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Detection of Antimicrobial Susceptibility and Integrons Among Extended-spectrum β-lactamase Producing Uropathogenic *Escherichia coli* Isolates in Southwestern Iran

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ABSTRACT

Objectives: Urinary tract infections (UTIs) are one of the most prevalent infectious diseases and can lead to a high rate of morbidity and mortality. The emergence of multiple-drug resistant strains, particularly extended-spectrum beta-lactamases (ESBLs) producing strains, has become a global healthcare concern. Our study sought to investigate the antimicrobial resistance pattern and presence of integrons and *fimH* determinants among uropathogenic *Escherichia coli* (UPEC) isolates obtained from hospitalized Iranian patients. ***Methods***: This cross-sectional study was performed on 121 *E. coli* isolates recovered from patients with clinical symptoms of UTIs, referred to Shiraz Nemazee Hospital, in 2016–17. The isolates were identified by standard microbiologic tests and confirmed by API 20E strip. Antimicrobial susceptibility testing was determined using the disk diffusion method. The presence of *fimH* and classes 1–3 integron encoding genes was determined using the polymerase chain reaction. ***Results:*** Ampicillin (9.1%) and nalidixic acid (19.0%) showed the lowest level of antibiotic susceptibility. The highest level of susceptibility was toward imipenem (77.7%). The rate of ESBL-producing isolates was 42.1%. There was a significant association between production of ESBLs and higher antibiotic resistance in the tested isolates. Of the investigated virulence and resistance genes, *fimH*, *intI1*, and *intI2* were positive in 98.3%, 59.5%, and 7.4% of isolates, respectively. ***Conclusions:*** The remarkable rate of ESBL-producing UPEC isolates accompanied with the presence of integrons suggest the necessity of restricted infection control policies to prevent further dissemination of resistant strains.

Urinary tract infections (UTIs) are one of the most prevalent infectious diseases in both hospital and community settings and can lead to a high rate of morbidity and mortality.[1,2] Various pathogens are responsible for causing UTIs, of which *Escherichia coli* account for the majority of infections.[3]

Among the array of antibiotics commonly used for the treatment of UTIs, β-lactams are the most extensively used agents.[1] However, the emergence of multiple-drug resistant (MDR) strains, particularly extended-spectrum beta-lactamases (ESBLs) producing strains, has become a global healthcare concern.[4–8] Recently, the trend of ESBL-producing *E. coli* strains has increased worldwide, including in Iran.[9,10] ESBLs are enzymes capable of hydrolyzing penicillins, broad-spectrum cephalosporins, and monobactams.[11] The specific ESBL-producing strains have different genetic characteristics, which may cause specific pathogenesis characteristics.[4,12]

The antibiotic resistance determinants can normally transfer among bacterial strains by different horizontal gene transfer mechanisms, including integrons.[13] These elements are responsible for the integration and dissemination of resistance genes among the bacteria. To date, several classes of integrons have been described based on the amino acid sequences of their integrase genes (*intI*).[13] Of them, class 1 and 2 integrons are the most prevalent classes of MDR gram-negative bacteria associated with antibiotic treatment failure.[14]

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Successful colonization and invasion of *E. coli* into host uroepithelial cells and bladder tissues is mostly dependent on fimbrial adhesions.[15] Among adhesions of uropathogenic *E. coli* (UPEC), *fimH* protein is a major virulence determinant, which plays an important role in host-pathogen interactions and biofilm formation.[15] These features made *fimH* a worthy therapeutic target for the development of new methods for the diagnosis and prevention of UTIs.

Awareness of the trends of antibiotic resistance and mechanisms of resistance is a rational way to overcome the risk of drug resistance and treatment failure. Thus, we investigated the antimicrobial resistance pattern and presence of integrons and *fimH* determinants among UPEC isolates obtained from hospitalized Iranian patients.

METHODS

This cross-sectional study was performed using 121 non-duplicated *E. coli* isolates obtained from hospitalized patients with symptomatic UTIs at Nemazee teaching hospital in Shiraz, Southwestern Iran from November 2016 to May 2017. This study was in accordance with the declaration of Helsinki and approved by the Ethics Committee of Shiraz University of Medical Sciences.

The isolation and identification of *E. coli* strains were performed by standard microbiological tests and confirmed by API 20E strip (API-bioMérieux, France). The confirmed isolates were stored at -80 °C for long-term preservation.

Antibiotic susceptibility of all isolates to amikacin (30 µg), ampicillin (10 µg), ceftazidime (30 µg), imipenem (10 µg), tetracycline (30 µg), levofloxacin (5 µg), ciprofloxacin (5 µg), nalidixic acid (30 µg), nitrofurantoin (300 µg), co-trimoxazole (25 µg), and gentamicin (10 µg) (Mast Co., UK) was carried out on Muller- Hinton agar (Merck, Germany) using the disk diffusion method as recommended by the Clinical and Laboratory Standards Institute (CLSI).[16] *E. coli* ATCC 25922 was used as a quality control strain for antibacterial susceptibility testing. MDR was estimated according to previously described definitions (i.e., non-susceptible to ≥ 1 agent in ≥ 3 different antimicrobial categories).[17]

All isolates were tested for ESBL production, using the double-disk synergy test using ceftazidime (30 µg) and ceftazidime-clavulanic acid (30/10 µg) disks as described by CLSI guidelines.[16] *E. coli* ATCC 25922 and *Klebsiella pneumoniae* ATCC 700603 were used as negative and positive control strains, respectively.

The template DNA used was extracted from freshly grown colonies by the boiling method as described previously.[18] Simplex polymerase chain reaction (PCR) was used to determine the presence of classes 1–3 integrons by detection of integrase genes *intI1*, *intI2* and *intI3*, and *fimH* (type-1 fimbriae), using the previously described primers [Table 1].[19,20] PCR amplifications for the studied genes were carried out in the following condition, initial denaturation at 95 °C for 5 minutes, followed by 30 cycles of denaturation at 95 °C for 60 seconds, annealing for 45 seconds (temperature dependent on primer sequences), extension at 72 °C for 50 seconds, and final extension at 72 °C for 5 minutes. PCR amplifications for the studied genes was carried out on a T100™ thermal cycler (Bio-Rad, Hercules, CA, USA). The amplifications were separated on 1.5% agarose gel prepared in 1X TAE (Tris/Acetate/EDTA) buffer and visualized using ultraviolet light after staining with safe stain load dye (CinnaGen Co., Iran) [Figure 1]. The purified PCR products of the amplified *intI1* and *intI2* genes were submitted for sequencing (Bioneer Co., South Korea), and

Table 1: List of primers used.

Primer	Oligonucleotide sequence (5' to 3')	Gene	Amplicon size (bp)	Reference
IntI1-Forward	GGTCAAGGATCTGGATTTCG	*intI1*	483	19
IntI1-Reverse	ACATGCGTGTAAATCATCGTC			
IntI2-Forward	CACGGATATGCGACAAAAAGGT	*intI2*	789	19
IntI2-Reverse	GTAGCAAACGAGTGACGAAATG			
IntI3-Forward	AGTGGGTGGCGAATGAGTG	*intI3*	600	19
IntI3-Reverse	TGTTCTTGTATCGGCAGGTG			
FimH-Forward	TGCAGAACGGATAAGCCGTGG	*fimH*	508	20
FimH-Reverse	GCAGTCACCTGCCCTCCGGTA			

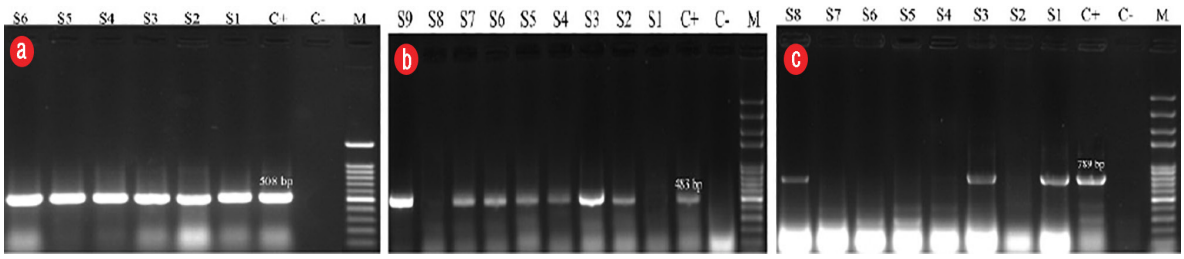

Figure 1: Agarose gel electrophoresis of polymerase chain reaction (PCR) products for **(a)** *fimH* gene, **(b)** *intI1* gene, and **(c)** *intI2* gene. Lane M: 100bp DNA size marker, column C-: negative control, C+: positive control, S: results of clinical samples.

the sequences were compared using online BLAST software. For *fimH* gene, *E. coli* ATCC 25922 was used as a positive control strain.

The analysis was performed using SPSS Statistics (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). The results are presented as descriptive statistics in terms of relative frequency. Values are expressed as the percentages of the group (categorical variables). Chi-square or Fisher's exact tests were used to determine the significance of the differences. A difference was considered statistically significant if the *p*-value was < 0.050.

RESULTS

Of 121 *E. coli* isolates included in our study, 74 (61.2%) and 47 (38.8%) isolates were obtained from females and males patients, respectively. The median age of the patients was 52.1±27.8 years, ranging from 1 month to 100 years old. The most frequent source of bacterial isolation was from intensive care units (59.5%) followed by internal wards (16.5%), neonatal intensive care units (14.9%), surgery wards (6.6%), and the transplantation ward (2.5%).

Imipenem (77.7%) and nitrofurantoin (76.9%) were the most effective *in vitro* antibiotics for *E. coli* isolates. Ampicillin (9.1%) and nalidixic acid (19.0%) showed the lowest level of susceptibility. The full results of antibiotic susceptibility pattern for UPEC isolates are shown in Table 2.

The rate of ESBL-producing isolates was 42.1% (51/121). There was a significant association between production of ESBLs and higher antibiotic resistance in the tested isolates [Table 2]. The most effective antibiotic against ESBL-producing isolates was nitrofurantoin followed by amikacin and imipenem. In total, 98.0% of the ESBL-producing isolates and 87.1% of non-ESBL-producing isolates were MDR ($p = 0.040$).

Seventy-two (59.5%) isolates were positive for *int1* gene and harboring class 1 integron; nine

Table 2: The results of antibiotic susceptibility pattern of *Escherichia coli* isolates.

Class	Antibiotics	Total n = 121		Non-ESBL-producing n = 70		ESBL-producing n = 51		*p*-value
		n	%	n	%	n	%	
Penicillins	Ampicillin	11	9.1	11	15.7	0	0.0	< 0.001
Cephalosporins	Ceftazidime	40	33.1	39	55.7	1	2.0	< 0.001
Tetracyclines	Tetracycline	39	32.2	28	40.0	11	21.6	0.032
Quinolones	Nalidixic acid	23	19.0	17	24.3	6	11.8	0.083
	Ciprofloxacin	50	41.3	37	52.9	13	25.5	0.003
	Levofloxacin	60	49.6	43	61.4	17	33.3	0.002
Sulfonamides	Co-trimoxazole	30	24.8	20	28.6	10	19.6	0.260
Aminoglycosides	Gentamicin	78	64.5	53	75.7	25	49.0	0.002
	Amikacin	86	71.1	51	72.9	35	68.6	0.610
Nitrofurans	Nitrofurantoin	93	76.9	56	80.0	37	72.5	0.340
Carbapenem	Imipenem	94	77.7	62	88.6	32	62.7	0.001

ESBL: extended-spectrum beta-lactamase.

Table 3: Antibiotic susceptibility pattern of the studied *Escherichia coli* isolates according to integron class 1 positivity.

Class	Antibiotics	Integron 1 negative n = 49		Integron 1 positive n = 72		*p*-value
		n	%	n	%	
Penicillins	Ampicillin	4	8.2	7	9.7	0.770
Cephalosporins	Ceftazidime	15	30.6	25	34.7	0.640
Tetracyclines	Tetracycline	19	38.8	20	27.8	0.200
Quinolones	Nalidixic acid	11	22.4	12	16.7	0.430
	Ciprofloxacin	21	42.9	29	40.3	0.780
	Levofloxacin	27	55.1	33	45.8	0.320
Sulfonamides	Co-trimoxazole	17	34.7	13	18.1	0.037
Aminoglycosides	Gentamicin	32	63.5	46	63.9	0.870
	Amikacin	33	67.3	53	73.6	0.460
Nitrofurans	Nitrofurantoin	42	85.7	51	70.8	0.057
Carbapenem	Imipenem	37	75.5	57	79.2	0.630

(7.4%) isolates were positive for *intI2* genes and harboring class 2 integron, and seven (5.8%) isolates contained both genes. Class 3 integron was not detected in any of the isolates by the absence of *intI3* gene. Integron class 1 was significantly associated with lower susceptibility to sulfonamides ($p < 0.050$) [Table 3]. Moreover, there was no significant association between ESBLs production and integron 1 or 2 positivity. The incidence of integron class 1 and 2 among MDR isolates was 95.8% and 100%, respectively. These rates in non-MDR isolates were 85.7% for class 1 integron and 91.1% for class 2 integron ($p > 0.050$). Type 1 fimbrial adhesin by detection of *fimH* gene was positive in 98.3% of UPEC isolates.

DISCUSSION

Nosocomial infections caused by drug-resistant *E. coli* spread rapidly in the world and can be associated with higher rates of morbidity and mortality in vulnerable populations, such as neonates, pregnant women, or immunocompromised patients.[21] To reduce the risk of complications associated with hospital-acquired UPEC infections and overcome the dissemination of drug-resistant strains, we strongly recommend periodic surveillance to identify the ESBL-producing strains to optimize available infection control policies.[22]

We report the antibiotic resistance and prevalence of ESBL-producing UPEC isolates in Southwestern Iran. The prevalence of ESBL-producing UPEC isolates was 42.1%, which in spite of the great discrepancy is consistent with the median values (24% to 72.9%) reported in previous studies from Iran.[23–30] The differences globally in the prevalence of ESBL-producing UPEC isolates can be due to differences in geographical regions, infection control policies, the origin of infection, and sample size.

ESBLs are plasmid-mediated β-lactamases that are capable of hydrolyzing β-lactams, except for carbapenems and cephamycins.[11,31] In this regard, the majority of our ESBL-producing isolates were resistant to penicillins and cephalosporins. Moreover, in accordance with previous reports,[23,24,31,32] our ESBL-producing isolates showed significantly higher resistance rates to most of the tested agents. Similar to our findings, several authors have introduced carbapenem, amikacin, and nitrofurantoin as a treatment option for UTIs caused by ESBL-producing *E. coli* strains.[29,32,33]

Class 1 and 2 integron-integrase genes were found in 59.5% and 7.4% of isolates, respectively. Numerous studies reported the prevalence of integrons among clinical isolates of *E. coli* from Iran and other parts of the world. Generally, those studies reported a higher incidence of class 1 integron[34–37]; however, there were some variations according to geographical distribution and source of infections. One report from Yasuj, southwest of Iran showed class 1 and 2 integrons in 52%, and 2.5% of UPEC isolates, respectively.[34] In the northern part of the

country, only 22% of UPEC isolates contained the class 1 integron gene.[38] In Northwest Iran, the prevalence of class 1 and 2 integrons was 22.05% and 5.08% of MDR UPEC strains, respectively.[39] The highest rate of integrons carrying UPEC isolates was reported from the west of Iran with 87% for class 1, and 7% for class 2.[37] It seems that the occurrence of integrons in the community and hospitals can be different. Another study conducted in our region (Fars province) showed the prevalence of class 1 and 2 integrons in community-acquired UPEC isolates to be 6.25% and 10.41%, respectively.[40]

In our results, in agreement with previous studies, almost all of the UPEC isolates (98.3%) carried the *fimH* gene.[41–44] Our observations suggest the potential of type 1 fimbrial adhesin as promising candidates for the development of new therapeutic strategies to prevent complications related to UPEC colonization.[45]

CONCLUSION

The remarkable rate of MDR and ESBL-producing UPEC isolates accompanied with the presence of integrons suggests the necessity of restricted infection control policies to prevent further dissemination of resistant strains. Several locally available antibiotics showed promising effects against our MDR isolates. Due to the continuous evolution of pathogens in hospital environments continuous updating of local data, such as this study, provide experimental evidence to improve the outcome of nosocomial infections.

Disclosure

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