# Bacteriological aspects and risk factors for the acquisition of ESBL producing *Enterobacteriaceae* in urinary tract infections in the elderly

## *Aspects bactériologiques et facteurs de risque d'acquisition d'EBLSE dans les infections urinaires du sujet âgé*

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**DOI** :https://doi.org/10.48087/BJMSoa.2022.9103

**Received** : December 21, 2021

**Accepted** : March 16, 2022

**Published** : June 05, 2022



**Citation :**

Benammar S, Segueni A, Courcol R et al. Bacteriological aspects and risk factors for the acquisition of extended-spectrum beta-lactamase-producing *Enterobacteriaceae* in urinary tract infections in the elderly in Batna, Algeria. Batna J Med Sci 2022;9(1):10-16. https://doi.org/10.48087/BJMSoa.2022.9103

## ABSTRACT

**Aim.** Our study aimed to know the antibiotic resistance of the isolated strains, as well as the risk factors for acquiring extended-spectrum beta-lactamase-producing *Enterobacteriaceae*, in the urinary tract infection of the elderly. **Methods.** All the urine specimens received from elderly people at the Microbiology Laboratory of Batna Hospital, Algeria, from March 2012 to March 2014 were included in a prospective observational study. The bacteria were identified by API gallery or mass spectrometry. The antimicrobial susceptibility testing was performed as per CLSI guidelines. Multi-drug resistant gram-negative bacilli were studied by PCR and sequencing to determine their resistance mechanisms. The risk factors for ESBL-E acquisition were determined by univariate analysis. **Results.** From a total of 1024 urinary specimens, 372 microorganisms were isolated. The resistance rates of the community *Escherichia coli* strains to amoxicillin-clavulanic acid (51.2%) and ciprofloxacin (26.5%) were high. In *Enterobacteriaceae*, ESBL (11.4%) were all of the CTX-M type, mainly the CTX-M-15 variant, often associated with the *qnrB* gene. The CTX-M-1 type predominated in *E. coli*. The carbapenemases produced by non-fermenting bacilli were of the oxacillinase-23 and VIM types while none were produced by *Enterobacteriaceae*. A recent history of surgery and antibiotic treatment were the main risk factors identified in the ESBL-E acquisition. **Conclusion.** This study is the first to describe the antibiotic resistance of UTI strains in the elderly in Algeria. Risk factors identified in the acquisition of resistant uropathogens highlight the importance of good hygiene practices and antimicrobial prescription.

**Keywords:** Urinary tract infection, Elderly, Antimicrobial resistance profiles, ESBL-E risk factors, Molecular typing.

## RÉSUMÉ

**Objectif.** Notre étude avait pour objectifs la connaissance du profil de résistance aux antibiotiques des souches isolées dans les infections urinaires du sujet âgé, ainsi que les facteurs de risque d'acquisition d'Entérobactéries productrices de bêta-lactamases à spectre étendu. **Matériels et méthodes.** Tous les échantillons urinaires reçus de personnes âgées au Laboratoire de Microbiologie du CHU- Batna (mars 2012 à mars 2014) ont été inclus dans une étude observationnelle prospective. Les bactéries ont été identifiées par galerie API ou spectrométrie de masse. Les tests de sensibilité aux antimicrobiens ont été effectués conformément aux directives du CLSI. Les bacilles à Gram négatif multirésistants ont été étudiés par PCR et séquençage pour déterminer leurs mécanismes de résistance. Les facteurs de risque d'acquisition de E- BLSE ont été déterminés par analyse univariée. **Résultats.** Sur un total de 1024 prélèvements urinaires, 372 micro-organismes ont été isolés. Les taux de résistance des souches communautaires d'Escherichia *coli* à l'amoxicilline-acide clavulanique (51,2 %) et à la ciprofloxacine (26,5 %) étaient élevés. Chez les *Enterobacteriaceae*, les BLSE (11,4 %) étaient toutes de type CTX-M, principalement le variant CTX-M-15, souvent associé au gène qnrB. Le type CTX-M-1 prédominait chez *E. coli.* Les carbapénémases produites par les bacilles non fermentants étaient de type oxacillinase-23 et VIM alors qu'aucune n'était produite par les Entérobactéries. Un antécédent chirurgical et un traitement antibiotique récents étaient les principaux facteurs de risque identifiés dans l'acquisition des E-BLSE. **Conclusion.** Cette étude est la première à décrire la résistance aux antibiotiques des souches d'IU chez les personnes âgées en Algérie. Les facteurs de risque identifiés dans l'acquisition d'uropathogènes résistants soulignent l'importance des bonnes pratiques d'hygiène et de prescription d'antibiotiques.

**Mots clés :** Infection urinaire, Sujet âgé, Profils d'antibiorésistance, Facteurs de risque d'E-BLSE, Typage moléculaire.

## INTRODUCTION

The profile of elderly population is ranging from healthy to fragile and polypathological **[1]**. Urinary tract infections (UTIs) in the elderly, the leading cause of bacterial and nosocomial infections, are a real problem of public health **[2]**. Several factors contribute to its increasing prevalence **[3]**. Changes in urinary functions and associated comorbidities influence the clinical course and the nature of the involved bacteria. These factors lead to delayed diagnosis and favor the involvement of specific and antibiotic-resistant micro-organisms. As a result, UTIs are responsible for significant morbidity and mortality in the elderly with a risk of severe sepsis elderly with a risk of severe sepsis and death **[4,5].**

Community-acquired urinary tract infections in the elderly have some bacteriological characteristics compared to young adults and may involve emerging opportunistic Gram-negative bacteria. In addition, bacterial resistance is higher due to the history of the elderly subject **[3,6].** The increasing worldwide antibiotic resistance of community uropathogens is a cause of concern, especially with regard to and third generation cephalosporins (3GC) and fluoroquinolones

(FQ). This is illustrated by the emergence and spread of the cefotaximase-Munich (CTX-M) type, community ESBLs, as well as that of plasmid determinants of resistance to FQ **[7-9]**.

In Algeria, a gradual trend towards an ageing population, as well as an increase in life expectancy at birth, are noted. Indeed, the group of elderly people represented 8.7% of the total population in 2015 and will represent more than 14% in 2030 **[10]**. UTIs in the elderly are of interest because of the scarcity of national epidemiological data specific to this age group. To this end, a prospective observational study was conducted in 2012-2014 at the Microbiology Department of the University Hospital of Batna, North-East of Algeria, with the aim of identifying the bacterial epidemiology of UTIs in the elderly together with the antibiotic resistance of isolated strains. A molecular study of multi-resistant bacteria was carried out. The risk factors for the acquisition of community ESBL-*Enterobacteriaceae* were also investigated.

## MATERIALS AND METHODS

### Type of study

This was a prospective study with a descriptive aim of UTIs in the elderly population, conducted in Batna University Hospital, from the 1st of March 2012 to the 31th of March 2014.

### Inclusion criteria

Patients aged of at least 65 years and living in Batna for whom a cytobacteriological examination of urine was requested to confirm a suspected UTI were included with their oral agreement. They consulted on an outpatient basis or were hospitalized in the Batna University Hospital. An information sheet filled up by the clinician accompanied the urine sample; it included basic socio-demographic (name, age and gender) and clinical (justification of microbiological examination of urine and clinical background) information.

### Criteria for non-inclusion

Subjects less than 65 years of age and those with recurrent infection with the same bacterium.

### Size of the study population

It corresponds to the total of urine samples received in the Microbiology department from the elderly patients included, during the study period (25 months).

### Cytobacteriological examination of urine (CBEU)

The urine was examined under a light microscope and seeded onto nutrient agar (NA) and chocolate blood agar (CBA). The plates were incubated at 35°C (under 5% $CO_2$ for CBA) for 24-48 h **[11].** Sabouraud medium was possibly added. The colonies were counted and the result was interpreted according to consensus recommendations. CBEU was considered sterile when less than $10^3$ colony-forming units (CFU)/ml were detected. It was considered positive in case of bacteriuria ≥ [$10^3$-$10^5$] CFU/ml, depending on species, gender and place of acquisition **[1,12].**

Identification of the isolated bacteria was carried out using Api® 20E, 20NE, 20Staph and 20Strep galleries (bioMérieux, France). *Candida* strains were identified after staining. For each identified bacterium, an antimicrobial test was performed using the Mueller-Hinton (MH) agar diffusion method, according to the recommendations and interpretations of the Clinical and Laboratory Standards Institute (CLSI). The validation of the results was ensured by the inclusion of reference strains: *Escherichia coli (E. coli)* ATCC 25922, *Staphylococcus aureus (S. aureus)* ATCC 25923 and *Pseudomonas aeruginosa* (*P. aeruginosa*) ATCC 27853 [18].

In Lille and Saint-Etienne laboratories (France), Gram-negative bacilli (GNB) resistant to 3GC or carbapenems were identified by MALDI-TOF (Matrix Assisted Laser Desorption Ionization - Time of Flight) mass spectrometry (Microflex, Bruker Daltonics, Germany), tested with automated method (VITEK-2, bioMérieux, France), and by diffusion in agar medium (for mecillinam and temocillin) according to the recommendations and interpretations of the Committee of Antibiogram of the French Microbiology Society (CA-SFM) **[14].** Detection of the synthesis of ESBL and/or AmpC at a high level in 3GC-resistant GNBs was carried out by the MAST Discs Combi test AmpC & ESBL Detection Set (Mast Group Ltd, United Kingdom). For carbapenemase-resistant GNBs, the search for carbapenemase production was carried out with the UPLC-MS/MS test as described **[15]**.

### Genotypic tests detecting antimicrobial resistances

In the Saint-Etienne laboratory, amplification of the gene coding for the CTX-M type ESBL was performed by conventional multiplex PCR using primer pairs CTX-M A1/A2 and CTX-825F/825R **[16]**. Amplicons were revealed by capillary electrophoresis (Bio Analyst 2100, Agilent).

Sequencing of the *bla CTX-M* genes was carried out according to the Sanger enzymatic method using a Beckman CEQ 8000 sequencer. The sequences obtained were compared with the database of nucleotide sequences from the NCBI (National Center for Biotechnology Information) site and its BLAST program.

The most prevalent carbapenemase genes were searched for by real-time multiplex PCR for *bla* KPC and *bla* NDM, and by independent real-time PCR for *bla* VIM and *bla* Oxa-48 genes, using Taqman probe for the first 3 genes and Sybr Green for the last one, on a Smart Cycler DX (II) apparatus (Cepheid, USA). The *bla* Oxa-23 gene was tested by real-time PCR on a 7500 thermal cycler (Applied Biosystems).

The detection of the *qnr* genes was carried out by *qnr* multiplex PCR (A, B and S) according to the technique described by Cattoir *et al*. **[17]** with revelation by capillary electrophoresis.

### Statistical analysis

Epidemiological, clinical information and results of bacteriological analysis were reported for each patient. Data processing and statistical analyzes were carried out with SPSS statistics 22 tool. Quantitative variables were expressed as means +/- standard deviations. The proportions were expressed in percentages. The Pearson Chi-2 ($X^2$) test in univariate analysis was used to determine patients' risk factors for the acquisition of ESBL-E by comparing ESBL-secreting *Enterobacteriaceae versus* non-ESBL *Enterobacteriaceae.* The $p$ values < 0.05 were considered to be statistically significant. The Odds ratio was calculated within 95% confidence interval.

## RESULTS

### 1. UTI rates and characteristics of infected patients

From 1024 included samples, 358 (35.0%) were tested positive. The number of infected patients was equally divided between the genders. The average age was 73.5 ± 7.3 years old. Mid-stream urinary samples were predominant, including 271 cases (75.7%).

These UTIs were considered to be community-acquired (CA-UTI) and healthcare-associated (HA-UTI) in 265 cases (74.0%) and 93 cases (26.0%), respectively. In the community setting, UTIs in women (n=140) were diagnosed as acute pyelonephritis (APN) in 37% of cases and considered

In men (n=125), prostatitis was more common than APN. The diagnosis of urosepsis was reported in 4% and 18% of CA and HA cases, respectively, with almost exclusively males.

### 2. Isolated microorganisms

The culture-positive urines were polymicrobial in 14 cases, which allowed the isolation of a total of 372 microorganisms, including 271 CA and 101 HA strains.

In the community setting, *E. coli* was the most prevalent strain (62.7%). A great variety of species were involved within the *Enterobacteriaceae* family, as well as the presence of *Pseudomonas* spp. and *Staphylococcus* spp. at frequencies equal to 3% and 7%, respectively. The four most frequently isolated species were in decreasing order *E. coli, Klebsiella, Proteus* spp. and *S. aureus* **(Table 1).** *E. coli* was predominant in the female UTI, while *Klebsiella* spp., *Serratia* spp. and the *Proteae* family (*Proteus* spp., *Morganella morganii*) were more frequently recovered in males than in females ($p < 0.05$).

In the hospital setting, GNB accounted for only 54.5% of isolates, the other half comprising Gram-positive cocci (23.8%) and *Candida* spp. (21.8%). Among the bacteria described as emerging and opportunistic in the UTI of the elderly, *Aerococcus urinae* and *Leuconostoc* spp. were isolated **(Table 1).**

The difference in bacterial distribution according to the presence or absence of a urinary catheter was statistically significant only for *E. coli* and *Candida* spp. ($p < 0.05$).

**Table1**. Distribution of microorganisms isolated in Community acquired -urinary tract infection (CA-UTI) and healthcare associated- urinary tract infection (HA- UTI) in the elderly.

| Microorganisms | Number (Percentage%) | |
|---|---|---|
| | **CA-ITU** | **HA-ITU** |
| *Escherichia coli* | 170 (62.7%) | 18 (17.8%) |
| *Klebsiella* spp. | 22 (8.1%) | 9 (8.9%) |
| *Proteus* spp. | 16 (5.9 %) | 2 (1.9%) |
| *Morganella morganii* | 10 (3.7%) | 4 (3.9%) |
| *Staphylococcus aureus* | 10 (3.7%) | 4 (3.9%) |
| Coagulase-negative staphylococci | 9 (3.3%) | 7 (6.9%) |
| *Pseudomonas aeruginosa* | 8 (3%) | 8 (7.9%) |
| *Serratia marcescens* | 7 (2.6%) | 1 (0.9%) |
| *Enterococcus* spp. | 6 (2.2%) | 11 (10.9%) |
| *Acinetobacter* spp. | 3 (1.1%) | 4 (3.9%) |
| *Citrobacter* spp. | 3 (1.1%) | - |
| *Streptococcus* spp. | 3 (1.1%) | - |
| *Enterobacter cloacae* | 3 (1.1%) | 8 (7.9%) |
| *Candida* spp. | 1 (0.4%) | 22 (21.8%) |
| *Stenotrophomonas maltophilia* | - | 1 (0.9%) |
| *Leuconostoc* spp. | - | 1 (0.9%) |
| *Aerococcus urinae* | - | 1 (0.9%) |
| **Total** | **271 (100%)** | **101 (100%)** |

***CA-UTI***: community-acquired urinary tract infection; ***HA-UTI***: healthcare associated- urinary tract infection.

### 3. Bacterial resistance to antibiotics

- **Community infections**

Strains of *E. coli* (n=170) were resistant to antibiotics frequently prescribed by general practioners, including amoxicillin-clavulanic acid (51%) and cotrimoxazole (49%). Percentages of resistance to ciprofloxacin exceeded 20%. The activity of cefotaxime, gentamicin, nitrofurantoin and fosfomycin was fairly good **(Figure 1)**.

The resistance of the 24 *Enterobacteriaceae* to 3GC (10.4%) was essentially due to the synthesis of ESBL (17 strains). These ESBL-E were isolated with a prevalence of 7.4%, and exhibited a higher resistance to fluoroquinolones (15/17), cotrimoxazole and gentamicin, but remained susceptible to fosfomycin (17/17), mecillinam (13/14) and temocillin (11/14).

Resistance to ertapenem was identified for a single strain of *Serratia marcescens* by a mechanism involving hyper-produced AmpC associated with ESBL and impermeability.

The resistance of *Enterobacteriaceae* to cephalosporins, gentamicin and quinolones was shown to be significantly higher in men than in women, in parenchymal urinary tract infection than in cystitis, and in complicated UTI than in uncomplicated ones ($p < 0.05$).

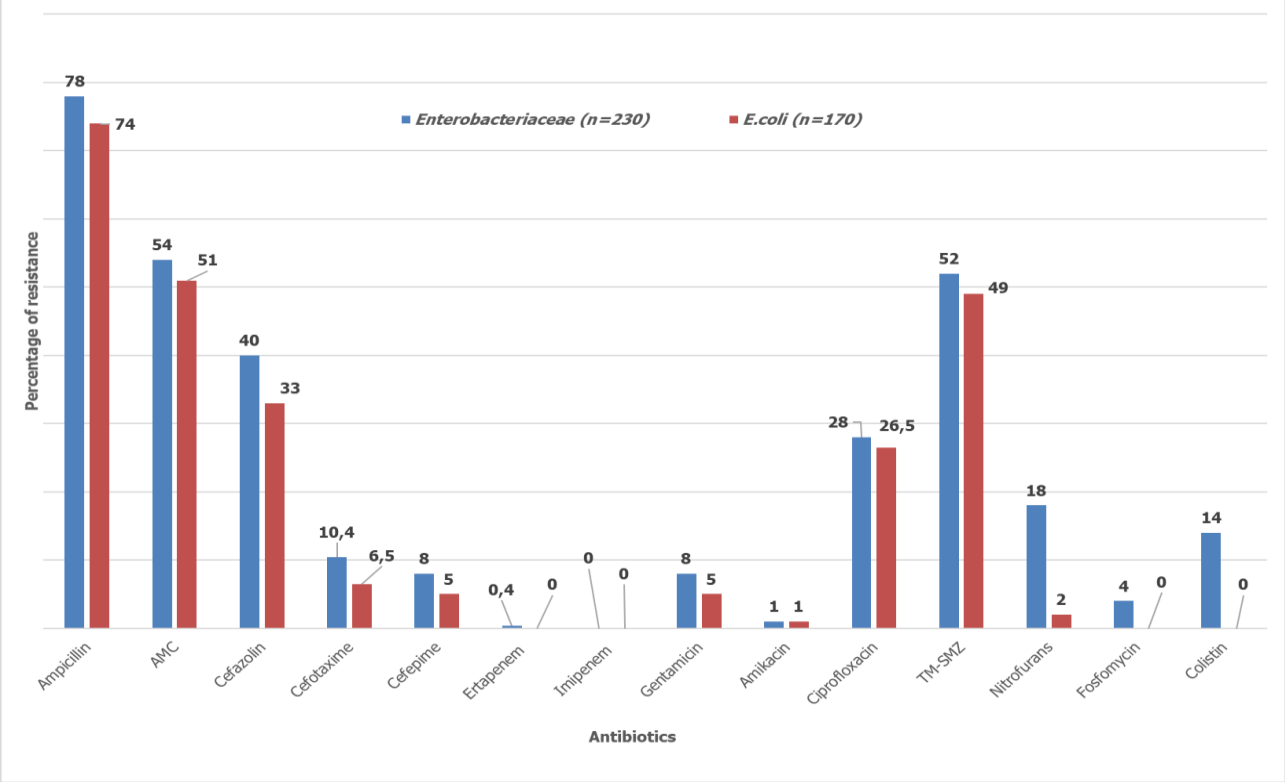
Strains of *Staphylococcus* spp. (n=19) were methicillin-resistant in 8 cases. These eight strains were characterized by associated resistance to ofloxacin, amikacin and cotrimoxazole. All these strains were susceptible to glycopeptides with low resistance rate to gentamicin (2/19) and fosfomycin (1/19).

*Enterococcus faecalis* (n=6) remained sensitive to ampicillin, fosfomycin and nitrofurantoin.

For *P. aeruginosa* (n=8), a low level of resistance to all antibiotics was observed. Only one strain produced a VIM metallo-β-lactamase (carbapenemase).

- **Healthcare-associated infections**

*Enterobacteriaceae* of hospital origin (n=42) were resistant to cefotaxime (38.1%), gentamicin (33.3%), ciprofloxacin (54.8%) and cotrimoxazole (67%), while amikacin, fosfomycin, and carbapenems maintained an excellent activity (95%, 95,3% and 100% respectively). Their resistance to 3GC was mainly due to the synthesis of ESBL




***AMC***: amoxicillin-clavulanic acid; ***TM/SMZ***: trimethoprim/sulfamethoxazole (cotrimoxazole).
Colistin (resistance = 14%): natural resistance of some species of *Enterobacteriaceae* to this antibiotic (no acquired resistance noted).

**Figure 1.** Percentage of *E. coli* and *Enterobacteriaceae* resistance to antibiotics in community acquired-urinary tract infection in elderly.

*P. aeruginosa* were poorly resistant to antibiotics, whereas a clear multiresistance was observed for *Acinetobacter baumannii* and *Stenotrophomonas* spp. Indeed, 4 strains out of 5 belonging to the last two species were resistant to carbapenems and/or 3GC (ESBL), and 3/5 to fluoroquinolones and aminosides. Only colistin and rifampicin remained active on these strains.

*Staphylococci* were mostly methicillin-resistant (8/11). *Enterococcus* spp. was also highly resistant to ampicillin (7/11) and levofloxacin (8/11).

- **Genotypic study of multi-resistant GNBs**

Screening of CTX-M in 27 strains of *Enterobacteriaceae* showed that they all belonged to the CTX-M group 1. Among them, there was a predominance (59.3%) of the CTX-M-15 type (16/27), followed by CTX-M-3 (6/27) and CTX-M-1 (5/27). These 3 types of CTX-M were equally divided between CA and HA strains. CTX-M-15 was the only type identified in *S. marcescens* and *M. morganii*, and predominated in *K. pneumoniae* while CTX-M-1 was only found in *E. coli.*

The *qnr* gene searched for in the ESBL CTX-M (+) strains was present in 7 strains (25.9%), 6 of them being resistant to fluoroquinolones. The *qnr*-positive strains belonged to type B; they were mostly isolated from the HA strains (5/7) and were associated with a very large predominance of the CTX-M-15 type and the *K. pneumoniae* species **(Table 2).**

The *P. aeruginosa* strain and the 2 carbapenem-resistant strains of *A. baumannii* were positive for VIM (metallo β-lactamase) and oxacillinase-23, respectively.

Carbapenemase testing by UPLC-MS/MS and PCR was

**Table2.** PCR results on *bla qnr,* PCR and sequencing *bla CTX-M* for multidrug resistant *Enterobacteriaceae.*

| Bacterial species | CTX-M clone | CA-UTI / HA-UTI | PCR gene *qnr* | N |
|---|---|---|---|---|
| *Klebsiella pneumoniae* | CTX-M-15 | HA-UTI | *qnr* B | 4 |
| *Klebsiella pneumoniae* | CTX-M-15 | CA-UTI | *qnr* B | 1 |
| *Klebsiella pneumoniae* | CTX-M-15 | CA-UTI | Negative | 2 |
| *Klebsiella pneumoniae* | CTX-M-15 | HA-UTI | Negative | 1 |
| *Klebsiella pneumoniae* | CTX-M-3 | CA-UTI | *qnr* B | 1 |
| *Klebsiella pneumoniae* | CTX-M-3 | CA- UTI | Negative | 2 |
| *Escherichia coli* | CTX-M-1 | CA- UTI | Negative | 3 |
| *Escherichia coli* | CTX-M-1 | HA-UTI | Negative | 2 |
| *Escherichia coli* | CTX-M-15 | CA- UTI | Negative | 2 |
| *Escherichia coli* | CTX-M-15 | HA-UTI | Negative | 1 |
| *Escherichia coli* | CTX-M-3 | HA-UTI | Negative | 1 |
| *Escherichia coli* | CTX-M-3 | HA-UTI | Negative | 2 |
| *Serratia marcescens* | CTX-M-15 | HA-UTI | *qnr* B | 1 |
| *Serratia marcescens* | CTX-M-15 | CA- UTI | Negative | 3 |
| *Morganella morganii* | CTX-M-15 | HA-UTI | Negative | 1 |

***CA-UTI***: community-acquired urinary tract infection; ***HA-UTI***: healthcare associated- urinary tract infection.

**Table2.** PCR results on *bla qnr,* PCR and sequençing *bla CTX-M* for multidrug resistant *Enterobacteriaceae.*

| Bacterial species | CTX-M clone | CA-UTI / HA-UTI | PCR gene *qnr* | N |
|---|---|---|---|---|
| *Klebsiella pneumoniae* | CTX-M-15 | HA-UTI | *qnr* B | 4 |
| *Klebsiella pneumoniae* | CTX-M-15 | CA-UTI | *qnr* B | 1 |
| *Klebsiella pneumoniae* | CTX-M-15 | CA-UTI | Negative | 2 |
| *Klebsiella pneumoniae* | CTX-M-15 | HA-UTI | Negative | 1 |
| *Klebsiella pneumoniae* | CTX-M-3 | CA-UTI | *qnr* B | 1 |
| *Klebsiella pneumoniae* | CTX-M-3 | CA- UTI | Negative | 2 |
| *Escherichia coli* | CTX-M-1 | CA- UTI | Negative | 3 |
| *Escherichia coli* | CTX-M-1 | HA-UTI | Negative | 2 |
| *Escherichia coli* | CTX-M-15 | CA- UTI | Negative | 2 |
| *Escherichia coli* | CTX-M-15 | HA-UTI | Negative | 1 |
| *Escherichia coli* | CTX-M-3 | HA-UTI | Negative | 1 |
| *Escherichia coli* | CTX-M-3 | HA-UTI | Negative | 2 |
| *Serratia marcescens* | CTX-M-15 | HA-UTI | *qnr* B | 1 |
| *Serratia marcescens* | CTX-M-15 | CA- UTI | Negative | 3 |
| *Morganella morganii* | CTX-M-15 | HA-UTI | Negative | 1 |

***CA-UTI***: community-acquired urinary tract infection**; *HA-UTI***: healthcare associated- urinary tract infection.

- **Risk factors associated to E-ESBL urinary tract infection**

A univariate analysis of the different variables included in this study (according to the literature) was carried out between patients infected with ESBL and non-ESBL *Enterobacteriaceae* in CA-UTI. The following risk factors were identified with a *p* value below < 0.05: male sex, recent history of hospitalization (< 6 months), antibiotic therapy (3GC and FQ), current or past urinary catheterization, recurrent UTI, recent (< 6 months) urinary tract procedures and other surgery **(Table 3).**

## DISCUSSION

This study shows that the resistance rates to usually-prescribed antibiotics of CA and HA bacteria were high. Recent surgery, antibiotic treatment and hospitalization were associated to ESBL-*Enterobacteriaceae* (ESBL-E), which were all of the CTX-M type (mainly variant 15) and widely associated with *qnrB* genes, while the CTX-M-1 variant predominated in ESLB-*E. coli*.

This is the first prospective study carried out on symptomatic UTI in the elderly in Algeria and taking into account clinical, bacteriological and molecular parameters. This study makes a distinction between CA-UTI and HA-UTI.

In terms of microbial epidemiology, the isolation of non-fermentative bacilli and Gram-positive cocci in a community environment was a specificity reported in the UTI of elderly subjects at a variable frequency. *S. aureus* is currently implicated with a high prevalence in patients without a history of hospitalization but suffering from a dermatological pathology **[18].** Our patients also included peritoneal dialysis and/or diabetic patients with skin infection. We also observed the presence of species of *Enterobacteriaceae* that are usually of care-acquired origin (*Serratia* spp., *Enterobacter* spp., *M. morganii*).

In our hospital cohort, the high prevalence of *Candida* spp. and Gram-positive cocci was explained by (i) the urinary catheterization which was very common, (ii) the numerous co-morbidities (diabetes, immunosuppression, chronic urological pathologies) suffered by the patients, (iii) the long duration of hospitalization, and (iv) the numerous

In the community setting, the prevalence of *E. coli* resistance to ampicillin, amoxicillin-clavulanic acid and cotrimoxazole was very high, exceeding the results of previous studies **[2, 19].** Resistance to ciprofloxacin was 26.5%, no longer allowing its use as a probabilistic treatment. In a recent Algerian study on UTI in the general population, resistance to FQ was found to be 22.7% for *E. coli* **[20].** This data was close to that of our results. In Europe, *E. coli* resistance to ciprofloxacin is generally lower, ranging from 4.8% to 30.8% with a north-south gradient **[21].**

The resistance of *E. coli* to cefotaxime (6.5%) and gentamicin (4.7%) was within the limits provided by the literature **[22].** The antibiotics that remained extremely active on *E. coli* were shown to be carbapenems, fosfomycin, nitrofurantoin and amikacin (< 3%).

In the case of *Enterobacteriaceae*, a gender-specific difference in resistance as well as a progressive development of resistance rates to almost all antibiotics has been reported in the literature **[21, 22].**

In a nosocomial environment, the rates of resistance of *Enterobacteriaceae* and staphylococci to antibiotics were higher than those found in European data. It is recognized that resistance levels depend on the frequency of antibiotic use, the quality of hospital care, social factors, underlying diseases and levels of immunization **[23].**

*A. baumannii* species was frequently multi-resistant, which is in line with Algerian epidemiology **[24]**, and raised the problem of alternative treatments. In France, the resistance rates of this species remain fairly low compared with our results **[23].**

ESBL-bacteria were isolated with a low prevalence in the community (4.7% for *E. coli* and 7.4% for *Enterobacteriaceae*), lower than in several studies **[25, 26],** whereas in the hospital environment, the frequency of ESBL-*E. coli* was very high.

It is essential to preserve the activity of 3GC, FQ and carbapenems. As shown in this study: fosfomycin exhibited an excellent activity against all species of ESBL *Enterobacteriaceae*, *Enterococcus* spp. and *Staphylococcus* spp. Nitrofurantoin was highly active against *Enterococcus*

spp. as well as all *E. coli* and 3GC-sensitive *Enterobacteriaceae*. Low resistance of community ESBL-E bacteria was detected against pivmecillinam and temocillin.

This study revealed the presence of the *bla CTX-M* gene for all ESBLs and the high prevalence of the CTX-M-15 type in our setting, in accordance with current Algerian and world epidemiology, both within the community and hospital **[8, 20].**

This study is the first to report the presence of the CTX-M-1 type in Algeria. CTX-M-1 was the first isolated type that led to the discovery of this new class of ESBL in Germany in 1989 and continues to circulate **[26, 27].** The *E. coli* strains isolated in our work mainly produced CTX-M-1, while multiple studies have reported the spread of the community *E. coli* O25-ST131 clonal group, which carries the CTX-M-15 type **[28]**. This relative predominance of the CTX-M-1 type for *E. coli* is difficult to generalize due to the small size of the effective.

The molecular analysis of the carbapenemases revealed the presence of the genes *bla OXA-23* in *A. baumannii* which seems to be endemic in Algeria **[29],** and *bla VIM* in *P. aeruginosa*, which was consistent with the literature **[7].**

Prevalence of *qnr* genes was 26.1%, higher than what was described in the literature **[27]**. The importance of these plasmid determinants of FQ resistance lies in their frequent association with CTX-M block on the same mobile element, which favors their co-selection, co-expression and co-transfer but also their ability, when present in bacteria, to facilitate the increase of stepwise mutations in the *gyrA* and *parC* genes, with the possible consequence of *in vivo* selection of ciprofloxacin-resistant strains **[30, 31]**. These *qnrB* genes were shown to be widely associated with the CTX-M-15 type, the hospital environment and the *K. pneumoniae* species **[32, 33].**

The risk factors that play a role in the acquisition of ESBL were widely explored, more frequently in hospital than in the community **[1, 34-40]**. During the study of risk factors in older people with UTI, it appeared that a recent urinary tract operation was a very important factor, multiplying the risk by a 16-fold factor (95% CI 3.96-66.86). Recent hospitalization multiplied the risk of ESBL by 10 (OR= 9.87; 95% CI 2.83-37.68). In fact, in hospital, patients were subjected to invasive procedures which were undoubtedly a gateway for multi-resistant bacteria **[35].**

A recent antibiotic treatment was implicated with an OR of 8.28 (95% CI 1.12-170.79). Among the antibiotics that were analyzed, only FQ and 3GC were significantly associated with increased risk. They are powerful co-selectors since the resistance genes to these two antibiotic families are located on the same plasmid **[8].** The excessive use of antibiotics in the elderly, combined with their low functional and immune status, strongly contributes to the establishment of a resistant microbiota. Other described risk factors have not been objectified in our study, including the notion of urinary tree abnormalities, diabetes or all forms of immunosuppression.

**Limitations to our study**: its focus on one university hospital (the only one in the city) without including the results of the private analysis laboratories for CA-UTI. In Algeria, specific geriatric structures are lacking. In addition, elderly subjects are not very demanding of consultations and analyzes with an obvious lack of compliance. It was therefore important to have an idea on the subject by analyzing all the samples received in the Microbiology department, over a substantial length of data collection (25 months).

## CONCLUSION

In elderly with UTI, the distribution of microorganisms and antibiotic resistance profiles depend on many parameters including gender, presence of a urinary catheter, topographical location, acquisition sites and prognostic forms. Also, the resistance rates of community and *a fortiori* hospital bacteria to the antibiotics usually prescribed are so high that probabilistic antimicrobial treatments become uncertain in elderly patients weakened by numerous co-morbidities and in whom the drug iatrogeny is significant. For this reason, UCBE should be systematically requested before prescribing an adapted antibiotic therapy from the outset. The initial presumptive treatment before adaptation according to the antimicrobial testing would then only be reserved for serious cases.

Additional work must be promoted to establish a consensus on the management of UTI in elderly subjects in Algeria, adapted to the specific characteristics of the national microbial epidemiology. The risk factors identified as statistically significant in the acquisition of a CA-UTI were mainly represented by a recent history (< 6 months) of surgery, hospitalization and antibiotic therapy (FQ, 3GC). Knowledge of these factors allows a better presumptive antimicrobial treatment in urosepsis. These observations also encourage the promotion of recommandations regarding the prevention of the spread of resistance and the correct use of antibiotics.

## CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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