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Resistance to Oral Antibiotics among Urinary Tract Infection Isolates of *Escherichia coli* from the United States and Europe in 2017

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ABSTRACT

Background: Clinical guidelines have recommended oral antibiotics such as the cephalosporins, fluoroquinolones, and trimethoprim-sulfamethoxazole (TMP-SMX) for the treatment of urinary tract infections (UTIs) caused by *Escherichia coli* (EC). The utility of these agents continues to be eroded by the increased prevalence of expanded spectrum β-lactamase (ESBL) genes and concomitant resistance determinants to other antimicrobial classes. This study assessed the prevalence of ESBL phenotypes among EC from UTIs in the US and Europe (EU) in 2017 and the impact of co-resistance to oral agents used to treat UTIs

Methods: 2422 unique EC from UTIs in the US and EU in the SENTRY Surveillance program were evaluated for susceptibility to various agents. All isolates were consecutively collected and centrally tested by CLSI methods and interpretive criteria were determined using both CLSI and EUCAST breakpoints. Isolates that met ESBL MIC screening criteria were characterized for the presence of β-lactamase genes.

Results: Among the 2422 isolates of EC from UTIs in the US and EU the resistance (R) rates for cefuroxime (CEF), levofloxacin (LEV) and TMP-SMX were 17.9%, 25.6% and 33.2%, respectively. The overall presence of ESBL phenotypes was 18.2% (18.7% in the US and 21.0% in EU). Among the 411 ESBL phenotypes, R to CEF, LEV and TMP-SMX were 94.3%, 70.6% and 61.6%, respectively. In contrast <0.1% of all EC or 0.2% of ESBL EC were meropenem (MER)-R. Only two carbapenemase-producing organisms were identified, an NDM-5 and a KPC-2-producing EC from Turkey and Greece, respectively. The CTX-M-15 was the most prevalent ESBL and identified among 167 isolates; with co-resistance to CEF, LEV and TMP-SMX noted in 100%, 82.6% and 70.7%, respectively. All CTX-M-15 isolates were susceptible to MER.

Conclusions: Oral agents such as CEF, LEV and TMP-SMX exhibit R rates ≥ 17.9%. Co-resistance to CEF, LEV and TMP-SMX were considerable higher among ESBL phenotypes (>61.6%) and confirmed $bla_{CTX\text{-}M\text{-}15}$ genotypes (70.7%). In contrast, the carbapenems remained active against ESBL phenotypes and genotypes, such as $bla_{CTX\text{-}M\text{-}15}$. New oral agents with the spectrum and potency of the carbapenems would address and unmet need to new options to treat multi-drug-resistant EC UTIs.

INTRODUCTION

Escherichia coli is the most prevalent pathogen associated with urinary tract infections (UTIs). Oral antibiotics including the cephalosporins, fluoroquinolones and trimethoprim sulfamethoxazole (TMP-SMX) have been historically used to manage UTIs but in recent years their utility has been eroded by the increasing prevalence of extended spectrum β-lactamase (ESBL)-producing organisms where extensive co-resistance has been reported. The management of UTIs caused by ESBL-producing *E. coli* is challenging due to limited oral treatment options being available outside the hospital setting. The carbapenem antibiotics are one of the few classes that have retained activity because of their stability to ESBL and Class C β-lactamases that are prevalent among Gram-negative uropathogens. Unfortunately, no oral options with the spectrum and potency of the carbapenems are currently available. The goal of the current study was to assess the susceptibility of UTI isolates of *E. coli* collected in the United States and Europe during 2017 to various antibiotics, including oral agents widely used to treat UTIs to assess rates of resistance in both continents. The prevalence of ESBL phenotypes among *E. coli* will also be assessed to determine the impact of co-resistance to oral antibiotics.

METHODS

E. coli from UTIs were collected as part of the SENTRY Surveillance Program (JMI Laboratories, North Liberty, IA) from participating medical centers geographically distributed across the nine US Census regions and from 11 countries in Europe. All isolates were centrally tested for susceptibility and the results were interpreted in accordance with CLSI and EUCAST criteria. All ESBL phenotypes were defined by CLSI criteria and were used to select isolates for follow up molecular characterization to confirm the presence of specific β-lactamase genes such as the CTX-M-15 ESBL. Molecular analyses were conducted using next generation sequencing (NGS). Susceptibility results for all UTI isolates including ESBL phenotypes, FQ-resistant, TMP-SMX-resistant phenotypes and CTX-M-15 genotypes were determined using the publicly available SENTRY Antimicrobial Surveillance online query tool (www.sentry-mvp.jmilabs/app/sentry-public).

RESULTS

Table 1: Susceptibility Results for 2,422 UTI isolates of *E. coli* collected in the US and EU in 2017 in the SENTRY Surveillance program

Antimicrobial Agent	MIC (µg/mL)			CLSI[a]			EUCAST[a]		
	Range	50%	90%	%S	%I	%R	%S	%I	%R
Ciprofloxacin	≤0.03 to >4	≤0.03	>4	70.3	1.6	28.1	70.3	1.6	28.1
Levofloxacin	≤0.03 to >16	≤0.03	16	71.7	0.9	27.4	71.7	0.9	27.4
Trimethoprim-sulfamethoxazole	≤0.5 to >8	≤0.5	>8	66.8		33.2	66.8	0.6	32.6
Amoxicillin-clavulanic acid	0.5 to >32	8	16	74.9	17.2	7.8	74.9		25.1 [b]
							97.7		2.3 [c]
Cefuroxime	≤0.12 to >64	4	>64	61.4	20.7	17.9 [d]	77.7		22.3 [e]
				77.7	4.4	17.9 [f]	77.7		22.3 [f]
Doripenem	≤0.06 to >8	≤0.06	≤0.06	>99.9	0	<0.1	>99.9	0	<0.1
Ertapenem	≤0.008 to >2	≤0.008	0.03	99.5	0.2	0.3	99.5		0.5
Imipenem	≤0.12 to >8	≤0.12	0.25	99.9	0	0.1	99.9	<0.1	<0.1
Meropenem	≤0.015 to >32	≤0.015	0.03	>99.9	0	<0.1	>99.9	0	<0.1
Amikacin	1 to >32	2	8	99.7	0.2	0.1	98.3	1.4	0.3
Piperacillin-tazobactam	≤0.06 to >128	2	8	96.7	1.9	1.4	94.3	2.4	3.3
Ampicillin-sulbactam	≤0.5 to >64	8	64	52.5	16.3	31.2	52.5		47.5
Cefepime	≤0.12 to >16	≤0.12	8	87.6	2.8	9.6 [g]	85.8	3.1	11.1
Ceftazidime	0.03 to >32	0.25	8	88.6	2.4	9	84.4	4.2	11.4

a. Criteria as published by CLSI [2019] and EUCAST [2019]
b. Using other than uncomplicated UTI breakpoints
c. Using uncomplicated UTI only breakpoints
d. Using oral breakpoints
e. Using oral, uncomplicated UTI only breakpoints
f. Using parenteral breakpoints
g. Intermediate interpreted as susceptible-dose dependent

Table 2: Co-resistance among TMP-SMX-R and levofloxacin-R *E. coli* from UTI's in US and EU

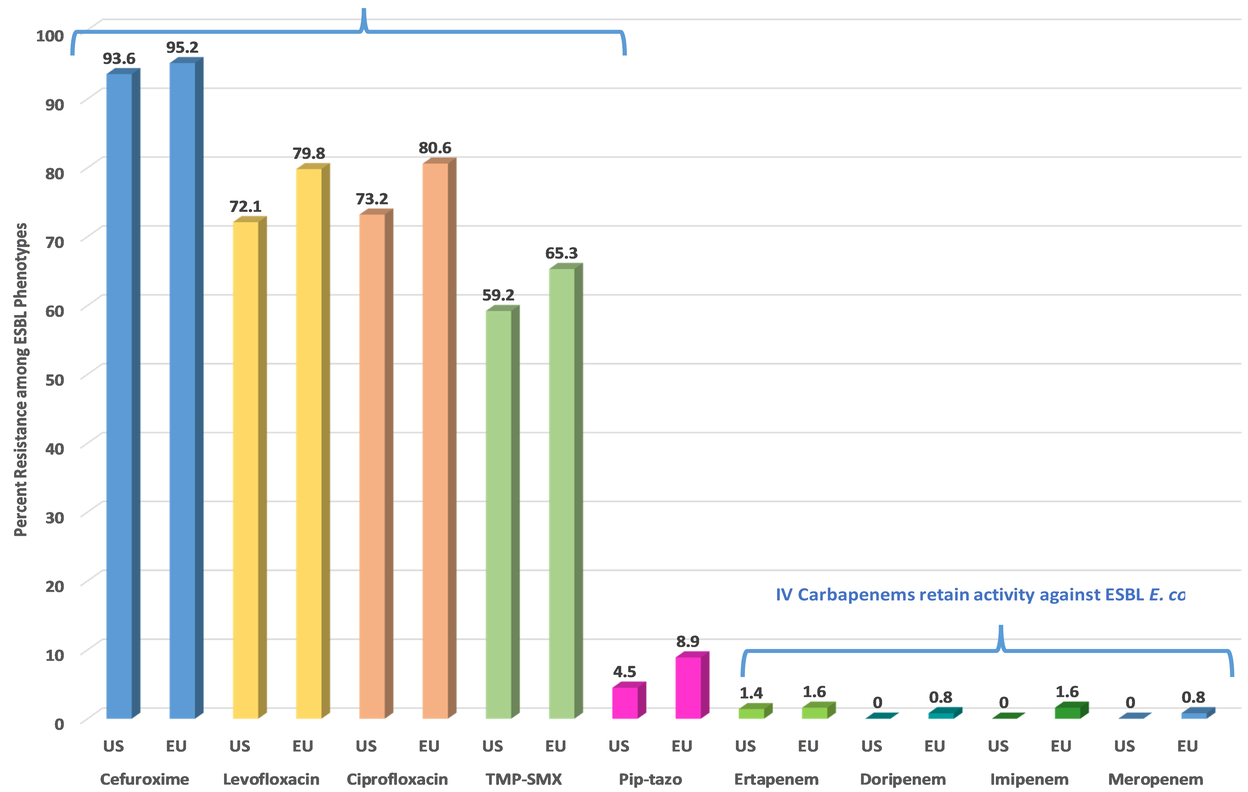
Agent	TMP-SMX-R *E. coli* (N = 805)	LEVO-R *E. coli* (N = 663)
Cefuroxime	34.3	49.5
Ceftazidime	15.9	24.9
Ciprofloxacin	48.9	100
Levofloxacin	48.0	100
Doripenem	0.0	0.2
Ertapenem	0.2	0.5
Imipenem	0.0	0.2
Meropenem	0.0	0.2
TMP-SMX	100	58.2

Table 3: Susceptibility Results for 167 CTX-M-15 β-lactamase-positive *E. coli* from UTIs in the US and EU during 2017

Antimicrobial Agent	MIC (µg/mL)			CLSI[a]			EUCAST[a]		
	Range	MIC_{50}	MIC_{90}	%S	%I	%R	%S	%I	%R
Cefuroxime	>64	>64	>64	0	0	100.0 [b]	0		100.0 [b]
				0	0	100.0 [c]	0		100.0 [c]
Ceftazidime	1 to >32	16	>32	16.2	13.8	70.1	1.2	15	83.8
Ciprofloxacin	≤0.03 to >4	>4	>4	9.6	3	87.4	9.6	3	87.4
Levofloxacin	≤0.03 to >16	16	>16	13.2	1.2	85.6	13.2	1.2	85.6
Trimethoprim-sulfamethoxazole	≤0.5 to >8	>8	>8	29.3		70.7	29.3	0.6	70.1
Doripenem	≤0.06 to 0.5	≤0.06	≤0.06	100	0	0	100	0	0
Ertapenem	≤0.008 to 1	0.03	0.25	97.7	2.3	0	97.7		2.3
Imipenem	≤0.12 to 0.5	≤0.12	≤0.12	100	0	0	100	0	0
Meropenem	≤0.015 to 0.5	0.03	0.06	100	0	0	100	0	0

[a] Criteria as published by CLSI [2019] and EUCAST [2019] [b] Using oral breakpoints [c] Using parenteral breakpoints

Figure 1: Antibiotic Resistance Rates among 411 ESBL Phenotypes of UTI Isolates of *E. coli* collected in the US and EU in 2017 (SENTRY Surveillance Program)



CONCLUSIONS

- Among the 2422 UTI isolates of *E. coli* resistance to FQs were 28.1% and 27.4%, respectively, for ciprofloxacin and levofloxacin. Using oral breakpoints 38.6% of *E. coli* were non-susceptible to cefuroxime and 33.2% of isolates were resistant to TMP-SMX (Table 1). 16.5% (400 isolates) were R to both levofloxacin and TMP-SMX.

- Overall prevalence of ESBL phenotypes among *E. coli* was 18.2% (18.7% in the US and 21.0% in the EU).

- Among the 411 ESBL phenotypes, R to cefuroxime, levofloxacin and TMP-SMX were 94.3%, 70.6% and 61.6%, respectively. Resistance to oral antibiotics were similar, regardless of continent (Figure 1) but trended slightly higher for isolates from the EU compared with US. Intravenous carbapenems were highly active against ESBL isolates of *E. coli* from both the US and EU. Only two carbapenem-resistant *E. coli* were identified in the EU; an NDM-5 β-lactamase-producing organism from Turkey and a KPC-2 producing organism from Greece.

- Levofloxacin-resistant *E. coli* exhibited high co-resistance to cefuroxime (49.5%) and TMP-SMX (58.2%). TMP-SMX *E. coli* exhibited high co-resistance to FQs such as levofloxacin (48.0%) and cefuroxime (34.3%). In contrast, all levofloxacin-R and TMP-SMX-R *E. coli* exhibited low or no co-resistance to the carbapenems (Table 2).

- CTX-M-15 ESBL genotypes were the most prevalent ESBL's and were identified among 167 *E. coli*. Among the CTX-M-15 genotypes FQ-R was 85.6% for levofloxacin and R to TMP-SMX was 70.7% (Table 3).

- The carbapenems retained activity with high susceptibility rates against UTI isolates of *E. coli* from both the US and EU including resistant phenotypes and conformed genotypes.

- New oral agents with the spectrum and potency of the intravenous carbapenems would address a substantial unmet need for new agents to treat UTIs caused by multi-drug-resistant ESBL-producing *E. coli*.