5% S), fosfomycin (99.0% S), mecillinam (94.1% S), nitrofurantoin (97.3% S), and trimethoprim-sulfamethoxazole (68.2% S; Table 2).
- The percentage of *E. coli* isolates displaying an ESBL or MDR phenotype was 17.3% and 5.9% respectively (Table 1).
- Gepotidacin inhibited 94.3% of ESBL and 96.7% of MDR isolates at concentrations ≤4 mg/L (Table 1).
- When tested against the drug-resistant subsets, including ESBL and MDR subsets, gepotidacin maintained similar $MIC_{50/90}$ values (2/4 mg/L), except against isolates resistant to fosfomycin (2/8 mg/L, Table 1).
- Against *S. saprophyticus* isolates, gepotidacin ($MIC_{50/90}$, 0.06/0.12 mg/L) inhibited all isolates at ≤0.25 mg/L (Table 3).
- Most oral agents showed S results of >97% against *S. saprophyticus* isolates, except for penicillin (3.5% S; Table 3).

Acknowledgements

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 OTA Agreement No. HHSO100201300011C.

References

Clinical and Laboratory Standards Institute (2021). *M100Ed31. Performance standards for antimicrobial susceptibility testing: 29th informational supplement.* Wayne, PA: CLSI.

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

Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT and Monnet DL.(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

Please find the online version of this poster by scanning the QR code or via http://tago.ca/-IDW13 (GSK) or https://www.jmilabs.com/data/posters/IDWeek2021_RtoOralSOCforUTI.pdf (JMI).

GSK JMI