

# Multidrug resistance of uropathogens at governmental hospitals in the Gaza strip/Palestine

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## Abstract

**Introduction:** Urinary tract infection is a public health problem worldwide. *Escherichia coli*, *E. coli* and *Klebsiella* spp. are among the main etiologic for UTI in the Gaza Strip. The growing variations in resistance patterns among uropathogens to antimicrobials is multifactorial and varies globally. It greatly reduces/limits or complicates treatment options.

**Aims:** To determine the pattern of antimicrobial resistance and multidrug resistance among uropathogens at governmental hospitals.

**Methods:** We analyzed the data of 11,890 urine samples processed in governmental hospitals in the Gaza Strip, Palestine during 2019. The percentage of resistance was calculated for uropathogens, and then multidrug resistance was calculated according to Centers for Disease Control and Prevention "CDC" definition.

**Results:** Of 11,890 urine samples, 2910 (24.5%) showed significant growth. *Escherichia coli* was most frequently isolated (1743; 59.9%), followed by *Klebsiella* spp. (725; 24.9%), *Pseudomonas* spp. (123; 4.2%), *Streptococcus* spp. (98; 3.4%), *Staphylococcus aureus* (41; 1.4%). Microorganisms' resistance was high against ampicillin (92.4%) and amoxicillin (91.1%), trimethoprim/sulfamethoxazole (68.2%), cefalexin (64.9%), doxycycline (61.9%), nalidixic acid (53.6%), cefuroxime (53.0%), ceftriaxone (48.9%), ceftazidime (43.1%), ciprofloxacin (36.9%), gentamicin (25.8%), amikacin (3.2%). The resistance of microorganisms in males is higher than females. Multidrug resistance was detected in 37% of *E. coli* and 53% in *Klebsiella* spp.

**Conclusion:** Resistance is high and variable among uropathogens isolated from patients in the Gaza strip. Both age and gender are risk factors in both infection and resistance pattern. The multidrug resistance percentage is growing remarkably in the Gaza Strip.

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## Keywords

Uropathogens; Resistance;  
Urinary Tract Infection;  
Multidrug Resistance;  
Gaza Strip; Palestine.

Received 9-03-12021; Accepted 19-04-2021

## Introduction

Urinary tract infection (UTI) is a public health problem, in both community and hospitals. It is more prevalent in women than men [1]. According to the American college of obstetricians and gynecologists, about 50-60% of the women suffer from an episode of UTI at least once during their lifetime [2]. Unmanaged UTI may result in a wide range of serious complications starting from kidney damage, renal scarring and may end with renal failure. In men, UTI become increasingly frequent with age and functional disability, but bacteriuria in elderly men tends to be intermittent, episodic, and more complex to be diagnosed [3].

Gram-negative bacteria are the most common causative agents of UTI, including *E. coli*, *Klebsiella* spp., and *Proteus* spp. While Gram-positive bacteria constitutes the minority of UTI infectious pathogens like *Staphylococcus saprophyticus*, *Enterococci* spp., and *Streptococcus* spp. [4, 5]. Antimicrobial resistance is becoming a major concern not only in nosocomial complicated UTI, but also in uncomplicated community-acquired UTI [6]. Concurrent resistance to antimicrobials of different structural classes has arisen in several of bacterial species and may complicate the therapeutic management of infections, including those of the urinary tract [7]. Multiple drug resistance (MDR) rate for 3 and more drugs is arising in *E. coli* isolates and often complicate therapeutic management of urinary tract infection (UTI) by this organism [7]. The extent of the problem in low-and middle-income countries is unknown because of the scarcity of data, but high levels of resistance are increasingly being reported worldwide [8].

In Palestine, antimicrobials are poorly regulated and available on the private market and can be accessed with or without a prescription [9]. Gaza Strip is one of the high-density populated area, in which governmental hospitals is the back bone of UTI infections treatment. In this study, the common uropathogens were determined and the pattern of

resistance of *E. coli* and *Klebsiella* spp. were detected and the MDR rates were determined.

## Methods and materials

### Study design and settings

This is a retrospective study in design that was conducted in four governmental hospitals (European, Al Shifa, Nassr, and Al Durra Hospitals) in Gaza Strip, Palestine over a period one year (1/1/2019 to 31/12/2019).

### Data collection

The study data were collected from urine culture records of samples that were sent to the Microbiology laboratory during the study period. All samples diagnosed with UTI infection by physicians in hospital were included. An approval from the Helsinki Ethical Committee was obtained before the study and a permission from the Ministry of Health was granted to use the data.

The records of 11,890 urine samples results were studied. According to the microbiology lab Standard Operation Procedure, midstream urine samples were collected in sterile containers and cultured on blood agar and MacConkey media with a standard calibrated loop and were incubated at 37°C overnight. A growth of  $\geq 10^5$  colony-forming units/mL was considered as significant bacteriuria. The identification of isolates was done through Gram-staining and conventional biochemical methods. Antimicrobial susceptibility was done by Kirby–Bauer disc diffusion method on Mueller–Hinton agar and the interpretations were carried out according to the Clinical and Laboratory Standards Institute guidelines [10]. Antibiotic disks used in the susceptibility testing varied according to their availability. Data were obtained in the form of Microsoft excel file containing all the recorded cases UTI cultures results contains susceptibility, resistance to the used antimicrobials, name of the uropathogen, age, gender, date of test, area of living, name of hospital, and diagnosis at the

four governmental hospitals, the data cleaned, coded and exported to SPSS to be analyzed.

### Data analysis

Data analysis was done, using SPSS 22 (2019). Cross tabulation was made; to detect any correlations, and/or differences among the investigated variables, using chi square, and independent T test. P-value equal or less than 0.05 was considered statistically significant, with confidence interval (CI) of 95%. Tables, histograms, and charts were used to present the data. Indicators which used in the study designed to reflect antimicrobial susceptibility situation in governmental hospitals.

## Results

### Distribution frequency of uropathogens

Only 2,910 (24.5%) exhibited significant growth and were considered as positive for UTI. Among the uropathogens isolated during the data collection period, *E. coli* constituted the majority with 59.9%, followed by *Klebsiella* spp. (24.9%), *Pseudomonas* spp. (4.2%), and *Proteus* spp. (2.4%). Gram-negative bacteria constituted 91% of the isolates, while Gram-positive (*S. aureus*, *Enterococcus* spp., and *Streptococcus* spp.) represented in less than 5.5%. In addition, less than 3% of the isolates were classified as "others" as shown in **Table 1**.

### Prevalence of UTI according to patients' gender

Females represented 71.4% of all positive urine cultures with an odds ratio of 1.863 (**Table 2**).

### The antibiogram of uropathogens recovered from patient samples

**Table 1** demonstrates that *E. coli* and *Klebsiella* spp. constitutes about 85% of the total isolates, which means that they are the main etiologic agents of UTI, therefore, the study will focus on these isolates as the main findings. A prominent finding is the high

**Table 1.** The distribution frequency of uropathogens isolates at the four governmental hospitals.

Organism isolated	n=2,910		Total	
	Frequency	%	N	%
Gram negative				
<i>Escherichia coli</i>	1,743	59.9	2672	91.8
<i>Klebsiella</i> spp.	725	24.9		
<i>Proteus</i> spp.	69	2.4		
<i>Enterobacter</i> spp.	12	0.4		
<i>Pseudomonas</i> spp.	123	4.2		
Gram positive				
<i>Staphylococcus aureus</i>	41	1.4	152	5.25
<i>Enterococcus</i> spp.	13	0.4		
<i>Streptococcus</i> spp.	98	3.4		
Others				
<i>Candida</i> spp.	70	2.4	86	2.95
Others	16	0.5		
Total	2,910	100	2,910	100

**Table 2.** Frequency of gender distribution of UTI cases from the four governmental hospitals in the Gaza Strip Palestine.

Variable	Gender distribution	
	Frequency	%
Female	2078	71
Male	832	29
Total	2910	100

resistance exhibited by uropathogens to penicillin group. The resistance to penicillin derivatives like ampicillin was 91% and amoxicillin was 90%, for *E. coli*, and the resistance is 95% for *Klebsiella* spp. to the same antimicrobials **Table 3**. As shown in **Table 3** *E. coli* is highly resistant to the cephalosporin group. Its resistance ranges from 41% to 60% against all of the cephalosporins. *E. coli* has the highest resistance against cephalexin (60%) and the lowest resistance against ceftazidime (41%). *Klebsiella* spp. has resistance (73%) and (49%) against the same antimicrobials, respectively. Also, **Table 3** shows that the antibiotic resistance patterns of *E. coli* to the listed tested antibiotics.

**Table 3.** Resistance pattern of uropathogens to antimicrobials at the four governmental hospitals in the Gaza Strip/Palestine during.

Antimicrobial	Disk charge	<i>E. coli</i>		<i>Klebsiella spp.</i>		<i>Proteus spp.</i>		<i>Enterobacter spp.</i>		<i>Pseudomonas spp.</i>		<i>S. aureus</i>		<i>Enterococci</i>		<i>Streptococcus spp.</i>	
	Microgram	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Penicillin G	6	-	-	-	-	-	-	-	-	-	-	3	75	4	36	1	100
Ampicillin	10	553	91	245	95	27	90	5	100	30	100	3	60	3	30	5	100
Amoxicillin	20	154	90	70	95	13	87	4	100	7	88	5	71	1	100	2	67
Cloxacillin	5	-	-	-	-	-	-	-	-	-	-	5	50	-	-	19	79
Piperacillin	100	148	74	90	79	2	50	1	50	19	79	-	-	-	-	-	-
Cephalexin	30	540	60	279	73	21	68	2	67	42	91	2	15	4	67	29	74
Cefuroxime	30	682	49	350	62	20	37	3	33	63	81	6	26	7	64	24	47
Cefotaxime	30	474	44	267	60	10	24	-	-	29	43	2	67	4	57	-	-
Ceftazidime	30	494	41	243	49	18	45	1	20	36	38	1	50	7	100	-	-
Ceftriaxone	30	681	46	364	59	16	29	2	22	49	49	3	50	5	56	-	-
Cefazolin	30	344	53	154	61	10	34	4	50	32	84	3	75	1	50	-	-
Doxycycline	30	304	59	151	66	16	80	0	0	41	85	4	29	-	-	12	48
Amikacin	30	15	2	14	4	1	3	-	-	5	8	1	17	5	63	-	-
Gentamicin	30	321	23	172	29	20	38	4	40	23	24	8	30	7	54	25	48
Co-Trimoxazole	1.25/23.75	959	66	420	69	47	80	8	80	78	91	14	54	4	67	46	78
Nalidixic acid	30	852	53	330	50	37	63	3	30	87	84	1	33	5	100	4	100
Ciprofloxacin	5	450	35	198	38	16	34	4	40	36	36	12	38	7	70	45	63
Rifampicin	5	-	-	1	50	-	-	-	-	-	-	1	3	-	-	27	36
Vancomycin	30	-	-	-	-	-	-	-	-	-	-	8	21	2	18	17	18
Co-amoxiclav	20/10	45	73	17	68	5	63	-	-	3	75	13	45	1	50	32	42
Meropenem	10	24	6	16	8	3	14	1	25	11	20	0	0	1	50	-	-
Nitrofurantoin	300	20	15	24	44	2	50	0	0	8	73	-	-	-	-	-	-
Piperacillin + tazobactam	100/10	13	9	9	11	0	0	0	0	0	0	-	-	-	-	-	-
Total R %		7082	45	3422	53	284	46	42	40	600	56	95	33	68	56	288	49

-: This antimicrobial did not used for this microorganism 00 This microorganism is 0% resistant to antimicrobial

**Table 4.** Antimicrobial resistance of uropathogens according gender at four governmental hospitals in the Gaza Strip- Palestine during 2019.

Isolate	<i>E. coli</i>				<i>Klebsiella spp.</i>				<i>Pseudomonas spp.</i>				<i>Proteus spp.</i>				P. value
	Female		Male		Female		Male		Female		Male		Female		Male		
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
Ampicillin	428	90	125	94	150	94	95	97	12	100	18	100	19	86	8	100	0.164
Amoxicillin	121	90	33	89	43	93	27	96	2	67	5	100	10	83	3	100	0.087
Piperacillin	107	70	41	85	57	73	33	92	10	77	9	82	1	33	1	100	0.052
Cephalexin	388	57	152	69	177	71	102	78	19	90	23	92	10	53	11	92	0.188
Cefuroxime	483	45	199	62	219	59	131	66	28	76	35	85	10	29	10	53	0.282
Cefotaxime	333	41	141	53	165	58	102	63	14	41	15	45	6	22	4	27	0.562
Ceftazidime	330	37	164	52	158	48	85	53	17	35	19	40	12	43	6	50	0.105
Ceftriaxone	473	42	208	56	233	56	131	65	18	38	31	60	10	28	6	30	0.272
Cefazolin	248	50	96	64	97	58	57	68	14	78	18	90	6	27	4	57	0.242
Amikacin	7	1	8	4	6	3	8	6	2	8	3	8	1	4	0	0	0.832
Gentamicin	225	20	96	30	113	29	59	30	11	23	12	25	13	38	7	37	0.545
Doxycycline	206	57	98	63	113	65	38	69	19	83	22	88	12	75	4	100	0.367
Co-Trimoxazole	731	66	228	66	291	69	129	71	36	86	42	95	29	73	18	95	0.389
Nalidixic acid	608	50	244	62	226	51	104	48	43	84	44	83	24	60	13	68	0.722
Ciprofloxacin	292	30	158	48	136	38	62	38	21	40	15	31	9	30	7	41	0.299
Co-amoxiclav	35	71	10	77	15	65	2	100	2	67	1	100	3	50	2	100	0.006
Meropenem	15	6	9	8	12	9	4	7	5	17	6	23	3	20	0	0	0.572
Nitrofurantoin	15	15	5	14	13	34	11	69	1	33	7	88	2	50	0	0	0.678
Piperacillin + tazobactam	8	7	5	14	6	10	3	13	0	0	0	0	0	0	0	0	0.610
Total	5053	43	2020	53	2230	51	1183	57	274	54	325	60	180	44	104	59	0.024

### Antimicrobial resistance pattern of uropathogen according to patient's gender

As shown in **Table 4**, among males, the resistance of *E. Coli* to antimicrobials was 10-15% higher than among females to the following antibiotics (piperacillin, cephalixin, cefotaxime cefuroxime, cefotaxime, ceftazidime, ceftriaxone cefazoline ciprofloxacin gentamicin, and nalidixic acid). The total resistance of *E. coli* to all antimicrobials in females was 43%, while in males it was 53%. According to *Klebsiella* spp., among males, its resistance to the following antimicrobials (cephalexin, cefotaxime cefuroxime, cefotaxime, ceftazidime, ceftriaxone cefazoline, amikacin, doxycycline, ciprofloxacin gentamicin, cotrimoxazole, and nalidixic acid) was 3-9% higher

than in females. The total antimicrobial resistance of *Klebsiella* among female isolates is 51% while in males 57%. Despite higher prevalence of UTI in the female than in males **Table 2**, the resistance percentage against antimicrobial is higher in male than in the female. By conducting independent T-test for all antimicrobials, P. values is statistically significant only for co-amoxiclav (P. value= 0.006) and marginally significant for piperacillin (P. value= 0.052) and the total antimicrobial resistance was statistically significant (P. value= 0.024) as shown in **Table 4**

### Antimicrobial resistance pattern of uropathogens according to patient's age

As shown in **Table 5**, there was fluctuation in the resistance of the microorganisms against anti-

**Table 5.** Percentage of antimicrobial resistance of all microorganisms at the four governmental hospitals distributed by age groups in the Gaza Strip-Palestine 2019.

Antimicrobials	Age groups								ANOVA	Scheffe test
	0-28 day		29d-1 year		1-12 y		Adult			
	R	%	R	%	R	%	R	%	P. value	P. value
Cefuroxime	22	47	99	46	463	44	577	66	0.300	.012
Ampicillin	30	97	86	91	485	90	277	96	0.046	.010
Amoxicillin	4	80	45	92	115	91	97	90	0.162	.003
Piperacillin	0	0	22	73	91	61	149	89	0.000	.009
Cephalexin	16	53	52	60	331	54	524	75	0.052	.013
Cefotaxime	13	43	57	39	279	37	441	62	0.035	.077
Ceftazidime	12	40	39	35	201	32	554	50	0.069	.303
Ceftriaxone	13	46	92	44	353	35	667	63	0.056	.052
Cefazolin	8	42	57	53	192	44	295	69	0.008	.015
Amikacin	1	3	6	4	14	2	22	6	0.036	.416
Gentamicin	7	16	24	12	146	14	407	41	0.000	.002
Doxycycline	6	67	7	64	12	52	504	62	0.097	.274
Co-Trimoxazole	26	60	131	67	564	63	859	73	0.436	.002
Nalidixic acid	17	39	78	36	394	38	835	71	0.000	.004
Ciprofloxacin	5	16	20	15	120	15	627	55	0.000	.000
Co-amoxiclav	2	100	11	69	37	71	68	46	0.815	.134
Colistin	0	0	17	85	106	60	9	28	0.000	.870
Meropenem	1	50	1	5	0	0	56	10	0.000	.371
Nitrofurantoin	1	25	2	33	4	13	49	29	0.984	.567
Piperacillin + tazobactam	0	0	5	21	11	10	6	5	.011	.896

ANOVA P. value: among all age groups; Scheffe test; P. Value between 0-28 days group & adult group.

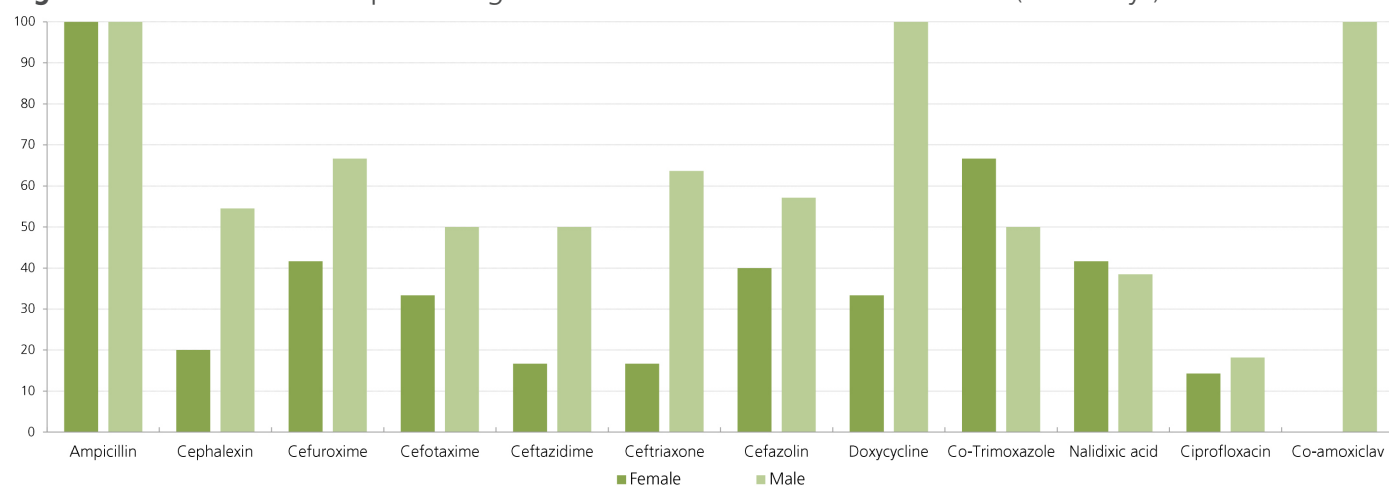
crobinals in different age groups. ANOVA test was used to determine the significance of this variation. The result of ANOVA revealed that the fluctuation among age categories is statistically significant for number of antimicrobials (ampicillin, piperacillin, cefotaxime, cefazolin, amikacin, gentamicin, nalidixic acid, ciprofloxacin, and piperacillin + tazobactam) at  $P$  value of  $< 0.05$ ). Two antimicrobials (cephalexin and ceftriaxone) at  $P$  value of  $< 0.05$ , while other antimicrobials were not statistically significant (e.g., cefuroxime, amoxicillin, ceftazidime, doxycycline, co-trimoxazole, co-amoxiclav, and nitrofurantoin). When Scheffe test was performed to test resistance variations among these age groups, it was found that there is a prominent correlation between age group 0-28 days and adult group with ( $P$  value of less than 0.05 (for cefuroxime, ampicillin, amoxicillin, piperacillin, cephalexin, cefazolin, gentamicin, co-trimoxazole, nalidixic acid, and ciprofloxacin) **Table 5**.

### Antimicrobial resistance pattern of uropathogen according to both gender and age

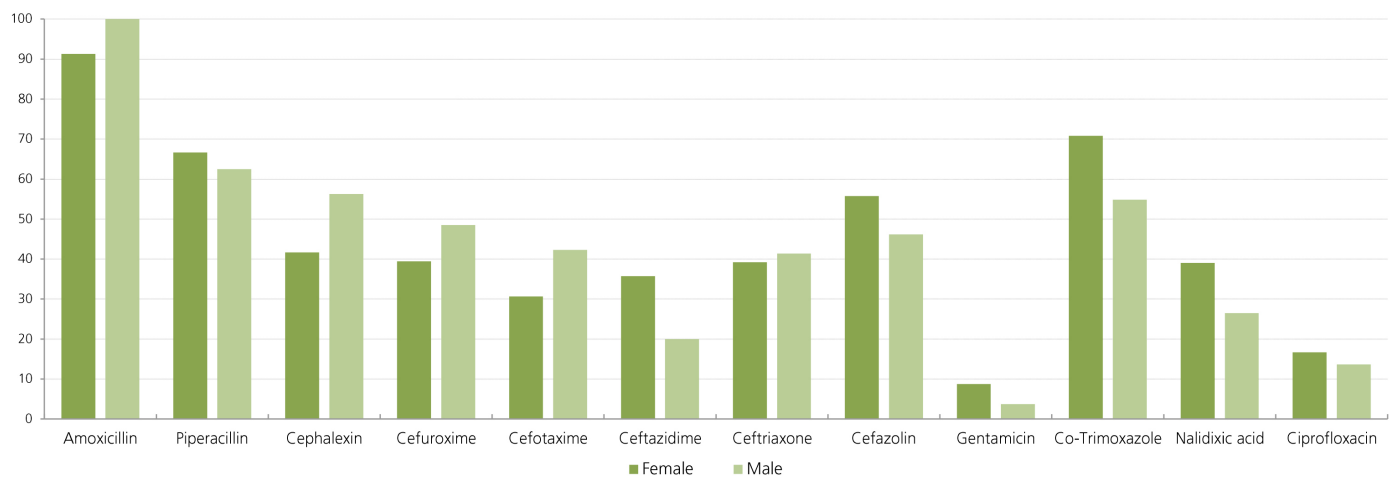
*E. coli* isolates were grouped according to age and gender, the difference is high between males and females in the age category of (0-28 days). Within the age category (29 days to 1 year), the resistance in females is higher than in males for most of

the antimicrobials. However, in the age categories (1 year to 12 years) and adults, the resistance is higher in males to most of the antimicrobials than in females. As shown in **Figure 1**, *E. coli* resistance to antimicrobials among male isolates was higher than females isolate in most of the age categories. In the age category (0-28 days), *E. coli* isolates were resistant to amoxicillin is closed 100% in both genders. There is a difference in resistance of the *E. coli* against these antimicrobials (cephalexin, ceftazidime, ceftriaxone, and cefuroxime) in this age category about 30-40% between genders, however, both co-trimoxazole, and nalidixic acid show resistance in females, is higher than males in this age category. Among the age category (29 days to 1 year), *E. coli* in males is more resistant than in female against amoxicillin, cephalexin, and cefotaxime, while the resistance in female is higher than males against ceftazidime, gentamicin cephazolin, co-trimoxazole, nalidixic acid, and piperacillin **Figure 2**. In the age category (1 year to 12 years), *E. coli* resistance in males is higher than in females against piperacillin, cephalexin, cefuroxime, cefotaxime, ceftazidime, cefazoline, nalidixic acid, and ciprofloxacin. The resistance of *E. coli* in female isolates higher than male against amoxicillin and co-trimoxazole. The resistance of *E. coli* to gentamicin is almost the same **Figure 3**.

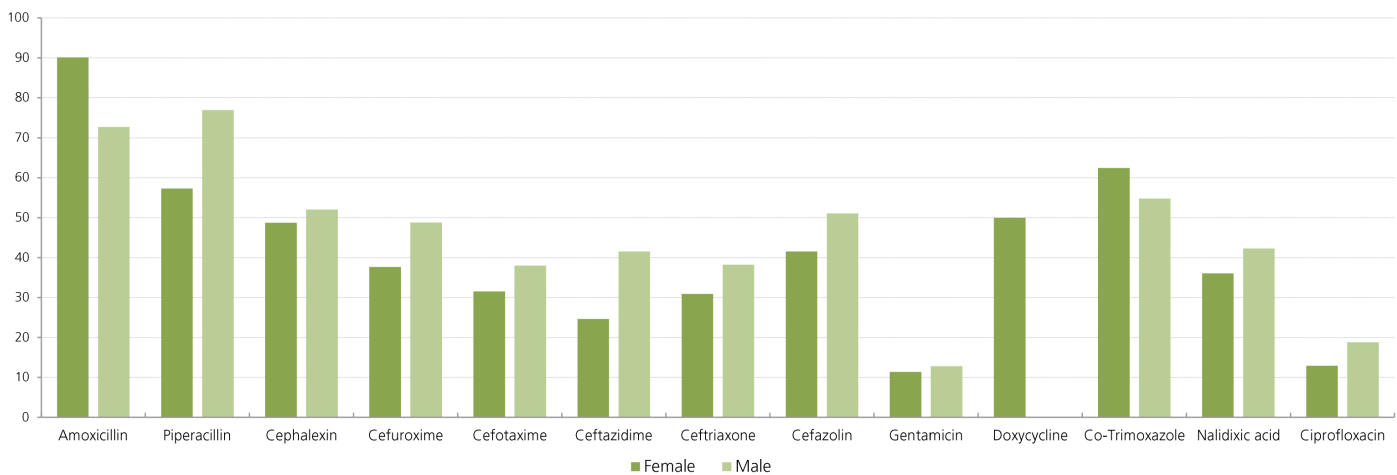
**Figure 1:** *E. coli* resistance percentage to antibiotics in males and females (0-28 days).



**Figure 2:** *E. coli* resistance percentage to antimicrobial in males and females (29 days-1 year).



**Figure 3:** *E. coli* resistance percentage to antimicrobial in male female (1-12 years).



In the age category, (adults) the resistance of *E. coli* in male is higher than in female against the all of the antimicrobials (amoxicillin, piperacillin, cephalixin, cefuroxime, cefotaxime, ceftazidime, ceftriaxone, cefazolin, gentamicin, co-trimoxazole, nalidixic acid, ciprofloxacin) **Figure 4**.

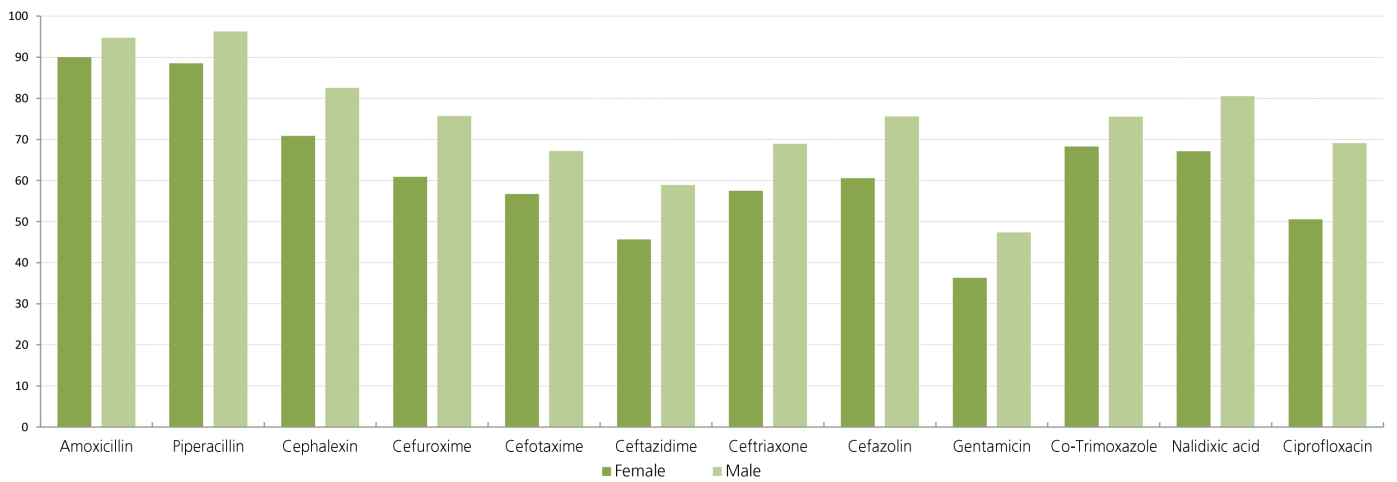
### Multiple drug resistance in uropathogens

Regarding to multidrug resistance definition [11], which is not yet agreed upon by the medical community. Many definitions are currently being used to characterize patterns. The most practical definition used for Gram-positive and Gram-negative bacteria is 'resistant to a single antibiotic in three or more

antimicrobial classes [12], these antibiotic groups have been chosen according to lists suggested by professionals for isolates have no intrinsic factors for resistance to these antibiotics, and according to the standard operating procedures SOPs that is followed by the laboratory technicians at the governmental hospital in the Gaza Strip/Palestine, these antibiotics are ampicillin, cefuroxime, co-trimoxazole, ciprofloxacin, gentamicin, the isolates of *E. coli* and *Klebsiella* spp. as shown in **Table 6**, the observation is the resistance for a single antibiotic (ampicillin) from the penicillin group of *E. coli* is (91%) and for *Klebsiella* spp. is (91%) and by adding another antibiotic (cefuroxime) from cephalosporin group the



**Figure 4:** *E. coli* resistance percentage to antimicrobial in male and female adults.



**Table 6.** Multidrug resistance percentage for uropathogens the same isolates for different antibiotic groups at governmental hospitals in Gaza Strip Palestine during 2019.

No	Antibiotic	<i>Escherichia coli</i>		<i>Klebsiella</i> spp.	
		N	%	N	%
1	Ampicillin	553	91	245	95
2	Ampicillin + Cefuroxime	242	45	131	58
3	Ampicillin + Cefuroxime + Co-Trimoxazole	162	37	90	53
4	Ampicillin + Cefuroxime + Co-Trimoxazole+ Ciprofloxacin	55	18	33	31
5	Ampicillin + Cefuroxime + Co-Trimoxazole+ Ciprofloxacin + Gentamicin	29	11	21	22

resistance percentage for isolates for penicillin and cefuroxime for the same isolates is (45%) for *E. coli* and (58%) for *Klebsiella* spp., after adding the third antibiotic (Co-Trimethoprim) from aminoglycoside group the resistance for the same isolates for these antibiotic groups is (37%) for *E. coli* and (53%) for *Klebsiella* spp., after addition of the fourth antibiotic group fluoroquinolone (ciprofloxacin) and according to the definition, the multidrug resistance is (18%) for *E. coli* and (31%) for *Klebsiella* spp., after

addition of the fifth antibiotic group (Gentamicin) multidrug resistance is (11%) for *E. coli* and (22%) for *Klebsiella* spp., from these findings multidrug resistance was detected in uropathogens, (37%) for *E. coli* and (53%) for *Klebsiella* spp. the same isolates by three different antibiotics in different groups. This is alarming and should be considered by any antibiotic stewardship programs. (Table 6)

## Discussion

This study aimed to determine the resistance pattern of uropathogens to antimicrobials and to explore the MDR at the governmental hospitals in the Gaza Strip/Palestine. Uropathogens were isolated from 24.5% of the requested urine cultures. *E. coli* constituted the majority of isolates with 59.9%, followed by *Klebsiella* spp. (24.9%) and all Gram-negative constituted 91% of the isolates. Females represented by 71.4% of all positive urine cultures. *E. coli* resistance rate to penicillin derivatives like ampicillin was 91% and amoxicillin 90%, while resistance rate of *Klebsiella* spp. was 95% for the same antimicrobials. *E. coli* is highly resistant to the cephalosporin group. Its resistance is between 41% and 60% against all of the cephalosporines, *Klebsiella* spp. has resistance (73%) and (49%) against the same antimicrobials, respectively. Both of *E. coli*

and *Klebsiella* have the minimal resistance against amikacin, which are (2%) and (4%), respectively. The resistance percentage against the tested antimicrobials is higher in male than in the female. Regarding to our study, MDR in Gaza governmental hospitals is (37%) for *E. coli* and (53%) for *Klebsiella* spp., respectively.

We demonstrated very high prevalence of Gram-negative isolates and this in agreement with a study in Lahore, Pakistan conducted between December 2018 and June 2019, which reported that prevalence of 92% Gram negative [13]. Another study in Ethiopia revealed that Gram-negative bacteria caused 90% of UTI cases while gram-positive bacteria cause only 10% of the cases [14]. In North Ethiopia, *E. coli* prevalence in UTI was 60.29% and *Klebsiella* spp. prevalence was 5.88% in a study conducted from 2002 to 2011 [15]. Another study reported 79% *E. coli* prevalence in UTI in Luxembourg [16] which higher than our findings.

In Sarajevo, *E. coli* had the highest antimicrobial resistance to trimethoprim/sulfamethoxazole (38.61%), followed by amoxicillin/clavulanic acid (19.62%), ciprofloxacin (9.49%), gentamicin (8.86%), cephalexin (8.23%), nitrofurantoin (8.23%), cefuroxime (7.52%), ceftazidime (6.33%), cefuroxime (89.87%), amikacin (4.43%) [17]. These findings are lower than our findings. A study from Iraq in 2016 demonstrated resistance pattern for *E. coli* similar to this study. The resistance was 100% for penicillin and 52% for cephalosporin [18]. In Saudi Arabia, the resistance of *Klebsiella* spp. was 91% against ampicillin, 57% against cefotaxime, and 46% against ceftazidime [19]. Another study from India revealed that *E. coli* resistance against amikacin was (16-38%), followed by cefotaxime (38-40%), gentamicin (42-68%), ciprofloxacin (54-73%), and co-trimoxazole (74-90%) during the period between 2000 and 2004 [20].

A study in Saudi Arabia found that the resistance of *E. coli* against meropenem was 7%, amikacin (9%) and gentamicin (18%) [19]. In south Iran, a

study conducted in 2019 found that the resistance of *E. coli* against nalidixic acid was 71.9% [21]. In Rajasthan, a 2012 study recorded an overall resistance of *E. coli* against nalidixic acid, norfloxacin, and ciprofloxacin as (94%), (77%), and 74.75%, respectively [22].

A retrospective study investigated 16,883 urine culture samples conducted in Palestine between 2001 and 2013, demonstrated that Gram-negative uropathogens showed good susceptibility towards ciprofloxacin, ofloxacin, norfloxacin, cefuroxime, nitrofurantoin, sulphathiazole/trimethoprim, nalidixic acid, and amoxicillin/clavulanic acid, (76.1%, 71.8%, 72.9%, 64%, 67.5%, 48.7%, 57.6%, 42.1%, respectively) [23].

In Turkey, a retrospective study, evaluated causative agents and antimicrobial resistance in urine isolates from the positive community period between 2014 and 2016, it revealed that the resistance of *E. coli* during these years against co-trimoxazole was (29.8%) [24]. In addition, higher resistance rates against ampicillin Bangladesh 2020 found (100%) [25].

These variations among various studies from different countries may be due to different geographical settings, variations in use or misuse of antimicrobials, different treatment protocols, and study sample size among many other causes. Resistance varies over time and many of the above listed studies were conducted in different settings and times.

According to 2020 CDC update, a microorganism protects itself from antibiotic in various ways. *K. pneumoniae* produce enzymes called carbapenems, which break down carbapenem drugs and most other beta-lactam drugs. *E. coli* bacteria with the *mcr-1* gene can add a compound to the outside of the cell wall so that the drug colistin cannot latch onto it [26].

Several risk factors are associated with UTIs, including gender. The shorter distance to the bladder in women makes it easier for bacterial colonizers to reach it [27]. Male patients, have a lower risk of contracting uncomplicated UTIs but are more prone

to contracting complicated or MDR infections [28]. Our data reflect the severe nature of UTI in men, in which infections are caused by MDR microorganisms

A study conducted in Pakistan in 2008 gave similar results, it reported variations among age groups with regard to resistance and it appeared that in the case of males, *E. coli* isolates were susceptible to nitrofurantoin in age groups 0+, 50+, and 70+, while in age groups 20+, 30+ and 60+ hundred percent resistance was recorded. *E. coli*. In females, showed no resistance to nitrofurantoin in age groups 10+, 50+, and 70+, while it showed 33% resistance in age groups 0+, 20+, and 30+. *E. coli* isolates from age groups 50+ and 70+ both in males and females were found to be 100% susceptible to the nitrofurantoin [29].

One study concluded that antibiotics that target DNA synthesis result in a progressively higher number of resistant isolates among the older population. The results emphasize the importance of patient age on antibiotic selection as a preventive measure to reduce the rate of resistant infections in each susceptible population. This pattern suggests that physicians should take into consideration patient age as another factor in determining the best antibiotic regiment with the aim of curtailing the emergence of newer resistant phenotypes in the future [30].

A study in southwest Washington in 2013 showed statistically significant differences between males and females in the age-specific susceptibilities of *E. coli* to ampicillin, co-amoxiclav, ciprofloxacin, and nitrofurantoin. Urinary *E. coli* isolates from male patients tend to exhibit increased antimicrobial resistance than isolates from female patients. Despite the statistical significance of time trends and differences in age-specific susceptibilities, the magnitude of these differences was generally less than 5% and thus may not represent clinically meaningful differences. The exception was susceptibility to amoxicillin-clavulanate, where

susceptibility was roughly 10% lower in males aging 18 to 64 years than females in the same age group [31]. A 10 year study of community UTI in Portuguese patients also identified differences in antimicrobial susceptibility according to patient gender. The authors reported that urinary isolates of *E. coli* were significantly more resistant to fluoroquinolones, penicillin's, nitrofurantoin, and first and second-generation cephalosporins among men compared to women [32]. Another study focused on pediatric patients, also identified significantly higher resistance to co-trimoxazole and ciprofloxacin in male versus female patients [33].

The NAUTICA (the North American Urinary Tract Infection Collaborative Alliance) surveillance study of outpatient UTIs, reported greater antimicrobial resistance to ciprofloxacin, levofloxacin, and co-trimoxazole among all urinary isolates from U.S. and Canadian male patients [34]. In the CANWARD (Canadian Ward) Surveillance Study, antimicrobial susceptibility among all *E. coli* isolates (not limited to urine isolates) collected from Canadian tertiary medical centers were compared and resistance was also observed to be significantly higher to ciprofloxacin, levofloxacin, and co-trimoxazole in isolates collected from male patients versus female patients [35].

Most studies of urinary tract infections (UTIs) focus on female patients because of the higher incidence in women than in men. For this reason, most UTI guidelines are based on studies performed on women, despite the obvious genito-urinary differences [36]. In men, UTIs become increasingly frequent with age and functional disability, but bacteriuria in elderly men tends to be intermittent, episodic, and more complex to diagnose. It is generally recognized that treatment recommendations for women are not usually appropriate for men. However, guidelines or recommendations for the management of men are mostly based on studies in women, children and institutionalized elderly people of both sexes [3].

A study conducted in Arabia Saudi in 2018 showed a slightly high level of multidrug resistance among the tested isolates if compared with our results with (67%) of all *E. coli* isolates showing the MDR phenotype. Of these isolates, (26.86%) isolates were resistant to 3 antibiotic groups (25.37%) were resistant to 4 antibiotic groups, and (14.92%) were resistant to 5 antibiotic groups [37]. A study conducted in Jordan, revealed that there is high percentage of uropathogenic *E. coli* isolates from outpatients and hospitalized Jordanian patients in Amman area, is multidrug resistant to at least 3 antibiotics [38].

## Conclusion

The main etiologic agents for UTI are *E. coli* and *klebsiella* spp. Penicillin is no longer be suitable treatment for UTI. Both age and gender are risk factors in both infection and resistance pattern. Antimicrobial stewardship program should be established under the MoH supervision, physicians should minimize the empirical use of antimicrobials in non-life-threatening infection and rely more on culture and sensitivity for specific treatment. This type of study should be performed regularly to monitor the resistance of microorganisms to antimicrobials, not only for UTI but also for all types of infections for humans and animals as well to find the proper way to minimize multidrug resistance.

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