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Susceptibility to Alternative Oral Antimicrobial Agents in Relation to Sequence Type ST131 Status and Coresistance Phenotype among Recent *Escherichia coli* Isolates from U.S. Veterans

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The rising prevalence of resistance to first-line antimicrobial agents in *Escherichia coli*, which has paralleled the emergence of *E. coli* sequence type ST131, has created a need for alternative oral options for use in treating outpatients with infections such as cystitis and chronic prostatitis. Accordingly, we determined susceptibility to six alternative oral agents (azithromycin, chloramphenicol, doxycycline, fosfomycin, minocycline, and rifampin) by Etest or disk diffusion for 120 recently obtained *E. coli* clinical isolates from Veterans Affairs Medical Centers across the United States. Isolates were randomly selected in three subgroups of 40 isolates each based on coresistance to fluoroquinolones with and without extended-spectrum cephalosporins (ESCs). Results were stratified according to trimethoprim-sulfamethoxazole (TMP-SMZ) phenotype. Overall, the prevalence of susceptible (or susceptible plus intermediate) isolates varied by agent, with rifampin being lowest (0%), fosfomycin highest (98 to 99%), and others in the mid-range (37 to 88%). Substantial proportions of isolates (15 to 27%) yielded intermediate results for azithromycin, chloramphenicol, doxycycline, and minocycline. Among isolates resistant (versus susceptible) to fluoroquinolones with or without ESCs, susceptibility to the above four agents declined significantly among non-ST131 isolates but not ST131 isolates. In contrast, in the presence of resistance to TMP-SMZ, susceptibility to azithromycin, doxycycline, and minocycline was significantly reduced among both ST131 and non-ST131 isolates. These findings identify potential alternative oral agents for use with *E. coli* isolates resistant to fluoroquinolones, ESCs, and/or TMP-SMZ and suggest that determination of ST131 status could help guide initial antimicrobial selection, pending susceptibility results.

The rising prevalence of antimicrobial resistance among *Escherichia coli* clinical isolates, which reflects largely the widespread emergence of *E. coli* sequence type ST131 (1, 2), increasingly complicates the management of *E. coli* urinary tract infections (UTIs), sometimes necessitating the use of parenteral therapy for ambulatory patients in whom oral therapy should suffice (3). Identification of alternative oral agents active against *E. coli* strains resistant to trimethoprim-sulfamethoxazole (TMP-SMZ), fluoroquinolones, and extended-spectrum cephalosporins (ESCs) is needed, especially if nitrofurantoin is contraindicated or unsuitable (3, 4).

Additionally, a growing number of patients have intractable recurrent same-strain UTI episodes caused by multidrug-resistant *E. coli*, typically *E. coli* ST131 (5). Each episode usually resolves with appropriate antimicrobial therapy but is followed within days to weeks by a repeat episode. This pattern suggests the presence of a persisting internal focus of the causative strain, possibly within the prostate gland (especially after transrectal prostate biopsy) (6) or within uroepithelial cells (possibly as intracellular bacterial communities) (7). To eradicate such persisting foci, antimicrobial agents that achieve adequate intraprostatic or intracellular concentrations might offer an advantage over conventional agents that penetrate poorly into such sites (7, 8).

Accordingly, for a panel of systematically selected recent ST131 and non-ST131 *E. coli* clinical isolates from Veterans Affairs medical centers (VAMCs) across the U.S., we determined the *in vitro* susceptibility to six oral antimicrobial agents with enhanced tissue or intracellular penetration, including azithromycin, chloramphenicol, doxycycline, fosfomycin, minocycline, and rifampin (Table 1) (8, 9). These agents can be considered alternative agents for UTI management, since susceptibility of *E. coli* isolates to these agents is not routinely tested or reported by clinical microbiology laboratories, and several (e.g., azithromycin) lack a Food and Drug Administration indication for treatment of UTI or *E. coli* infections.

MATERIALS AND METHODS

Isolates. The 120 study isolates were selected systematically from a 595-member parent collection of *E. coli* clinical isolates from 2011 from 24 VAMCs distributed broadly across the United States, including from states in the West (Idaho, Utah, Colorado, Washington, and California), Midwest (Wisconsin, Michigan, Indiana, Ohio, Missouri, Minnesota, and Iowa), South (District of Columbia, Mississippi, Florida, Tennessee, and Texas), and Northeast (Massachusetts and New York) (10). For the parent collection, each participating VAMC provided 10 recent deidentified fluoroquinolone-resistant and fluoroquinolone-susceptible extraintestinal *E. coli* isolates (chosen without regard for specimen type, patient location, patient characteristics, or coresistance) from 2011, plus up to 10 deidentified, extended-spectrum-beta-lactamase-producing *E. coli* isolates (as available) from 2010-2011. Results of standardized susceptibility testing from the source laboratories were submitted with the isolates. In the research laboratory, isolates were screened for ST131 status using PCR-based detection of ST131-specific polymorphisms in *gyrB* and *mdh* (11).

For the present study, 120 total isolates were selected from the parent

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TABLE 1 Selected pharmacokinetic properties of alternative antimicrobial agents

Antimicrobial agent or class	Vol of distribution (liters/kg)[a]	Intracellular concn/ extracellular concn[b]	% excreted unchanged in urine[a]
Azithromycin	18	40–300	6–12
Chloramphenicol	0.5–1.0	13	10
Fosfomycin	0.3[c]	No data	30–60[d]
Rifampin	0.9	2–10	15–30
Tetracyclines	Varies by agent	1–4	Varies by agent
Doxycycline	0.8	No data	35–45
Minocycline	1.0–1.5	No data	6–10

[a] Data from reference 13.
[b] Data from reference 17.
[c] Data from reference 18.
[d] Data from reference 9.

TABLE 2 Susceptibility profiles of 120 *Escherichia coli* clinical isolates in relation to fluoroquinolone and extended-spectrum-cephalosporin resistance group[a]

Antimicrobial agent or class	No. (%) of isolates susceptible to agent or class within resistance group ($n = 40$)[b]		
	FQ-S, ESC-S	FQ-R, ESC-S	FQ-R, ESC-R
Ampicillin	20 (50)	5 (12)	0 (0)
Ampicillin-sulbactam	26 (65)	13 (23)	0 (0)
Cefazolin	34 (85)	29 (12)	0 (0)
Gentamicin	34 (85)	27 (67)	20 (50)
Nitrofurantoin	38 (95)	37 (92)	28 (70)[c]
Trimethoprim-sulfamethoxazole	28 (70)	22 (55)	8 (20)

[a] All isolates were susceptible to carbapenems (based on reported ertapenem, imipenem, or meropenem result).
[b] FQ-S and FQ-R, fluoroquinolone susceptible and resistant; ESC-S and ESC-R, extended-spectrum-cephalosporin susceptible and resistant.
[c] For nitrofurantoin susceptibility among FQ-R, ESC-R ST131 isolates (20/20, 100%) versus non-ST131 isolates (8/20, 40%), $P < 0.001$ (Fisher's exact test). All other comparisons (ST131 versus non-ST131) yielded P values of >0.10.

collection, 20 per category for six different categories. Categories were defined based on a combination of ST131 status and reported phenotype for fluoroquinolones (represented by ciprofloxacin) and ESCs (represented by ceftriaxone). Specifically, 20 ST131 and 20 non-ST131 isolates (total of 40 per resistance category) were selected randomly, using a random number list, for each of three combined resistance categories: (i) susceptible to fluoroquinolones and ESCs, (ii) resistant to fluoroquinolones but susceptible to ESCs, and (iii) resistant to both fluoroquinolones and ESCs. The only exception involved ST131 isolates susceptible to fluoroquinolones and ESCs, of which only 14 isolates were available within the parent collection. Accordingly, an additional 6 such isolates were obtained from the Minneapolis VAMC clinical microbiology laboratory, selected randomly from a larger collection of this laboratory's *E. coli* isolates from 2011. Resistance phenotypes were confirmed selectively by disk diffusion, using methods, reference strains, and interpretive criteria as specified by the Clinical and Laboratory Standards Institute (CLSI) (12).

Susceptibility testing for alternative agents. Isolates underwent standardized testing for susceptibility to azithromycin, chloramphenicol, doxycycline, fosfomycin, minocycline, and rifampin, using either gradient elution (Etest strips; bioMérieux) for MIC determination or, if Etest strips were unavailable, disk diffusion. Methods, reference strains, and interpretive criteria (if available) were as specified by the manufacturer (for Etest) or CLSI (for disk diffusion) (12). For rifampin, interpretive criteria for *Haemophilus influenzae* were used. Given the uncertain clinical implications of an intermediate result, especially for urine isolates, susceptibility results were analyzed using two dichotomous classification schemes, i.e., susceptible versus (intermediate plus resistant), and (susceptible plus intermediate) versus resistant.

Statistical methods. Comparisons of proportions were tested using Fisher's exact test for unpaired data and McNemar's test for correlated proportions. Throughout, 2-tailed tests were used. The significance criterion was a P value of <0.05.

RESULTS

Conventional susceptibility profiles. Among the 120 *E. coli* study isolates, data provided by the submitting laboratories showed that the prevalence of susceptibility to each of the standard antimicrobial agents or classes (except carbapenems, for which there was no detected resistance) varied greatly not only by agent within each resistance group but also by resistance group, being highest among dually susceptible isolates, intermediate among fluoroquinolone-resistant but ESC-susceptible isolates, and lowest among dually resistant isolates (Table 2). Apart from carbapenems, the best-preserved susceptibility prevalence values across resistance groups occurred with gentamicin and nitrofurantoin, although even their susceptibility values were unacceptably low among the dually resistant isolates (Table 2). After stratification by resistance group, no statistically significant association of coresistance with ST131 status was evident, excepting a higher prevalence of nitrofurantoin resistance among non-ST131 isolates than ST131 isolates within the dual-resistance group.

Susceptibility to alternative agents. Susceptibility to the six alternative agents varied by agent, resistance group, intermediate result classification approach, and ST131 status (Table 3). All isolates were resistant to rifampin (MIC $\geq$ 8 mg/liter). The other agents yielded overall prevalence values ranging (by agent) from 30% to 98% for susceptible and from 57% to 99% for susceptible or intermediate, with susceptibility to azithromycin being lowest, susceptibility to doxycycline, minocycline, and chloramphenicol being intermediate, and susceptibility to fosfomycin being highest.

The prevalence of susceptible (and susceptible plus intermediate) isolates differed significantly in relation to ST131 status for three drugs: azithromycin (dually susceptible group only) and doxycycline and minocycline (fluoroquinolone-resistant, ESC-susceptible group and dually resistant group) (Table 3). In each instance, ST131 isolates were more commonly susceptible.

As noted for the conventional antimicrobial agents (Table 2), statistically significant declining prevalence gradients were evident across the three resistance groups for susceptibility to azithromycin, doxycycline, minocycline, and chloramphenicol (Table 3). However, this trend was evident only among the non-ST131 isolates; the ST131 isolates had quite stable values for susceptibility to alternative agents regardless of resistance group (Table 3).

Susceptibility versus TMP-SMZ phenotype and ST131 status. Because resistance to TMP-SMZ is a common reason to seek an alternative agent, and because different resistance phenotypes are often associated (for examples, see Tables 2 and 3), the analysis shown in Table 3 was repeated after stratification by TMP-SMZ phenotype. In most subgroups, the prevalence of susceptibility to the alternative agent did not vary significantly in relation to TMP-SMZ susceptibility (data not shown). However, in 12 comparisons (6 involving azithromycin, 4 involving doxycycline, and 2 involv-

TABLE 3 Susceptibility of 120 *Escherichia coli* clinical isolates to alternative antimicrobial agents in relation to ST131 status and resistance group[a]

Agent[b]	Phenotype	No. (%) of isolates with phenotype[d]							*P* value[e]			
			FQ-S, ESC-S (group 1)		FQ-R, ESC-S (group 2)		FQ-R, ESC-R (group 3)		ST131 vs. other			
		Total ($n = 120$)	ST131	Other	ST131	Other	ST131	Other	FQ-S, ESC-S	FQ-R, ESC-S	ESC-R, FQ-R	Group 1 vs. 2 vs. 3, other[c]
Azithromycin	S	45 (30)	9 (45)	13 (65)	8 (40)	6 (30)	6 (30)	3 (15)				0.004
	S or I	68 (57)	11 (55)	18 (90)	12 (60)	11 (55)	10 (50)	6 (30)	0.03			<0.001
Doxycycline	S	68 (57)	14 (70)	15 (75)	15 (75)	7 (35)	12 (60)	5 (25)		0.03	0.05	0.005
	S or I	90 (75)	18 (90)	16 (80)	20 (100)	11 (55)	17 (85)	8 (40)		0.001	0.008	0.04
Minocycline	S	81 (68)	17 (85)	15 (75)	16 (80)	9 (45)	18 (90)	6 (30)		0.048	<0.001	0.02
	S or I	99 (83)	18 (90)	16 (80)	20 (100)	15 (75)	19 (95)	11 (55)		0.047	0.008	
Chloramphenicol	S	73 (61)	13 (65)	16 (80)	12 (60)	8 (40)	13 (65)	11 (55)				0.04
	S or I	106 (88)	17 (85)	19 (95)	19 (95)	17 (85)	18 (90)	16 (80)				
Fosfomycin	S	118 (98)	20 (100)	20 (100)	19 (95)	20 (100)	19 (95)	20 (100)				
	S or I	119 (99)	20 (100)	20 (100)	19 (95)	20 (100)	20 (100)	20 (100)				

[a] FQ-S and FQ-R, fluoroquinolone resistant and susceptible; ESC-S and ESC-R, extended-spectrum-cephalosporin resistant and susceptible.
[b] Agents shown are those with ≥1 susceptible (S) or intermediate (I) isolate. All isolates were resistant to rifampin.
[c] No significant between-group susceptibility differences were found for ST131 isolates.
[d] For each group, $n = 40$.
[e] *P* values of ≤0.05 (determined by Fisher's exact test) are shown.

ing minocycline), susceptibility to the alternative agent was significantly more prevalent among TMP-SMZ-susceptible isolates (Table 4).

DISCUSSION

We assessed 120 recent clinical *E. coli* isolates from VAMCs across the United States for susceptibility to 6 alternative oral agents and, in contrast to previous similar studies (3, 4), analyzed the results in relation to the organisms' fluoroquinolone, ESC, and TMP-SMZ phenotype and ST131 genotype. We found a consistent hierarchy of activity among the study drugs regardless of resistance group (as defined by fluoroquinolone and ESC phenotype), with rifampin and azithromycin being least active, doxycycline, minocycline, and chloramphenicol being moderately active, and fosfomycin

TABLE 4 Susceptibility to alternative antimicrobials in relation to trimethoprim-sulfamethoxazole (TMP-SMZ) phenotype

Resistance group[a]	ST131 status	Alternative agent[b]	Phenotype[c]	No. (%) of isolates with phenotype		*P* value[d]
				TMP-SMZ susceptible	TMP-SMZ resistant	
FQ-S, ESC-S	ST131	Azithromycin	S	8/12 (75)	1/8 (13)	0.03
		Azithromycin	S or I	10/12 (83)	1/8 (13)	0.005
	Non-ST131	Azithromycin	S	16/16 (100)	2/4 (50)	0.03
		Doxycycline	S	14/16 (88)	1/4 (25)	0.03
FQ-R, ESC-S	ST131	Azithromycin	S	11/12 (92)	1/8 (13)	0.001
		Doxycycline	S	12/12 (100)	3/8 (38)	0.004
	Non-ST131	Doxycycline	S	7/10 (70)	0/10 (0)	0.003
		Doxycycline	S or I	9/10 (90)	2/10 (20)	0.005
		Minocycline	S	8/10 (80)	1/10 (10)	0.005
		Minocycline	S or I	10/10 (100)	5/10 (50)	0.03
FQ-R, ESC-R	ST131	Azithromycin	S	4/6 (67)	2/14 (14)	0.04
		Azithromycin	S or I	6/6 (100)	4/14 (29)	0.01

[a] FQ-S and FQ-R, fluoroquinolone susceptible and resistant; ESC-S and ESC-R, extended-spectrum-cephalosporin susceptible and resistant.
[b] Only drugs that yielded *P* values of <0.05 in at least one comparison are shown.
[c] S, susceptible; I, intermediate.
[d] Determined by Fisher's exact test.

being most active. Susceptibility to these alternative agents declined in association with resistance to fluoroquinolones and ESCs only among the non-ST131 isolates and declined in association with TMP-SMZ resistance among ST131 and non-ST131 isolates alike. These findings identify potential novel treatment options for problematical *E. coli* UTI isolates but also point out the limitations of these agents for extensively coresistant strains, particularly among non-ST131 isolates.

An encouraging finding was the high prevalence of susceptibility to fosfomycin in all subgroups, as defined by coresistance phenotype and ST131 status. Fosfomycin has excellent distribution in the bladder wall, kidneys, and prostate and is excreted primarily into the urine (9). This suggests that in many clinical settings, at least among U.S. veterans, fosfomycin could be used empirically to treat *E. coli* UTI with a high likelihood of susceptibility, even without confirmatory testing, which not all laboratories provide.

In contrast, the other alternative agents encountered resistance with sufficient frequency, especially in the dually resistant group and among non-ST131 isolates, to make empirical therapy chancy, particularly if the patient has more than trivial symptoms or is frail. Despite sharing generally good tissue penetration with fosfomycin, only 6 to 45% of the other agents' active drug forms are excreted into the urine, compared to up to 60% for fosfomycin (9, 13). Although this may lead to comparatively lower urine concentrations than for renally cleared drugs, if even 10% of a drug (e.g., chloramphenicol) is excreted unchanged in the urine, it can reach therapeutically relevant urine concentrations. For example, if 10% (100 mg) is excreted into a daily urine volume of 2 liters, a daily drug dose of 1 g yields a mean urine concentration of 50 mg/liter, well above the susceptible MIC threshold for most drugs. Prior to use of these agents, at least as the sole therapy, it would be prudent to confirm susceptibility. How a clinical laboratory could provide such data for some of these agents with *E. coli*, in the absence of guidance from regulatory bodies such as CLSI and the FDA, is unclear. Furthermore, some of these agents lack an indication for UTI therapy (e.g., azithromycin) or are approved in the United States for UTI but have limited availability (e.g., chloramphenicol), making their use challenging.

The dramatic differences in susceptibility associated with ST131 status are potentially important clinically. Although ST131 has gained notoriety as a multidrug-resistant disseminated pathogen (1, 2, 14, 15), it apparently is actually less likely to be resistant to these alternative agents than non-ST131 *E. coli* isolates, when matched for coresistance to fluoroquinolones and ESCs. Therefore, a rapid test that could determine whether an *E. coli* isolate (or *E. coli*-containing urine sample) involves ST131 could allow reasonably confident empirical use of an alternative agent that otherwise would be excluded from empirical use because of the unacceptably high prevalence of resistance to it among non-ST131 isolates.

The burden of *E. coli* infection, particularly ST131, is high among U.S. veterans, and population-specific susceptibility data for alternative agents can provide valuable guidelines for clinicians. The susceptibility data demonstrate that identifying ST131 status allows selection of an alternative agent with resistance rates similar to those for drugs currently used for empirical treatment. For example, the estimated overall prevalence of resistance in *E. coli* within the VA population to ciprofloxacin and TMP-SMX is 29% and 22%, respectively (10), and our data show that doxycycline and minocycline offer similar resistance prevalence (25% and 20%, respectively) among fluoroquinolone-resistant, ESC-susceptible ST131 isolates. For organisms known to be ST131, the only conventional drugs with less than 25% resistance prevalence are ceftriaxone, imipenem, and nitrofurantoin (10), making oral doxycycline and minocycline potentially attractive alternative options. Furthermore, both doxycycline and minocycline are known to have excellent prostatic penetration, with concentrations as high as 40 to 100% and 60% of serum levels, respectively (16).

Consideration of possible combination therapy also is warranted, e.g., using a classic UTI agent (e.g., a fluoroquinolone or TMP-SMZ) plus an alternative agent, or two alternative agents, in an effort to achieve synergy, to compensate for intermediate activity of one or both agents or to eradicate a possible intracellular or intrabiofilm focus. For example, because azithromycin is widely distributed throughout the body and is concentrated primarily intracellularly (Table 1), these types of agents may offer adjuncts for patients suspected of harboring intracellular bacterial reservoirs (7). Although the efficacy of such approaches would require assessment in appropriately designed *in vitro*, animal model, and human clinical studies, our data support contemplating and designing such studies.

Study limitations include the small subgroups due to multiple stratifications, the use of conventional susceptibility data as reported by the submitting laboratories, the uncertain interpretive criteria for rifampin, and the unknown clinical relevance of *in vitro* susceptibility data. Study strengths include the broadly distributed (within the United States), recent, and representative (of U.S. veterans) study population, the attention to ST131 genotype and coresistance phenotypes, and the use of unconventional antimicrobial agents.

In summary, we documented multiple potential alternative oral antimicrobial therapy options for *E. coli* isolates recently obtained from veterans across the U.S. that are resistant to fluoroquinolones and/or ESCs and showed that ST131 isolates are more likely to be susceptible to such alternative agents than are similarly coresistant non-ST131 isolates. These findings should assist providers and clinical laboratories in coping with the rising prevalence in *E. coli* of resistance to conventional UTI agents and the increasing numbers of patients with recurrent or persistent antimicrobial-resistant *E. coli* UTI. Clinical correlation of these findings is needed.

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