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ORIGINAL ARTICLE

Bacterial Pattern of Community acquired Urinary Tract Infections: A Challenge for Antimicrobial Resistance

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ABSTRACT

Background*: Urinary tract infection (UTI) is considered one of the most common bacterial infections seen in health care. To our knowledge, there is no available antimicrobial resistance surveillance system for monitoring of community-acquired UTIs (CA- UTIs) in our country.* ***Objectives****: we aimed to discuss the bacterial pattern and resistance profile of CA-UTIs in Ismailia, Egypt.* ***Methods:*** *This cross-sectional study included 400 patients suffering from symptoms of acute UTIs. Urine specimens were collected by clean-catch mid-stream method, examined microscopically and inoculated immediately on blood agar and MacConkey's agar plates. Colony counting, isolation and identification of the urinary pathogens were performed by the conventional biochemical tests according to the isolated organism. Antibiotic susceptibility testing was performed by Kirby Bauer disk diffusion method. Interpretation was performed according to Clinical Laboratory Standard Institute (CLSI) guidelines.* ***Results:*** *out of 400 specimens, 136 of them revealed no bacterial growth or insignificant bacteriuria. Most of participants with UTI were females (81.8%) (p=0.008) and 54.5% of them were married (P=0.1). Gram negative bacteria were more common than Gram positive representing 66 % and 34% respectively. E. coli was the most common isolated organism (39%) followed by S. aureus (32%), K. Pneumoniae and Pseudomonas (10.5% for each), Proteus (6%) and Enterococci (2%). E. coli isolates showed the highest susceptibility to imipenem, meropenem, amikacin, nitrofurantoin, levofloxacin and ciprofloxacin. Most of our patients were diabetics (64.8%) (p=0.004). The mean ± SD of HbA1c was 6.4±2.0 with 4 to 12.6 range, S.E was 0.1 and 95% C.I was 6.2- 6.7. The highest mean ± SD of HbA1c was in S. aureus infections.* ***Conclusion:*** *Gram negative bacteria were most common than Gram positive with predominance of E. coli with significant relation to the presence of diabetes.*

INTRODUCTION

Urinary tract infection (UTI) is one of the most important causes of morbidity in the general population with increased lifetime frequency in adult women (50-60%)[1,2]. The occurrence of UTI, at least one time during life, is estimated to be higher in women than men (40% vs 12%) with high recurrence rate especially in women (27 to 48%), In the United States, UTIs are considered an economic problem that cost about $6 billion per year[3-5].

Colonization of bacteria around the urethral opening in both men and women are naturally washed out during micturition. The short urethra in women makes it probable for bacterial colonizers to reach the bladder more easily. In addition, the urethral opening in women is nearby to the vaginal opening and rectum, which are contaminated areas with large and different bacterial population. Bacterial factors affect the progression to UTIs including the virulence characteristics of the bacteria and its ability to evade the human immune system[5].

Urinary Tract Infections are classified according to the clinical presentation and level of severity into upper and lower UTIs. According to the source of infection, UTIs were classified into Community Acquired (CA-UTIs) and Health Care associated infections (HA-UTIs). Clinically, UTIs were reported as complicated or uncomplicated according to the risk factors [6].

Inadequate empirical antibiotic prescription without urine culture and susceptibility testing result in emergence of multi-drug resistant (MDR) pathogens and ineffective UTI treatment and development of persistence or recurrent infections [7]. The use of prophylactic antimicrobial therapy is considered a main risk factor in development of MDR which occurred frequently in Asia, Africa, and Latin America (86%, 85%, and 84%, respectively), followed by Europe (67%) [8,9].

Enterobacteriaceae and *Candida albicans* also can cause UTIs [4,10]. Meanwhile, Uropathogenic *Escherichia coli* strains (UPEC) are the most common bacterial causes of uncomplicated UTIs, community-acquired infections, and hospital-acquired infections (80%, 95% and 50% respectively) [11].

The first-line antimicrobials for empiric treatment of UTIs are selected based on the local resistance rates with resistance not exceeding 10–20% [12]. So, local surveillance of uropathogens and their resistance pattern are serious for notifying empirical antimicrobial choices. Inappropriately, there is no antimicrobial resistance surveillance system for monitoring of community-acquired uropathogens in Egypt resulting in lack of a local protocol for the proper treatment of CA-UTIs in Egypt. In the present study, we aimed to discuss the bacterial pattern and resistance profile of community-acquired uropathogens in Ismailia, Egypt.

METHODOLOGY

Patients:

This cross sectional study was carried out in Outpatient's Clinics in Ismailia city, Egypt and included 400 patients suffering from symptoms of acute UTIs. Patients who received antibiotics in the last 2 weeks, hospitalized (for more than 48 hr) or with urinary catheter were excluded from our study. All age groups were included. Informed consent was taken from each patient to use their data in the current research work. The ethics committee of Faculty of Medicine, Suez Canal University had reviewed and approved the study (approval number: Research 4417#).

Collection, examination, and culture of urine samples:

Each patient was carefully instructed regarding the sterile collection of urine samples as a clean-catch mid-stream specimen. The urine specimens were transported within 2 hours to the Microbiology and Immunology laboratory, Faculty of Medicine, Suez Canal University.

Specimens were examined for pus cells, epithelial cells and red blood cells, and then inoculated immediately on blood agar and MacConkey's agar plates using a 0.001ml calibrated loop. Colony count, isolation and identification of the urinary pathogens were performed by the conventional biochemical tests according to the isolated organism [13,14]. Patients with nonsignificant bacteriuria or mixed growth of bacteria indicating contamination were excluded.

Antibiotic susceptibility test

Antibiotic susceptibility testing was performed by Kirby Bauer Disk Diffusion method and interpreted according to Clinical Laboratory Standard Institute (CLSI) guidelines. The antibiotics used (Oxoid, Basingstoke, UK) were selected according to the type of organism isolated and interpreted according to CLSI guidelines [15].

Statistical Analysis

All statistical analyses were performed using Statistical Package for Social Science program (SPSS version 22 for windows). Continuous data such as age were summarized by mean, standard deviation and range while qualitative data such as gender and marital status were summarized by frequencies. In analytical data, the chi-square test was used to detect the difference between qualitative data, while Kruskal-Wallis test was used to detect the difference between quantitative data. Statistical significance was considered at p.value ≤ 0.05.

RESULTS

A total of 400 patients suffering from signs and symptoms of acute UTI were included in our study ranging from 3 months to 92 years age. Midstream urine samples were collected from all participants and 136 of them revealed no bacterial growth or insignificant bacteriuria. Most of participants with UTI were females (81.8%) (p=0.008) and 54.5% of them were married (p=0.1) (table 1). Gram negative bacteria were more common than Gram positive bacteria representing 66 % (174/264) and 34 % (90/264) respectively. *E. coli* was the most common isolated organism (39%) followed by *S. aureus* (32%), *K. pneumoniae* and *pseudomonas* (10.5% for each), *proteus* (6%) and *enterococci* (2%).

Socio-demographic data and the type of detected organisms:

We found that age and gender were significantly related to the type of detected organism detected (p= 0.046 and 0.008 respectively) (table 1).

Table 1: Relation between socio-demographic data and detected organisms

Organism	No.	Age				P value	Gender (No., %)		P value	Marital status		P value
		Mean ± SD	S.E.	95% C.I.	Range		Female	Male		Married	Not married	
E. coli	102	33.6±23.6	2.3	29.0-38.2	1-84	0.046*§	86(84.3%)	16(15.7%)	0.008*¶	64(62.7%)	38(373%)	0.100¶
K. pneumoniae	28	30.5±12.1	2.3	25.8-35.2	0.5-58		26(92.9%)	2(7.1%)		18(64.3%)	10(35.7%)	
Proteus	16	25.1±28.9	7.2	9.7-40.4	2-91		14(87.5%)	2(12.5%)		6(37.5%)	10(62.5%)	
Pseudomonas	28	38.9±31.6	6.0	26.7-51.1	3-92		16(57.1%)	12(42.9%)		14(50.0%)	14(50.0%)	
S. aureus	84	25.7±21.7	2.4	21.0-30.4	0.3-72		68(81.0%)	16(19.0%)		38(45.2%)	46(54.8%)	
Enterococci	6	37.3±10.7	4.4	26.1-48.6	24-50		6(100.0%)	0(0.0%)		4(66.7%)	2(33.3%)	
Total	264	30.9±23.4	1.4	28.0-33.7	0.3-92		216(81.8%)	48(18.2%)		144 (54.5%)	120(45.5%)	

* Statistically significant at p<0.05
§ Kruskal-Wallis test used
¶ Chi-square test used (Exact p value)

Abdominal pain and fever were the most common presentation in our patients (51.5% for each) with statistically significant relation to infection (p=0.04) (table 2).

Table 2: Relation between clinical symptoms and detected organisms

Organism	Vaginal discharge (No., %)		P value	Abdominal pain (No., %)		P value	Fever (No., %)		P value
	Present	Absent		Present	Absent		Present	Absent	
E. coli	69(80.2%)	17(19.8%)	0.001*¶	50(49.0%)	52(51.0%)	0.040*¶	50(49.0%)	52(51.0%)	0.040*¶
Enterococci	1(16.7%)	5(83.3%)		4(66.7%)	2(33.3%)		4(66.7%)	2(33.3%)	
K. pneumoniae	21(80.8%)	5(19.2%)		9(32.1%)	19(67.9%)		9(32.1%)	19(67.9%)	
Proteus	11(78.6%)	3(21.4%)		5(31.3%)	11(68.8%)		5(31.3%)	11(68.8%)	
Pseudomonas	16(100.0%)	0(0.0%)		18(64.3%)	10(35.7%)		18(64.3%)	10(35.7%)	
S. aureus	59(86.8%)	9(13.2%)		50(59.5%)	34(40.5%)		50(59.5%)	34(40.5%)	
Total	177(81.9%)	39(18.1%)		136(51.5%)	128(48.5%)		136(51.5%)	128(48.5%)	

* Statistically significant at p <0.05
¶Chi-square test used (Exact p value)

Most of isolates were more than 100.000 CFU/ml (80.3%) while 17.4% counted 10.000 to 100.000 CFU/ml and only 2.3% were less than 10.000 CFU/ml. We noticed that all E. coli, *K. pneumoniae and proteus* isolates were count more than 100.000 CFU/ml while 50% of *S. aureus* was counted 10.000 to 100.000 CFU/ml (p=0.001) (table 3).

Table 3: Bacterial counts of isolated organisms

Organism	Count (No., %)			P value
	>100,000	10,000-100,000	<10,000	
E. coli	102(100.0%)	0(0.0%)	0(0.0%)	<0.001*¶
Enterococci	2(33.3%)	2(33.3%)	2(33.3%)	
K. pneumoniae	28(100.0%)	0(0.0%)	0(0.0%)	
Proteus	16(100.0%)	0(0.0%)	0(0.0%)	
Pseudomonas	26(92.9%)	2(7.1%)	0(0.0%)	
S. aureus	38(45.2%)	42(50.0%)	4(4.8%)	
Total	212(80.3%)	46(17.4%)	6(2.3%)	

* Statistically significant at p <0.05
¶Chi-square test used

Diabetes and UTI:

In our work most of our patients were diabetics (64.8%). The mean ± SD of HbA1c was 6.4±2.0 with range (4-12.6), S.E was 0.1 and 95% C.I was 6.2- 6.7. The highest mean ± SD glycated hemoglobin (HbA1c) was in *S. aureus* infections. We also studied the relation of the diabetes (as a risk factor) with the isolated organisms. We found that there was a significant statistical relation between the presence of diabetes and development of acute UTI (p=0.004), while the HbA1c was not statistically significant in the presence of acute UTIs (p= 0.07) (table 4).

Table 4: Relation between diabetes and detected organisms

Organism	Diabetes (No., %)		P value	HbA1c				P value
	Not Diabetic	Diabetic		Mean ± SD	S.E.	95% C.I.	Range	
E. coli (102)	42(41.2%)	60(58.8%)	0.004*¶	6.6±2.2	0.2	6.1-7.0	4.0-12.6	0.070§
Enterococci (6)	6(100.0%)	0(0.0%)		6.5±1.8	0.4	5.8-7.3	4.9-9.8	
K. pneumoniae (28)	10(35.7%)	18(64.3%)		6.2±1.5	0.4	5.4-7.0	4.9-9.6	
Proteus (16)	6(37.5%)	10(62.5%)		6.3±2.0	0.4	5.6-7.1	4.6-11.0	
Pseudomonas (28)	8(28.6%)	20(71.4%)		6.1±1.8	0.2	5.7-6.5	4.5-12.0	
S. aureus (84)	21(25.0%)	63(75.0%)		9.1±1.9	0.8	7.1-11.1	6.8-12.0	
Total	93(35.2%)	171(64.8%)		6.4±2.0	0.1	6.2-6.7	4.0-12.6	

* Statistically significant at p <0.05
¶Chi-square test used
§ Kruskal-Wallis test used

Antimicrobial susceptibility of uropathogenic isolates:

Investigation of antimicrobial susceptibility of uropathogenic *E. coli* isolates exhibited the highest susceptibility to imipenem, meropenem, amikacin, nitrofurantoin, levofloxacin and ciprofloxacin (86.3%, 80.4%, 62.7%, 62.7% 49% and 49% respectively) (table 5). Most of isolated strains (92%) were MDR.

Table 5: Antibiogram of *E. coli* isolated from the studied samples.

Name of antibiotic	Sensitive %	Intermediate %	Resistant%
ampicillin	2%	-	98%
Cefazolin	37.3%	-	62.7%
Gentamycin	37.3%	33.3%	29.4%
Tobramycin	45.1%	5.9%	49
Amikacin	62.7%	31.4%	5.9%
Ciprofloxacin	49%	3.9%	47.1%
Levofloxacin	49%	-	51%
Trimethoprim sulphamethoxazole	37.3%	-	62.7%
trimethoprim	37.3%	-	62.7%
Aztreonam	47.1%	17.6%	35.3%
Meropenem	80.4%	3.9%	15.7%
Imipenem	86.3%	9.8%	3.9%
Cefoxitin	37.3%	-	62.7%
Nitrofurantoin	62.7%	19.7%	17.6%
Cefotaxime	29.4%	13.7%	56.9%
Ceftazidime	3.9%	11.8%	84.3%
Ceftriaxone	37.3%	9.8%	52.9%
Cefepime	11.8%	54.9%	33.3%
Ampicillin sulbactam	25.5%	25.5%	49%
Amoxicillin clavulanic acid	31.4%	15.7%	52.9%

Among *klebsiella* species, high susceptibility was detected to meropenem, imipenem, ciprofloxacin and amikacin (92.9%, 85.7%, 82.1% and 78.6% respectively) (table 6).

Table 6: Antibiogram of *Klebsiella* pneumoniae detected in the examined samples

Name of antibiotic	Sensitive%	Intermediate%	Resistant%
Ampicillin	36%	7.1%	56.9%
Cefazolin	32.2%	7.1%	60.7%
Gentamycin	42.9%	32.1%	25%
Tobramycin	32.2%	7.1%	60.7%
Amikacin	78.6%	10.7%	10.7%
Ciprofloxacin	82.1%	0	17.9%
Levofloxacin	32.2%	7.1%	60.7%
Trimethoprim sulphamethoxazole	35.7%	7.2%	57.1%
trimethoprim	35.7%	7.2%	57.1%
Aztreonam	53.6%	14.3%	32.1%
Meropenem	92.9%	7.1%	0
Imipenem	85.7%	14.3%	0
Cefoxitin	25%	7.1%	67.9%
Nitrofurantoin	7.1%	14.3%	78.6%
Cefotaxime	25%	21.4%	53.6%
Ceftazidime	14.3%	17.9%	67.9%
Ceftriaxone	42.9%	17.9%	39.3%
Cefepime	0	46.4%	53.6%
Ampicillin sulbactam	32.2%	46.4%	21.4%
Amoxicillin clavulanic acid	21.4%	10.7%	67.9%

Most of *pseudomonas* species were sensitive to meropenem and imipenem (92.9%), nitrofurantoin (64.3%) and amikacin (50%) (Figure 1). On the other hand, 75% of *proteus* species were sensitive to amikacin and 62.5% were sensitive to meropenem, imipenem and amoxicillin sulbactam (Figure 2).

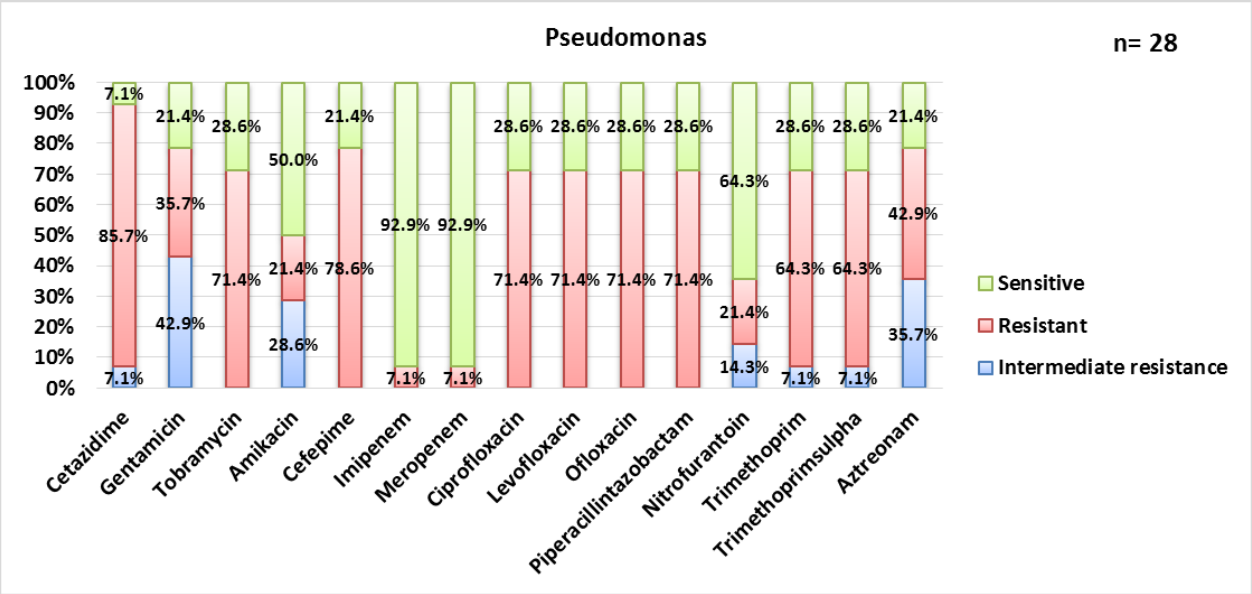

Fig. 1: Antibiogram of *pseudomonas* detected in the studied samples

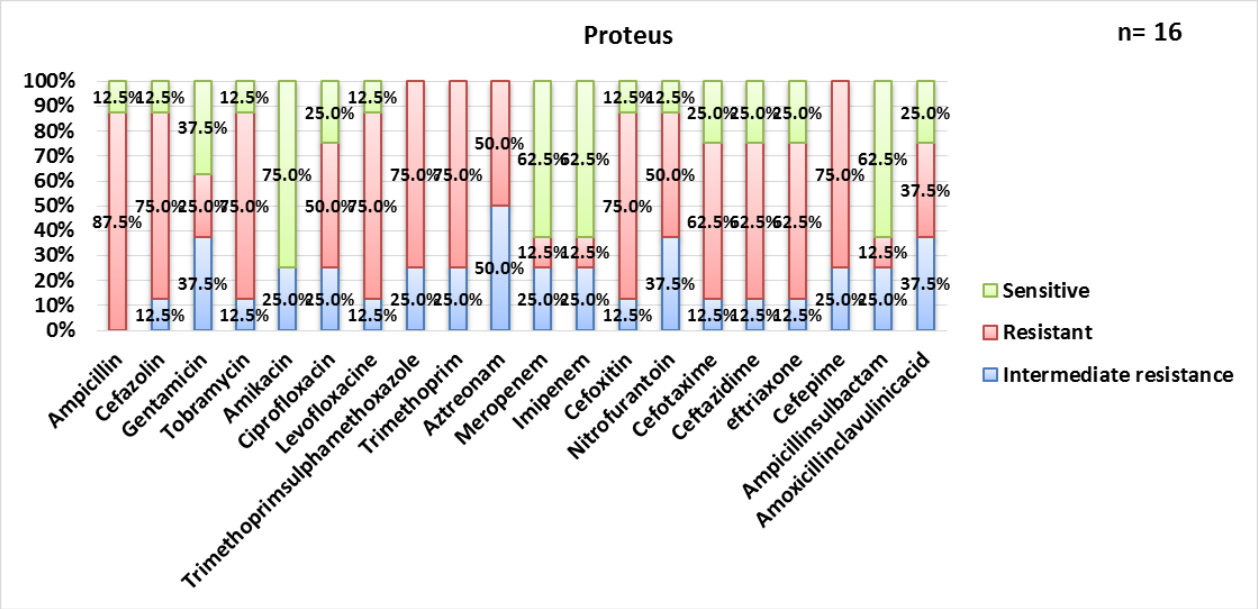

Fig. 2: Antibiogram of *Proteus* detected in the studied samples

We noticed that the rate of resistance was high among Gram positive bacteria as 92.9% of *S. aureus* were resistant to ampicillin and 88.1% were resistant to cefoxitin. Ofloxacin and doxycycline resistance was noticed among 76.2% of *S. aureus* isolates (Figure 3). Interestingly, all *enterococci* isolates were resistant to penicillin and most of them (66.7%) were resistant to ampicillin, vancomycin, linezolid, nitrofurantoin and ciprofloxacin (Figure 4).

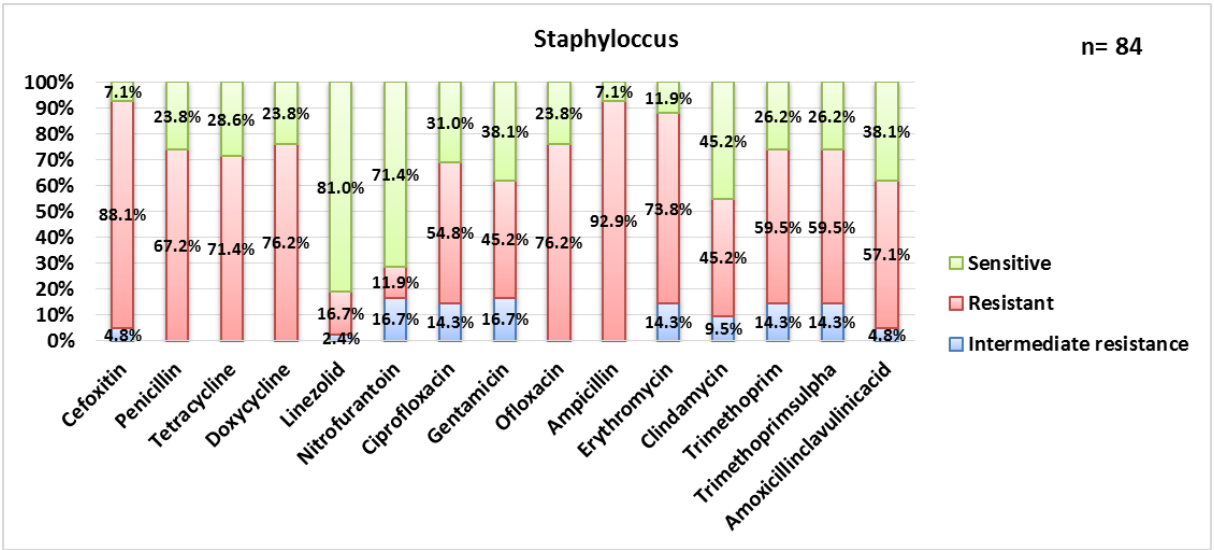

Fig. 3: Antibiogram of *Staphylococcus* detected in the studied samples

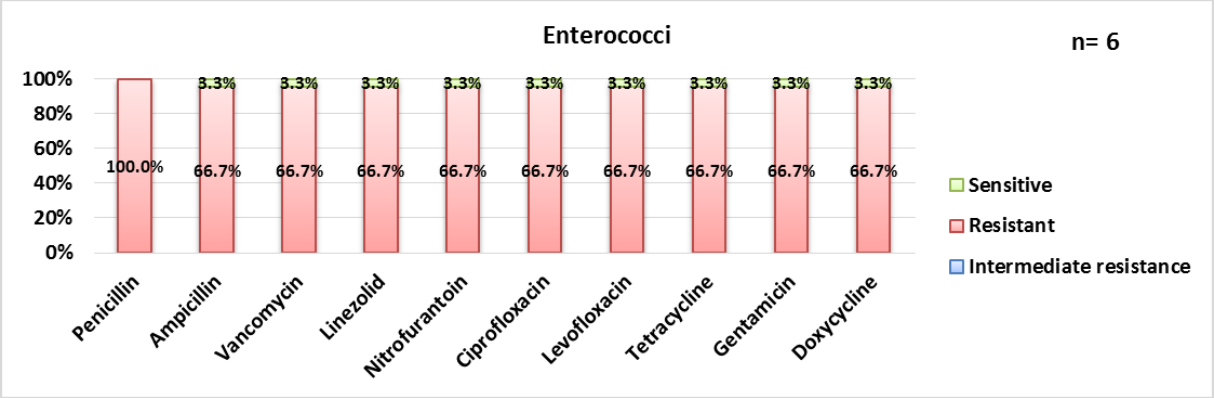

Fig. 4: Antibiogram of *Enterococci* detected in the studied samples

Relation between the type of organism, socio-demographic data, clinical presentation, presence of diabetius and antibiogram:

According to age, there was a statistically significant difference between the different types of bacteria and age. There is female predominance found in all types of bacteria under study with statistical difference ($P < 0.05$) especially in *pseudomonas* ($P < 0.001$). There were no statistical difference between different types of bacteria in relation to marital state except for the *S. aureus* which was more in non-married patients ($p<0.05$). Diabetics were more affected by different types of bacteria ($p<0.05$). *Enterococci* was the only exception which was more predominant in non-diabetics ($p<0.05$). *Enterococci* was also exception in the presence of vaginal discharge ($p< 0.001$), which is present in all types of infection under the study ($p<0.001$). Abdominal pain and fever were present in most types of infections except for *E. coli*, *K. pneumoniae*, *proteus* ($p< 0.05$). The count of bacterial colonies exceeds the 10^5 in all types of infections under the study ($p <0.001$).

DISCUSSION

The microbiological testing for uncomplicated UTIs is not performed on a routine basis resulting in under-representation of uncomplicated UTIs. Meanwhile, Antimicrobial Resistance Surveillance System (ARS) data represent the prevalence of complicated UTIs wherever cultures are done in the community setting. A wide bacterial pattern of infection and increase extents of resistance can be predictable in cases of complicated UTIs, so the incidence of antibiotic resistance in patients with uncomplicated UTIs is likely overrated[16–18]

Our study included 400 patients with signs and symptoms of acute UTI. We noticed that the frequency of females (81.8%) were higher than of males ($p=0.008$). This finding is compatible with another study done in Egypt reported that female patients represented 58% in CA-UTI and 52% in HA-UTI[19]. These findings may be due to shorter urethra of females with proximity to the anus that allows bacterial access to the bladder and the absence of prostatic fluid which had an antibacterial effect [20]. In our study, we found that Gram negative bacteria were more common than Gram positive representing 66 % (174/264) and 34 % (90/264) respectively. *E. coli* was the most common isolated organism (39%) followed by *S. aureus* (32%), *K. pneumoniae* and *pseudomonas* (10.5% for each), *proteus* (6%) and *enterococci* (2%).

Our study revealed a high incidence of MDR phenotype (92%) among uropathogenic *E. coli* isolates. In Egypt, Gawad and his colleagues reported a higher incidence of MDR in uropathogenic *E. coli* (90.85%) being higher in Mansoura hospital (Dakhalia governorate, rural, 96.77%) than in Giza governorate (urban, 76.47%). Other studies in Egypt, reported a high incidence of MDR phenotype among UPEC; where it was recorded in 95%, 84%, and 47.9% of tested UPEC isolates in Cairo, Dakhalia, and Minia governorates, respectively [21–23].

Other studies, from developing countries, also reported a high incidence of MDR phenotype among UPEC 78%, 32.2% and 92.9%, of UPEC isolates from Tehran, Libya, and Bangladesh, respectively[24–26]. Another Egyptian study reported high resistance to ampicillin (93.1%) and ceftazidime (86.2%) in uropathogenic *E. coli* isolates. As regards imipenem and meropenem only 1 isolate (3.5%) was resistant to either one of them.

Trimethoprim and co-trimoxazole (trimethoprim/ sulfamethoxazole) were used in the past as first-line antimicrobials for empirical treatment of UTIs. Resistance should be lower than 20% to safeguard best benefits from these antimicrobials [(27,28)]. In our study, we found high resistance to trimethoprim and co-trimoxazole among *E. coli* isolates (62.7%) compared to other studies. In 2018, Klingeberg and his colleagues reported low prevalence of trimethoprim and co-

trimoxazole resistance among *E. coli* (15.2% and 13% respectively). Accordingly, they recommend trimethoprim as a choice for the treatment of uncomplicated UTIs. Co-trimoxazole is considered the second choice for its side effects [29]. In recent studies from Germany, low prevalence of resistance was noticed against Trimethoprim and co-trimoxazole (17.5% and 15.0% respectively). Studies from other countries reported low prevalence compared to our results (7, 26–28). In our study, high resistance to both drugs may be due to the frequent use of trimethoprim which should be observed, bearing in mind that trimethoprim is nowadays again suggested as a first-line agent.

K. pneumoniae is a clinically frequent pathogen and cause both HA-UTI and CA-UTI. The increased resistance of this pathogen leads to restricted therapeutic opportunities [(30)]. The emergence of virulent organisms, with K1/K2 capsular serotypes, has been detected over the last 20 years in community[(31)]. In our study, we found that *S. aureus* was second frequent bacterial causes of CA-UTIs (32%), while *K. pneumoniae* and *pseudomonas* represented 10.5% of the bacterial causes. In 2007, Keynan and Rubinstein reported a changing pattern of *K. pneumoniae* infections in the community, describing this organism as the second most common etiological pathogen involved in CA-UTIs [(31)]. It is one of the topmost three pathogens of worldwide concern documented in the 2017 World Health Organization's (WHO)[32].

Most of the community acquired *K. pneumoniae* pathogens characterized in our study were susceptible isolates; the antimicrobial susceptibility was >80% in meropenem, imipenem and ciprofloxacin (92.9%, 85.7% and 82.1% respectively). This finding matched with another study in Portugal, one of the top carbapenems consumers in Europe. They stated an increase in the frequency of the susceptible isolates to carbapenems with change in pattern of resistance (5.2% and 8.6% respectively)[30,33,34,35].

In our study, the patients with UTI caused by *K. pneumoniae* were mostly female (92.9%), married (64.3%), diabetics (64.3%) with HbA1c mean ± SD was 6.5±1.8 (range: 4.9-9.8, P= 0.417). Another study reported that old age and female gender were dominant. They also reported that diabetes mellitus was the most common underlying disease (53.7%) [(36)].

In our study, we noticed unusual increase in the frequency of *S. aureus* (32%) isolated from patients with UTIs. This finding was not matched with several studies reported *S. aureus* as an unusual cause of UTI[37–39]. Baraboutis and his colleagues reported a relation between *S. aureus* bacteriuria and bacteremia, but primary *S. aureus* UTI may also occur due to catheterization. Other pathogenetic mechanisms were reported as unrecognized preceding bacteremia related to intravascular device exposure or other healthcare-related factors [37]. Furthermore, we noticed that the rate of resistance was high among *S. aureus* isolates, 92.9% was resistant to ampicillin and 88.1% was resistant to cefoxitin. Ofloxacin and doxycycline resistance were noticed among 76.2% of *S. aureus* isolates.

In our study, assessment of combination therapy in treatment of CA-UTIs was not performed. On the other hand, we didn't evaluate the genotypes characterization of the isolates especially MDR organisms. As, empirical treatment must be based on both antibiogram and clinical conditions, this study shortage in the severity of the infection and vulnerability of the patients such as underlying diseases.

CONCLUSION

Results of our study should be interpreted with caution due to the small sample size, the limited site of the study, and the geographic variability in resistance pattern of uropathogens. However, results analysis according to patient characteristics and severity of the infection were not performed, results of our study are unlikely to be generalized to every adult patient presenting with UTI. In our area, urine sample of patients with UTI are not routinely tested, and susceptibility testing is recommended only in cases of treatment failure or suspected complications. Accordingly, in the absence of local antimicrobial susceptibility pattern, the results of our study could serve as a respected source for antibacterial drugs prescription in empirical treatment of UTI.

Data Sharing Statement

All authors claim that all data and materials as well as software application or custom code support our published claims and comply with field standards.

- The authors declare that they have no financial or non-financial conflicts of interest related to the work done in the manuscript.
- Each author listed in the manuscript had seen and approved the submission of this version of the manuscript and takes full responsibility for it.
- This article had not been published anywhere and is not currently under consideration by another journal or a publisher.

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