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Epidemiology of *Escherichia coli* Surveillance Isolates Causing Urinary Tract Infections in Europe and *In Vitro* Activity of Gepotidacin (2019-2020)

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Introduction and Methods

- Gepotidacin is a novel, 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.
- This study evaluated the epidemiology of *E. coli* causing UTI in patients seen in Europe and the activity of gepotidacin and comparators against subsets of *E. coli*, including those with characterized β-lactam resistance mechanisms, as part of the gepotidacin global surveillance study.
- 1,143 *E. coli* were collected from 34 medical centres in Europe, Russia, Turkey and the UK.
- Susceptibility testing followed CLSI broth microdilution methods, except that fosfomycin (with glucose-6-phosphate) and mecillinam were tested by agar dilution in a central laboratory (JMI Laboratories).
- MIC results for all comparator agents were interpreted per EUCAST guidelines, except amoxicillin-clavulanic acid which was interpreted according to CLSI breakpoints.
- Isolates displaying aztreonam, ceftazidime, or ceftriaxone MIC values ≥2 mg/L were subjected to genome sequencing and *in silico* screening of β-lactamase encoding genes, including extended-spectrum β-lactamases (ESBL), oxacillinases and carbapenemases.
- Isolates that met the MIC criteria for screening of β-lactamase were also subjected to epidemiology typing by multilocus sequence typing (MLST), O:H serotyping and *fimH* typing.

Activity of gepotidacin against UTI isolates by genotype

Table 1 Activity of gepotidacin and comparator agents against various genetic subsets of *E. coli* causing UTI

Organism/group (no. of isolates)	Gepotidacin MIC$_{50/90}$	Gepotidacin %S	A/C MIC$_{50/90}$	A/C %S	Ciprofloxacin MIC$_{50/90}$	Ciprofloxacin %S	Nitrofurantoin MIC$_{50/90}$	Nitrofurantoin %S	Fosfomycin MIC$_{50/90}$	Fosfomycin %S	Mecillinam MIC$_{50/90}$	Mecillinam %S	T/S MIC$_{50/90}$	T/S %S
E. coli (1,143)														
Non-ESBL (962)	2/2	—	4/16	83.7	0.015/>4	84.0	16/32	99.2	0.5/1	97.7	0.5/4	93.3	≤0.12/>4	75.9
ESBL[a] (181)	2/4	—	16/32	49.7	>4/>4	27.1	16/32	97.2	0.5/2	93.9	1/4	96.1	>4/>4	39.2
CTX-M[a] (155)	2/4	—	8/16	56.8	>4/>4	21.3	16/32	96.8	0.5/2	93.5	1/4	96.8	>4/>4	36.1
ST131[b] (88)	2/4	—	16/32	44.3	>4/>4	4.5	16/32	94.3	0.5/2	92.0	0.5/2	100	>4/>4	42.0
O25:H4/*H*30[c] (75)	2/4	—	16/32	42.7	>4/>4	0.0	16/32	96.0	0.5/2	93.3	0.5/2	100	>4/>4	40.0
Non-ST131[d] (93)	2/8	—	8/>32	54.8	0.5/>4	48.4	16/32	100	0.5/1	95.7	1/8	92.5	>4/>4	36.6

ESBL, extended spectrum-β-lactamase; A/C, amoxicillin-clavulanate (2:1); T/S, trimethoprim-sulfamethoxazole; EUCAST breakpoints applied, except for amoxicillin-clavulanate (i.e., CLSI); "—" breakpoint not available.

[a] Includes 155 *bla*$_{CTX-M}$, 7 *bla*$_{CMY}$, 6 *bla*$_{DHA-1}$, 2 *bla*$_{OXA-48}$-like, 2 *bla*$_{SHV-12}$, 1 *bla*$_{TEM-52}$, 6 with overexpression of AmpC, and 2 with negative β-lactamase results. *bla*$_{CTX-M}$ includes 94 *bla*$_{CTX-M-15}$, 34 *bla*$_{CTX-M-27}$, 10 *bla*$_{CTX-M-14}$, and 17 isolates each with a distinct *bla*$_{CTX-M}$ allele.

[b] Includes 87 ST131 and 1 single locus variant ST2279. O antigens detected were: O25b (79 isolates), O16 (6), and O non-typeable (3).

[c] Includes 75 O25b:H4 (*fimH*30), which carried 51 *bla*$_{CTX-M-15}$, 23 *bla*$_{CTX-M-27}$, 1 *bla*$_{DHA-1}$.

[d] 35 ST types.

- An ESBL phenotype was noted in 15.8% (181/1,143) of *E. coli.*
  - ESBL rates within Eastern- and Western-European countries of 29.2% (n=62) and 12.8% (n=119), respectively.
  - Most ESBL isolates carried CTX-M alleles (85.6%; 155/181) with a small number (7.2%; 13/181) carrying plasmid AmpC genes.
  - Two isolates from Turkey carried *bla*$_{OXA-48}$ or *bla*$_{OXA-244}$.
  - 48.6% (88/181) of ESBL isolates belonged to clonal complex 131 (87 ST131 and 1 ST2279), of which 88.6% (78/88) were O25b:H4 and 75 carried *fimH*30 (68.0% *bla*$_{CTX-M-15}$).
  - Other O:H serotypes comprised 8 strains or less, including O75:H5 (4.4%; 8/181) and O16:H5 (3.3%; 6/181).
  - Gepotidacin had MIC$_{50}$ and MIC$_{90}$ values of 2–4 mg/L against non-ESBL, ESBL and other *E. coli* subsets, except against non-ST131 (MIC$_{90}$, 8 mg/L).
  - Nitrofurantoin, mecillinam and fosfomycin showed susceptibility ≥92% against all subsets, whereas other oral agents had compromised activity (≤84% susceptible).
  - For the ESBL subset, %S ranges between 39% - 50% for T/S, ciprofloxacin, and A/C and >/=94% for fosfomycin, mecillinam, and nitrofurantoin.

Conclusions

- Gepotidacin demonstrated potent activity against non-ESBL and ESBL, and various characterized *E. coli* subsets, including the resistant ST131 O25(b):H4 clone.
- These data support the clinical development of gepotidacin as a treatment option for UTI caused by *E. coli* including when other oral treatment options are limited due to resistance.

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