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ADVANCED RESEARCH IN LIFE SCIENCES
7, 2023, 46 - 53

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DOI: 10.2478/arls-2023-0006
Research Article

Antibiotic Resistance Pattern of *Enterobacteriaceae* Strains Isolated from Community Urinary Tract Infections in Algiers, Algeria

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Received February, 2023; Revised March, 2023; Accepted April, 2023

Abstract
Urinary tract infections (UTIs) are currently one of the most important medical practice visits. The spread of antibiotic-resistant bacteria in the community complicates the therapeutic management. The aim of this study is to investigate the bacteria associated with community acquired urinary tract infections (CA-UTIs) and the antibiotic resistance pattern of bacterial isolates during 2021 in Algiers, northern Algeria. A total of 548 urine samples from patients with CA-UTIs symptoms were analyzed. Pure bacterial isolates were identified using morphological and biochemical characteristics, and subjected to antibiogram evaluation using the disk diffusion method. A total 133 out of 548 patients (24.27%) had positive CA-UTIs, mainly affecting women (84.21%). A percentage of 87.22% of isolates were identified as *Enterobacteriaceae*, which were represented mostly by *Escherichia coli* (76 isolates), *Klebsiella pneumoniae* (13 isolates), and *Proteus mirabilis* (13 isolates). A number of 125 isolates (93.98%) were resistant to at least one antibiotic tested. The results showed the highest antibiotic resistance to ampicillin (92.24%) and amoxicillin-clavulanic acid (91.37%), and revealed the most sensitivity to cefotaxime and nitrofurantoin (95.69%) and colistin (93.11%). The results of this study revealed high concerns about CA-UTIs caused by multidrug-resistant *Enterobacteriaceae*.

Keywords: community UTI, Algiers, multidrug resistance.

Introduction

Urinary tract infections (UTIs) are a common type of infection that affects millions of people worldwide. According to the World Health Organization [1], UTIs are a health security problem for many countries, especially developing ones, and they are among the most common types of infection seen in primary and acute care. UTIs are on the rise globally and estimated to account for around 8.6 million healthcare visits annually [2]. Moreover, antibiotic resistance has risen to dangerously high levels globally, and by 2050, it is estimated that 10 million deaths will be due to antimicrobial resistance and that $100 trillion of the global economy will be lost if consistent efforts are not made to contain this threat [4, 5]. In Algeria, the incidence of UTIs has increased significantly since the early 1990s, especially in vulnerable healthcare settings such as intensive care units and surgeries [5]. Furthermore, several published works reported the alarming appearance of new multi-resistant bacterial strains in Algeria [6]. The challenge of

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this multiple resistance occurs mainly with Gram-negative bacilli, which occupy a considerable place among microorganisms [7]. Multi-resistant bacteria, including *Enterobacteriaceae*, have been frequently observed in urology and nephrology services, causing 40% of nosocomial urinary tract infections [8]. Treatment of UTIs is made more difficult by the spread of multidrug resistant (MDR) bacterial uropathogens in the community [9]. Moreover, the impact of nosocomial infections is seen not only at the individual patient level but also at the community level, as it is associated with multidrug-resistant infections [10]. In light of the above information, we conducted this study to determine the frequency of antibiotic resistance of *Enterobacteriaceae* isolated from the urine of patients infected by CA-UTIs in Algiers (Algeria).

Materials and Methods

Sample Collection

A total of 548 urine samples from patients (aged from 15 days to 88 years) were collected between December 2020 and December 2021. The patients have not been in contact with the hospital in the 48 hours preceding the urine sampling to avoid all samples from patient affected by nosocomial infection based on the definition given by Van Duin and Paterson [11], Todorovic Marcovic et al. [12] and Odoki et al. [13].

Bacteria Isolation and Identification

All collected samples were cultured on a nutrient agar medium using the calibrated loop/surface streak method [14]. After 18–24 h of incubation (at 37 °C), pure cultures of *Enterobacteriaceae*-like colonies were first subjected to standard bacteriological techniques (morphology, Gram stain, catalase and oxidase tests). Strains with coccobacilli morphology, Gram-negative, catalase-positive, and oxidase-negative were considered presumptive *Enterobacteriaceae* and later identified to species level by commercial API 10S kits (BioMérieux) [15].

Antimicrobial Susceptibility

The antibacterial resistance of *Enterobacteriaceae* strains was determined for 15 antibiotics by the disk diffusion method. The sensitivity of each strain to antibacterial drugs was determined according to the guidelines of the Clinical and Laboratory Standard Institute [16]. Pure colonies were suspended in 10 ml of sterilized physiological water from a fresh overnight culture of each isolate. The bacterial suspension density was adjusted to a concentration of 0.5 McFarland. A cotton swab was used to inoculate the agar plate surface, and the procedure was repeated three times by rotation of the plate (60°). The antibiotic disks were placed on the inoculated plates and incubated for 24 h (at 37°C). The following antibiotics were tested: ampicillin (10 µg), amoxicillin + clavulanic acid (20/10 µg), cefazolin (30 µg), cefoxitin (30 µg), cefotaxime (30 µg), imipenem (10 µg), gentamicin (120 µg), amikacin (30 µg), nalidixic acid (10 µg), ofloxacin (5 µg), ciprofloxacin (5 µg), trimethoprim/sulfamethoxazole (1.25/23.75 µg) and chloramphenicol (30 µg).

Results and discussion

Distribution of Clinical Isolates

Our study found the prevalence of CA-UTIs is 24.27% among symptomatic patients. The observed rate is higher than the levels recorded previously in Italy (20.4%) [17], and in Morocco (17.9%) [18]. UTIs are one of the most common CA-bacterial infectious diseases worldwide, affecting patients of both genders [19].

During the study period, a total of 133 bacterial isolates were collected. There were 116 strains (87.22%) of *Enterobacteriaceae* (Figure 1), among which 76 (65.51%) were identified as *Escherichia coli*. These findings are in agreement with results found in some regions of Algeria [5, 14] and other countries [15, 16]. The second most common species were *Klebsiella pneumoniae* and *Proteus mirabilis*, each of which was represented by 13 strains (11.20%). Al-Naqshbandi and Chawsheen [23] and Orrett [24] have mentioned similar results for *K. pneumoniae* and *P. mirabilis*, respectively [17, 18]. Other bacterial species were infrequently isolated, namely *Klebsiella* oxytoca (n = 3) and *Enterobacter cloacae* (n = 3) followed by *Enterobacter aerogenes* (n= 2). Only one strain was isolated for each of the following species: *Yersinia enterocolitica*, *Salmonella typhi*, *Escherichia vulneris*, *Citrobacter koseri*, *Citrobacter* sp., and *Enterobacter* sp.

Species distribution by gender

Among the 116 confirmed patients affected by UTI caused by *Enterobacteriaceae*, 98 (84.48%) were female and 18 (15.52%) were male (a sex ratio of 0.18) (Figure 1). We note that the distribution of the causative species of UTIs is not dependent on gender; indeed, the abundant species were isolated from both genders. The reason behind this high prevalence of UTIs in females is their short urethra and certain behavioral factors, which include delay in micturition, sexual activity, and the use of diaphragms and spermicides, which promote colonization of the periurethral area with coliform bacteria [25], especially the close proximity of the urethral meatus to the anus [26].

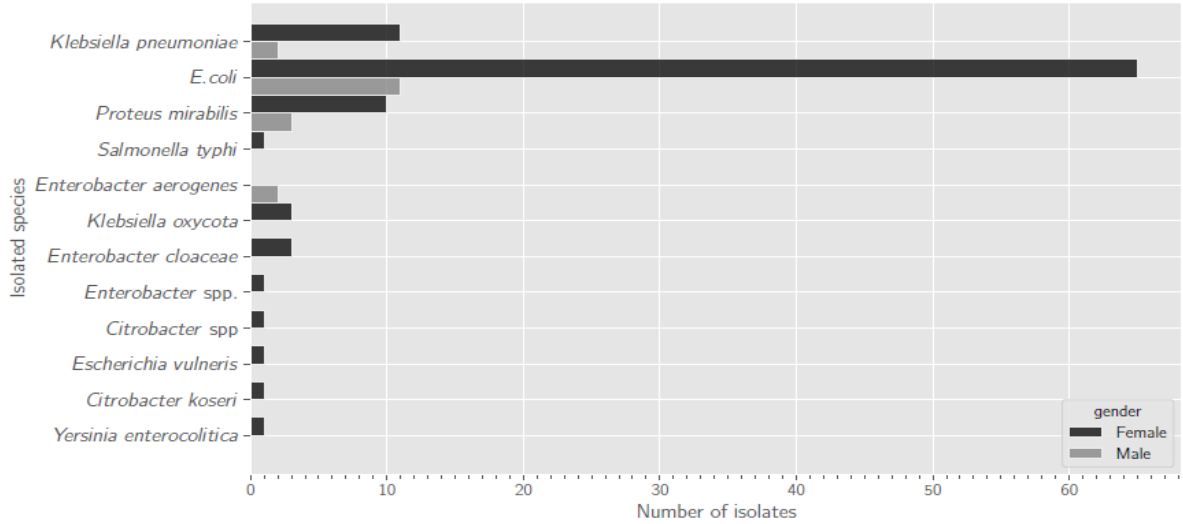


Figure 1. Species frequency and distribution by gender

Disk diffusion susceptibility testing

The majority of isolated *Enterobacteriaceae* were penicillin-resistant, with more than 91% being resistant strains (Table 1). The majority of strains of bacteria have become resistant to this class of antibiotic due to the overuse and misuse of antibiotics. This leads to selection pressure, where bacteria that are resistant to the drug survive and multiply, while susceptible bacteria are killed [27]. We discovered significantly lower resistance to the cephalosporin class, which has declined in recent generations (13.97%, 10.34%, and 4.31% of resistant strains for the first, second, and third generations, respectively). In the same context, Lo et al. [28] found that, when moving from the first to the third generation, the antibacterial activity of cephalosporins increases against *Enterobacteriaceae* isolates. First-generation cephalosporins are first-line drugs for uncomplicated lower UTI treatment, according to several international consensuses [29]. The second-generation cephalosporin is an effective antibiotic against the bacterial species involved in CA-UTIs [30]. However, due to their greater stability to β-lactamases than first- or second-generation cephalosporins [31], extended-spectrum cephalosporins have become more commonly used for the treatment of UTIs since the introduction of third-generation cephalosporins in the mid-1980s [30]. Only carbapenem (imipenem) was effective against all tested strains in the β-lactam class. The absence of resistance to this antibiotic was previously reported by Yandai et al. [32] in Chad and Kotb et al. [33] in Egypt.

Our isolates show the highest rate of resistance against trimethoprim/sulfamethoxazole in the non β-lactam group, with 33.62% of resistant strains. This antibiotic is important and widely used as first-line for the treatment of uncomplicated cystitis [34] because of its effectiveness and its availability at a low cost. However, its excessive use increases bacterial resistance in several countries [35].

Most *Enterobacteriaceae* isolates are susceptible to quinolones and phenicols, which have been considered highly effective treatments for UTIs. Naomi et al. [36] obtained the same results. Quinolones are the most frequently selected antibacterials for treating uncomplicated UTIs in many countries [31, 32]. According to the scientific literature, the resistance rate to chloramphenicol is less than 20% [39]. Despite the fact that chloramphenicol appears to be a useful medication for urinary infections, it is no longer a first-line antibacterial agent in developed countries due to severe toxicity to human serum albumin [40].

Polymyxins and nitrofurans resistance affects a small percentage of our isolates (6.89 and 4.31%, respectively). The low resistance against polymyxins may be explained by the limited use of the treatment for severe infections caused by Gram-negative and multidrug-resistant bacilli. This reaffirms the need for its continued appropriate use [41]. Nitrofuran has shown its effectiveness in the treatment of lower UTIs, namely recurrent urinary tract infections, when it was suggested and frequently prescribed by general practitioners [42].

The aminoglycosides were effective against all bacterial isolates tested. Jung et al. [43] obtained the same result. This may be explained by the less frequent use of aminoglycosides than broad-spectrum cephalosporins or fluoroquinolones.

Table 1.

Antibiotic resistance of isolated species of *Enterobacteriaceae*

Species (number of strains)	Number of strains resistant to:														
	β-lactams						Aminogly-cosides		Quinolones			Phenicols	Sulfonamides and associated antibiotics	Nitrofurans	Polymyxins
	AMP	AMC	CZ	FOX	CTX	IPM	GEN	AK	NA	OFX	CIP	C	SXT	NIT	CS
***Klebsiella pneumoniae* (13)**	11	11	3	2	1	0	0	0	4	4	3	1	7	1	0
***Escherichia coli* (76)**	71	71	8	6	3	0	0	0	9	9	7	7	22	1	0
***Proteus mirabilis* (13)**	12	12	0	0	0	0	0	0	0	0	0	5	5	2	8
***Salmonella typhi* (1)**	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0
***Enterobacter aerogenes* (2)**	2	1	0	1	0	0	0	0	0	0	0	0	1	0	0
***Klebsiella oxytoca* (3)**	3	3	0	0	0	0	0	0	0	0	0	1	0	0	0
***Enterobacter cloacae* (3)**	3	3	2	1	0	0	0	0	1	1	1	1	1	0	0
***Enterobacter* sp. (1)**	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0
***Citrobacter* sp. (1)**	1	1	1	1	1	0	0	0	0	0	0	0	1	1	0
***Escherichia vulneris* (1)**	1	1	1	0	0	0	0	0	0	0	0	0	1	0	0
***Citrobacter koseri* (1)**	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
***Yersinia enterocolitica* (1)**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	107	106	16	12	5	0	0	0	14	14	11	15	39	5	8

AMP - ampicillin (10 µg); AMC - amoxicillin- clavulanic acid (20/10 µg); CZ - cefazolin (30 µg); FOX – cefoxitin (30 µg); CTX– cefotaxime (30 µg); IPM – imipenem (10 µg); GEN – gentamicin (120 µg); AK - amikacin (30 µg); NA - nalidixic acid (10 µg); OFX - ofloxacin, (5 µg); CIP- ciprofloxacin (5 µg), C – chloramphenicol (30 µg); SXT - trimethoprim/sulfamethoxazole (1.25/23.75 µg); CS - colistin (25 µg); NIT – nitrofurantoin (300 µg).

Among the studied strains, 7 strains of *E. coli*, 3 strains of *K. pneumonia*, and 5 strains of *P. mirabilis* showed a multi-resistance to three or more families of antibiotics. The dissemination of multidrug-resistant *Enterobacteriaceae* (MDRE) in community settings is becoming a great concern [44]. MDR bacteria are often associated with hospital-acquired infections. However, some multidrug-resistant bacteria have become common causes of community-acquired infections. This is an important development because the spread of MDR bacteria in the community has led to an increase in the number of infections caused by MDR bacteria [11]. The spread of MDR bacteria in community settings is becoming a major problem because it is more difficult to be controlled in hospitals. CA-UTIs data related to MDRE are not well defined. To this end, it is necessary to have reliable predictors and susceptibility data for CA-UTI caused by MDRE.

Several factors can explain the development of antibiotic resistance and its progressive increase. The primary outcome was the abusive use and inappropriateness of the antibiotic prescription for UTI, including self-medication, the antibiotic type, as shown by the evidence that these drugs are frequently given to patients who do not suffer from bacterial diseases or do not have an infectious disease [25, 40].

The distribution of resistance to different families of antibiotics with a focus on the age of the patients revealed marked heterogeneity (Figure 2). This result has been also reported by Rocha et al. [46], indicating that the stratification of susceptibility results by gender and age revealed a marked heterogeneity among subgroups. Our data showed a higher number of resistant strains for β-lactams (107 patients) and sulfonamides (39 patients). The age distribution indicated that all ages are affected by this resistance with relative concentration around 30 and 70 years for β-lactams and sulfonamides, respectively. No relationship can be found between age and antibiotic resistance to phenicols, quinolones, polymyxins and nitrofurans due to the relatively low number of patients. In contrast, the investigation of Pulcini et al. [47] carried out in France, revealed that the age around 70 years showed a high resistance against β-lactams. Furthermore, Rocha et al. [46] indicated that the resistance of 30 years patient was observed against sulfonamides. These differences could be explained by the sampling size of the investigated population.

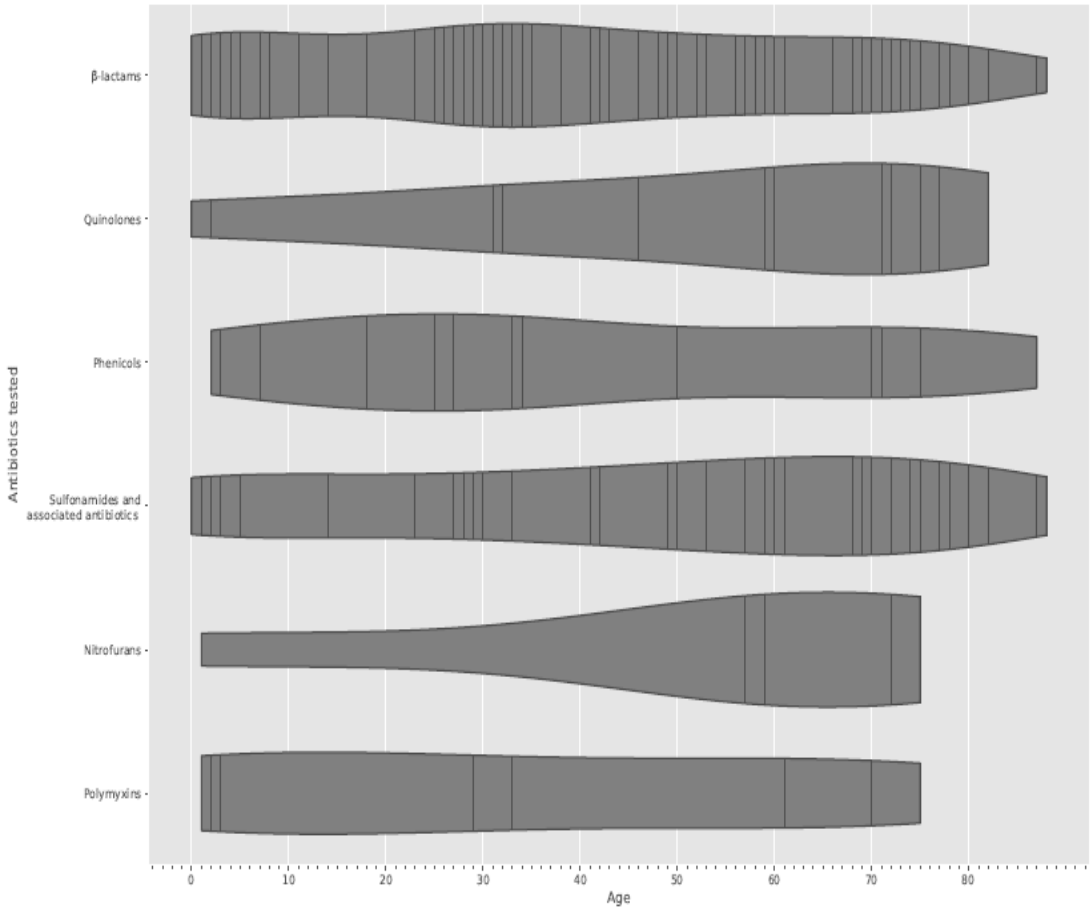


Figure 2. Antibiotic resistance pattern according to patient age

Conclusions

The current study demonstrates that *E. coli* is the primary causative agent of urinary tract infections (UTIs) at a rate of 65.51%, followed by *K. pneumoniae* and *P. mirabilis*. UTIs are more prevalent among females than males. The study found that carbapenems and aminoglycosides demonstrated strong antibiotic activity against 116 community-acquired *Enterobacteriaceae* isolates, which are commonly isolated organisms in UTIs. However, the study also found high resistance levels to penicillin and trimethoprim/sulfamethoxazole. The rate of multidrug-resistant *Enterobacteriaceae* (MDRE) in the studied region was alarming at 14.70%. The rate of MDRE in community-acquired UTIs is increasing in the area. To address this issue, regular evaluations of enterobacterial resistance trends will be necessary in the coming years, as resistance to newer antibiotics such as β-lactams and quinolones may increase.

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