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Original Article

The prevalence and risk factors of fluoroquinolones and co-trimoxazole resistant *Escherichia coli* in the Northwest Iran: A retrospective cohort

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Abstract

Introduction: Fluoroquinolone (FQ) and co-trimoxazole (STX) are the most effective antibiotics for *Escherichia coli*; however, antibiotic resistance has become an ever-increasing challenge. The current study investigates the prevalence rate and risk factors for developing FQ and STX resistance in Northwest Iran.

Methods: This is a retrospective cohort study of 314 patients admitted to Sina Hospital, the academic hospital affiliated with Tabriz University of Medical Sciences, Iran, between 21st March 2017 to 20th March 2018. Based on specimen culture, patients were divided into two groups, i.e., FQ or SXT-resistant *E. coli* and the antibiotics sensitive. The potential risk factors for developing FQ or SXT-resistant *E. coli* were studied in the included patients.

Results: FQ and SXT-resistant *E. coli* prevalence was 66.3% and 70%, respectively. Univariate analyses showed that type II diabetes mellitus, prior antibiotic use, prior FQ administration, prior admission, prior urinary tract infection, urinary catheterization, and anemia were the significant risk factors for developing FQ-resistant *E. coli* infection. The univariate analyses indicated that prior antibiotic use, hospitalization in an intensive care unit (ICU), and urinary catheterization were the significant risk factors for developing SXT-resistant *E. coli* infection. FQ and SXT-resistant *E. coli* infections are prevalent in our region. Prior antibiotic use and urinary catheterization are the common risk factors for developing FQ and SXT-resistant *E. coli* in our region.

Conclusion: Type II diabetes mellitus, prior urinary tract infection, gentamicin resistance, prior FQ administration, and extended-spectrum β-lactamases (ESBL) production are risk factors for developing FQ-resistant *E. coli* and ESBL production is the risk factor for developing STX-resistant *E. coli* in our region.

Introduction

Escherichia coli, the most common pathogen of the *Enterobacteriaceae* family, accounts for common clinical infections. Following antibiotic resistance, *E. coli* has become a significant public health challenge.[1-3] Co-trimoxazole (SXT) and fluoroquinolones (FQs) are commonly administered antibiotics to treat infections mediated by *E. coli*. These antibiotics have been the first line of empiric therapy, especially in urinary tract infections; however, antibiotic resistance mechanisms have resulted in the development of FQ and SXT-resistant *E. coli* in clinical settings.[4-7] Resistance to SXT has been increasingly reported among all *E. coli* strains isolated from community-acquired and nosocomial infections.[2] Resistance to SXT appeared soon after its use was initiated in patients; the SXT-resistance rate was < 1% in early 1970 for *E. coli* strains from the urinary tract,[8] while this number was reported at 84.4% for *E. coli* isolated from urine and wound specimens in 2012.[9] In 2014-2018, 62.5% of uropathogenic *E. coli* was resistant to STX.[10] In the United States, the SXT resistance rate varies from 20% to 25%.[2] In a systematic review conducted in Iran on studies published from 1992 to 2015, the prevalence of SXT resistance in uropathogenic *E. coli* isolates was 62%.[11] Therefore, its use in urinary tract infections as an empirical therapy has been restricted.[2,7,12] Following the worrisome increase of SXT-resistant *E. coli*, FQs were considered as the first line of treatment agents; however, the excessive use of

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FQs has also led to FQ-resistance development in recent years.[2,13] The prevalence of FQ-resistant *E. coli* in the USA and Europe was below 10%[14] and 15.8%,[15] respectively. Our previous research on uropathogenic *E. coli* isolates indicated that 54% were ciprofloxacin resistant.[16]

Although early reports of FQ and SXT resistance in *E. coli* suggested an association between FQ and SXT resistance,[17] little consensus is present on the factors that enhance the risk of FQ and SXT-resistant infections. Few studies highlighted different risk factors for SXT or FQ-resistant *E. coli*.[1,8,18-23] For SXT, recent hospitalization, the use of SXT,[8] and recurrent urinary tract infection [23] have been listed as the risk factors. The risk factors for FQ-resistant development include older age, urinary catheterization,[21] immunosuppression, previous infection,[1] aminoglycoside use,[24] antimicrobial therapy, and urinary tract infection.[1] However, the prevalence and antimicrobial resistance patterns vary among different geographical regions; understanding the risk factors of antimicrobial resistance is crucial for identifying the high-risk groups.[25] Therefore, the present study aimed to investigate the prevalence rate of FQ and SXT-resistant in *E. coli* isolates and risk factors for developing resistance to FQ and SXT in hospitalized patients in Northwest Iran.

Methods

This is a retrospective cohort study of 314 patients admitted to Sina Hospital, the academic hospital affiliated with Tabriz University of Medical Sciences, Iran, between 21st March 2017 to 20th March 2018. Following the study of microbiological reports, all patients with a positive culture of *E. coli* were selected for further analysis. These *E. coli* isolates were isolated from community-acquired or nosocomial infections. Identification of *E. coli* was performed using standard bacteriological techniques.[26,27] The antimicrobial susceptibility testing was performed, and results were interpreted as described by the Clinical Laboratory Standard Institute (CLSI).[27] *E. coli* isolates demonstrating FQ and/or SXT-resistance were considered as the case, and sensitive ones as the control group. Each patient was included as a case or control only once. If *E. coli* culture was positive on multiple occasions, only the first episode of infection was considered.

The medical records of included patients were reviewed to extract age, sex, source of infection, presence of an urinary catheter, history of smoking, nephrolithiasis, type II diabetes mellitus, hypertension, ischemic heart diseases, chronic renal failure, cancer, immunosuppressive therapy such as chemotherapy or corticosteroid therapy, benign prostatic hyperplasia, prior urinary tract infection, ICU admission, previous hospitalization in the last six months, prior FQ or SXT or another antibiotic use in the past 90 days, infecting with a nosocomial infection or colonization in the ICU, white blood cell count, hemoglobin, platelet, creatinine, erythrocyte sedimentation rates, procalcitonin, and antibiogram-based factors. This study was approved by the Ethics Committee of Tabriz University of Medical Sciences and the informed consent was obtained from the included patients. The protocol of this study is in line with the Helsinki Declaration of 1975, as revised in 2008 and is accordance with the ethical standards.

The obtained data were subjected to statistical analysis and represented as mean ± standard deviation (SD) and frequency (%). Univariate analysis was conducted to study the association between potential risk factors and FQ or SXT-resistant infection. All P-values were calculated using logistic regression. An odds ratio (OR) and 95% confidence interval (CI) were calculated to investigate any correlation between risk factors and FQ or SXT resistance. Adjusted ORs were calculated using unconditional logistic regression analysis with variables significance at a *P* value of ≤ 0.1, as assessed by univariate analysis, to control for all the confounding factors. Variables were included in the multivariate analysis in a stepwise manner to construct the final model. *P* values of less than 0.05 were considered as significant. SPSS v.22 was used for all statistical analysis.

Results

A total of 314 microbiologically confirmed *E. coli* isolates were collected from 173 women (55.1%) and 141 men (44.9%). The mean age of included patients was 64.1 years (range, 2 to 95 years). Forty-six (17.8%) of the included patients were hospitalized in the ICU, and 258 (82.2%) in non-ICU wards. The source of infection was asymptomatic and symptomatic urinary tract infection in 250 (79.6%) patients and the source of infection for the remaining patients was the bloodstream, respiratory, and wound site. In the urine isolates, 39.5% of patients had a urinary-catheter. The *E. coli* resistance rates to different antibiotics tested are depicted in Figure 1. Among the antibiotics investigated in the present study, the highest rates of resistance were observed for cefazolin (73.91%), cefotaxime (71.06%), co-trimoxazole (70%), ceftazidime (69.45%), fluoroquinolone (66.3%), gentamicin (33.55%),

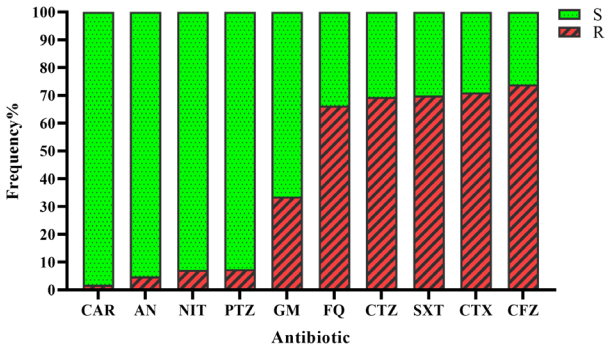

Figure 1. Rates of resistance to different antibiotics tested against 314 E. coli strains isolated from urine, bloodstream, respiratory samples, and wounds. Abbreviations: CAR, carbapenem; AN, amikacin; NIT, nitrofurantoin; PTZ, piperacillin tazobactam; GM, gentamicin; FQ, fluoroquinolone; CTZ, ceftazidime; SXT, cotrimoxazole; CTX, cefotaxime; CFZ, cefazolin; S, sensitive strains; R, resistant strains

piperacillin-tazobactam (7.5%), nitrofurantoin (7.2%), amikacin (AN) (4.84%) and carbapenem (1.82%) (Figure 1). Among all *E. coli* isolates, 205 (65.3%) were extended-spectrum β-lactamases (ESBL) producing bacteria.

FQ resistance

FQ resistance was observed in 66.3% of *E. coli* isolates. Among these, univariate analysis showed a history of type II diabetes mellitus (*P* value = 0.003, OR = 2. 1, 95% CI = 1.28-3.45), prior antibiotic administration (other than FQ and SXT) (P-value = 0.000, OR = 2.96, 95% CI = 1.75-5.1), prior FQ use (*P* value = 0.000, OR = 3.75, 95% CI = 1.82-7.71), prior admission (*P* value = 0.000, OR = 3.16, 95% CI = 1.77-5.65), prior urinary tract infection (*P* value = 0.005, OR = 5.59, 95% CI = 1.66-18.81), urinary catheterization (*P* value = 0.006, OR = 2.36, 95% CI = 1.28-4.34) (Table 1), anemia (*P* value = 0.006, OR = 2.16, 95% CI = 1.23-3.77) (Table 2), ESBL production (*P* value = 0.000, OR = 9.01, 95% CI = 5.23-15.53), gentamicin (*P* value = 0.000, OR = 11.69, 95% CI = 5.17-26.43) and SXT (*P* value = 0.000, OR = 2.98, 95% CI = 1.77-5.03) use (Table 3), were statistically significant risk factors associated with FQ resistance. It is worth mentioning that there was a trend toward significance for age > 65 years (*P* value = 0.068, OR = 1.56, 95% CI = 0.97-2.51) and hypertension history in patients (*P* value = 0.059, OR = 1.59, 95% CI -0.98-2.56) (Table 1).

STX resistance

Regarding SXT, 70% of *E. coli* isolates were resistant. Univariate analysis demonstrated that prior antibiotic (other than FQ and SXT) use (*P* value = 0.002, OR = 2.3, 95% CI = 1.34-3.92), ICU admission (*P* value = 0.004, OR = 3.23, 95% CI = 1.41-7.48), urinary catheterization (*P* value = 0.049, OR = 1.86, 95% CI = 1-3.44) (Table 1), ESBL production (*P* value = 0.000, OR = 3.14, 95% CI = 1.88-5.26), FQ resistance (*P* value = 0.000, OR = 2.98, 95% CI = 1.77-5.03) were found to be statistically significant risk factors for SXT resistance. There was a trend toward significance for the male sex (*P* value = 0.081, OR = 1.57, 95% CI = 0.946-2.607), prior FQ (*P* value = 0.065, OR = 1.84, 95% CI = 0.96-3.53) (Table 1), gentamicin (*P* value = 0.083, OR = 1.63, 95% CI = 0.94-2.83), and AN administration (*P* value = 0.076, OR = 6.38, 95% CI = 0.83-49.31) (Table 3).

Furthermore, multivariate analysis of independent risk factors for *E. coli* resistance to FQs and SXT are displayed in Table 4. Our findings showed that type II diabetes mellitus, prior urinary tract infection, gentamicin resistance, prior FQ use, and ESBL were statistically significant risk factors for *E. coli* resistance to FQs and SXT.

Discussion

The prevalence of antibiotic resistance, resistance patterns, and associated risk factors may vary among different geographic locations. This study investigated the prevalence of FQs and STX-resistant *E. coli* and the related risk factors in the Northwest of Iran. The present study investigated *E. coli* isolates from community-acquired and nosocomial infections obtained from urine, blood, respiratory secretion, and wound.

In the United States, Fluit et al reported that the resistance rate of *E. coli* to FQ was 4.7-7.9% in 2000[14]; however, there was no resistance to FQ among *E. coli* isolates in 1997.[28] In 2008, Talan et al indicated that the prevalence of FQ and SXT-resistant *E. coli* was 5% and 24% among patients with pyelonephritis in the United States.[15] In the United States, the rate of resistance to SXT increased from 15.4% to 25.1% from 1997 to 2018,[14,15,28] and the resistance for FQ increased from < 1% to approximately 30% from 1997 to 2015.[14,15,28,29] In India, the prevalence rate of FQ and SXT was 89% and 94% among patients with gastrointestinal infections.[13] It has been reported that antimicrobial resistance in community-acquired uropathogenic *E. coli* isolates to FQ and SXT was 17.8% and 34.2%, respectively.[6] In Iran, the rate of *E. coli* resistance to SXT and FQ was 64% and 28%,[11] which was approximately retained at 62% in 2019.[16] In our study, the prevalence rate of *E. coli* resistance to FQ and SXT was 66.3% and 70%, respectively. The widespread use of SXT and the increasing *E. coli* resistance to this antibiotic encouraged clinicians to use FQs as suitable alternatives for most infections because of their high potency, broad spectrum, and tolerability. Our results have demonstrated worrisome emergence of *E. coli* resistant to FQs.

The present study also investigated the potential risk factors for developing FQs and STX-resistant *E. coli* in the Northwest of Iran. The current study is among the few studies investigating the relationship of underlying diseases with *E. coli* resistance to FQ and SXT. Our results have indicated that among nephrolithiasis, diabetes mellitus, hypertension, ischemic heart diseases, chronic renal failure, and cancer, only type II diabetes mellitus is a risk factor for FQ-resistant *E. coli*. In line with the previous findings,[1,23] our results have shown that prior urinary tract infections and urinary catheterization are risk factors for FQ-resistant *E. coli*. Consistent with previous reports,[1,3,4] our results have indicated that the resistance to FQ and SXT is related to the recent administration of FQ and other antibiotics. Consistent with the study by Sotto et al,[30] our findings have indicated that ICU admission was associated with SXT resistance but not with FQ. In addition, the administration of immunosuppressive drugs and smoking, similar to earlier findings, were not associated with FQ or SXT resistance[4]; however, Zhu et al reported that immunosuppressive drugs were risk factors for FQ resistance.[1] Our study has demonstrated that 74%-81% of ESBL-producing *E. coli* were significantly resistant to FQ and SXT; these results were compatible

Table 1. Clinical factors associated with E. coli resistance to FQ and SXT as assessed by univariate analysis [a]

Risk Factors	Category	FQ OR (95% CI)	FQ *P* [b] value	SXT OR (95% CI)	SXT *P* [b] value
Age	<65	1		1	
	>65	1.56 (0.97-2.51)	**0.068**	1.49 (0.91-2.44)	0.118
Sex	Female	1		1	
	Male	1.23 (0.76-1.98)	0.4	1.57 (0.946-2.607)	0.081
Smoking	No	1		1	
	Yes	0.715 (0.39-1.3)	0.27	1.105 (0.573-2.129)	0.766
Nephrolithiasis	No	1		1	
	Yes	1.46 (0.75-2.85)	0.26	1.199 (0.614-2.343)	0.595
DM	No	1		1	
	Yes	2.1 (1.28-3.45)	**0.003**	1.088 (0.66-1.792)	0.741
HTN	No			1	
	Yes	1.59 (0.98-2.56)	0.059	1.35 (0.82-2.22)	0.237
IHD	No			1	
	Yes	1.25 (0.62-2.5)	0.53	0.607 (0.31-1.184)	0.143
CRF	No	1		1	
	Yes	1.37 (0.67-2.79)	0.39	1.385 (0.648-2.96)	0.4
BPH	No	1		1	
	Yes	1.91 (0.76-4.81)	0.17	2.051 (0.722-5.83)	0.178
Cancer	No	1		1	
	Yes	1.49 (0.69-3.2)	0.31	1.13 (0.52-2.45)	0.76
ISD	No	1		1	
	Yes	1.02 (0.47-2.19)	0.97	0.573 (0.261-1.254)	0.163
Prior AB use	No	1		1	
	Yes	2.96 (1.75-5.01)	**0.000**	2.3 (1.34-3.92)	**0.002**
Prior FQ use	No	1		1	
	Yes	3.75 (1.82-7.7)	**0.000**	1.84 (0.96-3.53)	0.065
Prior SXT use	No	1		1	
	Yes	0.50 (0.1-2.5)	0.41	0.425 (0.059-3.07)	0.4
Prior admission	No	1		1	
	Yes	3.16 (1.77-5.65)	**0.000**	1.54 (0.89-2.66)	0.12
Prior UTI	No	1		1	
	Yes	5.59 (1.66-18.81)	**0.005**	1.61 (0.67-3.87)	0.28
ICU hospitalization	No	1		1	
	Yes	0.79 (0.43-1.44)	0.43	3.23 (1.41-7.48)	**0.004**
Uro E. coli	Without catheter	1		1	
	With catheter	2.36 (1.28-4.34)	**0.006**	1.86 (1-3.44)	**0.049**
E. coli source	Non-urine	1		1	
	Urine	0.95 (0.52-1.73)	0.87	0.52 (0.26-1.033)	0.062

[a] Abbreviations: DM, Diabetes mellitus; HTN, Hypertension; IHD, ischemic heart diseases; CRF, chronic renal failure; BPH, benign prostatic hyperplasia; ISD, immunosuppressive drug; AB, antibiotic; UTI, urinary tract infection; ICU, intensive care unit; Uro, Uropathogenic; odds ratio; CI, confidence interval.
b All p values were calculated using binary logistic regression.
[c] other than FQ and SXT

Table 2. laboratory factors associated with E. coli resistance to FQ and SXT as assessed by univariate analysisa

Risk Factors	Category	FQ OR (95% CI)	FQ *P* [b] value	SXT OR (95% CI)	SXT *P* [b] value
WBC	Normal	1		1	
	Leukocytosis	0.750 (0.45-1.24)	0.26	0.95 (0.56-1.6)	0.85
Hb	Normal	1		1	
	Anemia	2.16 (1.23-3.77)	**0.006**	1.42 (0.79-2.55)	0.25
Plt	Normal	1		1	
	Thrombocytopenia	0.74 (0.43-1.27)	0.28	0.86 (0.49-1.52)	0.61
Creatinine	Normal	1		1	
	High	1.15 (0.7-1.89)	0.58	1.23 (0.74-2.06)	0.43
ESR	Normal	1		1	
	High	1.42 (0.68-2.97)	0.35	0.85 (0.38-1.9)	0.69
PCT	Normal	1		1	
	High	1.11 (0.51-2.42)	0.79	1.34 (0.57-3.16)	0.51

[a] Abbreviations: WBC, white blood cell; Hb, Hemoglobin; Plt, platelet; ESR, Erythrocyte sedimentation rate; PCT, procalcitonin, OR, odds ratio; CI, confidence interval
[b] All p values were calculated using binary logistic regression.

Table 3. Antibiogram- based factors associated with E. coli resistance to FQ and SXT as assessed by univariate analysis[a]

Risk Factors	Category	FQ OR (95% CI)	FQ P [b] value	SXT OR (95% CI)	SXT P [b] value
ESBL	No	1		1	
	Yes	9.01 (5.23-15.53)	**0.000**	3.14 (1.88-5.26)	**0.000**
PTZ	S	1		1	
	R	5.77 (0.73-45.37)	0.069	1.57 (0.42-5.83)	0.503
CAR	S	1		-	-
	R	0.71 (0.65-0.77)	0.559	-	-
AN	S	1		1	
	R	2.89 (0.63-13.32)	0.17	6.38 (0.83-49.31)	0.076
GM	S	1		1	
	R	11.69 (5.17-26.43)	**0.000**	1.63 (0.94-2.83)	0.083
NIT	S	1		1	
	R	2.48 (0.69-8.91)	0.163	1.5 (0.47-4.78)	0.49
CTZ	S	1		1	
	R	10.52 (5.96-18.56)	**0.000**	3.12 (1.84-5.27)	**0.000**
CTX	S	1		1	
	R	10.65 (5.99-18.93)	**0.000**	3.34 (1.96-5.69)	**0.000**
CFZ	S	1		1	
	R	8.38 (3.18-22.06)	**0.000**	2.3 (0.92-5.78)	0.076
SXT	S	1		-	
	R	2.98 (1.77-5.03)	**0.000**	-	

[a] Abbreviations: PTZ, piperacillin tazobactam; CAR, carbapenem; AN, amikacin; GM, gentamicin; NIT, nitrofurantoin; CTZ, ceftazidime; CTX, cefotaxime; CFZ, cefazolin; FQ, fluoroquinolone; SXT, cotrimoxazolee, OR,odds ratio; CI, confidence interval.
[b] All p values were calculated using binary logistic regression.

Table 4. Multivariate analysis of independent risk factors for E. coli resistance to FQs and SXT [a]

Risk Factors	Category	OR (95% CI)	*P* [b] value
For FQ			
DM	No	1	
	Yes	2.24 (1.05-4.8)	0.038
Prior UTI	No	1	
	Yes	5.92 (1.25-28.1)	0.025
GM	S	1	
	R	11.68 (3.63-37.6)	0.000
Prior FQ use	No	1	
	Yes	3.1 (0.86-10.65)	0.049
ESBL	No	1	
	Yes	9.43 (4.32-20.59)	0.000
For SXT			
ESBL	No	1	
	Yes	3 (1.62-5.57)	0.000

[a] Abbreviations. OR, odds ratio; CI, confidence interval
[b] All *p* values were calculated using logistic regression.

with the previous studies.[9,14,24] Furthermore, our findings have indicated that resistance to gentamicin and SXT is associated with FQ resistance, and resistance to FQ is associated with resistance to SXT. However, our results have shown that sex and age are the risk factors for developing STX-resistant *E. coli*, probably due to their excessive use in all age groups in our region. In accordance with our findings, it has been reported that sex and age were not related to FQ or SXT resistance.[13] In contrast, earlier studies demonstrated that male sex and age above 65 were independent risk factors for resistance to FQ or SXT.[1,3,4,6] To the best of our knowledge, the current study is among the studies that investigated the association of the laboratory parameters, including leukocytosis, anemia, thrombocytopenia, creatinine, erythrocyte sedimentation rate, and procalcitonin levels, with FQ and SXT-resistant *E. coli*. Our results have demonstrated that only anemia is associated with FQ and SXT-resistant *E. coli*. However, due to the possibility of having different risk factors for colonization and infection, it is recommended that these two groups be separately investigated further in future studies.

Conclusion

With a prevalence rate above 65%, FQ and SXT-resistant *E. coli* infections have become an emerging concern in our region. Based on multivariant analyses, type II diabetes mellitus, prior urinary tract infection, gentamicin resistance, prior FQ administration, and ESBL production are risk factors for developing FQ-resistant *E. coli* and ESBL production is the risk factor for developing STX-resistant *E. coli* in our region.

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Competing Interests

The authors have no conflicts of interest to declare.

Ethical Approval

This study was approved by the Ethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran (IR.TBZMED.REC.1400.084) and the informed consent was obtained from the patients.

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