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In vitro activity of gepotidacin against urine isolates of *Escherichia coli* from outpatient departments in Germany

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Disclosures

- The authors declare the following real or perceived conflicts of interest during the last 3 years in relation to this presentation: MK is a partner and CEO of Antiinfectives Intelligence GmbH (AI), a research organisation providing services to pharmaceutical companies; EW is an employee of AI.
- This study was funded by GlaxoSmithKline plc.

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Introduction

- *Escherichia coli* is the leading causative pathogen of community-acquired urinary tract infections (UTI).[1]
- The management of UTI in the community is empiric in most cases but acquired antimicrobial resistance in *E. coli* has complicated effective treatments.[2]
- Gepotidacin (GEP), a first in class triazaacenaphthylene antibacterial targeting both bacterial DNA gyrase and topoisomerase IV by a different mechanism from fluoroquinolone (FQ) antibiotics, is currently in Phase 3 clinical development for the treatment of gonorrhoea and uncomplicated urinary tract infections (UTI) and represents a promising drug for oral treatment of acute uncomplicated UTI.[3, 4]
- The purpose of this study was to evaluate the *in vitro* activity of gepotidacin in comparison to ciprofloxacin against a collection of German *E. coli* isolates from urine.

Methods

- A total of 460 *E. coli* isolates collected at 23 laboratories during a laboratory surveillance study conducted by the Paul Ehrlich Society in 2019/20 were studied.
- Susceptibility testing was performed at a reference laboratory by the broth microdilution method according to ISO 20776-1.
- EUCAST breakpoints (v.12.0) were applied to interpret the ciprofloxacin MICs. Preliminary breakpoints for gepotidacin have not been defined yet.
- Production of extended-spectrum β-lactamases (ESBLs) was detected by broth microdilution (EUCAST) and confirmed by PCR.

- **Overall, $MIC_{50/90}$s were 2/4 mg/L for gepotidacin and 0.016/>2 mg/L for ciprofloxacin (Table 1).**
- **The gepotidacin concentrations required to inhibit 50% and 90% of the ESBL-producing and ciprofloxacin-resistant isolates were also 2 and 4 mg/L, respectively (Table 1).**

Gepotidacin showed promising *in vitro* activity against *E. coli* urine isolates, including ESBL-producing and ciprofloxacin-resistant isolates.

Table 1 MIC distributions of gepotidacin and ciprofloxacin against *E. coli* isolates from urine

Phenotype/ Drug	MIC [mg/L]															%R
	≤0.002	0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	≥32	
All (n=460)																
Gepotidacin							1	4	3	44	242	141	24	1		-[1]
Ciprofloxacin	**1**	6	46	243	50	7	9	30	15	2		*51*				11.5
ESBL-negative (n=414)																
Gepotidacin							1	2	3	39	217	129	22	1		-[1]
Ciprofloxacin	**1**	6	46	235	48	6	9	25	10	2		*26*				6.8
ESBL-positive (n=46)																
Gepotidacin								2		5	25	12	2			-[1]
Ciprofloxacin				8	2	1		5	5			*25*				54.3
Cirofloxacin (S+I; n=407)																
Gepotidacin							1	2	2	37	218	125	21	1		-[1]
Ciprofloxacin (R; n=53)																
Gepotidacin								2	1	7	24	16	3			-[1]

S+I, isolates classified as S (susceptible at standard dose) or I (susceptible at increased exposure); R, resistant isolates; %R, percentage of resistant isolates. The underlined numbers indicate the MIC50/90 values. Numbers in bold include isolates with MIC < value shown; numbers in italic include isolates with MIC > the highest concentration tested. The solid vertical lines indicate the EUCAST breakpoint defined for ciprofloxacin resistance.
[1] No EUCAST breakpoint defined.

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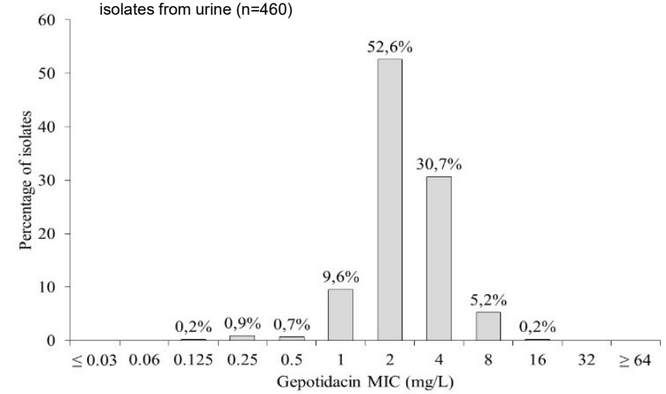
Results

- Three hundred and ninety-three (85.4%) and 67 (14.6%) isolates were obtained from female and male patients, respectively. Median (interquartile range) patients' age was 63 (45–78) years.
- Forty-six isolates (10.0%) produced an ESBL (CTX-M-type), 25 of which also produced other β-lactamases (TEM [n=12], DHA [n=1], OXA-1 [n=10], OXA-244 [n=2]). Thirty, 15 and 1 isolates were positive for CTX-M group 1, CTX-M group 9 and CTX-M group 8, respectively.
- Two isolates were AmpC producers only, with CMY and DHA. Fifty-three (11.5%) isolates were ciprofloxacin-resistant, 25 (47.2%) of which also produced an ESBL.
- Nineteen and four ESBL-producing isolates belonged to the O25b-ST131 and O16-ST131 subgroup, respectively.

Figure 1 Distribution of gepotidacin MIC values (in %) for all *Escherichia coli* isolates from urine (n=460)



- Unimodal frequency distribution of gepotidacin MIC values (all *E. coli* isolates, n=460). MICs ranged from 0.125 – 16 mg/L with a mode of 2 mg/L.

Conclusions

- Gepotidacin showed promising *in vitro* activity against *E. coli* isolates from urine, including ESBL-producing and ciprofloxacin-resistant isolates.

References

1. Stamm WE et al., J Infect Dis. 2001;183 (Suppl 1)
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4. ClinicalTrials.gov Identifiers: NCT04020341 and NCT04187144

Disclosures

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This study was funded by GlaxoSmithKline plc.

Background and Methods

- Gepotidacin (GEP): Gepotidacin is a novel, first-in-class triazaacenaphthylene antibiotic
  - 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
  - In Phase 3 clinical development: treatment of *Neisseria gonorrhoeae* and uncomplicated urinary tract infections (UTI)

- E. coli isolates (n=460)
  - Collected at 23 laboratories during a laboratory surveillance study conducted by the Paul Ehrlich Society in 2019/20
  - Susceptibility testing: broth microdilution method (ISO 20776-1)
  - MIC interpretation of ciprofloxacin: EUCAST breakpoints (v.12.0)
  - MIC interpretation of gepotidacin: No MIC breakpoints or interpretive criteria are currently available

- Characterization of isolates with production of extended-spectrum β-lactamases (ESBLs)
  - Identified via broth microdilution (EUCAST)
  - Confirmed by PCR detection of β-lactamase genes encoding TEM, SHV, CTX-M, DHA, CMY, OXA-48, VIM, KPC
  - PCR-based determination of sequence type subgroups ST131-O25b and ST131-O16 (Johnson et al. 2014, J Clin Microbiol;52(5):1358-65)

Results and Conclusions

Table 1: MIC distributions of gepotidacin and ciprofloxacin against *E. coli* isolates from urine

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Isolate population/source

Median (IQR) patients' age: 63 (45–78) years

- female (n=393; 85.4%)
- male (n=67: 14.6%)

Results

- $MIC_{50/90}$ gepotidacin: **2/4 mg/L**
- $MIC_{50/90}$ ciprofloxacin: **0.016/>2 mg/L**
  - ESBL-producers: **>2 mg/L**
- $MIC_{50/90}$ gepotidacin in challenging isolates:
  - ESBL-producers: **2/4 mg/L**
  - $Ciprofloxacin^R$ isolates: **2/4 mg/L**

Promising *in vitro* activity of gepotidacin against *E. coli* isolates from urine, including ESBL-producing and ciprofloxacin-resistant isolates