

# Antibiotic resistance profiling of Uropathogenic Enterobacteriaceae, Casablanca, Morocco

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## Abstract.

**Introduction:** the urinary tract infection is a pathology frequents as well in community as at the hospital. In last years, there has been increased the incidence of antibiotic resistance in Uropathogenic Enterobacteriaceae. This development explains the need for periodic regional surveillance of this resistance to antibiotics, which poses a real problem of public health, because it affects several molecules ranging from  $\beta$ -lactam to quinolones.

**Objective:** the aims of this study is to determine the profile of antibiotic resistance of Uropathogenic Enterobacteriaceae isolated from medical analysis laboratories in Casablanca, Morocco.

**Materials and methods:** This is a prospective study that was conducted on patients who visited medical analysis laboratories in Casablanca city, for urinalysis test from 01 January 2017 to 30 December 2018 (a two full years). The culture was performed according to the usual techniques, and the antibiogram was done according to the recommendations of the Antibiogram Committee of the French Society of Microbiology. The statistical analysis was performed using Microsoft Excel (**Microsoft 2016**).

**Results:** During our study, we reported 18% of urinary tract infections, Sex ratio F/M was 1.79. In addition, Enterobacteriaceae were the most common germs. Of all the strains isolated, we noted a predominance of *Escherichia coli* with 75.41%) and *Klebsiella spp* with 17.05%.

In the course of this study period, we observed high rates of resistance to the main classes of antibiotics, and an overall increase between 2017 and 2018 in this resistance to the majority of  $\beta$ -lactam antibiotics, quinolones and aminoglycosides for almost all species of Uropathogenic Enterobacteriaceae. However, amikacin was the most active molecule against the Uropathogenic Enterobacteriaceae strains isolates.

**Conclusion:** The development of resistance of Uropathogenic Enterobacteriaceae to antibiotics is a worrying phenomenon that exposes us to difficulties in the therapeutic management of infections. The current control of antimicrobial resistance is a real emergency and requires the involvement of public awareness before government instructions.

**Key Words:** Urinary tract infection, Cytobacteriological Urine Examination (ECBU), Enterobacteriaceae, antibiogram, antibiotic resistance.

## 1 Introduction

Urinary tract infections (UTIs) are a severe public health problem and are caused by a range of pathogens, but most commonly by Enterobacteriaceae family: *Escherichia coli*, *Klebsiella spp*, *Proteus spp*, *Enterobacter spp* [1]. According to the world health organization "WHO", urinary Enterobacteriaceae infection is one of the most common infections acquired in community and hospital [2].

The routine therapy of UTIs is based on the use of antibiotics such as  $\beta$ -lactams, quinolones and aminoglycosides in many countries. Unfortunately, the widespread and misuse of these antibiotics resulted in the increasing rate of resistance to them in the societies [3].

In the last years, the increase in rates of antibiotic resistance among Enterobacteriaceae has posed

challenges in choosing regimens, especially when infection due to multidrug resistant Enterobacteriaceae are suspected or endemic. Also, it's become a major international public health issue, raising fears of therapeutic impasses, that's why it has the priority for surveillance and resistance studies given their high frequency and severity [4, 5].

In Morocco, the data on resistance to antibiotics of Uropathogenic Enterobacteriaceae are very limited and needs further investigations [6, 7].

Therefore, the global purpose of our study is to describe the antibiotic resistance profiling of Uropathogenic Enterobacteriaceae strains isolated at medical analysis laboratories in Casablanca, Morocco, in order to supervise their emergence and to restrict the spread in the population.

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## 2 Materials and methods

### Setting

This study was designed as a point-prevalence survey performed between **01 January 2017 and 31 December 2018**, it was conducted in medical analysis laboratories, Casablanca, Morocco. Casablanca is the economical capital of Morocco and the largest city in country.

The activities of those laboratories consist in carrying out medical analyzes on behalf of private clients, clinics and hospitals, it admitted patient from all specialties and all ages from all regions of Morocco.

### Study population and data Collection

2090 urines samples were collected throughout Casablanca from the health facilities, for each patient who came to the laboratory for a cyto bacteriological examination of urines, a sterile sampling tube was given.

Patients were assisted with strict hygiene measures to ensure an aseptic sample. Prior to the collection, a survey form was made available to capture patient's details, these were related to personal and medical information.

### Collection and identification of strains

The biologic criteria of inclusion were a pure bacterial culture with a colony count  $\geq 105$  CFU/ml associated with a leukocytes count  $\geq 104$ /ml. Culture was performed by inoculating 10 mL of urine onto CLED (Cystine Lactose Electrolyt Deficien) agar. After incubation at 37°C aerobically overnight, bacteria were identified using routine microbiologic procedures including biochemical test (API 10E or 20E *system-bioMerieux*®, Marcy l'Etoile, France and Vitex 2 compact 15 *system-bioMerieux*®).

### Antimicrobial drug susceptibility testing

The study of antibiotic susceptibility was carried out by the Muller Hinton agar (*Bio-Rad, Marnes-la-Coquette, France*) diffusion technique and VITEK 2 compact 15 *system bioMerieux*® cards. Following overnight incubation, the inhibition zone diameters were measured, each strain was classified as susceptible (S), intermediate (I) or resistant (R) with interpretative reading according to the recommendations of the antibiogram committee of the French Microbiology Society (CA-SFM) [8].

All Uropathogenic Enterobacteriaceae strains were subjected to antimicrobial susceptibility testing against five antibiotic classes: Penicillin, cephalosporin, fluoroquinolones, aminoglycosides and folate pathway inhibitors (Trimethoprim-sulfamethoxazole).

### Statistical analysis

Data were analyzed using the statistical software Excel, Microsoft 2016. This data included the identification number, the patient's name, the date of isolation, the

germ identified, as well as the antibiotics tested with their susceptibility profile (S, I, R).

Categorical variable were expressed as percentages, and continuous variable were expressed as means  $\pm$  SD or median or median. Prevalence of infected patients were calculated.

## 3 Results

### Patient characteristics

During the study period, 2090 urine samples were collected, included 374 infected patients had urinary tract infection (18% of positivity).

The average age of patients infected in our series was  $34.77 \pm$  years old with extremes age ranging from 1 month to 97 years.

The most common symptoms observed among patients infected are fever and urinary and kidney problems. Urinary cytology showed erythrocytes, polynuclear neutrophils infiltrates, epithelial cells, yeasts and urinary crystals, of which calcium oxalate crystals were the most numerous.

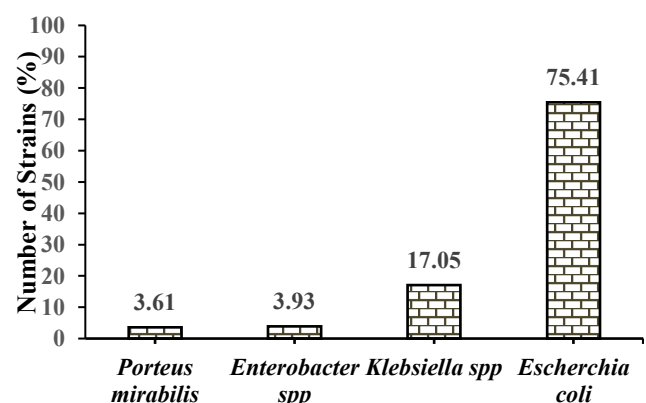
The female sex was predominant with 64.17% female compared to 35.83% male, with a F/M sex ratio of 1.79 (240 females and 134 males patient).

### Prevalence and pathogens of infections

We isolated 381 bacteria with 306 (80,31 %) Enterobacteriaceae, 35(9,19 %) Non fermenting Gram-negative Bacilli ferment and 40 (10,5%) Gram positive cocci.

There were 306 non-duplicate Enterobacteriaceae isolates recovered from the infected patients (some of these patients had UTIs caused by more than one organism in the same episode).

The majority of uropathogens were *Escherichia coli* with 72% (230 strains, followed by *Klebsiella spp* (17.05%). On the other hand, the other Uropathogenic species (*Enterobacter spp*, *Proteus spp*) were also isolated but with very low proportion. The distribution of the bacteria in patients with UTIs is shown in **Figure 1**.



**Figure 1** : The frequency of distribution of isolated bacterial strains

**Antibiotic Resistance of Uropathogenic Enterobacteriaceae**

In the course of our study, we sought to determine and interpret the profiling of Uropathogenic Enterobacteriaceae to various antibiotics tested according to CASFM standards.

**Profile and development of  $\beta$ -lactams antibiotics resistance**

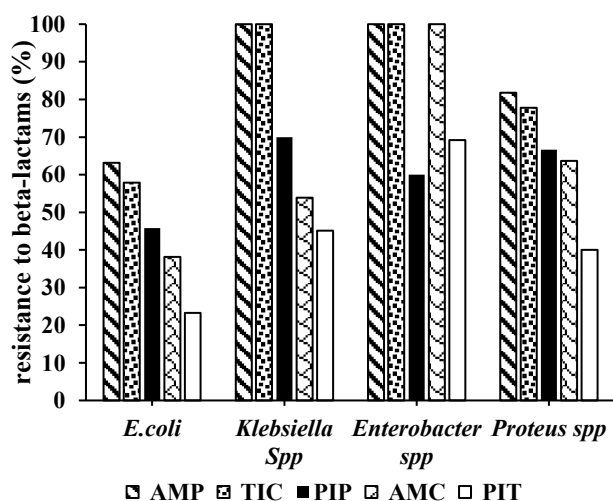
The antibiotic resistance profiling of the different Uropathogenic germs shows a high resistance rate of *E. coli* for ampicillin (63.16%), Ticarcilin (57.87). As well as, for the amoxicillin-clavulanic acid combination (38.16%). The resistance rate of *E. coli* strains to 3rd generation cephalosporin was 16.9% and 16.96 % for Cefoxitin (2nd generation cephalosporin).

With regard to *Klebsiella spp* strains, resistance was representatively of 53.84%, 46.77%, 39.22% for the combination of Amoxicillin-Clavulanic acid, 3rd generation cephalosporin and Cefoxitin.

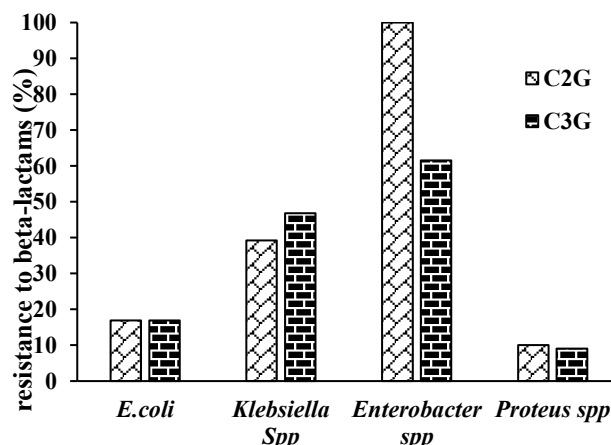
In addition, *Enterobacter spp* had significant resistance to  $\beta$ -lactams with percentages of 76.72%, 61.54% respectively for the combination of Amoxicillin-Clavulanic acid and 3rd generation cephalosporin.

We also noted that 77.77% of *Proteus spp* strains are resistant to the combination of Amoxicillin-Clavulanic acid. While cephalosporin remains the most active antibiotics on these strains.

Rate of  $\beta$ -lactams antibiotics resistance for Enterobacteriaceae summarized in **Figure 2** and **3**.



**Figure 2** : Beta-lactam (penicillin) resistance profile, of uropathogenic isolates (%)

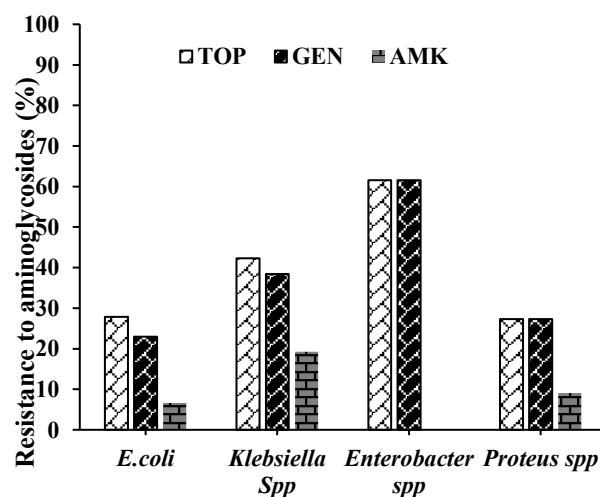


**Figure 3** Beta-lactam (cephalosporin) resistance profiling of uropathogenic isolates (%)

**Profile and development of aminoglycosides antibiotic resistance**

For *E. coli* strains, we recorded 27.85% resistance for Tobramycin and 22.93% for Gentamicin. we also noted that *Klebsiella spp* strains register a moderate resistance to aminoglycosides which reaches a prevalence of 42.31% to Tobramycin and 38.46% to Gentamicin. Whereas, *Enterobacter spp* strains showed significant resistance to Tobramycin and Gentamicin (61.54%). The level of resistance of *Proteus spp* to aminoglycosides is 27.27% for Tobramycin and Gentamicin. Amikacin retains good activity against strains of Uropathogenic Enterobacteriaceae.

Rate of aminoglycosides antibiotics resistance for Enterobacteriaceae summarized in **Figure 4**.



**Figure 4** : Aminoglycosides resistance profiling of uropathogenic isolates (%)

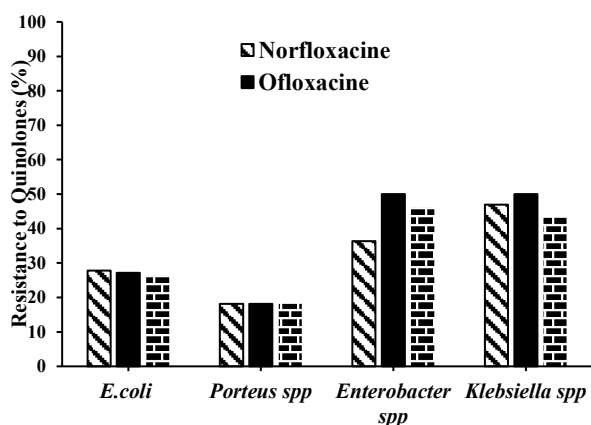
**Profile and development of Quinolones antibiotic resistance**

*E. coli* strains have mild resistance to Quinolones (Ofloxacin 27.19%, Norfloxacin 27.78%, Ciprofloxacin 26.52%). With regard to *Klebsiella spp* strains, we noted

46.94% of resistance for Norfloxacin, 50% for Ofloxacin and 43.14 for ciprofloxacin.

In addition, quinolones resistance in *Enterobacter spp* strains has been identified with 50% of strains resistant to Ofloxacin, 46.15% of strains resistant to ciprofloxacin and 36.36% of strains resistant to Norfloxacin. However, 18.18% of *Proteus spp* strains are resistant to all fluoroquinolones.

Rate of quinolones antibiotics resistance for Enterobacteriaceae summarized in **Figure 5**.



**Figure 5** : Quinolone resistance profiling of uropathogenic isolates (%).

### 3 Discussion

Antibiotic resistance of bacteria a serious threat to global public health. The spread of resistant bacteria leads to a dramatic increase in mortality, morbidity and the cost of treatment [5].

It's an increasingly serious threat to global public health that requires action across all government sectors and society [9].

Among the germs responsible for urinary tract infections, Enterobacteriaceae are the most formidable, because they have mechanisms of resistance to many antibiotics, the high concentration of these germs in the digestive tract, promotes the exchange and dissemination of resistance genes [10].

Thus, for our study with a sample of 2090 patients, we obtained 1716 negative urine cultures (82.11%) and 374 positive cultures, giving a frequency of urinary tract infection of 17.889%. This positivity rate is slightly lower than that obtained in subsequent studies by **Hailaji et al., 2016** in Nouakchott city, Mauritania (18,4%) [4],

and a slightly higher than that found by **Mahmoud et al., 2010** in Fes city, Morocco [10] and **Lahlou et al., 2009** in Meknes city, Morocco [11], who obtained positive urine, and culture rates of 14% and 12,2%, respectively. This situation is justified by the fact that urinary tract infection is one of the most frequent community bacterial infections [12]. The negative urine culture rate represents more than three-quarters of all the examinations carried out in our study. This can be explained by the fact that these patients are subjected to self-medication without medical consultation, which contributes to hide the pathogenic bacterial flora and hinders its multiplication on the culture media in the laboratory [13].

The high frequency of urinary tract infections in women compared to that in men is consistent with that reported in the literature review [13, 4]. In infected patients on our study, 63,17 % were women, whereas 35.83 % were men. This is explained by the fact that urinary tract infection in women can be interpreted by several factors related to the anatomical and physiological nature of their urinary tract since the length of their urethra is much reduced (4 cm). Also, hormonal and physiological changes can promote the occurrence of these infections [13, 4, 14]. Man is relatively more protected because of the anatomical structure of his urinary system. Fecal contamination is then reduced since there is a distance between his anus and his urinary meat [13, 4].

The ascending pathophysiology of urinary tract infection and the strong colonization of the perineum by Enterobacteriaceae of digestive origin, and in particular *Escherichia coli*, associated with specific factors of uropathogenicity such as bacterial adhesins capable of binding to the urinary epithelium explain that the species *Escherichia coli* dominate the epidemiological profile with 75, 41 % followed by *Klebsiella spp* strains with 17.05%. Our results were consistent with a recent notional study, Maghreb and European [1, 4, 14, 11].

Gram-positive bacteria have an adhesion factor, which is lipoteichoic acid, which may explain why Gram-positive cocci is represented with a rate of 10,5 %. Indeed, the

authors of latest study in Madagascar reported 11,4% [15]. However, the authors recent studies in India reported 20 to 30 % of Gram-positive cocci causing UTI and similar result were reported in Nigeria with a High prevalence of *S. aureus* [16, 17]. The epidemiological data of Uropathogens is quite important for countries and towns with poor access to healthcare services and commonly used empirical antibiotic.

The routine therapy of UTIs is performed based on the use of antibiotics, and appropriate antibiotics should be selected by considering the characteristics such as the antibiotic susceptibility pattern of the causative isolate, infection type ( community-acquired or hospital-acquired infections), the patient's conditions including age, gender, history of allergy, underlying diseases, previous antibiotic consumption, taking the other drug, history of previous UTIs, site of UTI and also the pathogenic or normal flora of the causative isolate [18].

Unfortunately, the widespread and misuse of these antibiotics resulted in the increasing rate of resistance to them in the societies. There are different risk factors associated with acquiring multi-drug resistance including the use of antibiotics before causing to UTI, hospitalization for a long time, the use of medical devices such as urinary catheters, having underlying diseases as well as an old age [18].

The study of the antibiotic resistance of strains of uropathogenic Enterobacteriaceae revealed the rate of variable resistance to the antibiotics tested.

In our study, we noted that the majority of *E. coli* strains are resistant to Ampicillin (63.15%), Ticarcillin (57.87%) and Amoxicillin / clavulanic acid (38.16%). These results are consistent with the results of various national and European studies [1, 14]. Furthermore, 16.91% of *E. coli* strains are resistant to cephalosporin, this resistance rate is comparable to the results of some authors including **Hailaji et al., 2016** who reported that resistance in *E. coli* strains to cephalosporins was 19.8% [4].

Résistance to  $\beta$ -lactamins antibiotics usually is acquired due to the production of various types of  $\beta$ -lactamase

enzyme [18]. A group of  $\beta$ -lactamases, called Extended Spectrum  $\beta$ -lactamases is produced after mutations in the ancestral enzymes *bla TEM-1*, *bla TEM-2*, and *blaSHV-1*, and are often transferred by plasmids [18].

This general situation of résistance to  $\beta$ -lactamins antibiotics is the consequence of the selection pressure due to the wide use of  $\beta$ -lactamins in health facilities but also through self-medication.

Quinolones and fluroquinolones are among the most common antibiotics in treatment of UTIs and their excessive use has led to an increased resistance in UTI pathogens [19, 18].

The rate of resistance to quinolones is 27.16% in our study in Casablanca. 20 % in that noted in El Jadida [20] and 27% in Rabat [21].

The global epidemiological situation of resistance of *E. coli* strain to quinolones remains variable, in fact the resistance rate is 10% in the United State [22] s and 50% in China [23].

Mutations in DNA topoisomerases II and IV, decreased uptake of the antibiotics, extrusion of antibiotics via efflux pumps, and plasmid mediated quinolones resistance genes are the major of resistance mechanisms to these antibiotics [18]. *Qnr* genes (*qnr A*, *qnr B* and *qnrC*) are the most important plasmid mediated quinolones resistance genes that cause the antibiotic resistance by inhibiting the binding of quinolones to DNA gyrase and topoisomerases [24]. *Qnr* genes due to locating on different integrons resultats in the disseminated resistance in Enterobacteriaceae strains [24].

With regard to *Klebsiella spp* strains, From the results obtained, 53.85% of the strains studied are resistant to the combination of amoxicillin and clavulanic acid and 45.26% are resistant to cephalosporins. These results are different from those found by **M. Mahmoud et al., 2011** in Algeria, which report resistance rates of 70 % for Amoxicillin and Clavulanic acid, and 11% for Cefotaxime. On the other hand, this observation is reported by several notional studies, Maghreb and European, including that carried out in Nouakchott city,

Mauritania [4] and in Tunisia [25]. In addition, we recorded 41.67% resistance for Ciprofloxacin, 43.14% for Norfloxacin, and 50% for Ofloxacin. These results are consistent with the studies by Haillaji et al., 2016 in Mauritania where approximately 36.5% of *Klebsiella ssp* strains were resistant to ofloxacin and 33.6% for ciprofloxacin [4].

Regarding *Proteus ssp* are naturally resistant to tetracycline. For other antibiotics conventionally used in urinary tract infections, the development of resistance rates over the past decade is worrying. In our study, the resistance rates of *Proteus ssp* strains to Ampicillin, Piperacillin and Amicillins / Clavulanic acid were higher. This finding is consistent with that found by A. Mahamat., 2006 et al in the town of Naim, France [26]. The significant increase in the rate resistance to AMC, Ampicillin and Piperacillin could be explained by the ability of *Proteus ssp* to secrete a wide variety of plasmid  $\beta$ -lactamases which are responsible for lower amino-penicillin activity.

In addition, 9.27% of *Proteus ssp* strains are resistant to cephalosporin, results close to those reported by M. Mahmoud et al., 2010 [27]

Fortunately, quinolones retain excellent activity on *Proteus ssp* strains (18% of resistant strains), this result is similar to that found by M. Mahmoud et al., 2010 in Fez, which reports a resistance rate to ciprofloxacin of 15% [27].

The resistance of *Proteus ssp* strains to quinolones could be linked to the emergence and extension of new resistance mechanisms, including the accumulation of mutations in genes encoding DNA gyrase and topoisomerase IV, the decrease in their intracellular concentration by an increase in the activity of efflux pumps and / or decrease in membrane permeability, and expression of the *Qnr* gene (Quinolone resistance) [28].

Currently, *Enterobacter ssp* strains are beginning to take an important place as opportunistic pathogens responsible for urinary tract infections. We noted an alarming rate of resistance to quinolones, in fact 46.15% of the *Enterobacter ssp* strains are resistant to

ciprofloxacin, 50% resistance to ofloxacin and 36.36% resistance to Norfloxacin. Our rates are a little high compared to several studies, in fact the resistance to quinolones in national studies varies from 0 to 50% [29, 27, 30]. On the other hand, our result is similar to the studies by TOUDJI et al., 2017 in Togo where approximately 63.89% of the *Enterobacter ssp* strains were resistant to Ciprofloxacin, 63.64% to Ofloxacin and 63.64% to Norfloxacin [31].

In our study, we noted an alarming rate of resistance to Aminoglycosides. Indeed, 27.83% of *E. coli* are resistant to Tobramycin, 42.30% of *Klebsiella ssp* strains are also resistant to the same molecule, 61.54 of *Enterobacter ssp* strains and 27.27 of *Proteus ssp* strains are resistant to Tobramycin and Gentamycin. Our rates are very high compared to foreign studies. Indeed, the resistance to aminoglycosides detected in Beirut city, Lebanon and Sousse city, Tunisia remains low and varies from 4 to 10% [25, 32].

The mechanism of resistance to aminoglycosides is essentially the acquisition of modifying enzymes. These enzymes belong to 3 classes corresponding to phosphorylation, acetylation and nucleotidylation activities [33].

In the present study, the presence of phenotypes resistant to all aminoglycosides should be taken into account. Indeed, the current emergence of 16S RNA methyltransferases conferring a high level of resistance to all aminoglycosides used in practice is a worrying phenomenon that requires epidemiological monitoring [33].

Amikacin maintains good activity against Uropathogenic Enterobacteriaceae. However, the rational use of this molecule is mandatory in order to avoid the emergence of multidrug resistant strains.

This study underlines the importance of cytobacteriological examination of urine with antibiogram before any treatment for urinary tract infections to avoid empirical and probabilistic treatments which can promote the emergence and resistance of germs to antibiotics.

Bacterial resistance to antibiotics poses the problem of choice of antibiotic therapy. In Africa, and in particular in Morocco, the majority of patients do not have access to the laboratory and the management of infectious syndromes is probabilistic.

In addition, this resistance is the consequence of selection pressure due to the excessive prescription and sometimes abusive use of broad-spectrum antibiotics both in hospitals and in community settings (dispensing without prescription, self-medication, free sample, etc. ...), without forgetting the impact of poorly controlled food where more and more antibiotics are used in agriculture and breeding. The predominant plasmid determinism of these acquired resistances also favors their dissemination.

#### 4 Conclusion

Uropathogenic Enterobacteriaceae constitute, in our city, an increasing infectious risk with high levels of resistance to antibiotics and the emergence of resistance to last resort molecules in antibacterial therapy, they can lead, in many cases to a therapeutic impasse.

This phenomenon of multi-resistance to antibiotics is a major public health problem in Morocco, worrying and alarming because of the potential risks (increased morbidity and mortality, additional economic costs and installation of highly resistant bacteria in hospital services and in the community).

Better control in terms of strict compliance with hygiene measures, isolation of carriers, the reasoned use of antibiotics and defining therapeutic and prophylactic strategies adapted to local epidemiology are the key actions to slow down their emergence and dissemination. In addition, compliance with the rules of good pharmacy practice for the delivery of drugs, the major role that city pharmacists must play as advisers in antibiotic therapy are all elements to be promoted in controlling the spread of multi-resistance in the community.

The intra- and extra-hospital spread of multidrug-resistant Enterobacteriaceae in urinary tract infections

requires all healthcare establishments to monitor all patients infected with these strains.

Despite everything, other studies are necessary to determine if we are not there in the presence of the emergence of multidrug resistant Enterobacteriaceae and to associate the clinical parameters, therapeutic and the confrontation with the molecular tool allowing the classification and the typing. genes implicated in these resistances.

#### Conflicts of Interest

Authors declare no conflict of interest.

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