Scientific Research Publishing

Advances in Bioscience and Biotechnology, 2023, 14, 91-105
https://www.scirp.org/journal/abb
ISSN Online: 2156-8502
ISSN Print: 2156-8456

# Urinary Tract Infections in a Tunisian Orthopedic Institute: Major Strain Microbiological Profile

**Hajer Kilani[1,2*], Salma Kaoual[1,3], Fatma Kaabi[1], Sophia Bouhalila Besbes[1,3]**

[1]Microbiology Unit, Clinical Biology Laboratory, Mohamed Kassab Institute of Orthopedics, Tunis, Tunisia
[2]Faculty of Medicine, LR99ES09 Laboratory of Antibiotic Resistance, University of Tunis El Manar, Tunis, Tunisia
[3]Department of Biology B, Faculty of Pharmacy, University of Monastir, Monastir, Tunisia
Email: *hajerkilani@yahoo.fr

**How to cite this paper:** Kilani, H., Kaoual, S., Kaabi, F. and Besbes, S.B. (2023) Urinary Tract Infections in a Tunisian Orthopedic Institute: Major Strain Microbiological Profile. *Advances in Bioscience and Biotechnology*, **14**, 91-105.
https://doi.org/10.4236/abb.2023.143006

**Received:** January 13, 2023
**Accepted:** March 5, 2023
**Published:** March 8, 2023



## Abstract

**Background:** Urinary Tract Infection (UTI) detected in the hospital and in the community is one of the most common reasons for consultation in everyday practice; it represents a major source of antibiotic consumption. This study's objectives were to outline the microbiological profile of Tunisian patients with UTI and assess antibiotic resistance over the course of three years at the Orthopedic Institute. **Methods:** All strains identified in urine samples between January 1st, 2019, and December 31st, 2021, were included. Standard laboratory procedures were used to identify the bacterium. The Microscan Walkway 40 Plus was used to do biochemical assays and antibiotic susceptibility testing. The EUCAST criteria were used to interpret the findings. **Results:** A total of 1313 strains were isolated. The bacteriological study showed the predominance of enterobacteria (96.8%), especially *E. coli* (52.2%) and *K. pneumoniae* (19.3%). Overall resistance rates to antimicrobial agents were as follows: for hospital, *E. coli* strains were in descending order amoxicillin (73.05%), trimeth/sulfamethoxazole (46.9%), ofloxacin (40.3%), amoxicillin/clavulanic acid (35.05%) and gentamicin (20.5%). Our results showed low resistance to fosfomycin for *E. coli* 2.6% in hospitals while ≥12.1% for *K. pneumoniae*. Amikacin resistance remains medium-low for *E. coli* being ≥20% and 10% for *K. pneumonia*. Nitrofuran resistance has affected 1.06% of *E. coli* strains in hospital settings and 21.5% of *K. pneumoniae*. Extended Spectrum Beta-Lactamases (ESBLs) production was present in a number of enterobacteria (19.3% of *K. pneumoniae* and 14.4% of *E. coli*). **Conclusion:** The prevalence of *E. coli* and *K. pneumoniae* producers ESBLs in UTI is increasing. Rigorous surveillance of resistance rate is necessary to determine appropriate empirical treatment and limit the spread of multiresistant strains.

**Keywords**

Gram-Negative, UTI, Hospital, Community, Bacteria

## 1. Introduction

Urinary Tract Infection (UTI) is a common pathology, both in the community and in the hospital [1]. It is the second most common bacterial infection managed in primary care, accounting for approximately 8.1 million visits to healthcare providers each year [1] [2].

The urinary tract is essentially contaminated upwards from the perineal flora, with the invasion of the bladder, then possibly one or both kidneys and/or the prostate [2]. The migration of bacteria along the urinary tract, despite the urinary flow, requires many virulence factors (somatic antigens, fimbrial and afimbrial adhesins, hemolysin, siderophores, etc.) [2].

Initially, commensal strains were sensitive to the majority of antibiotics with good diffusion in the urinary tract. However, the massive and often abusive use of antibiotics continues to exert strong selection pressure on bacteria, especially those of the intestinal microbiota [3], not to mention the effect of diet and lack of hygiene which exacerbate the problem. Thus, Bacteria Resistant or even Multi-Resistant (BMR) to antibiotics is selected in the digestive flora. The use of fluoroquinolones, cephalosporins, especially taken orally, ceftriaxone and the amoxicillin-clavulanic acid combination increases the risk of developing resistant bacterial UI [3] [4]. This strong selection pressure, therefore, has a major clinical impact. In Tunisia, the digestive carriage of Extended-Spectrum $\beta$-Lactamase (ESBL)-producing *E. coli* in healthy volunteers is 7.5% in adults [5] and 5% in children [6].

The microorganisms most frequently isolated during these infections are Gram-negative bacilli with *Escherichia coli* at the top of the list [2] [3] [4] [5].

UTI should be treated with appropriate antibiotics to avoid aggravation or relapse. However, a recent increase in antibiotic resistance of bacteria responsible for UTI has been observed [2]. Knowledge of the current state of antibiotic resistance of bacteria isolated in UTI optimizes the therapeutic choice and therefore improves the prognosis of these infections. In adults, this infection is mainly due to uropathogenic commensal bacteria such as *E. coli*, *Klebsiella* spp, *Proteus* spp and *Staphylococcus saprophyticus*, *Enterococcus* spp and *Pseudomonas* spp. In children, *E. coli* is responsible for nearly 70% of UTI. *Proteus mirabilis* and *K. pneumoniae* are involved in 7% - 8% of cases, and *Enterococcus* spp is present in 10% of cases. Infections with *Pseudomonas aeruginosa* and *Staphylococcus aureus* occur in specific contexts, underlying uropathy or prior antibiotic therapy. In recent years, Multidrug-Resistant (MDR) bacteria has emerged and been disseminated in the community, initially confined to the hospital setting (6). Among these MDR, enterobacterales produced ESBLs constitute an alarming problem

affecting many countries. To treat UTI, empirical antibiotic treatment is frequently initiated, since antibiotic susceptibility necessitates a minimum of 48 h for testing [7]. However, this strategy of treatment leads to the emergence of resistance to several first-line antimicrobial agents, multidrug resistance and ESBLs, which are raising major concerns worldwide [7] [8].

The purpose of our work is to clarify the germs responsible for UTI in inpatient and outpatient patients over three years and study antibiotic resistance of *Escherichia coli* and *Klebsiella pneumoniae* strains to better guide first-line antibiotic therapy.

## 2. Material and Methods

The work focused on urine cytobacteriological examinations performed in the laboratory of medical biology from January 2019 to December 2021 at Mohamed Kassab Institute of Orthopedics.

The urine comes from patients hospitalized in different departments or attending outpatient consultation.

### 2.1. Bacteriological Study

Each urine was subjected to a routine cytobacteriological examination consisting of:

- Uroculture with germ count bacteriuria.
- A direct examination to assess leukocytology and the figurative elements of the urine (red blood cells, crystals).

The diagnosis of UTI has retained on the basis of a leucocyteuria > $10^4$/ml, clinical signs of the bacterial species and positive bactereuria [9].

The identification of bacteria has been done on cultural characters and biochemical tests through Microscan walkway 40 plus® [10].

### 2.2. Study of Antibiotic Sensitivity

The antibiotic susceptibility study was conducted using the Mueller-Hinton (MH) liquid. The resulting broth will be inoculated into the microplate wells and incubated in the MicroScan Walkaway 40 plus® for 16 to 24 hours at 35˚C ± 1˚C. These are "combo" microplates, with specific panels, containing bacterial identification wells and antibiotic-containing wells at increasing concentrations dedicated to the determination of ATB sensitivity by the measurement of the Minimum Inhibitory Concentration (MIC).

Themicroplates used for enterobacteria were Nuc57, Nc71 for non-fermentative gram-negative bacteria, PBC32 for stapylococci and enterococci and PC37 for streptococci. Well readings are automated based on inhibition of bacterial growth. The results were interpreted by the expert system according to the recommendations of the Committee of Antibiogram of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [11].

*E. coli* ATCC 25922, *Enterococcus feacalis* ATCC 29212, *Pseudomonas aeru-*

*ginosa* ATCC27853, *Staphylococcus aureus* ATCC29213 were used as a control strains.

## 3. Results

Over the course of three years, 5969 cytobacteriological tests were conducted. A total of 1313 cases of UTI have been reported.

### 3.1. Distribution of UI Species Diagnosed during the Study Period

The bacteriological study showed the predominance of enterobacterales (96.8%) especially *Escherichia coli* (52.2%), *Klebsiella pneumoniae* (19.3%) *Enterococcus faecalis* (5.4%). Similar percentages were detected for *Proteus mirabilis* and *Pseudomonas aeruginosa* with 2.2%, both for *Enterobacter cloacae* and *Acinetobacter baumami* complex with 2.1%. When it comes to isolated Gram-positive Cocci, *Staphylococcus aureus* comes in second place behind *Enterococcus faecalis* with 1.1% (Table 1).

### 3.2. Distribution of Major Bacteria by Sex

The average prevalence of *E. coli* strains was higher in women than in men over the course of three years (68%), while the average prevalence of *K. pneumoniae* strains in men over the course of two years was 52.8% (Figure 1).

Our results showed that *K. pneumoniae* were present with the same percentage in women for two years 47% (Figure 1). The sex ratio was 0.4 (216/470) for *E. coli* and 0.9 (121/133) for *K. pneumoniae.*

### 3.3. Distribution of *E. coli* and *K. pneumoniae* by Service

According to our findings, *E. coli* predominates in outpatient services and physical medicine with a comparable percentage of 34.6%, whereas *K. pneumoniae* predominates in the surgical department with a higher percentage of 57%, followed by the physical medicine department with a lower rate of 40.5% (Figure 2).

### 3.4. Antibiotic Resistance of Major Germs Isolated in UTI

The antibiotics most affected by hospital *E. coli* strains were amoxicillin (73.05%), trimeth/sulfamethoxazole (46.9%), ofloxacin (40.3%), amoxicillin/clavulanic

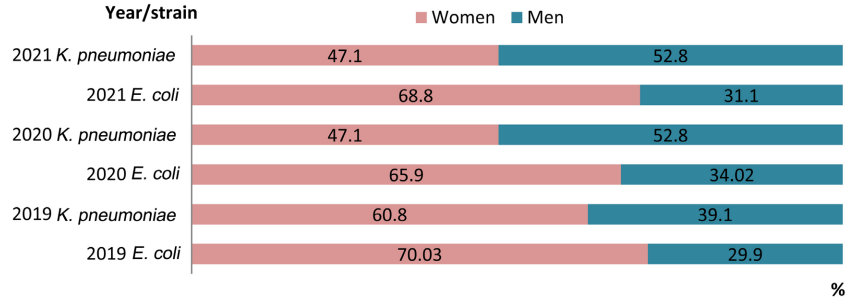


Figure 1. Distribution of *E. coli* and *K. pneumoniae* according to sex.

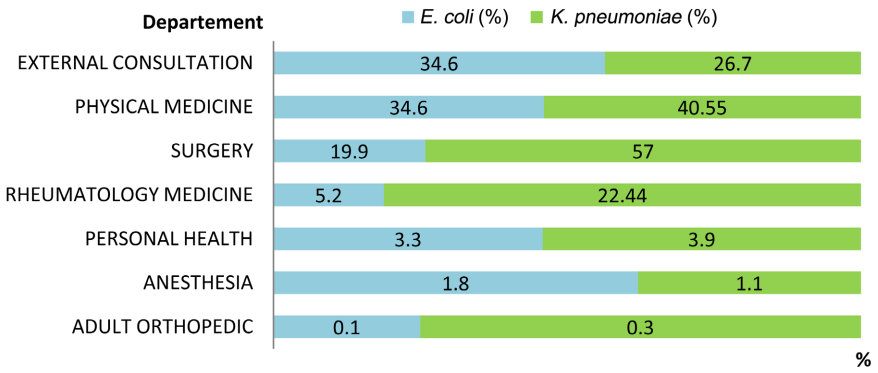


**Figure 2.** Distribution of *E. coli* and *K. pneumoniae* by department.

**Table 1.** Distribution of species isolated in the UTI during the study period.

| Germ | Number | % |
|---|---|---|
| **Gram-negativebacilli** | | |
| ***Escherichia coli*** | 686 | 52.2 |
| ***Klebsiella pneumoniae*** | 254 | 19.3 |
| ***Proteus mirabilis*** | 46 | 3.5 |
| ***Pseudomonas aeruginosa*** | 45 | 3.4 |
| ***Enterobacter cloacae*** | 29 | 2.2 |
| ***Acinetobacter baumami complex*** | 29 | 2.2 |
| ***Citrobacter koseri*** | 18 | 1. 3 |
| ***Klebsiella oxytoca*** | 12 | 0.9 |
| ***Citrobacter freundii*** | 10 | 0.7 |
| ***Serratia* spp** | 10 | 0.7 |
| ***Enterobacter* spp** | 10 | 0.7 |
| ***Providencia stuarti*** | 9 | 0.6 |
| **Gram-positive cocci** | | |
| ***Enterococcus feacalis*** | 72 | 5.4 |
| ***Staphylococcus aureus*** | 15 | 1.1 |
| ***Staphylococcus coagulasenegatif*** | 15 | 1.1 |
| ***Enterococcus* spp** | 12 | 0.9 |
| ***Streptocoques groupe B*** | 8 | 0.6 |
| **Others germs:** ***Proteus vulgaris, Pseudomonas fluroescens/pudita, Groupe Acinetobacter lwoffii, Morganella morganii, Providencia rettgeri, Providencia rustigiani, Streptococcus species, Streptococcus bovis, Streptococcus dys-galactiae*** | 33 | 2.5 |
| **TOTAL** | 1313 | |

acid (35.05%) and gentamicin (20.5%). Resistance was slightly lower for the community strains amoxicillin 66.7%, trimeth/Sulfamethoxazole 42.6%, ofloxacine 35.3%, amoxicillin/clavulanic acid 27.3% and gentamicine 13.4% (Table 2).

The antibiotics most affected by hospital *K. pneumoniae* strains were amoxicillin amoxicillin/clavulanic acid andtrimeth/sulfamethoxazole (40.6%), ofloxacin (34.7%) and gentamicin (22.8%). Resistance was slightly lower for the community strains, amoxicillin/clavulanic acid 19.6% ofloxacin 21.6%, gentamicin 10.9% and trimeth/sulfamethoxazole 9.4% (Table 3).

Resistance to third-generation cephalosporins through ESBLs production was present in a number of enterobacteria (19.3% of *K. pneumoniae* and 14.4% of *E. coli*) (Table 4 and Figure 3). We noted an increase in isolation of ESBL-producing *E. coli* from 10.8% in 2019 to 16% in 2021 and ESBL-producing *K. pneumoniae* from 18.6% in 2019 to 25.2% in 2021 (Table 4 and Figure 3).

Table 2. Percentage of resistance to antibiotics of *E. coli* isolated from the UTI during the study period.

| Year | 2019 | 2020 | 2021 | Moyenne N | 2019 | 2020 | 2021 | Moyennne N |
|---|---|---|---|---|---|---|---|---|
| Isolat (N) | 154 | 144 | 150 | 149.3 | 113 | 50 | 75 | 79.3 |
| ATB | Hospital N (%) | | | | Community N (%) | | | |
| Amoxicillin | 111 (72.07) | 115 (79.8) | 101 (67.3) | 109 (73.05) | 79 (69.9) | 36 (72) | 44 (58.6) | 536 (6.7) |
| Amoxicillin/ Clavulanic Acid | 54 (35.06) | 55 (38.1) | 48 (32) | 52.3 (35.05) | 34 (30.08) | 14 (28) | 18 (24) | 22 (27.3) |
| Ticarcillin | 32 (20.7) | 36 (25) | 99 (66) | 55.6 (37.2) | 30 (26.5) | 35 (70) | 44 (58.6) | 36.3 (51.7) |
| Ticarcillin/ Clavulanic Acid | | 44 (30.5) | 40 (26.6) | 28 (19.03) | 30 (26.5) | 11 (22) | 14 (18.6) | 18.3 (22.3) |
| Pip/Tazo | 2 (1.2) | 18 (12.5) | 8 (5.3) | 9.3 (6.3) | 8 (7.07) | 4 (8) | 6 (8) | 6 (7.6) |
| Mecillinam | 70 (45.4) | 69 (47.9) | 73 (48.6) | 70.6 (47.3) | 52 (46.01) | 28 (56) | 29 (38.6) | 36.3 (46.8) |
| Imipenem | 1 (0.6) | 2 (1.3) | 0 | 1 (0.6) | 1 (0.8) | 0 | 0 | 0.3 (0.2) |
| Ertapenem | 2 (1.2) | 6 (4.1) | 0 | 2.6 (1.7) | 2 (1.7) | 1 (2) | 0 | 1 (1.2) |
| Cefalotin | 43 (27.9) | 47 (32.6) | 47 (31.3) | 45.6 (30.6) | 26 (23) | 11 (22) | 13 (17.3) | 16.6 (20.7) |
| Cefixime | 32 (20.7) | 37 (25.6) | 34 (22.6) | 34.3 (22.9) | 16 (14.1) | 8 (16) | 8 (10.6) | 10.6 (13.5) |
| Cefotaxim | 4 (2.5) | 8 (5.5) | 4 (2.6) | 5.3 (3.5) | 2 (1.7) | 1 (2) | 1 (1.3) | 1.3 (1.6) |
| Cefuroxim | 33 (21.4) | 41 (28.4) | 36 (24) | 36.6 (24.6) | 18 (15.9) | 9 (18) | 8 (10.6) | 11.6 (14.8) |
| Cefepim | 28 (18.1) | 35 (24.3) | 30 (20) | 31 (20.8) | 14 (12.3) | 7 (14) | 7 (9.3) | 9.3 (11.8) |
| Fosfomycin | 4 (2.5) | 5 (3.4) | 3 (2) | 3.6 (2.6) | 0 | 0 | 0 | 0 |
| Gentamicin | 34 (22.07) | 34 (23.6) | 24 (16) | 30.6 (20.5) | 14 (12.3) | 8 (16) | 9 (12) | 10.3 (13.4) |
| Amikacin | 0 | 6 (4.1) | 1 (0.6) | 2.3 (1.5) | 3 (2.6) | 0 | 0 | 1 (0.8) |
| Ciprofloxacin | 46 (29.8) | 64 (44.4) | 55 (36.6) | 55 (36.7) | 38 (33.6) | 18 (36) | 22 (29.3) | 26 (32.9) |
| Norfloxacin | 53 (34.4) | 68 (47.2) | 62 (41.3) | 61 (40.9) | 41 (36.2) | 21 (42) | 23 (30.6) | 28.3 (36.2) |
| Ofloxacin | 54 (35.06) | 69 (47.9) | 57 (38) | 60 (40.3) | 37 (32.7) | 20 (40) | 25 (33.3) | 27.3 (35.3) |
| Trimeth/Sulfa | 69 (44.8) | 74 (51.3) | 67 (44.6) | 70 (46.9) | 49 (43.3) | 19 (38) | 35 (46.6) | 34 (42.6) |
| Nitrofurantoïn | 2 (1.2) | 0 | 3 (2) | 1.6 (1.06) | 2 (1.7) | 0 | 0 | 0.6 (0.5) |

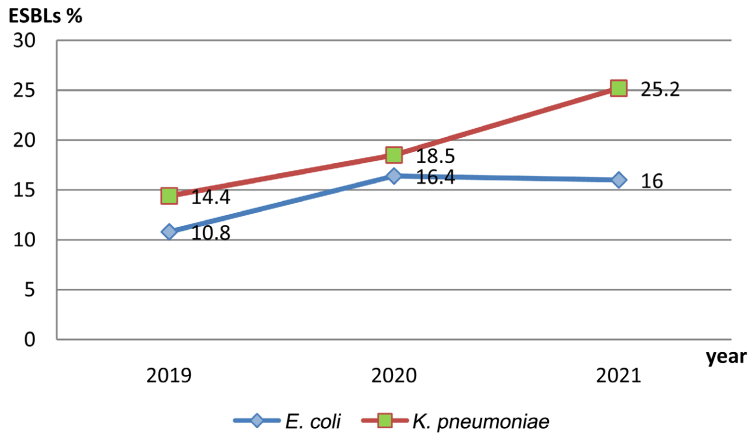


**Figure 3.** Percentages of ESBLs-producing by *E. coli* and *K. pneumoniae*.

**Table 3.** Percentage of resistance to antibiotics of *K. pneumoniae* isolated from the UTI during the study period.

| Year | 2019 | 2020 | 2021 | Moyennne | 2019 | 2020 | 2021 | Moyennne |
|---|---|---|---|---|---|---|---|---|
| IsolatNumber | 60 | 61 | 65 | 62 | 37 | 9 | 22 | 22.6 |
| ATB | Hospital N (%) | | | | Community N (%) | | | |
| Amoxicillin | 60 (100) NR | 61 (100) NR | 65 (100) NR | 62 (100) NR | 37 (100) NR | 9 (100) NR | 22 (100) NR | 22.6 (100) NR |
| Amoxicillin/ Clavulanic Acid | 19 (31.6) | 26 (42.6) | 31 (47.6) | 25.3 (40.6) | 11 (29.7) | 1 (11.1) | 4 (18.1) | 5.3 (19.6) |
| Ticarcillin | 60 (100) NR | 61 (100) NR | 65 (100) NR | 62 (100) NR | 37 (100) NR | 9 (100) NR | 22 (100) NR | 22.6 (100) NR |
| Ticarcillin/ Clavulanic Acid | 19 (13.6) | 26 (42.6) | 30 (46.1) | 25 (34.1) | 7 (18.9) | 2 (22.2) | 4 (18.1) | 4.3 (19.7) |
| Pip/Tazo | 13 (21.6) | 13 (21.3) | 18 (27.6) | 14.6 (23.5) | 5 (13.5) | 1 (11.1) | 2 (9.09) | 2.6 (11.2) |
| Imipenem | 5 (8.3) | 3 (4.9) | 6 (9.2) | 4.6 (7.4) | 0 | 1 (11.1) | 0 | 0.3 (3.7) |
| Ertapenem | 8 (13.3) | 7 (11.4) | 12 (18.4) | 9 (14.3) | 2 (5.4) | 1 (11.1) | 0 | 1 (5.5) |
| Cefalotin | 22 (36.6) | 28 (45.9) | 33 (50.7) | 27.6 (27.5) | 7 (18.9) | 2 (22.2) | 9 (40.9) | 6 (27.33) |
| Cefixim | 21 (35) | 23 (37.7) | 27 (41.5) | 23.6 (38) | 7 (18.9) | 2 (22.2) | 10 (45.4) | 6.3 (28.8) |
| Cefotaxime | 10 (16.6) | 12 (19.6) | 0 | 7.3 (12.06) | 4 (10.8) | 2 (22.2) | 16 (72.7) | 7.3 (35.2) |
| Cefuroxim | 23 (38.3) | 23 (37.7) | 30 (46.1) | 25.3 (40.7) | 8 (8.1) | 2 (22.2) | 9 (40.9) | 6.3 (20.7) |
| Cefepim | 18 (30) | 21 (34.4) | 16 (24.6) | 18.3 (29.6) | 6 (16.2) | 2 (22.2) | 7 (31.8) | 5 (23.4) |
| Fosfomycin | 7 (11.6) | 3 (4.9) | 10 (15.3) | 6.6 (10.6) | 6 (16.2) | 1 (11.1) | 2 (9.09) | 3 (12.1) |
| Gentamicin | 4 (6.6) | 19 (31.1) | 20 (30.7) | 14.3 (22.8) | 3 (8.1) | 1 (11.1) | 3 (13.6) | 2.3 (10.9) |
| Amikacin | 1 (1.6) | 4 (6.5) | 13 (20) | 6 (9.3) | 0 | 1 (11.1) | 0 | 0.3 (3.7) |
| Norfloxacin | 19 (31.6) | 21 (34.4) | 29 (44.6) | 23 (36.8) | 4 (10.8) | 2 (22.2) | 7 (31.8) | 4.3 (21.6) |
| Ciprofloxacin | 15 (25) | 18 (29.5) | 23 (35.3) | 18.6 (29.9) | 1 (2.7) | 2 (22.2) | 5 (22.7) | 2.6 (15 .8) |
| Ofloxacin | 19 (31.6) | 20 (32.7) | 26 (40) | 21.6 (34.7) | 3 (8.1) | 2 (22.2) | 8 (36.3) | 4.3 (21.6) |
| Trimeth/Sulfa | 19 (31.6) | 22 (36.06) | 25 (38.4) | 22 (35.3) | 7 (18.9) | 0 | 5 (22.7) | 4 (13.8) |
| Nitrofurantoïn | 10 (16.6) | 10 (16.3) | 15 (23.07) | 11.6 (18.6) | 3 (8.1) | 1 (11.1) | 2 (9.09) | 2 (9.4) |

NR: Natural Resistance.

**Table 4.** Frequencies of the major ESBL-producing strains.

| Year | 2019 | | 2020 | | 2021 | | Moyenne | |
|---|---|---|---|---|---|---|---|---|
| **Strain** | *E. coli* | *K. pneumoniae* | *E. coli* | *K. pneumoniae* | *E. coli* | *K. pneumoniae* | *E. coli* | *K. pneumoniae* |
| **Isolat (N)** | 267 | 97 | 194 | *70* | 225 | 87 | 228.6 | 84.6 |
| **ESBL N (%)** | 29 (10.8%) | 14 (14.4%) | 32 (16.4%) | *13* (*18.5%*) | 36 (16%) | 22 (25.2%) | 32.3 (14.4) | 16.3 (19.36) |

Aminoglycosides maintain good efficacy on enterobacteria (amikacin resistance ≥ 20 for *E. coli* and 10% for *K. pneumoniae*, our results showed low fosfomycin resistance for *E. coli* in hospital 2.6% and no resistance was observed in community settings while there is a mean resistance ≥ 12.1% for *K. pneumoniae*). Ofloxacin keeps a good action on urinary isolates. Resistance to this molecule was between 35% and 40% for *E. coli* and 21% to 34% for *K. pneumonia*. Resistance to nitrofurans has affected 0.5% of *E. coli* strains in community and 1.06% in hospital settings and 18.06% for *K. pneumoniae* in hospital (Table 2 and Table 3).

## 4. Discussion

Bacterial epidemiology of UTI is characterized by the predominance of enterobacteria in both our series and the literature [1] [2] [3] [4] [7] [8]. This is explained by the pathophysiological mechanism of the UTI, occurring mainly by ascending, the fecal flora is the usual source of the germs responsible for this infection. Uropathogenic germs from the fecal flora colonize the proximal vagina enter the urethra and bladder and stimulate the host response.

The migration of microorganisms to the bladder is facilitated by certain factors including sexual intercourse, which are the main risk factor for the development of uncomplicated UTI in women. The use of spermicide contraception methods including diaphragms withspermicides is an additional risk factor for UTI by modifying the local microbial environment and promoting colonization by uropathogenic agents [9]. Like other studies around the world [2] [7] [8]. *E. coli* dominates the etiology of UTI with a 52.2% frequency in our study. The major determinism of uropathogenicity of *E. coli* is the presence of essentially fimbrial adhesions ensuring bacterial fixation to uroepithelial cells via specific receptors [8].

In our series and earlier research, *K. pneumoniae* and *P. mirabilis* rank second among gram-negative bacilli in UI [3] [4] [8]. Both of these bacteria produce urease which alkalizes urine, the acid pH of which prevents the proliferation of germs [5] [8]. The study of the sensitivity of enterobacteria to betalactamines shows high resistance rates especially for amoxicillin 73.05% of hospital *E. coli* and 66.7% of community *E. coli*. These rates are comparable to those reported by other authors [4] [8] [12].

These results are consistent with those reported worldwide, showing that amoxicillin was the least active antimicrobial agent against *E. coli*, with resistance

rates ranging from 50% to 75% [12] [13] [14] [15] [16]. However, these rates vary considerably from region to region and can increase by up to 89% in developing countries, while in European countries they were estimated to be between 21% and 34% [17] [18].

In Tunisia, *E. coli* resistance to amoxicillin-clavulanic acid was 35.05% in hospital and 27.3% in community settings. For *K. pneumoniae*, the resistance rate was 40.6% in a hospital setting and low 19.6% in a community setting. This percentage is therefore not compatible with its use in probabilistic complex UtI-treatment [17].

Resistance to Third-Generation Cephalosporins (C3G) by ESBL production was 19.3% of *K. pneumoniae* and 14.4% of *E. coli*. We noted an increase in the isolation of ESBL-producing *K. pneumoniae* from 18.6% in 2019 to 25.2% in 2021 and *E. coli* producers of BLSE rose from 10.8% in 2019 to 16% in 2021. Acquired resistance to C3G from *E. coli* and *K. pneumoniae*is primarily due to ESBL. More rarely, it may be a chromosomal or plasmid cephalosporin. This resistance is around 18% for *E. coli* and 36% for *K. pneumoniae*, according to LART2017 [19].

BLSE are enzymes capable of hydrolysing all $\beta$-lactams with the exception of cephalomycins (cefoxitin, cefotin), moxalactam and carbapenems. They are partially inhibited by $\beta$-lactamase inhibitors (clavulanic acid, tazobactam, sulbactam). Resistance is often associated with several antibiotic families (aminoglycosides, Trimethoprim-Sulfamethoxazole (TMP-SMX), Fluoroquinolones (FQ).

The most common risk factors reported in the literature for ESBL-producing are recent antibiotic use, hospitalization within 3 months or being in a long-term structure, the presence of a permanent probe and recent travel to endemic BLSE area. Other risk factors were more rarely identified: male sex, prostate disease, recurrent urinary infections, co-morbidities, diabetes, and cancer. History of digestive or urinary colonization with EBLSE was considered by some authors as a risk factor [19] [20].

The prevalence of this resistance in the community is currently increasing, and it is no longer limited to strains acquired only in hospitals [21] [22]. Due to the widespread use of betalactamines, there is a selection pressure that has resulted in this overall condition. Additionally, these resistances developed by their plasmid determinism have a powerful ability to spread.

Increased prevalence of *E. coli* and *K. pneumoniae* ESBLs producers in UTI exposes the risk of increased carbapenem requirements. An increase in the prevalence of BLSE-producing *E. coli* has also been reported in other countries, with rates ranging from 2.5% to 24% [13] [14] [15] [22] [23].

The resistance of *E. coli* to imipenem is 0.6% and ertapenem is 1.7% in hospital. For *K. pneumoniae*, imipenem resistance is 7.6% and ertapenem resistance is 14.3% in hospital.

The Aziza Othmena hospital in Tunis contained 4.7% of isolates producing ESBLs; the incidence increased from 2012 to 2015 and then decreased starting in 2016. In 2018, the rate grew to 2.7%. (12). Previously, Tunisian prevalence rates

of this type of isolate ranged from 0.6% to 10.2% (19). Prevalence increased from 1.6% to 10.2% in the governorate of Sfax (southern Tunisia) between 2004 and 2015 [14].

For fluoroquinolones (FQ), the resistance of *E. coli* affected 40% of isolates on average, this rate is higher than in two other Tunisian studies that report a sensitivity rate of 0.3% to 0.8% [3] [7]. According to various Tunisian studies, FQ resistance rates range from 6.9% to 29.5% for ofloxacin and it averages 25.2% (*E. coli*) to 31.3% (*K. pneumoniae*) for ciprofloxacin [12].

In European countries, sensitivity rates ranged from 0.5% to 7.6% [18], while in Türkiye, 50% of *E. coli* isolates were resistant to ciprofloxacin [13]. Fluoroquinolone resistance has become a growing concern worldwide [24]. The risk factors for acquiring FQ-resistant strains reported in the literature are: age > 50 years, male sex, complicated urinary tract infection, antibiotic therapy in the previous 3 - 6 months, prior FQ exposure (<6 months), history of recent hospitalization, history of urinary tract infection < 1 year, relapse within 30 days, recurrent urinary tract infections, therapeutic failure, uroinvasive gestures, urinary catheterization, community prescription of levofloxacin, institutionalization [24].

FQ have a broad spectrum of activity and are sometimes essential for example to treat intracellular germ infections, so it is essential to try to preserve them [24]. The pharmacodynamic and pharmacokinetic characteristics of the FQ have prompted a wide use of these molecules, which was quickly followed by the emergence of resistant strains that are widely disseminated in recent years.

Rates of *E. coli* and *K. pneumoniae* resistance to TMP-SMX are high (46.9% for *E. coli* and 40.6% for *K. pneumoniae* in hospital). This against indicates its use in probabilistic IU processing. The TMP/SXT sensitivity assessment showed a high level of resistance, exceeding the agreed threshold of 20%, eliminating this antibiotic as a first-line treatment for ITU. Similar results have already been reported [20] [25]; resistance rates to TMP/SXT varied widely between countries, ranging from 19.6% in France [18] to 70.4% in Ethiopia [24]. Although the susceptibility rate to TMP/SXT in this study remained constant over the study period, some authors reported an increase in sensitivity, attributed to a decrease in the use of this antibiotic [12] [18]. Aminoglycosides remain active in our study as well as in other series [3] [9] [24].

In Tunisia the frequency of resistance of *E. coli* to gentamicin was 12.9%, that has amikacin is 0.2%. As for *K. pneumoniae*, the frequency of resistance to gentamicin is 27.9% and amikacin 2.1% (reference) these results are consistent with our study which showed resistance rates as follows: for gentamycin averaging 20% for *E. coli* and *K. pneumoniae* and 1.5% resistance to amikacin for hospital settings and 9.3ù for hospital *K. pneumoniae*. For amikacin, sensitivity rates range from 96.1 (29) to 100% [26].

According to available Tunisian data, fosfomycin is very active on strains *E. coli*, which allows its use in the probabilistic treatment of adult UCI. *E. coli* fosfomycin resistance rates range from 0% to 12.1% and 10.6% for hospital *K. pneu-*

*moniae*. What is remarkable in our study is that the resistance rate was 0% in hospital for *E. coli*. The use of this former antibiotic in the first line in the treatment of simple UCI is justified by the low resistance rates. Fosfomycin, a low resistance rate was reported (3.4% in Portugal) [27].

For nitrofurantoin, reported susceptibility rates exceeded 80%; it was estimated to be 83.6% in India, 88% in Morocco and 94.1% in Iran [6] [20] [24]. These rates ranged from 96% to 99% in western countries [4] [7] [18].

These results were similar with our study which shows a low level of resistance to this molecule with 1.06% for hospital *E. coli* and 18.6% for hospital *K. pneumoniae*. The French Society of Infectious Diseases guidelines recommend the use of these molecules in combination with 3rd generation intravenous cephalosporin for the treatment of complex forms of pyelonephritis [28].

Currently, some authors recommend the use of old molecules (furans, fosfomycin) in the treatment of IU which is in agreement with the results of this study. Indeed, these molecules have the advantage of having no mechanism of cross-resistance with other families of antibiotics.

So the selection of a resistant strain under treatment with furans or fosfomycin does not affect the choice of an alternative using another family of antibiotics to goodurinary diffusion [26] [29] [30] [31] [32].

The Molecules that can be used in first intention in the treatment of UTA in adults: fosfomycin, nitrofurantoin, gentamicin, amikacin and C3G if there are no risk factors for ESBL acquisition as well it must to avoid in first intention in the treatment of UTI in adults this molecules: Amino-openicillins, combination amoxicillin-clavulanic acid, TMP-SMX and FQ [26] [32].

There was a potential side effect; for fluoroquinolones: very specific monitoring of adverse effects (tendinopathies, neuropsychiatric disorders more frequent in the elderly, prolongation of the QT interval), for aminoglycosides: daily monodose treatments to be preferred, according to Afssaps recommendations (Review of the proper use of aminoglycosides administered by injection: gentamicin, tobramycin, netilmicin, amikacin, Assaps, Mars 2011). In the rare cases where an aminoglycoside monotherapy is indicated, the estimation of the creatinine clearance is essential to determine the spacing of the doses. The duration of treatment should not exceed 3 - 5 days and for nitrofurantoin: The contraindication must be respected in the event of renal insufficiency with creatinine clearance < 40 ml/min [33] [34].

## 5. Conclusions

Our research supports the use of fosfomycin, nitrofuran, gentamicin and amikacin as first-line agents in the treatment of adult UTI. C3G can also be used if there are no BLSE risk factors. BLSE-producing *E. coli* prevalence in UTI is increasing. To minimize the spread of these strains as much as possible, regular surveillance is essential.

To say goodbye to burning, frequent urination, and other unpleasant symptoms, start with these changes today. The key is to keep bacteria out of your system.

1) Drink plenty of water, and relieve yourself often. The simplest way to prevent a UTI is to flush bacteria out of the bladder and urinary tract before it can set in. If you're well-hydrated, it will be tough to go too long without urinating. Wipe from front to back. Bacteria tend to hang around the anus. If you wipe from front to back, especially after a bowel movement, they're less likely to make it to the urethra.

2) Wash up before sex and urinate after it. Use soap and water before sex. This keeps bacteria away from the urethra. And urinating afterward pushes, any bacteria that entered the urinary tract back out.

3) Steer clear of irritating feminine products. Skip douches, deodorant sprays, scented powders, and other potentially irritating feminine products.

4) Rethink your birth control. Some types of birth control might promote an overgrowth of harmful bacteria. This includes: diaphragms, non-lubricated condoms, spermicides and spermicide condoms.

5) Take probiotics; they are live microorganisms that can increase good gut bacteria. They may also help promote the growth of good bacteria in the urinary tract. This could help protect you from getting a UTI [35].

Clinico-bacteriological studies with a high level of scientific evidence must be carried out to increase the strength of the recommendations.

## Funding

This study was funded by the authors.

## Authors' Contribution

Original draft preparation writing: Hajer Kilani; review and editing: Salma Kaoual, Sophia Bouhalila Besbes and Hajer Kilani; methodology: Hajer Kilani, Salma Kaoual, Fatma Kaabi and Sophia Bouhalila Besbes; validation visualization supervision: Sophia Bouhalila Besbes. All authors read and approved the final version of the manuscript for submission.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

## References

[1] Bitew, A., Molalign, T. and Chanie, M. (2017) Species Distribution and Antibiotic Susceptibility Profile of Bacterial Uropathogens among Patients Complaining Urinary Tract Infections. *BMC Infectious Diseases*, **17**, Article No. 654. https://doi.org/10.1186/s12879-017-2743-8

[2] Córdoba, G., Holm, A., Hansen, F., Hammerum, A.M. and Bjerrum, L. (2017) Prevalence of Antimicrobial Resistant *Escherichia coli* from Patients with Suspected Urinary Tract Infection in Primary Care, Denmark. *BMC Infectious Diseases*, **17**, Article No. 670. https://doi.org/10.1186/s12879-017-2785-y

[3] Guermazi-Toumi, S., Boujlel, S., Assoudi, M., Issaoui, R., Tlili, S. and Hlaiem, M.E.

(2018) Susceptibility Profiles of Bacteria Causing Urinary Tract Infections in Southern Tunisia. *Journal of Global Antimicrobial Resistance*, **12**, 48-52. https://doi.org/10.1016/j.jgar.2017.09.004

[4] Farrell, D.J., Morrissey, I., De Rubeis, D., Robbins, M. And Felminghan, D. (2003) A UK Multicentre Study of the Antimicrobial Susceptibility of Bacterial Pathogens Causing Urinary Tract Infection. *Journal of Infection*, **46**, 94-100. https://doi.org/10.1053/jinf.2002.1091

[5] Mahamat, A., Lavigne, J.-P., Bouziges, N., Daurès, J.-P. and Sotto, A. (2006) Profils de résistance des souches urinaires de Proteus mirabilis de 1999 à 2005 au CHU de Nîmes. *Pathologie Biologie*, **54**, 456-461. https://doi.org/10.1016/j.patbio.2006.07.015

[6] Bouallègue, O., Saidani, M., Ben Mohamed, S. and Mzoughi, R. (2004) Particularités bactériologiques des infections urinaires chez l'enfant dans la région de sousse, Tunisie. *Tunisie Médicale*, **82**, 742-746.

[7] Diagnostic et antibiothérapie des infections urinaires bactériennes communautaires de l'adulte. https://www.infectiologie.com/UserFiles/File/spilf/recos/infections-urinaires-spilf.pdf

[8] Farrell, J., Morrissey, I., Rubeis, D., Robbins, M. and Felminghan, D. (2003) A UK Multicentre Study of the Antimicrobial Susceptibility of Bacterial Pathogens Causing Urinary Tract Infection. *Journal of Infection*, **46**, 94-100. https://doi.org/10.1053/jinf.2002.1091

[9] Société Française de Microbiologie (2018) Référentiel en Microbiologie Médicale (Rémic). Volume 6.2, 5ème Edition, Société Française de Microbiologie, Paris. https://www.sfm-microbiologie.org/boutique/referentiel-en-microbiologie-medicale-remic/

[10] MicroScan WalkAway plus System. Beckman Coulter, Brea. https://www.beckmancoulter.com/en/products/microbiology/microscan-walkaway-plus-system

[11] Société Française de Microbiologie (2018) Détermination de la sensibilité aux antibiotiques. CASFM/EUCAST, Société Française de Microbiologie, Paris, 7-15.

[12] Daoud, N., Hamdoun, M., Hannachi, H., Gharsallah, C., Mallekh, W. and Bahri, O. (2020) Antimicrobial Susceptibility Patterns of *Escherichia coli* among Tunisian Outpatients with Community-Acquired Urinary Tract Infection (2012-2018). *Current Urology*, **14**, 200-205. https://doi.org/10.1159/000499238

[13] Yilmaz, N., Agus, N., Bayram, A., Samlioglu, P., Sirin, M.C., Derici, Y.K. and Hancı, S.Y. (2016) Antimicrobial Susceptibilities of *Escherichia coli* Isolates as Agents of Community-Acquired Urinary Tract Infection (2008-2014). *Turkish Journal of Urology*, **42**, 32-36. https://doi.org/10.5152/tud.2016.90836

[14] Smaoui, S., Abdelhedi, K., Marouane, C., Kammoun, S. and Messadi-Akrout, F. (2015) Antibiotic Resistance of Community-Acquired Uropathogenic *Enterobacteriaceae* Isolated in Sfax (Tunisia). *Médecine et Maladies Infectieuses*, **45**, 335-337. https://doi.org/10.1016/j.medmal.2015.07.004

[15] Den Heijer, C.D., Donker, G.A., Maes, J. and Stobberingh, E.E. (2010) Antibiotic Susceptibility of Unselected Uropathogenic *Escherichia coli* from Female Dutch General Practice Patients: A Comparison of Two Surveys with a 5 Year Interval. *Journal of Antimicrobial Chemotherapy*, **65**, 2128-2133. https://doi.org/10.1093/jac/dkq286

[16] Shariff, V.A., Shenoy, M.S. and Yadav, T. (2013) The Antibiotic Susceptibility Patterns of Uropathogenic *Escherichia coli*, with Special Reference to the Fluoroquinolones.

*Journal of Clinical and Diagnostic Research*, **7**, 1027-1030. https://doi.org/10.7860/JCDR/2013/4917.3038

[17] Mamani, M., Nobari, N., Alikhani, M.Y. and Poorolajal, J. (2015) Antibacterial Susceptibility of *Escherichia coli* among Outpatients with Community-Acquired Urinary Tract Infection in Hamadan, Iran. *Journal of Global Antimicrobial Resistance*, **3**, 40-43. https://doi.org/10.1016/j.jgar.2015.01.003

[18] Kahlmeter, G. and Poulsen, H.O. (2012) Antimicrobial Susceptibility of *Escherichia coli* from Community-Acquired Urinary Tract Infections in Europe: The ECO·SENS Study Revisited. *International Journal of Antimicrobial Agents*, **39**, 45-51. https://doi.org/10.1016/j.ijantimicag.2011.09.013

[19] Observatoire National de l'Epidémiologie de la Résistance Bactérienne aux Antibiotiques (ONERBA) (2017) Rapport d'activité/Annual Report. http://onerba.org/publications/rapports-onerba/

[20] Société Tunisienne de Pathologie Infectieuse (2016) Antibiothérapie des infections urinaires communautaires de l'adulte. Recommandations de la STPI. Société Tunisienne de Pathologie Infectieuse, Tunis.

[21] Bonacorsi, S., Bruyère F., Cariou G., Clouqueur E., Cohen R., Doco-Lecompte T., Elefant E., Faure K., Gauzit R., Gavazzi G., Lemaitre L., Raymond J., Senneville E., Sotto A., Subtil D., Trivalle C., Merens A. and Etienne M. (2018) Practice Guidelines for the Management of Adultcommunity-Acquired Urinary Tract Infections. *Médecine et Maladies Infectieuses*, **48**, 327-358. https://doi.org/10.1016/j.medmal.2018.03.005

[22] Marzouk, M., Ferjani, A., Haj Ali, M. and Boukadida, J. (2015) Profile and Susceptibility to Antibiotics in Urinary Tract Infections in Children and Newborns from 2012 to 2013: Data from 1879 Urine Cultures. *Archives de Pédiatrie*, **22**, 505-509. https://doi.org/10.1016/j.arcped.2015.02.015

[23] El Bouamri, M.C., Arsalane, L., Kamouni, Y., Yahyaoui, H., Bennouar, N., Berraha, M. and Zouhair, S. (2014) Current Antibiotic Resistance Profile of Uropathogenic *Escherichia coli* Strains and Therapeutic Consequences. *Progrès en Urologie*, **24**, 1058-1062. https://doi.org/10.1016/j.purol.2014.09.035

[24] Heytens, S., Boelens, J., Claeys, G., DeSutter, A. and Christiaens, T. (2017) Uropathogen Distribution and Antimicrobial Susceptibility in Uncomplicated Cystitis in Belgium, a High Antibiotics Prescribing Country: 20-Year Surveillance. *European Journal of Clinical Microbiology & Infectious Diseases*, **36**, 105-113. https://doi.org/10.1007/s10096-016-2776-8

[25] Huang, L.-F., Lo, Y.-C., Su, L.-H. and Chang, C.-L (2014). Antimicrobial Susceptibility Patterns among *Escherichia coli* Urinary Isolates from Community-Onset Health Care-Associated Urinary Tract Infection. *Journal of the Formosan Medical Association*, **113**, 970-973. https://doi.org/10.1016/j.jfma.2014.01.009

[26] Honderlick, P., Cahen, P., Gravisse, J. and Vignon D. (2006) Quelle sensibilité aux antibiotiques pour les bactéries responsables d'infections urinaires? Que penser de fosfomycine et nitrofuranes. *Pathologie Biologie*, **54**, 462-466. https://doi.org/10.1016/j.patbio.2006.07.016

[27] Passadouro, R., Fonseca, R., Figueiredo, F., Lopes, A. and Fernandes, C. (2014) Evaluation of the Antimicrobial Susceptibility of Community-Acquired Urinary Tract Infection. *Acta Médica Portuguesa*, **27**, 737-742. https://doi.org/10.20344/amp.5352

[28] Le Conte, P., Elkharrat, D. and Potel, G. (2004) Prise en charge des infections urinaires communautaires dans les Service d'Accueil et d'Urgence Français. *Antibiotiques*, **4**, 237-239. https://doi.org/10.1016/S1294-5501(04)94270-7

[29] Sastry, S. and Doi, Y. (2016) Fosfomycin: Resurgence of an Old Companion. *Journal of Infection and Chemotherapy*, **22**, 273-280. https://doi.org/10.1016/j.jiac.2016.01.010

[30] Lemort, M.-L., Neuville, S., Medus, M., Gueudet, P., Saada, M., Aumaître, H. and Lecaillon, E. (2006) Evolution comparée de la sensibilité de souches de *Escherichia coli* isolées d'infections urinaires de patientsconsultants aux urgences et de patients hospitalisés en 2002 et 2004 à l'hôpital de Perpignan. *Pathologie Biologie*, **54**, 426-430. https://doi.org/10.1016/j.patbio.2006.07.007

[31] Muratani, T. and Matsumoto, T. (2006) Urinary Tract Infection Caused by Fluoroquinolone- and Cephem-Resistant Enterobacteriaceae. *International Journal of Antimicrobial Agents*, **28**, 10-13. https://doi.org/10.1016/j.ijantimicag.2006.05.009

[32] Bergogne-Bérézin, E. (2006) Antibiothérapie des infections urinaires basses: Bases cliniques, microbiologiques et pharmacologiques. *Antibiotiques*, **8**, 51-62. https://doi.org/10.1016/S1294-5501(06)70797-X

[33] Infectiologie.com. https://www.infectiologie.com

[34] Flores-Mireles, A., Walker, J., Caparon, M. and Hultgren, S.J. (2015) Urinary Tract Infections: Epidemiology, Mechanisms of Infection and Treatment Options. *Nature Reviews Microbiology*, **13**, 269-284. https://doi.org/10.1038/nrmicro3432

[35] Machalinski, A. (2021) Best Ways to Help Prevent UTIs. WebMD. https://www.webmd.com/women/guide/avoid-uti