RISK FACTORS OF FLUOROQUINOLONE RESISTANCE IN COMMUNITY-ACQUIRED ACUTE PYELONEPHRITIS CAUSED BY *ESCHERICHIA COLI*.

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INTRODUCTION

Acute pyelonephritis (AP) is a very common community infection. The diagnosis of AP is easy. *Escherichia coli* is the principal pathogen. Many antibiotics are used to treat AP such cephalosporins and fluoroquinolones (FQ). Furthermore, several practice guidelines recommend oral FQ as empirical treatment particularly if TMP/SXT resistance rate is higher than 20%. However, *E. coli* resistance to FQ increased in recent years and spread gradually worldwide. In some reports, FQ-resistance rates are higher than 10-20% in North America and Europe.

This increasing resistance limits treatment options and may affect the prognosis of the *E. coli* infections. Thus, precise information about the antimicrobial susceptibility of the community strains of *E. coli* is essential for selecting appropriate empirical agents.

This study was undertaken to describe the resistance rate to antibiotics of *E. coli* community-AP (CAP) and to identify the predictive factors for the isolation of FQ-resistant strains.

PATIENTS AND METHODS

Study design and population

This was a retrospective analytic study of patients admitted for CAP at infectious diseases department in the teaching hospital of Monastir (Tunisia) between 1999 and 2009. All the patients over 14 years old who were diagnosed CAP and whose pathogen was confirmed to be *E. coli* by urine culture were enrolled. Only patients treated as inpatients were included. Healthcare-associated infections were excluded. This study was performed by reviewing the medical records and conducting an analysis of the antimicrobial susceptibility data of our microbiology laboratory.

Definitions

AP was defined as 1) fever ≥ 37,8°C, 2) flank pain and/or costovertebral tenderness, 3) urinary tract symptoms, 4) more than 10^4 white blood cells /ml and 5) quantitative urine culture with bacterial growth of more than 10^5 CFU/ml.

Resistance to FQ was defined by resistance to ciprofloxacin and/or ofloxacin.

Laboratory methods

Identification of *E. coli* was performed by API 20E (bioMérieux, France). The study of antibiotic susceptibility was performed by agar diffusion according to Antibiogram Committee of the French Microbiology Society (CA-SFM).

Statistical methods

Categorical variables were analysed by chi-square test or Fisher's test. Univariate analyses were run to describe the distribution, central tendency and variability. Covariates found to be associated with FQ resistance on univariate analysis at a level of significance $p < 0.2$ were eligible for inclusion in a multivariate logistic regression model. SPSS version 17.0 was used for analysis.

RESULTS

Study population

A total of 433 cases of CAP were included. The mean age was 44.4 years (15 – 89) and 128 (29.6%) were male. Dominant comorbid conditions were diabetes (90, 20.8%) and urinary abnormalities (65, 15%) particularly urinary stone (35, 53.8%). AP was complicated in 271 cases (62.6%) (Table 1).

Table 1: Characteristics of 433 *E. coli* CA-AP and univariate analysis of fluoroquinolone resistance.

	All (n = 433)	FQ-Resistant (n = 31)	FQ-Susceptible (n = 402)	*p-Value*
Age, years (Mean ± SD)	44.4 ± 20.4	47.5 ± 20.6	44.2 ± 20.4	0.38
Age ≥ 65 years	101 (23.3%)	9 (29%)	92 (22.8%)	0.43
Male gender	128 (29.6%)	6 (19.3%)	122 (30.3%)	0.09
Diabetes	90 (20.8%)	9 (29%)	81 (20.1%)	0.24
Menopause	77 (24.9%)	10 (32.2%)	67 (16.6%)	0.069
Pregnancy	27 (8.7%)	2 (6.4%)	25 (6.2%)	0.95
History of UTI	118 (27.3%)	11 (34.3%)	107 (26.6%)	0.28
Hospitalisation in the last year	27 (6.2%)	5 (15.6%)	22 (5.4%)	**0.024**
Antibiotic therapy in the last year	66 (15.2%)	9 (29%)	57 (14.1%)	**0.038**
Urinary catheterisation	9 (2.1%)	3 (9.3%)	6 (1.5%)	**0.002**
Uropathology	83 (19.2%)	5 (15.6%)	78 (19.4%)	0.66
Urolithiasis	35 (8%)	3 (9.3%)	32 (7.9%)	0.53
Chronic renal failure	9 (2.1%)	1 (3.1%)	8 (2%)	0.64
Complicated AP	271 (62.6%)	20 (62.5%)	251 (62.4%)	0.81
Bacteraemia	38 (8.7%)	1 (3.1%)	37 (9.2%)	0.25
Temperature on admission, °C	38.5 ± 0.8	38.1 ± 0.9	38.6 ± 0.85	**0.002**
C-reactive protein, mg/ml (Mean ± SD)	106.1 ± 75.6	72.8 ± 60.1	109.3 ± 76.2	**0.014**
Leucocyte count, $10^3/mm^3$ (Mean ± SD)	12.8 ± 5.9	12.4 ± 8.4	12.8 ± 5.7	0.72
Creatinine, µmol/l (Mean ± SD)	92.6 ± 45.3	88.7 ± 42.6	92.9 ± 45.6	0.61

Microbiologic data

The antimicrobial susceptibility profiles are displayed in Figure 1. The highest resistance rates are noted for amoxicillin (58.7%), amoxicillin/clavulanic acid (37.9%) and trimethoprim/sulfamethoxazole (TMP/SXT) (35.9%).

Thirty one strains (7.1%) were resistant to FQ. Of them, **12 (38.7%) were extended-spectrum betalactamase (ESBL)-producing** (Figure 2). All ESBL-producing strains are resistant to FQ ($p < 0.001$) (Table 2).

Figure 1: Resistance rates of *E. coli* strains.

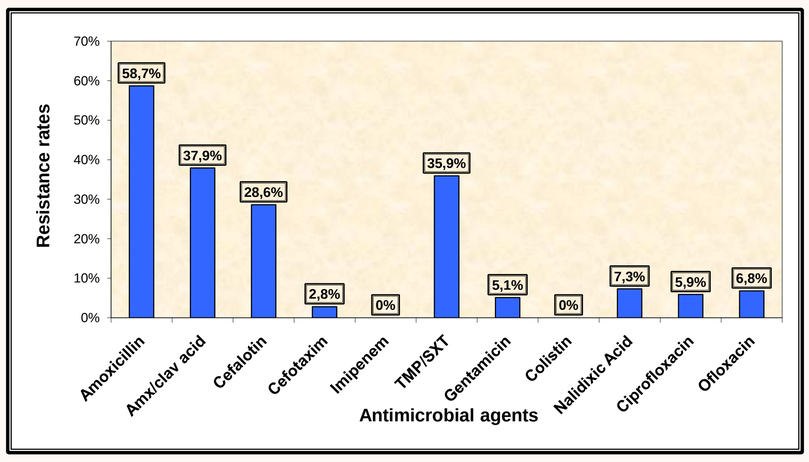

Figure 2: Distribution of *E. coli* ESBL and FQ-R during period 1999-2009.

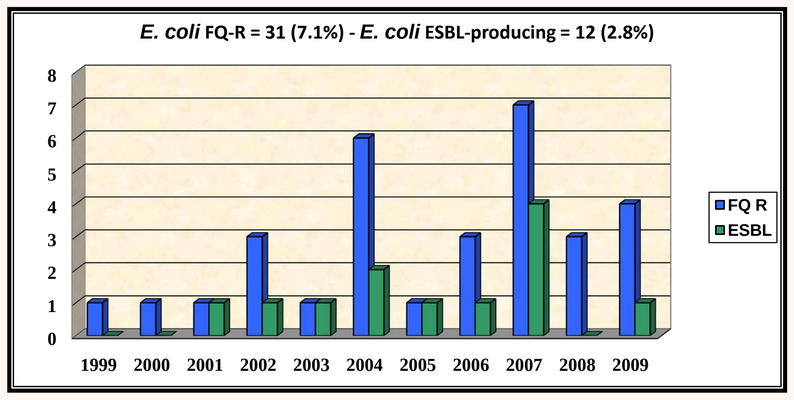

Table 2: Susceptibility of *E. coli* ESBL strains to fluoroquinolones.

	Fluoroquinolone resistance		Total
	Susceptible	Resistant	
ESBL –	402 (92.8%)	19 (4.4%)	421 (97.2%)
ESBL +	0 (0%)	12 (2.8%)	12 (2.8%)
Total	402 (92.8%)	31 (7.2%)	433 (100%)

Risk factor analysis

All the 433 patients enrolled were analysed for the risk factors to FQ resistance (Table 1). In univariate analysis FQ resistance was correlated to urinary catheterization ($p = 0.002$), antibiotic use in the previous 12 months ($p = 0.038$) and hospitalization in the previous 12 months ($p = 0.024$).

Independent risk factors associated with the isolation of an *E. coli* FQ-resistant strain were male sex (OR 3.5, $p = 0.023$, 95% CI 1.19–10.35) and menopause (OR 2.8, $p = 0.01$, 95% CI 1.23–6.53), if we analyze only women (Table 3).

Table 3: Multivariate analysis of FQ resistance among *E. coli* strains.

Characteristics	OR	95% CI	*p-Value*
Male gender	**3.5**	**1.19 – 10.35**	**0.023**
Menopause	**2.8**	**1.23 – 6.53**	**0.01**
Hospitalisation in the last year	**1.2**	**0.26 – 6.42**	**0.75**
Antibiotic therapy in the last year	**0.9**	**0.27 – 2.81**	**0.82**
Urinary catheterisation	**5.6**	**0.91 – 34.8**	**0.063**
Temperature on admission	**0.99**	**0.98 - 1**	**0.07**
C-reactive protein	**0.69**	**0.42 – 1.11**	**0.12**

CONCLUSION

❖ CAP due to FQ resistant *E. coli* strains are increasing in Tunisia. Comparatively to Europe, where resistance rates to FQ is >10%, our resistance rates permit to prescribe FQ as empirical treatment for CAP. However, we assist to an increasing of resistance. Thus, efforts are needed to limit FQ prescriptions.

❖ According to our data, male gender and menopause were independent predictive factors for *E. coli* FQ-resistant isolation. Male patients are exposed to prostatic pathology leading to recurrent UTI and antibiotic use, mainly FQ, and urinary catheterisation. In literature, main predictive factors associated to FQ-resistance were: abnormalities of the urinary tract, age >65 years, urinary catheterisation, complicated AP, history of hospitalisation in the last year and previous treatment with antibiotics particularly FQ.

❖ There are several limitations to our study. First, we reported the results of retrospective analysis of a database collected for more than 10 years, in several cases there were several lost values. Second, 62.6% of AP were complicated, probably due to the fact that our hospital is a tertiary university hospital. Therefore, our results may exaggerate the antimicrobial resistance.