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Activity of Tebipenem against *Escherichia coli* collected from Urinary Tract Infections in Europe in 2020

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Background

- *Escherichia coli* is frequently implicated in urinary tract infections (UTI) where increasing antibiotic resistance threatens empiric utility of oral agents such as the cephalosporins, fluoroquinolones and trimethoprim-sulfamethoxazole (TMP-SMX).[1,2]
- The increase in antibiotic resistance to oral agents makes the management of UTIs increasingly difficult outside the hospital setting that may result in hospitalization of otherwise healthy patients.[2-4]
- UTIs caused by extended-spectrum β-lactamase (ESBL)-producing *E. coli* are increasingly problematic to treat as they exhibit high-levels of co-resistance to fluoroquinolones and TMP-SMX.[1,2]
- The most prevalent ESBL's include CTX-M variants, which are present in strains of clonal complex ST131 that are important causes of both community-onset and nosocomial UTIs.[5]
- The goals of the study were to assess the prevalence of antibiotic resistance among UTI isolates of *E. coli* collected from patients with from UTIs in Europe during 2020 as part of the STEWARD Surveillance Program and evaluate the activity of tebipenem, an oral carbapenem, and comparator agents against *E. coli* from UTIs, including organisms that are resistant to currently available oral agents.

Methods

- In total, 764 isolates of *E. coli* were collected from UTI patients in 18 countries in Europe during 2020 as part of the STEWARD Surveillance Program.
- All isolates were shipped to a central laboratory (JMI Laboratories, North Liberty, IA, USA) for identification confirmation, antimicrobial susceptibility testing by broth microdilution in accordance with CLSI guidelines and susceptibility results were interpreted using EUCAST criteria[6] (No interpretive criteria are yet available for tebipenem).
- All *E. coli* isolates that showed an ESBL phenotype based on CLSI criteria were sequenced to identify β-lactamase genes and characterized by multi-locus sequence typing (MLST).
- The activity of tebipenem and comparators were assessed against different phenotypes and genotypes of *E. coli*.

Results

Figure 1. Prevalence of ESBL Phenotypes of UTI *E. coli* by Country

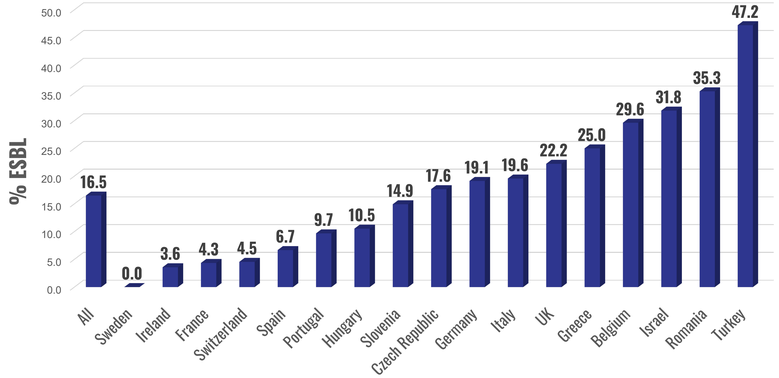


Table 1. Activity of Tebipenem and Comparators Against Resistant Phenotypes and Genotypes of *E. coli* from UTI's in Europe in 2020

Phenotype/ Genotype (N,%)	Agent	MIC (mg/L)			EUCAST		
		Range	50%	90%	S	I	R
All (764, 100%)	Tebipenem	≤0.004 - 0.5	0.015	0.015	NA	NA	NA
	Ertapenem	≤0.004 - >2	≤0.008	0.03	99.9		0.1
	Meropenem	≤0.015 - 0.5	≤0.015	0.03	100	0	0
	Mecillinam	≤0.06 - >8	0.5	>8	88		12
	Levofloxacin	≤0.015 - >32	0.03	16	77.3	2.1	20.6
	TMP-SMX	≤0.12 - >4	≤0.12	>4	69.3	0.5	30.1
ESBL (126, 16.5%)	Tebipenem	0.008 - 0.5	0.015	0.03	NA	NA	NA
	Ertapenem	≤0.008 - >2	0.03	0.12	99.2		0.8
	Meropenem	≤0.015 - 0.5	0.03	0.03	100	0	0
	Mecillinam	0.12 - >8	1	>8	87.3		12.7
	Levofloxacin	≤0.015 - >32	8	16	31.7	4.8	63.5
	TMP-SMX	≤0.12 - >4	>4	>4	39.7	0	60.3
Levofloxacin-Resistant (157, 20.6%)	Tebipenem	0.008 - 0.5	0.015	0.03	NA	NA	NA
	Ertapenem	≤0.008 - >2	0.015	0.06	99.4		0.6
	Meropenem	≤0.015 - 0.5	≤0.015	0.03	100	0	0
	Mecillinam	≤0.06 - >8	1	>8	87.9		12.1
	Levofloxacin	2 - >32	8	32	0	0	100
	TMP-SMX	≤0.12 - >4	>4	>4	38.1	0	61.8
TMP-SMX-Resistant (234, 30.1%)	Tebipenem	≤0.004 - 0.25	0.015	0.015	NA	NA	NA
	Ertapenem	≤0.008 - 0.5	≤0.008	0.03	100		0
	Meropenem	≤0.015 - 0.25	≤0.015	0.03	100	0	0
	Mecillinam	≤0.06 - >8	2	>8	80.8		19.1
	Levofloxacin	≤0.015 - >32	0.5	16	54.7	3.8	41.5
	TMP-SMX	4 - >4	>4	>4	0	0	100
(MDR) ESBL, Levofloxacin-Resistant, and TMP-SMX-Resistant (53, 6.9%)	Tebipenem	0.008 - 0.25	0.015	0.03	NA	NA	NA
	Ertapenem	≤0.008 - 0.5	0.03	0.25	100		0
	Meropenem	≤0.015 - 0.25	0.03	0.03	100	0	0
	Mecillinam	0.12 - >8	1	>8	88.7		11.3
	Levofloxacin	2 - >32	16	32	0	0	100
	TMP-SMX	>4	>4	>4	0	0	100
E. coli ST131 (169, 22.1%)	Tebipenem	0.008 - 2	0.015	0.03			
	Ertapenem	≤0.008 - >2	0.03	0.12	98.2		1.8
	Meropenem	≤0.015 - 4	0.03	0.03	99.4		0.6
	Mecillinam	0.12 - >8	1	8	91.1		8.9
	Levofloxacin	0.06 - >32	16	32	7.7		91.7
	TMP-SMX	≤0.12 - >4	>4	>4	42		58
E. coli CTX-M-15 alone and in combination (174, 22.8%)	Tebipenem	0.008 - 0.5	0.015	0.03			
	Ertapenem	≤0.008 - >2	0.03	0.12	97.7		2.3
	Meropenem	≤0.015 - 1	0.03	0.03	100		0
	Mecillinam	0.25 - >8	1	>8	89.1		10.9
	Levofloxacin	0.03 - >32	16	32	24.7		75.3
	TMP-SMX	≤0.12 - >4	>4	>4	43.1		56.9

Figure 2. Prevalence of Levofloxacin-Resistant Phenotypes of UTI *E. coli* by Country

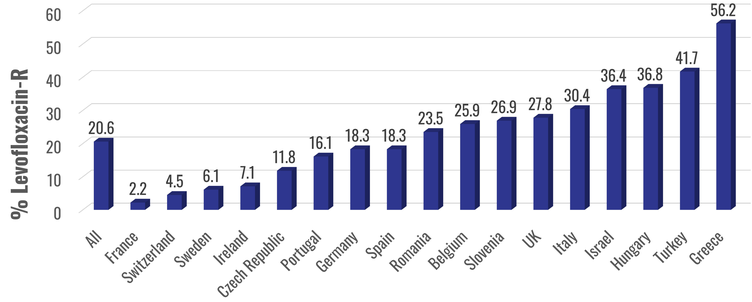
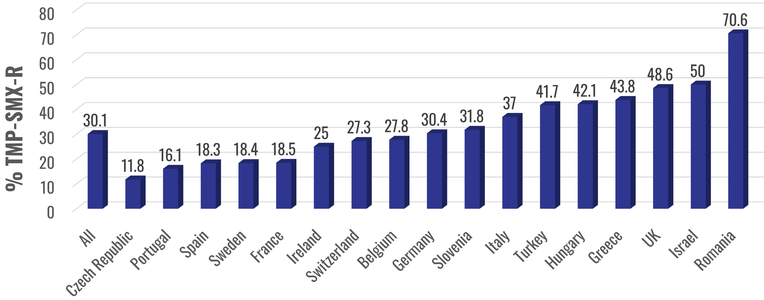


Figure 3. Prevalence of Trimethoprim-sulfamethoxazole-resistant phenotypes of UTI *E. coli* by Country



Conclusions

- Prevalence of ESBL, levofloxacin-resistance and TMP-SMX-resistance were 16.5%, 20.6% and 30.1%, respectively.
- Among ESBL phenotypes of *E. coli*, high co-resistance: >60% to levofloxacin and TMP-SMX were observed.
- Among all *E. coli*, the MIC_{90} values for tebipenem, ertapenem and meropenem were 0.015, 0.03 and 0.03 mg/L, respectively and >99.9% if isolates were susceptible to ertapenem and meropenem.
- The MIC_{90} values for tebipenem ranged from 0.015 to 0.03 mg/L against all resistant subsets including ESBL, levofloxacin-resistant, TMP-SMX-resistant, MDR, *E. coli* ST-131 including isolates with $bla_{CTX\text{-}M\text{-}15}$ alone and in combination.
- Activity of tebipenem is similar to intravenous carbapenems against UTI isolates of *E. coli* that includes ESBL phenotypes that exhibit high co-resistance to oral agents such as levofloxacin and TMP-SMX.

References

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