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## Epidemiology of Extended Spectrum B-Lactamase Producing Gram Negative Bacilli of Community Acquired Urinary Tract Infection in Tabriz, Iran

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### ABSTRACT

Bacteria which produce extended spectrum  $\beta$ -lactamase (ESBLs) are resistant to all kinds of  $\beta$ -lactam antibiotics and may also induce resistance to some other antibiotics including aminoglycosides, quinolones and trimethoprim-sulfamathoxazoles. Infection with these bacteria is very crucial among patients with urinary tract infection. In this study urine samples were collected from all administered patients who were clinically diagnosed with urinary tract infection and had positive urinary analysis. The urine samples of these patients undergone bacteriological tests for ESBL producing gram negative bacilli. Among 893 patients, 763 met the inclusion criteria and entered the study. A total of 587 samples of these patients were positive for four gram negative studied bacilli. The urine samples of 106 individuals (49 male (46%) and 61 female (54%) with mean age of 61 (Range: 19-90) years) were positive to extended spectrum  $\beta$ -lactamase producing bacteria. All isolates were susceptible to colistin and resistant to cefotaxime, ceftriaxone and cephalotine. The rate of resistance to Tazobactam as a  $\beta$ -lactam antibiotic was relatively low. Enterobacter and Citrobacter had the highest multi drug resistance (MDR). In conclusion the prevalence of infection with ESBLs producing gram negative bacilli in patients with community acquired urinary tract infection (CA-UTI) relatively high in our sampled population. The antibiogram test suggest that colistin is an appropriate antibiotic for these patients, and tazobactam is the most efficient  $\beta$ -lactam antibiotic in this case. However it would be preferable to carry out antibiogram test for high risk patients.

**Keywords:** Antimicrobial Resistance, Extended Spectrum B-Lactamase, Risk Factor, Urinary Tract Infection

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### INTRODUCTION

Urinary tract infection is the most prevalent bacterial infection worldwide [1]. Antibiotics are commonly used against this problem; therefore infection with antibiotic resistant strains of bacteria is a growing concern.

Gram negative bacteria such as Escherichia coli are identified as the major agents causing urinary tract infection [2]. This group of bacteria may develop resistance to all kind of  $\beta$ -lactam antibiotics by producing extended spectrum  $\beta$ -lactamase (ESBLs). This enzyme is produced by bacteria carrying CTX-M genes. The gene can be transferred via plasmid in a relatively short time, consequently it can spread the antibiotic resistance which may cause a crucial problem especially in hospital settings [3].

ESBLs producing organisms may also induce resistance to some of non  $\beta$ -lactam antibiotics including aminoglycosides (e. g. gentamycin), quinolones (e. g. ciprofloxacin) and trimethoprim-sulfamathoxazoles. If the resistance occurred to more than two groups of antibiotics, the isolates are called multidrug resistant (MDR) [4].

The frequency of ESBLs producing organisms among patients with urinary tract infection has been estimated to be 2%-60% in different countries [1, 5]. The antibiotic

resistance is generally growing especially in developing countries. The main risk known factors of infection with ESBLs producing organisms are recent antibiotic use [5, 6], recent hospitalization [7] and diabetes [1].

In this study we tried to identify the prevalence of urinary tract infection with ESBLs producing microorganisms and the distribution of some risk factors among the infected patients. This information provides an overview of this problem for practitioners and helps them to improve health care of patients with urinary tract infection.

#### MATERIALS AND METHODS

This descriptive study was approved by Tabriz University of medical sciences Review Board. A written consent form was obtained from each patient and we tried to keep the personal information of patients confidential.

This study carried out during December 2014 to September 2016 in Tabriz. All the patients diagnosed with urinary infection who were hospitalizes in infectious diseases ward in Imam Reza and Sina hospital of Tabriz were assessed. The urinary analysis of all of these patients was positive (the growth of  $10^5$  CFU bacteria in urine culture and presence of at least 10 WBC in urine analysis) and they had at least one of the following symptoms: fever, dysuria, frequent urination and urgent need for urination. Information about age, gender, underlying disorders and recent antibiotic consumption was documented in special forms for each patient.

Patients with history of hospitalization or residence in long term facilities in the preceding three months and patients who were bed ridden

due to spinal cord injuries and using indwelling urinary catheters were excluded.

The urine specimens of these patients was cultured on blood agar and Eosin Methylene Blue (EMB) agar (Lioflichem, Italia), and incubated at 37°C for 24 hours. Suspected colonies on these environments were identified by API20E system (Biomero, France). Patients who were infected with bacteria other than gram negative bacilli, were excluded from further examinations.

Isolated gram negative bacilli were then undergone antibiotic susceptibility test. In this procedure the susceptibility of isolates was examined through standard agar disk diffusion method according CLSI guideline (2014) [8].

At the first stage, the susceptibility of bacilli was assessed using disks of ceftazidime (30 $\mu$ g), cefotaxime (30 $\mu$ g), ceftriaxone (30 $\mu$ g) and aztreonam (10 $\mu$ g). If the growth of the isolates was inhibited by these antibiotics the test considered positive and the next stage was carried out.

At the second stage the combined disk test (CDT) was used to confirm extended spectrum  $\beta$ -lactamase production. In this stage disks containing caphalosporines (ceftazidime (30 $\mu$ g), cefotaxime (30 $\mu$ g)) with or without clavulanic acid was applied. The test was considered positive if the inhibition zone was more than 5mm larger around the disks with clavulanic than without clavolanic acid ones.

For the isolates confirmed to be extended spectrum  $\beta$ -lactamase producers, susceptibility to 18 antibiotics was examined, again by the disk diffusion method: amikacin (30 $\mu$ g), aztreonam (10 $\mu$ g), cefotaxime (30 $\mu$ g), ceftazidime (30 $\mu$ g), ceftriaxone (30 $\mu$ g), cephalotine (30 $\mu$ g), ciprofloxacin (5 $\mu$ g), colostin (10 $\mu$ g), cotrimaxazole (1.25/23.75  $\mu$ g), gentamicin (10 $\mu$ g), imipenem (10 $\mu$ g), levofloxacin (10 $\mu$ g), meropenem (10 $\mu$ g), nalidixic acid (30 $\mu$ g), nitrofurantion (30 $\mu$ g), ofloxacin (5 $\mu$ g), piperacilin (10 $\mu$ g), tetracilin (30 $\mu$ g).

The resistance rate and the distribution of assessed underlying factors are shown as percentage in the result section.

## RESULTS

Among 893 patients with urinary infection symptoms and positive urinary analysis, 763 met the inclusion criteria and entered the study. A total of 587 samples of these patients were positive in bacteriological tests (isolation of four gram negative bacilli) (table 1). The urine samples of 106 individuals (49 male (46%) and 61 female (54%) with mean age of 61 (Range: 19-90) years) were positive to extended spectrum  $\beta$ -lactamase producing bacteria (see fig 1 and table1).

**Table 1: The extended spectrum  $\beta$ -lactamase production distribution of isolated gram negative bacilli from 763 patients with urinary infection symptoms and positive urinary analysis (Iran, Tabriz-2015, 2016)**

Microorganism	Isolates (%)	Resistance rate (%)	Multiple drug resistance (MDR) rate (%)
<i>E. coli</i>	116 (19.7)	74 (63.8)	59 (79.7)
<i>Klebsiella pneumoniae</i>	24 (4.1)	18 (75.0)	8 (44.4)
<i>Enterobacter agglomerans</i>	444 (75.6)	12 (2.7)	12 (100)
<i>Citrobacter freundii</i>	3 (0.5)	2 (66.7)	2 (100)
Total	587 (100)	106 (18.1)	81 (76.4)

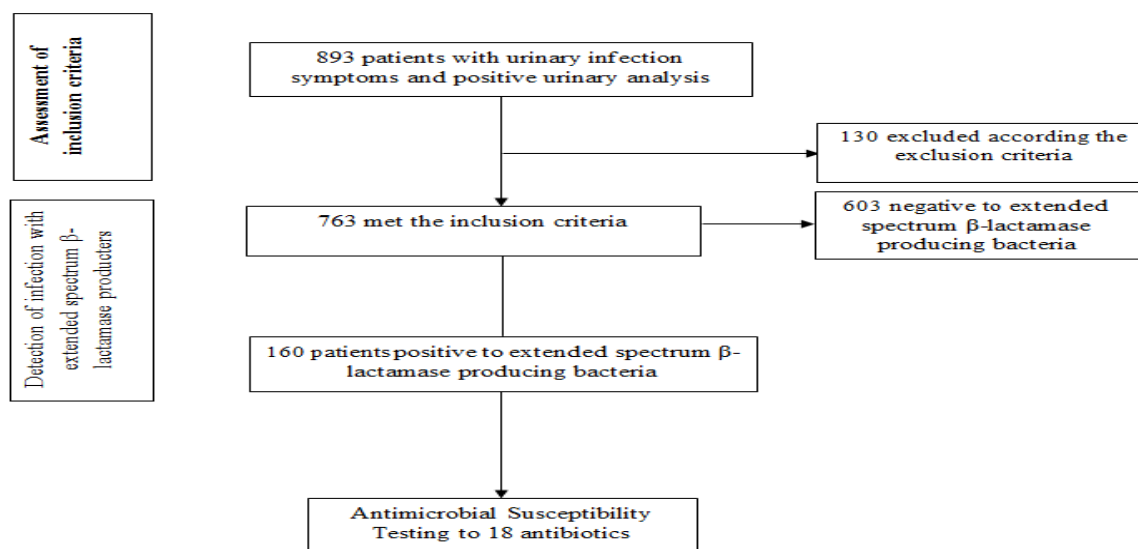
The distribution of some factors which have been recognized to be associated with urinary infection caused by  $\beta$ -lactamase producer gram negative bacteria are demonstrated in table 2.

**Table 2: Distribution of associated factors with infection to  $\beta$ -lactamase producer gram negative bacteria in 160 patients by gender (Iran, Tabriz-2015, 2016)**

Factor	Male (%)	Female (%)	Total (%)
Urolithiasis	9 (18.3)	15 (26.3)	24 (22.6)
Urologic operation	17 (34.6)	7 (12.2)	24 (22.6)
Prostate disease	14 (28.5)		
Diabetic mellitus	13 (26.3)	23 (40.3)	36 (33.9)
Renal insufficiency	12 (24.4)	20 (35)	32 (30.1)
Malignancy	10 (20.4)	6 (10.5)	16 (15)
Consumption of $\beta$ -lactam antibiotics in preceding 3 months	18 (36.7)	17 (29.8)	35 (33)
Consumption of quinolons in preceding 3 months	22 (44.8)	19 (33.3)	41 (38)

Consumption of quinolones was the most frequent factor in overall and in male patients. Diabetes mellitus was the second most frequent factor in overall and the first in female patients.

All isolates were susceptible to colistin and resistant to cefotaxime, ceftriaxone and cephalotine. Enterobacter showed the highest MDR (fig. 2).



**Figure 1: Flow diagram of the process of assessing ESBLs infection in patients with CA-UTI (Iran, Tabriz-2015, 2016)**

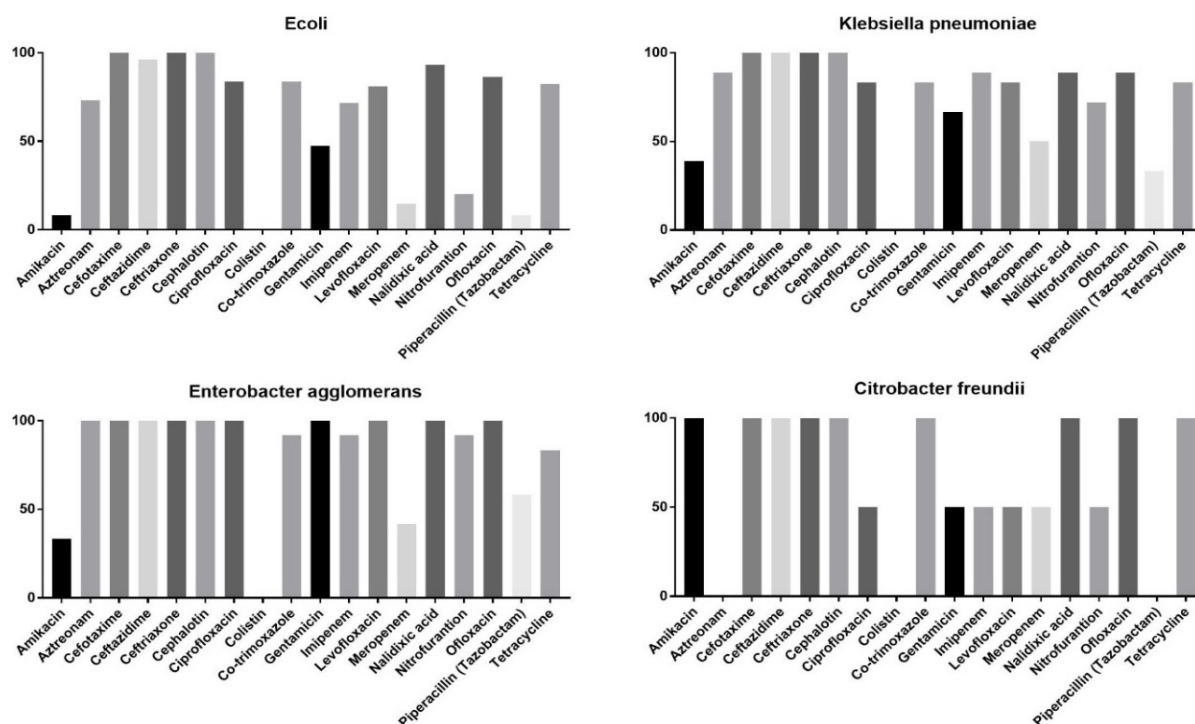


Figure 2: Resistance rate of isolations of four studied bacteria (Iran, Tabriz-2015, 2016)

**DISCUSSION**

In our samples population about one fifth of the CA-UTI patients were infected with ESBLs. In other studies carried out in china and Africa the ESBLs rate was even higher and about 50% [9, 10], however in developed countries like Canada and United States this rate is lower and about 10% [11]. In our study we excluded urinary specimens of bedridden patients, patients who were recently hospitalized and who were using urinary catheters. We aimed to identify the infection with ESBL which had not been acquired from hospital settings; therefore we defined these exclusion criteria. The results of the present investigation support this idea that infections with ESBLs are not a nosocomial infection any more, and are getting a growing concern in the society. Almost all the patients infected with ESBL need to be hospitalized for at least 2 weeks, and this will have economic and social consequences. Therefore, it is crucial to prevent antibacterial resistance and to limit the antibiotic consumption.

The most frequent ESBLs producing isolate was *E. coli* however the resistance rate of *E. coli* was

lower in comparison with *Klebsiella pneumoniae* and *Enterobacter agglomerans*.

In this study all the ESBLs producing organisms were resistant to ceftriaxone, cefotaxime, and cephalotin and more than 80% were resistant to quinolone and trimethoprim-sulfamethoxazole. The most effective antibiotic was colistin with 100% followed by amikasin and piperacilin [tazobactam] with 84% and 81% efficacy rate respectively.

Theoretically the ESBLs gram negative bacilli are not expected to be susceptible to  $\beta$ -lactam antibiotics, however the results of the presented study suggest that this resistance has not been developed to the piperacilin [tazobactam]. This finding is in accordance with other studies which assessed the antibiotics against antibiotic resistant bacteria [12, 13].

We found an unexpectedly high resistance among ESBLs producers against imipenem with only 23.6% of isolates sensitive to this antibiotic. The susceptibility to imipenem has been higher in other similar studies. For example in a study carried out in India all the isolates were sensitive to imipenem [13] and in another study performed

in China the susceptibility rate was more than 95% [9].

In this study the most frequent factors in patients with urinary tract infection caused by ESBLs producing gram negative bacilli were quinolone use in the preceding 3 months followed by diabetes mellitus, consumption of  $\beta$ -lactam antibiotics in the preceding 3 months and renal insufficiency.

### CONCLUSION

The result of this study shows a relatively high prevalence of infection with ESBLs producing gram negative bacilli in patients with CA-UTI. The antibiogram test suggest that colistin, amikasin and piperacilin (tazobactam) are appropriate antibiotic for these patients, however it would be preferable to carry out antibiogram test for high risk patients.

### Conflict of Interest

None

### Financial Disclosure

The authors have no financial disclosure.

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### Implication of the Manuscript

In this study we have provided some information to describe community acquired urinary tract infection due to extended spectrum B-lactamase producing gram negative bacilli in a sample population in Iran. The antibiotic resistance pattern of these patients and the potential risk factors are also demonstrated.

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