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Prevalence and Antimicrobial Susceptibility Patterns of Gram-negative Uropathogens Isolated in Public Hospital Establishment «Saad Guermech Saoudi Amar Hmaida» Skikda-Algeria

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Authors' contributions

This work was carried out in collaboration among all authors. Author MSK designed the study, performed the statistical analysis, wrote the protocol and wrote the manuscript. Authors RZ, MY and BS managed the analyses of the study and managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Urinary tract infections (UTI$_{s)}$ are a serious world-wide health problem whose treatment becomes highly difficult due to the emergence of antibiotic-resistant bacterial strains.
Aims: Herein, a retrospective study was conducted with the aim to determine the prevalence, the identification of the bacteria responsible of UTIs, and the antimicrobial resistance profile.
Study Design: All Patient samples, including either external samples or samples taken from patients admitted to Public Hospital Establishment "Saad Guermech Saoudi Amar Hmaida" in Skikda-Algeria were used in this study for a period extending from January 2018 – March 2020.

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Methodology: The identification of bacterial strains and the antibiotic susceptibility testing was carried out using Analytical Profile index galleries (API) system and disk diffusion method.
Results: Among the 1203 samples, 206 (17.12%) were positive, and 997 (82.88%) were negative for bacterial growth. Regarding the pathogenic strains, 26 (12.62%), and 180 (87.38%) were found respectively, Gram-positive and Gram-negative strains. Among the 180 Gram negative strains, 104 (57.83%) were reported in female patients, 68 (37.72%) were in male patients, and 8 (4.45%) whose gender was not mentioned. The most representative Gram-negative strains are *Escherichia coli* (*E. coli*) (43.33%), *Klebsiella pneumoniae* (*K. pneumoniae*) (13.33%), *Proteus mirabilis* (*P. mirabilis*) (7.77%), *Enterobacter sp* (*E. sp*) (6.66%), since the other strains were less frequent. Moreover, 6 bacterial strains belonging to 3 genera (*Escherichia*, *Klebsiella*, and *Enterobacter*) were ESBLs producers with an overall prevalence of 3.33% of pathogenic strains isolated from urine. ESBLs were produced in 4.00%, 5.88%, and 6.25% of *E. coli*, *K. pneumoniae*, and *E. cloacae* strains respectively.
Conclusion: *E. coli* was found to be the most predominant strain, while most of the Gram-negative strains were highly resistant to Amoxicillin/clavulanic acid, Ampicillin, penicillin and tobramycin.

Keywords: Urinary tract infection; Gram-negative; antibiotic; antimicrobial resistance.

1. INTRODUCTION

The urinary tract is vulnerable to microbial mediated infections threatening human health, and inducing mortality [1]. The urinary tract infections (UTIs) affect about 150 million people/year in the world [2]. In addition, this disease becomes the second mortality cause in the world, in case of respiratory tract infections [3]. Noteworthy, several studies have reported age, sex, hospitalization, and misuse of antimicrobials as biological parameters that can remarkably affect the distribution of UTIs [4], as well as bacterial organisms were proved as the main cause of this disease [5,6]. In fact, Gram –negative bacteria are responsible for 90% of UTI cases, and the other 10% cases are the cause of Gram-positive bacteria. The French Agency for Sanitary Safety of Health Products (FASSHP) have proved that UTIs are commonly occurred in females, while 50% of women would show at least one case of UTIs in a lifetime [7]. As previously reported [8,9], *Escherichia coli* (*E. coli*) is the main cause of UTIs, representing thus, 65%-90% of this infection prevalence. Further, the emergence of antimicrobial resistance (AMR) effectively results in the urinary infection caused by the uropathogens [10], and hence nearly of 9% of all prescribed antibiotics were intended to UTIs in Europe [11]. This study was, therefore, devoted to examine the UTIs pathogens, and their antimicrobial susceptibility profile in external patients and patient admitted at the Public Hospital Establishment "Saad Guermech Saoudi Amar Hmaida" in Skikda-Algeria.

2. MATERIALS AND METHODS

2.1 Sample Collection and Culture Selection Criteria

The retrospective study was performed between January 2018 and March 2020, at the Public Hospital Establishment of "Saad Guermech Saoudi Amar Hmaida" in Skikda- Algeria. Here, a total of 1203 urinary specimens were collected, and then the epidemiological data of sex and symptoms were recorded.

In case of the bacterial count is greater than 10^5 CFU/mL in the urine, the culture is considered significantly positive, since the bacterial count less than 10^3 CFU/mL in medium flow urine, or patients presenting urinary catheter refers to negative bacterial culture.

2.2 Bacterial Culture and Identification

The bacterial culture was prepared using urine samples spread on blood agar, nutrient agar and Hektoen agar medium, and incubated overnight at 37°C. When the growth count is less of 10^3 CFU/mL and when the growth of two or more bacterial species was observed in a case of urinary catheter, the samples were considered, respectively as negative and contaminated. Bacteriuria was positive by the number of $\geq 10^5$ CFU/mL and hence, the identification of bacterial strain and antimicrobial sensitivity test was executed [12]. Also, bacterial identification was noticed via cultural and biochemical criteria through the Analytical Profile Index API 20E system (BioMérieux). Further, the following biochemical test characters; mainly applied on all Gram-negative strains are recapitulated in Table 1.

Table 1. Reading table of the different tests of the Api 20E gallery [13]

Tests	Substrates	Enzymatic reactions	Results	
			Positive	**Negative**
ONPG	Ortho-nitro-phenyl-galactoside	B-galactosidase	colorless	Yellow
ADH	Arginine	Arginine Dihydrolase	Yellow	Red/Orange
LDC	Lysine	Lysine Decarboxylase	Yellow	Orange
ODC	Ornithine	Ornithine Decarboxylase	Yellow	Red/Orange
CIT	Sodium citrate	Utilization of Citrate	Pale green / Greyish	Blue-green/ Green
H2S	Hydrogen sulfide	Production of H2S	Colorless/ Greyish	Black deposit/ End border
URE	Urea	Urease	Yellow	Red/ Orange
TDA	Tryptophan	Tryptophan deaminase	Yellow	Dark brown
IND	Indole	Production of indole	Colorless	Pink
			Pale green/ Yellow	Red ring
VP	Glucose	Production of acetoin	VP1 + VP2 (10mn)	
			Colorless	Pink/ Red
GEL	Gelatin	Gelatinase	No diffusion	Diffusion with black pigment
GLU	Glucose	Fermentation/Oxidation	Blue/ Blue-green	Yellow
MAN	Mannitol	Fermentation/Oxidation	Blue/ Blue-green	Yellow
INO	Inositol	Fermentation/Oxidation	Blue/ Blue-green	Yellow
SOR	Sorbitol	Fermentation/Oxidation	Blue/ Blue-green	Yellow
RHA	Rhamnose	Fermentation/Oxidation	Blue/ Blue-green	Yellow
SAC	Sucrose	Fermentation/Oxidation	Blue/ Blue-green	Yellow
MEL	Melibiose	Fermentation/Oxidation	Blue/ Blue-green	Yellow
AMY	Amygdalin	Fermentation/Oxidation	Blue/ Blue-green	Yellow
ARA	Arabinose	Fermentation/Oxidation	Blue/ Blue-green	Yellow
OX		Cytochrome oxidase	Ox (1-2 mn)	
			Colorless	Purple
NO_3^-	Glu tube	Production of NO_2^-	NIT1 + NIT2 (2-3 mn)	
NO_2		Production of NO_3	Yellow	Red
			+ ZN	
			Red	Yellow

2.3 Antibiotic Susceptibility

The antibiotic susceptibility of the isolates was carried out by using disk diffusion according to the EUCAST criteria (version 1.0 valid from January, 2019) [14]. The tested antibiotics in this study were: ampicillin, amoxicillin/clavulanic acid, benzylpenicillin, tobramycin, amikacin, cefotaxime, gentamicin, cefazoline, ciprofloxacin, chloramphenicol, cefalotine, ceftazidime, colistin, cotrimoxazole, penicillin. Whilst, extended-spectrum beta-lactamases (ESBLs) producing strains were using synergy test between a central disk of amoxicillin/clavulanic acid 30mm from the disk of cefotaxime or ceftazidime. The presence of ESBLs is suspected in front of a “Champagne cork” appearance [15].

2.4 Statistical Analyses

Statistical analyses were performed SPSS software (version 22.0; IBM SPSS Inc., New York, USA) [16]. The categorical variables were tested by using Chi-square test, where $p< 0.05$ was considered significant.

3. RESULTS

3.1 Occurrence of UTIs in Examined Samples

In this study, 1203 urinary specimens were collected and examined. Patient’s clinical symptoms, urine strips, presence of leucocytes and bacteria in the urine are commonly used criteria to diagnosis the UTIs. Among all these samples, 206 (17.12%) exhibited positive growth of uropathogen strains, since 997 (82.88%) samples showed negative growth (Table 2). Furthermore, the 206 uropathogenic isolates showed 26 (12.62%) Gram-positive, and 180 (87.38%) Gram-negative bacteria (Table 2). In addition, the positive cultures for women and men were 104 (57.83%) and 68 (37.72%), respectively, while 8 (4.45%) of the gender was not indicated. The bacterial isolation and identification showed that species belonging to 13 genera are responsible for 180 positives cultures of Gram-negative bacteria. Also, *E. coli* was found to be the most predominant bacterium (43.34%) followed by *K. pneumoniae* (13.33%), *P. mirabilis* (7.77%), *Enterobacter sp* (*E. sp*) (6.66%), *Klebsiella sp* (*K. sp*) (4.44%), Citrobacter species (3.88%), *Pseudomonas sp* (*P. sp*) (3.33%), *Pseudomonas aeruginosa* (*P. aeruginosa*) (3.33%), Serratia species (2.77%), *Enterobacter cloacae* (*E. cloacae*) (1.66%), *Yersinia sp* (*Y. sp*) (1.66%), *Acinetobacter sp* (*A. sp*) (1.11%), *Aeromonas sp* (*A. sp*) (1.11%), *Klebsiella oxytoca* (*K. oxytoca*) (1.11%), *Proteus sp* (*P. sp*) (1.11%), *Photobacterium* species (1.11%), *Hafnia sp* (*H. sp*) (0.55%), *Klebsiella ozaenae* (*K. ozaenae*) (0.55%), *Morganella morganii* (*M. morganii*) (0.55%), *Klebsiella ornithinolytica* (*K. ornithinolytica*) (0.55%), *Enterobacter gergoviae* (*E. gergoviae*) (0.55%) (Fig. 1).

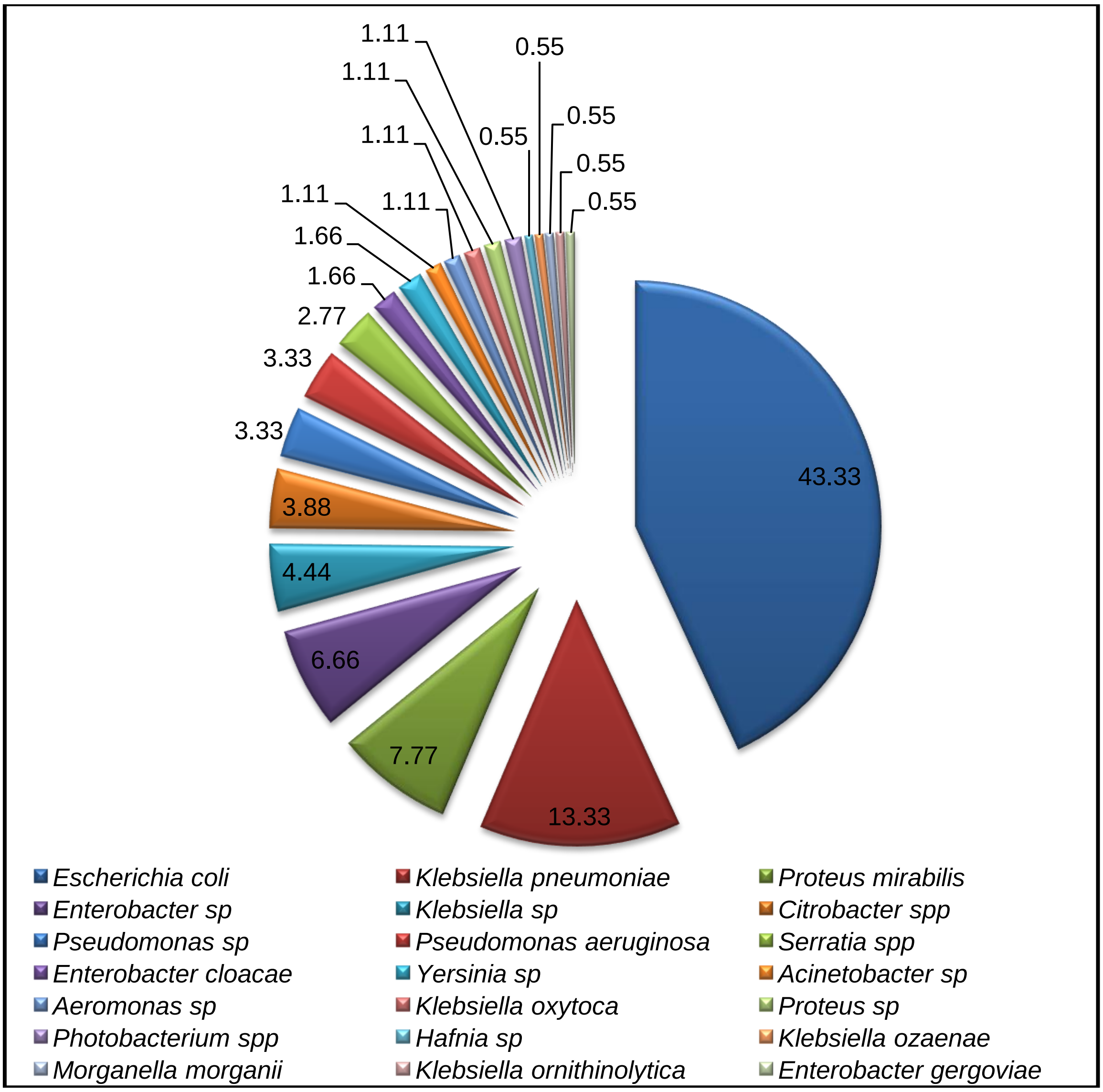


Fig. 1. Prevalence of Gram-negative uropathogens isolated from urine samples

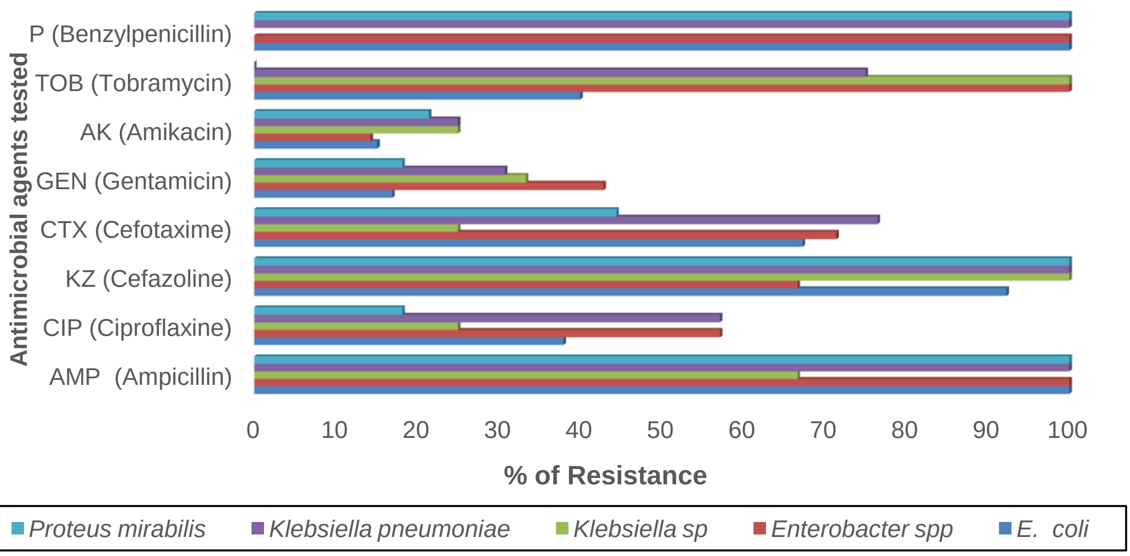
Table 2. Distribution of uropathogenic and non-uropathogenic bacteria among the tested patients in function of gender

Character	n (%)
No growth bacteria	977 (82.88)
Uropathogenic bacteria	206 (17.12)
Gram +	26 (12.62)
Gram -	180 (87.38)
Gender	**n (%)**
Female	104 (57.83)
Male	68 (37.72)
Gender not mentioned	8 (4.45)

3.2 Prevalence of Antimicrobial Resistance among Identified Uropathogens

E. coli, *P. mirabilis*, *K. pneumoniae*, *Klebsiella sp*, and *Enterobacter* spp antimicrobial resistance patterns were identified in this study. Also, the antimicrobial resistance profile is displayed in Fig. 2a, and 2b, showing a high resistance rate of Gram- negative strains to the analyzed antibiotics. Although, *E. coli* is the most common strain in terms of frequency, but Enterobacter spp are the most resistant bacterium. The results showed a total resistance (100%) to ampicillin, amoxicillin/clavulanic acid, tobramycin, colistin, penicillin, and benzylpenicillin, followed by cefotaxime, cefazoline, and ciprofloxacin with resistance rates of 71.42%, 66.66%, and 57.14% respectively. Additionally, most *E. coli* strains are 100% resistant to ampicillin and 15,09% resistant to amikacin. *K. pneumoniae* showed 100% of resistance to ampicillin, followed by amoxicillin/ clavulanic acid (90.9%). However, *K. pneumoniae* had a significant rate of resistance to cefotaxime (76.47%). *P. mirabilis* exhibit 100% resistance to three antibiotics: ampicillin, amoxicillin/clavulanic acid, and cefazoline. The data showed also, that 6 bacterial strains belonged to 3 genera (*Escherichia*, *Klebsiella*, and *Enterobacter*) are ESBLs producers with an overall 3.33% prevalence of pathogenic strains isolated from urine. ESBLs were produced in 4.00%, 5.88%, and 6.25% of *E. coli*, *K. pneumoniae*, and *E. cloacae* strains respectively. The distribution of ESBLs producing *E. Coli* shows a predominance of *E. cloacae* with 6.25% (Fig. 3). Although, all Gram-negative strains revealed a total sensitivity to chloramphenicol. Nevertheless, its toxicity to the bone marrow, as well as the availability of other antimicrobials make chloramphenicol as a useless option for the treatment of bacterial infections, especially UTIs.

a)



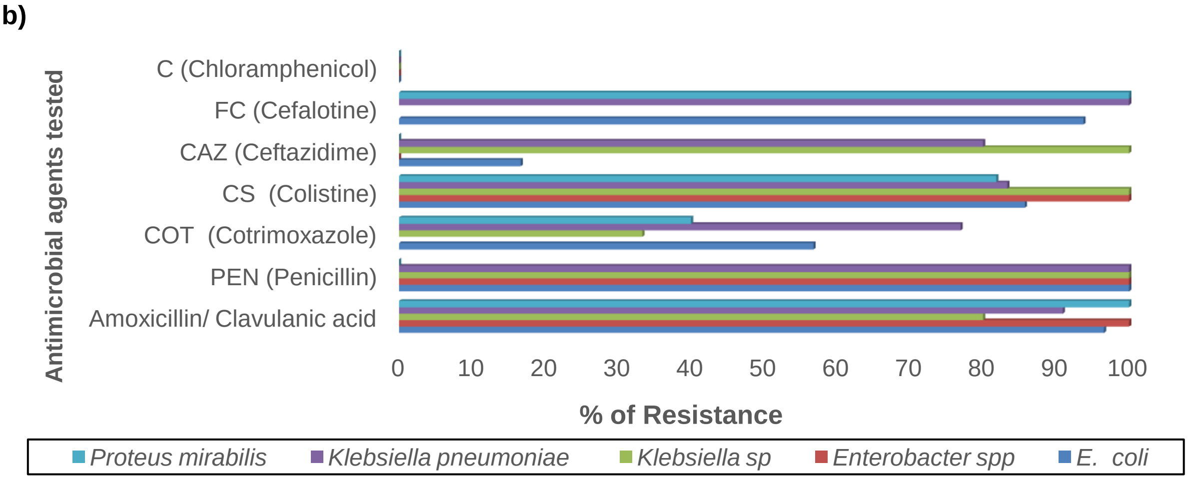


Fig. 2. Resistant strains of most representative Gram-negative uropathogens isolated from patients at Public Hospital Establishment "Saad Guermech Saoudi Amar Hmaida"

Antimicrobial agent tested is illustrated by a single bar. Different colored bars indicate the strain tested. The absence of the color in the colored bars means 0% of resistance for the relative strain.

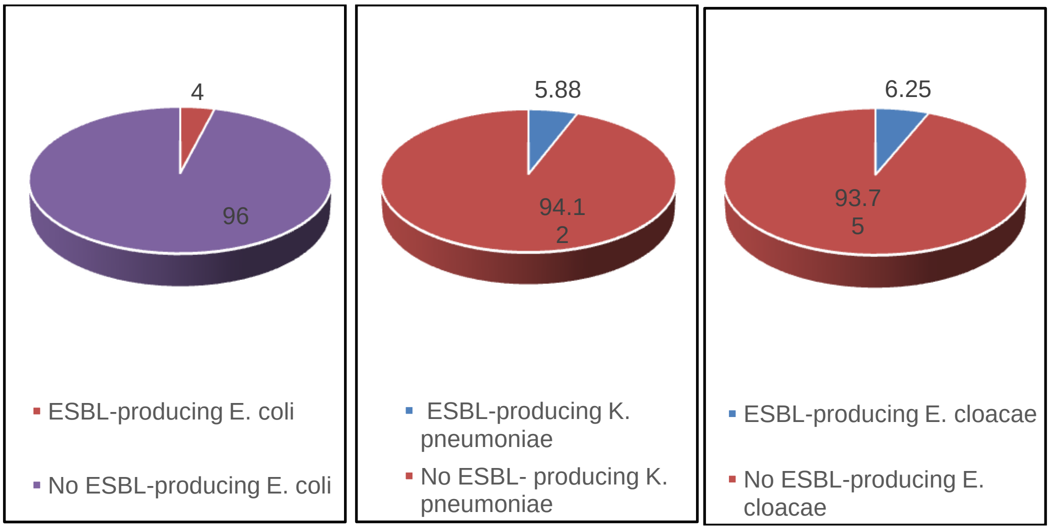


Fig. 3. Distribution and prevalence of ESBLs producing uropathogens strains

4. DISCUSSION

The study was basically aimed to evaluate the incidence of pathogens causing UTIs, through estimation of their sensitivity profile. From 1203 urinary samples collected during this study, 206 (17.12%) of patient's urine samples show marked bacteriuria. Also, a high frequency was found in Italy (31%), and Saudi Arabia (32.6%) [17,18], meanwhile the low frequency of UTIs with significant bacteriuria was observed at the National Hospital Abuja in Nigeria (13.1%), and the Ibn -Zohr Public Hospital Establishment of Guelma (northeast Algeria) (9.4%) [19], (Benoumhani B, Kismoune N, Skikda University, Algeria, Unpublished data). In accordance with previous results [17,20,21], female patients with UTI were found to be most frequent (57.83%). Indeed, females are highly exposed to the urinary infection because of their genital anatomy, age, sexual activity, postmenopausal phase, and hormonal changes [22]. Among the 206 pathogenic isolates, 12.62% are Gram-positive and 87.38% are Gram-negative, and these results concord with those found in Italy, showing 19.7% Gram-positive and 78.5% Gram-negative bacteria [17]. *E. coli* (43.33%) was the most detected strain among the Gram-negative bacteria, while *E. gergoviae* (0.55%) was the least isolated organism. The prevalence of isolated uropathogens was alike to that reported in other studies in different countries, including Italy. *E. coli* was involved in 53.5% of the UTIs and was the most frequent isolate [17]. in South America, the frequency of *E. coli* makes it as the most strain isolated, responsible for 39.7% of UTI cases [23]. Additionally, E. *coli*, was the cause of 66.01% of UTIs cases in China [24]. Furthermore, bacterial resistance profile showed that among Gram-negative uropathogens, Enterobacter spp were identified as the most resistant bacterium. Those strains revealed 100% resistance to ampicillin, amoxicillin/clavulanic acid, tobramycin, colistin, penicillin, and benzylpenicillin. The majority of the isolated strains showed strong resistance to ampicillin with a rate of (80%). Similarly, 72% and 78% of Gram-negative isolates found, respectively in Italy and Ethiopia showed a marked resistant to ampicillin [17,25]. Ampicillin, gentamicin, fosfomycin, and trimethoprim-sulfamethoxazole show some of the first-empirical treatment purposes. In almost of all UTIs cases, empirical antibiotic treatment begins before the urine culture results. Hence, the improper use of antibiotics (dosing, antibiotic intake interval, and prolonged use of antibiotics) increases antibiotic resistance among uropathogens. Several studies have reported the need to the appropriate use of antibiotics to overcome the antibiotic resistance problems [26]. The detection of ESBLs producing strains was established by the synergy test between the central amoxicillin/clavulanic acid disk 30 mm from the cefotaxime, ceftazidime, or ceftriaxone disks. Our findings showed also, that among of 180 identified Gram-negative strains, only 6 (3.33%) are potentially ESBLs producing strains. Previous studies have reported higher rates of ESBLs producing strains in Morocco and Mauritania with frequency of 12.2% and 12.8%, respectively [27,28]. In fact, this rate varies from country to country and from medical centre facility to another, for example: The countries of Southern Europe recorded rates exceeding 10%, since those of the north of Europe countries recorded only lower rates than 5% (Dadoun M, Rahmani A, Blida University, Algeria, Unpublished results) [29]. Our results showed that amikacin, gentamicin, or even cefotaxime is likely used for the treatment of Gram-negative strains who's the resistance rate to these antibiotics remains relatively low. On the other hand, the rate of resistance to penicillin, and amoxicillin/clavulanic acid is the highest rate with an increasing trend. This data is similar to those of the study conducted in Italy [17]. Hospitalized patients involved in this retrospective study may suffer from several infections due to multi-resistant bacterial strains, including urinary tract infections, affecting generally this type of patients. This study can bring new understanding knowledge that may influence the choice of empirical treatment of UTIs. Our study promotes information on the current health states at "Saad Guermech Saoudi Amar" Public Hospital Establishment, and at the Eastern region of Algeria, leading to establish new guidelines for the proper use of antibiotics.

5. CONCLUSION

In conclusion, the study proved that *E. coli* is the predominant strain among Gram-negative bacteria, followed by *K. pneumoniae* and, *P. mirabilis*. In addition, Enterobacter species are the most resistant strains to antibiotics with total resistance (100%) to ampicillin, amoxicillin/clavulanic acid, tobramycin, and penicillin. Interestingly, amikacin, gentamicin, or even cefotaxime could be used in the treatment of Urinary Tract Infections caused by Gram-negative strains, where the resistant rate of the main uropathogens to these antibiotics remains relatively low.

CONSENT AND ETHICAL APPROVAL

As per university standard guidelines, participant consent and ethical approval have been collected and preserved by the authors

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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