

Trends of antimicrobial resistance in *Escherichia coli* isolates from urine cultures of women in Jordan: A 10-year retrospective study

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Abstract

Background: Urinary tract infection (UTI) is a common medical condition among women. *E. coli* is the most common causative organism. Appropriate understanding of the development of antimicrobial resistance over the past helps to establish efficient treatment strategies in the future. The study aims to determine the antimicrobial resistance trends exhibited by *E. coli* isolates from women urine cultures over the past 10 years.

Methods: A total of 1874 positive urine samples over the years 2009 to 2018 were reviewed and classified according to the response to 24 different antimicrobial drugs in the laboratory. Relations between time and resistance evolutionary profiles were calculated.

Results: Gentamicin (p value =0.039), amoxicillin (p value =0.017), cefoxitin (p value =0.001) and cefixime (p value =0.026) fulfilled satisfactory figures in terms of average resistance, regression of resistance, speed of resistance evolution, steadiness of performance, side effects, spectrum range and cost with high significance.

Conclusion: Antibiotics that showed satisfactory susceptibility in culture are recommended for future treatment protocols of urinary tract infection in Jordan.

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Introduction

Antimicrobial resistance is a mounting threat to human societies [1]. Understanding the patterns of resistant traits evolution and regression according to the change in the treatment protocols and antimicrobial usage gives strong predictions of how the resistance course will change over time, which helps in reformulating future strategies that could slow the progression of resistance.

Escherichia coli is one of the most commonly opportunistic bacteria associated with humans today [2]. When *E. coli* is exposed to antibiotics, their cells developing resistant traits to survive and reproduce rapidly [3]. Prolonged exposure to antibiotics increases the activity of specific regulatory proteins that work on gene segments leading to the extrusion of antimicrobials out of the bacterial cell before reaching their target organelles [3]. The fastest way for bacteria to acquire resistance is through cell horizontal transfer of genetic structures called plasmids that contain specific DNA segments [4]. Plasmids can spread through an entire community of bacterial population within about 30 minutes [4]. They are capable of sharing genetic segments for specific efflux pumps that work on the cell wall of the bacteria to extrude antimicrobial molecules [5]. Bacteria can lose their acquired resistance if the selective pressure applied is changed or eliminated but this biological process occurs more slowly [6].

Urinary tract infections (UTI) due to *E. coli* occurs mostly in the lower parts of urinary system, the bladder and the urethra, causing cystitis and urethritis respectively. At times, it can be transferred to the kidneys causing pyelonephritis [7]. Women have much higher chance of acquiring UTI than men because they have a shorter urethra, since *E. coli* is heavily present in fecal matter, and can easily be transferred to the urethra through the urethral opening [8]. Infection can occur by sexual contact [9], improper wiping techniques after defecation;

wiping from back to front [9] and holding of urine; frequent urination allows flushing of *E. coli* and decreases the risk of infection [10]. Many other direct causes of infection can be present, like having a urinary catheter, using birth control methods or taking regular courses of antibiotics [11].

A total of 1-3% of all medical consultations in Great Britain compromises UTIs [12]. *E. coli*, on average is responsible for nearly 85% of UTI infections [13]. The average annual UTIs is 150 million cases globally [11]. Although the average is rising in both sexes, the increase rate in women is twice as men [14]. A total of 60% of women worldwide are estimated to develop UTI at least once in their lifetime [15]. Recent studies in Jordan, reported increased antibiotics resistance among *E. coli* uropathogens [16].

The aim of this study is to present a useful informative data for future establishment of antimicrobial usage in Jordan. To the best of our knowledge, this is the first study in Jordan to incorporate data of UTI in women into establishing local protocols for antibiotic usage.

Method and Materials

Study design

This study was conducted at The Jordan University Hospital (JUH), a tertiary hospital in Amman, Jordan. It gained acceptance by the Institutional Review Board (IRB No.10/2019/25180). Our inclusion criteria consisted of nonpregnant women who regularly visited JUH and were covered by the hospital insurance system. This is to ensure that patients followed unified treatment protocols and strategies and the bacterial urine cultures were subjected to the same laboratory conditions over the 10 years period. Men were excluded due to anatomical variables and different aetiologies and treatment protocols. Other body fluid cultures were excluded due to different treatment strategies. **Table 1** shows

Table 1. Antimicrobial drugs arranged according to their market availability in Jordan and current role for UTI treatment.

Antibiotic	Market availability years [17]	Current role in treatment protocols [18]
Amikacin	2009-2018	Resistant ESBL infections
Amoxicillin	2009-2018	First line agent in UTI in pregnancy
Ampicillin	2012-2018	First line agent in pregnancy
Cefepime	2009-2012	No current role
Cefixime	2015-2018	No current role
Cefotaxime	2011-2018	No current role
Cefoxitin	2017-2018	Second line agent for cystitis
Cefpodoxime	N/A	No current role
Ceftazidime	N/A	No current role
Ceftriaxone	2009-2018	First line agent in severely ill patients, Third line agent in pyelonephritis
Cefuroxime	2009-2018	Second line agent for cystitis
Cephalothin	N/A	Second line agent for cystitis and UTI in pregnancy
Ciprofloxacin	2009-2018	Second line agent for pyelonephritis
Cotrimoxazole	2011-2018	First line agent for cystitis and pyelonephritis
Ertapenem	2010-2018	Severe, complicated and resistant pyelonephritis, ESBL infection
Gentamicin	2009-2018	Second line agent in severely ill patients
Imipenem	2009-2018	Severe, complicated and resistant pyelonephritis, ESBL infection
Meropenem	2009-2018	No current role
Nalidixic acid	N/A	No current role
Nitrofurantoin	2009-2016	First line agent for cystitis and UTI in pregnancy
Norfloxacin	N/A	No current role
Piperacillin / tazobactam	2014-2018	Severe, complicated and resistant infections
Tetracycline	2009-2018	No current role
Tobramycin	2009-2018	No current role

the list of enrolled 24 antibiotics, the sample size for each antibiotic, the years of market availability in Jordan and the current role in UTI treatment protocols.

Data collection and analysis

Retrospective collection of 1874 urine sample results from January 2009 to December 2018 was done. Culture and sensitivity reports were obtained from the records of Microbiology Department at The JUH. Response of *E. coli* to 24 different antibiotics was categorized to susceptible (S) or resistant (R). Susceptibility or resistance to extended spectrum β lactamase (ESBL) results were interpreted according to the Clinical Laboratory Standard Institute (CLSI) 2017 protocols [19]. ESBL percentages were calculated since the start of conducting the test (May, 2017 to December, 2018).

Data was analyzed by SPSS version 23 program and presented by Microsoft Excel program, office 2019. Descriptive statistics and frequencies were applied. Moreover, linear regression analysis was done to investigate the change in resistance over ten years and Pearson's *r* was calculated. P-value < 0.05 was considered to indicate statistically significant difference.

Interpretation

Results interpretation took accredited international and national antimicrobial resistance recommendations into consideration. Antimicrobial market drug availability and usage during the 10-year period was also considered. Final recommendations for future treatment protocols were constructed using rationale of antimicrobial stewardship strategy formulary restrictions accredited by Ontario public health [20]. North York general antimicrobial restriction guidelines (accredited in 2015) are applied in JUH and were also taken into consideration [21].

Results

The mean age of patients was 37.1 ± 14.6 years. Median age was 32 years. Among 26537 collected urine samples, 9970 (37.6%) samples showed bacterial growth. After exclusion of mixed growth samples. Out of 4164 samples were left, 1874 sam-

ples showed *E. coli* growth (45%). Annual results of sensitivity and resistance to each antibiotic are shown in **Table 2**.

Analysis of data collected showed that 10 out of 24 antibiotics have P-values of less than 0.05 as shown in **Table 3**. Out of these ten antibiotics, the

highest average resistance rate was to amoxicillin (68.5%; P-value=0.017) followed by cefotaxime and ceftriaxone with average resistance rates of (65.9% and 65.7%, respectively) and P-value of 0.004 and 0.452, respectively, while the average resistance rate to gentamicin was (22.1%; P-value =0.039).

Table 2. The percentage of antimicrobial resistant *E. coli* isolates among the total number of samples per year.

Year	2009		2010		2011		2012		2013		2014		2015		2016		2017		2018	
	n	r %	n	r %	n	r %	n	r %	n	r %	n	r %	n	r %	n	r %	n	r %	n	r %
Amikacin	13	7.69	19	21.05	22	9.09	55	38.18	70	5.71	212	8.49	162	14.81	160	14.38	103	4.85	18	27.78
Amoxicillin	89	75.28	123	70.73	157	82.80	142	82.39	158	75.32	264	81.82	239	69.87	219	69.41	237	45.15	246	32.11
Ampicillin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	136	78.68	221	71.04
Cefepime	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	135	72.59	221	64.25
Cefixime	13	53.85	19	68.42	22	77.27	55	69.09	70	68.57	212	49.06	162	41.98	160	44.38	103	30.10	18	27.78
Cefotaxime	88	43.18	123	35.77	157	42.04	142	38.03	158	44.94	264	50.38	239	43.51	219	52.05	101	46.53	31	48.39
Cefoxitin	13	69.23	19	89.47	22	100.00	55	72.73	71	78.87	211	54.03	161	54.04	160	59.38	235	40.43	244	40.57
Cefpodoxime	13	30.77	19	31.58	22	31.82	55	25.45	71	23.94	211	20.85	161	13.04	160	24.38	235	16.17	242	11.98
Ceftazidime	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	135	40.74	221	40.27
Ceftriaxone	13	61.54	19	73.68	22	86.36	55	70.91	70	65.71	212	51.89	162	44.44	160	55.63	236	39.41	244	40.57
Cefuroxime	13	69.23	19	89.47	22	100.00	55	72.73	70	78.57	212	54.72	162	54.94	160	61.88	103	37.86	21	38.10
Cephalothin	88	44.32	123	38.21	157	45.22	142	50.70	158	50.00	264	57.58	239	44.35	219	53.42	234	45.73	244	44.26
Ciprofloxacin	13	76.92	19	78.95	22	95.45	55	74.55	69	66.67	211	47.39	162	45.68	160	47.50	236	29.24	244	28.69
Cotrimoxazole	89	57.30	123	60.98	157	61.15	142	59.86	158	54.43	264	60.98	239	54.81	219	62.10	237	53.59	245	46.12
Ertapenem	-	-	9	22.22	19	10.53	55	0.00	70	1.43	212	2.36	162	2.47	160	0.63	103	0.97	18	5.56
Gentamicin	89	25.84	124	27.42	157	26.75	142	19.01	158	17.09	264	26.89	239	20.50	219	21.46	236	19.49	246	16.26
Imipenem	13	0.00	19	5.26	22	0.00	55	0.00	70	0.00	211	1.90	162	1.23	160	1.88	236	0.42	242	0.83
Meropenem	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	136	0.00	222	0.45

Year	2009		2010		2011		2012		2013		2014		2015		2016		2017		2018	
	n	r %	n	r %	n	r %	n	r %	n	r %	n	r %	n	r %	n	r %	n	r %	n	r %
Nalidixic acid	89	57.30	123	56.10	157	57.32	142	59.86	158	56.33	264	68.18	239	65.27	219	66.67	100	68.00	21	66.67
Nitrofurantoin	89	3.37	123	2.44	157	8.92	142	23.94	158	32.91	264	39.77	239	17.99	219	33.79	237	24.47	246	17.07
Norfloxacin	88	32.95	123	35.77	157	34.39	142	35.21	158	34.81	264	41.67	239	38.08	219	42.47	237	32.07	245	27.35
Piperacillin / tazobactam	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	134	11.19	222	8.11
Tetracycline	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	133	52.63	221	47.51
Tobramycin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	133	18.80	219	15.98

n: Total sample numbers; r%: Percent of resistant cases.

Table 3. The average antibiotic resistance of *E. coli* isolates, P -value, Pearson's r, variance and trend for each antibiotic over the 10-year period.

Antibiotic	Average resistance	P value	Pearson's r	Variance	Trend	Antibiotic	Average resistance	P value	Pearson's r	Variance	Trend
	%						%				
Amikacin	15.20	0.902	0.045	0.011746	+	Ertapenem	5.10	0.094	-0.59	0.005173	-
Amoxicillin*	68.50	0.017	-0.726	0.028271	-	Gentamicin*	22.10	0.039	-0.656	0.001838	-
Ampicillin	74.90	-	-	-	-	Imipenem	1.20	0.722	-0.129	0.000266	-
Cefepime**	53.00	0.004	-0.814	0.030014	-	Meropenem	0.30	-	-	-	-
Cefixime*	44.50	0.026	0.693	0.002643	+	Nalidixic acid**	62.20	0.002	0.855	0.002708	+
Cefotaxime**	65.90	0.004	-0.817	0.039546	-	Nitrofurantoin	20.50	0.095	0.556	0.016684	+
Cefoxitin**	23.00	0.001	-0.879	0.00547	-	Norfloxacin	35.50	0.816	-0.085	0.001997	-
Cefpodoxime	40.50	-	-	-	-	Piperacillin / tazobactam	9.70	-	-	-	-
Ceftazidime**	59.00	0.005	-0.801	0.023945	-	Tetracycline	50.10	-	-	-	-
Ceftriaxone**	65.70	0.004	-0.817	0.041746	-	Tobramycin	17.40	-	-	-	-
Cefuroxime	47.40	0.452	0.269	0.00309	+	* : A significance of < 0.05 is marked by , ** : while if < 0.005, it is marked by P- value, Pearson's r, variance and trend were not calculated for antimicrobial drugs that were tested through a period of ≤ 2 years.					
Cephalothin	68.40	-	-	-	-						
Ciprofloxacin**	59.10	0	-0.916	0.051082	-						
Cotrimoxazole	57.10	0.083	-0.574	0.002493	-						

Overall trends of antimicrobial resistance were noticed to be positive for five antibiotics (amikacin, nitrofurantoin, nalidixic acid, cefuroxime and cefixime) but negative for other twelve antibiotics (gentamicin, cotrimoxazole, ciprofloxacin, norfloxacin, amoxicillin, imipenem, ertapenem, ceftazidime, cefotaxime, ceftriaxone and cefepime).

Figure 1 shows trends of antimicrobial resistance in *E. coli* isolates for antibiotics with significant P-value of < 0.05.

The remaining seven antibiotics (tobramycin, tetracycline, piperacillin / tazobactam, ampicillin, meropenem, cephalothin and cefpodoxime) were tested at The JUH laboratories for only two years

(2017-2018). Through this period, the average resistance to ampicillin was the highest among this group of antibiotics and among all 24 antibiotics too with average resistance rate of (74.9%) while meropenem had the least average resistance rate (0.3%).

ESBL positivity test was added by The JUH laboratory protocols in the period from May 2017 to December 2018. Results of positive and negative ESBL were calculated monthly. The average rate of positive ESBL strains of *E. coli* over 20 months was (33.1%) and its overall trend was positive as shown in **Figure 2**.

Discussion

Many concerns have been rising due to the emergence of new bacterial strains that are resistant to multiple antibiotics which are considered as the first line of treatment in UTI. The most common among these strains is the ESBL producers, which has developed resistance against penicillins and tetracyclines [22]. ESBL adaptation still has not worked against carbapenems [22], whereas many other resistant strains of *E. coli* are rising in recent years. For example, UTIs caused by ciprofloxacin-resistant *E. coli* have increased from 3% to 17% between the years 2000 to 2010 [23], pushing up the importance

Figure 1: Overall trends of *E. coli* resistance 2009-2018.

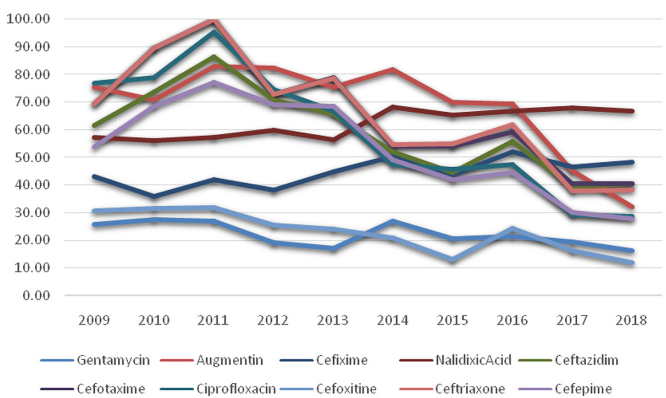
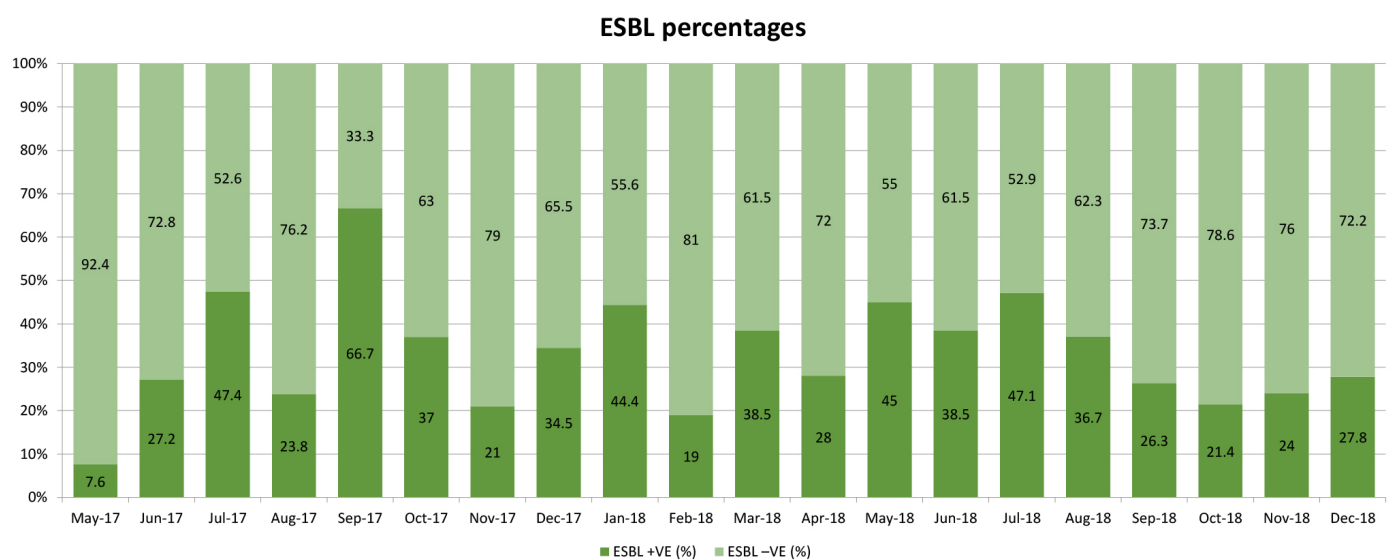


Figure 2: Percentages of ESBL in the period from May 2017 to December 2018.



of understanding the patterns of resistance in this type of bacteria and the urge to counter it.

The accredited protocols for prescribing antibiotics in JUH are according to the recommendations of National Antimicrobial Resistance Plan [24], World Health Organization (WHO) Antimicrobial Resistance (AMR) Plan [25], Joint Commission International (JCI) protocols of antimicrobial descriptions [26], and Pharmaceutical drugs description and awareness protocols of pharmacy department at The JUH [27].

In this study, we will discuss each antimicrobial class on an individual basis as follow:

Amikacin

It can be used as a therapeutic option for resistant ESBL *E. coli* isolates in case of limited resources [28]. Following accreditation of AMR plan in 2016, amikacin has shown minimal variance in resistance profiles.

Gentamicin

E. coli resistance to gentamicin can vary on institutional basis [29]. There is a slow trending down in resistance with overall low average resistance (22.1%). Gentamicin is used as a second line agent in severely ill patients. AMR plans restricted the usage of gentamicin to severe infections; this approach may has helped in the low rate of resistance values following 2016.

Tobramycin and tetracycline

Both have no current role in UTI treatment guidelines [18], but this approach should follow further studies on their performances in the following years.

Cotrimoxazole

It has an overall negative trend and is used as a first line agent. Cotrimoxazole has shown steadiness in performance over many years even to other

E. coli infections [30]. Though it has a high average resistance (57.1%), the application of good antimicrobial usage plans could control the resistance towards it as shown in the years following 2016.

Nitrofurantoin

It showed a great increase in resistance between the years of 2009 (3.4%) to 2014 (39.8%) followed by a period of slow regression in resistance since nitrofurantoin was unavailable in The JUH during the years 2015-2017. This fact may explaining the mild regression in resistance that took place in the following years. The overall trend of resistance is positive which emphasizes the revision of treatment protocols that consider nitrofurantoin as a first line agent. This antibiotic is also recommended for empiric therapy for community-acquired and nosocomial lower UTI caused by *E. coli* susceptible to it. Additionally, nitrofurantoin is also active against most strains of multidrug-resistant gram-negative bacilli including most ESBL-producing strains except *Proteus spp.* and *Pseudomonas aeruginosa* [31].

Ciprofloxacin

There is an evident increase in resistance in the period 2009 (76.9%) to 2011 (95.5%), then a near steady state took over in the years 2012 to 2016, followed by regression of resistance in the following years. Though the average resistance of ciprofloxacin remains high (59.1%), and the overall trend of resistance is negative which makes ciprofloxacin a reliable antimicrobial choice. It is evident that a significant drop in resistance followed the accreditation of AMR plans in 2016. Ciprofloxacin is a good candidate for present and future strategies in treating UTIs caused by *E. coli*. Though its resistance has regressed. Rates of ciprofloxacin resistant of uropathogenic *E. coli* in this study and other Jordanian studies are much higher than many other studies worldwide [23]. A recent study carried out in Jordan has indicated alarming high rates recovery of multi-drug resistant uropathogenic *E. coli* from Jordanian patients associated with high rates of positive ST131 clone and fluoroquinolone resistant and important types of *blaCTX-M* [16]. Also, it has been shown that multi-drug resistant *E. coli* to 3 or

more antibiotic classes causing urinary tract infections will be often associated with treatment failure, particularly in association with bacterial strains carrying CTX-M extended spectrum β -lactamases [32]. In addition, it has been reported that CTX-M-15 extended spectrum β -lactamases encoding genes are widely spread among *Enterobacteriaceae* in the Middle Eastern region [33].

Norfloxacin and Nalidixic acid

Though both drugs have high average resistance (35.5% and 62.2%, respectively), the resistance rates showed steadiness towards them over the 10-year period. Both antibiotics were never used in treating UTIs caused by *E. coli* in The JUH. Nevertheless, Nalidixic acid resistance is rising. Norfloxacin showed favorable susceptibility results and is a good candidate for future treatment protocols.

Amoxicillin

A relatively steady resistance is shown between the years 2009-2016 with a great decline in resistance profile following 2016. This trend is probably in relation to the accreditation of AMR plans and the restrictions over amoxicillin use as over-the-counter drug. Though amoxicillin has a high average resistance (68.5%), the inclusion of amoxicillin in future strategies in treating UTI depends on other factors as this antibiotic has minimal side effects and a rapid recovery profile, this is consistent with its traditional usage as oral treatment of UTI [34]. Amoxicillin resistance profile is a good example of reversing the resistance process rapidly when the selective pressure on the bacteria is eliminated.

Piperacillin/tazobactam and ampicillin

These antibiotics were added to the laboratory protocols in 2017. There were no significant changes in their resistance profiles over the following year with average resistance rates of (9.7% and 74.9%) respectively. Previous Jordanian studies reported also the prevalence of high resistance rates of *E. coli* isolates to ampicillin over the last 10-year [16, 39].

Imipenem, Ertapenem and Meropenem

Overall, the averages of resistance for all carbapenems are low (1.2%, 5.1% and 0.3%, respectively). Imipenem showed a steady performance against *E. coli*, with a negative annual trend. The restrictions applied by infection control departments at The JUH on the usage of imipenem as an empirical antimicrobial treatment helped in the regression of imipenem-resistant *E. coli* seen in the years 2017 to 2018. Resistance towards ertapenem showed a significant decline over the years between 2010 to 2018 with a negative overall trend. A progression in resistance was noted following the application of the new protocols in 2016, which enforces the statement that more restrictions should be put on prescribing this antibiotic. Ertapenem resistance worldwide have shown a significant increase following the year 2015 [35]. Carbapenems should be always reserved as the last lines of treatment for severe life-threatening cases. We advice the need for prudent and rational use of carbapenems in our country.

Cephalosporins

ESBLs are most common in *E. coli* and *K. pneumoniae*. The most typical type of infection they cause is urinary tract infections. Also, they can cause other serious infections and are most likely to be resistant to many of the empirical antibiotics used for these infections [36]. Infections with ESBL-producers are most common amongst elderly people or those who have recently been in hospital and received antibiotic treatment. The incidence of these infections has been increasing worldwide including Jordan [16,36]. Therefore, minimizing the spread of resistant organisms relies in part on only using antibiotics when necessary and at appropriate doses and duration in both the community and hospitalized patients [37].

First generation cephalosporins

Cephalothin was used widely since mid seventy of the last century at The JUH and recently added to

the laboratory protocols in 2017. Overall, it shows a high resistance profile with average resistance of (68.4%).

Second generation cephalosporins

E. coli exhibited a steady resistance profile towards cefuroxime over the 10 years period with a minimal annual growth rate; hence, cefuroxime is still considered one of the effective antimicrobials in the treatment of UTIs caused by *E. coli* at The JUH. The resistance profile of cefuroxime showed minimal regression in resistance after applying AMR plans during 2016. The latest treatment strategies helped in decreasing the selective pressure applied by ciprofloxacin and ceftriaxone but led to increase usage of cefuroxime which in turn might lead to increased resistance towards it. A relatively high average resistance (47.4%) that is trending up might enforce a revision of future treatment protocols that contain cefuroxime and encourage the switch to other drugs in the same class with lower resistance. Although with minimal variance and mild side effects, it is still counted as a recommended drug for any future strategies. *E. coli* exhibited regression of resistance towards cefoxitin, with negative overall trend of resistance, as the drug has not been available for usage in JUH since 2009. Recently in 2018, cefoxitin has replaced cefuroxime in many major departments in the hospital in a hope to reduce the resistance towards cefuroxime. Rates of resistance towards cefuroxime in this study seem to be less than worldwide reports [38]. In a former multicenter study conducted in Jordan, cefuroxime resistance rate was 61.7%, notably, 21.2% were resistant to cefoxitin [39].

Third generation cephalosporins

An increase in resistance towards cefixime is noted (43.2% to 48.4%) over the 10-year. Though it was used in many treatment protocols, it showed minimal variance with near steady performance. According to low cost and mild side effects, cefixime might play a role in future treatment protocols.

ceftazidime and cefotaxime were used in the years 2009-2012 in many treatment protocols at The JUH, hence, we can relate the rapid development of resistance seen in these two antibiotics in the years mentioned. But since 2012, ceftriaxone largely took over and replaced these two antibiotics in all major departments in the hospital. Ceftriaxone resistance evolution has a negative trend. Since 2016, there were major restrictions on the prescription of broad-spectrum antibiotics at The JUH, including ceftriaxone with new strategies that encourage the use of cefuroxime in the treatment of UTI instead of ceftriaxone. This probably helped in regression of resistance towards ceftriaxone in the years 2016 to 2018. ESBL bacteria is the most common cause for ceftriaxone resistance [40].

Fourth generation cephalosporins

A significant regression in resistance towards cefepime is evident with a negative overall trend. Cefepime was never available for prescription at The JUH after 2009, explaining the significant regression of resistance towards this antibiotic. With a high average resistance (53.0%) and variance, cefepime is not recommended in the near future protocols but might be one of our few weapons in the far future [41].

Due to the high prevalence of ESBL-positive isolates of *E. coli* in our region [16, 42]. ESBL test for positivity was added to the laboratory protocols in May, 2017. Overall, there is a mild increase in the percentage of *E. coli* isolates that showed positivity for ESBL testing over a period of 20 months. Strict antimicrobial strategies and protocols helped in decreasing the development of ESBL positive traits.

According to the data analysis, *E. coli* has shown different degrees of resistance. Understanding the patterns of this evolutionary process, the speed of it and the variance of growth rates exhibited in relation to changing the treatment strategies determines the best drug to use when carrying out

continuous analyses of bacterial cultures and their antibiotics susceptibility results.

Recommendations

Summarizes our recommendations, the antimicrobials labelled in C are recommended for any ap-

proach to future treatment strategies. The scale is based on rationale of antimicrobial stewardship strategy formulary restrictions, accredited by Ontario public health [20]. **Table 4**

Table 4. Summary of recommendation for future use of antibiotics against E. coli urinary tract infections based on the current average and trend of resistance, cost and side effects.

Antibiotic	Average resistance	Overall trend	Cost*	Extreme adverse effects [43]	Current Role [18]	Level of recommendation for future protocols**	P value
	%						
Amikacin	15.2	+	(11-20) USD	Neurotoxicity / Nephrotoxicity / Ototoxicity	Resistant ESBL infections	B	0.902
Amoxicillin	68.5	-	(11-20) USD	Diarrhea / Nausea / Vomiting	First line agent in UTI in pregnancy	C	0.017
Cefepime	53.0	-	(21-30) USD	Positive coombs test without hemolysis / Rash Diarrhea	First line agent in pregnancy	B	0.004
Cefixime	44.5	+	<10 USD	Diarrhea / Fever / Elevated liver enzymes / Headache	No current role	C	0.026
Cefotaxime	65.9	-	(11-20) USD	Nephrotoxicity / Fever / Elevated liver enzymes / Pain at the site of injection	No current role	B	0.004
Cefoxitin	23.0	-	(21-30) USD	GIT upset / Blood dyscrasias	Second line agent for cystitis	C	0.001
Ceftazidime	59.0	-	>30 USD	Increase in liver transaminases / Eosinophilia / Phlebitis / Immune hypersensitivity reactions	No current role	B	0.005
Ceftriaxone	65.7	-	(21-30) USD	Blood dyscrasias / Elevated liver enzymes / Diarrhea / Indurations at the site of injection	First line agent in severely ill patients / Third line agent in pyelonephritis	B	0.004
Cefuroxime	47.4	+	<10 USD	GIT upset / Anemia / Thrombophlebitis	Second line agent for cystitis	C	0.452
Ciprofloxacin	59.1	-	<10 USD	Nausea / Rash / Diarrhea	Second line agent for pyelonephritis	B	0.000
Cotrimoxazole	57.1	-	<10 USD	Seizure / Immune hypersensitivity reaction / Fulminant hepatic necrosis	First line agent for cystitis and pyelonephritis	B	0.083

Antibiotic	Average resistance	Overall trend	Cost*	Extreme adverse effects [43]	Current Role [18]	Level of recommendation for future protocols**	P value
	%						
Ertapenem	5.1	-	>30 USD	GIT upset / Phlebitis / Fever / Edema	Severe, complicated and resistant pyelonephritis / ESBL infections	B	0.094
Gentamicin	22.1	-	<10 USD	Neurotoxicity / Nephrotoxicity / Ototoxicity / Gait instability / Edema / Rash / Itching	Second line agent in severely ill patients	C	0.039
Imipenem	1.2	-	(21-30) USD	Phlebitis / Eosinophilia / Rash / Seizure	Severe, complicated and resistant pyelonephritis / ESBL infections	A	0.722
Nalidixic acid	62.2	+	(11-20) USD	Neurological symptoms / GIT upset	No current role	B	0.002
Nitrofurantoin	20.5	+	<10 USD	Methemoglobinemia / Arthralgia / Rash / Vasculitis	First line agent for cystitis and UTI in pregnancy	C	0.095
Norfloxacin	35.5	-	<10 USD	Tendinitis / Neurological symptoms / GIT upset / Skin	No current role	C	0.816

*: Cost per single antibiotic course, obtained by Jordan University Hospital pharmacy reports of imported drugs quantities in the years (2009-2018) (17).

** level of recommendation: a scale of 6 points represented by the preceding columns was constructed: 2 favorable figures: A, 3 favorable figures: B, ≥4 favorable figures: C. C code represents our recommendations for the near future protocols. Favorable figures: average resistance of less than 50% but higher than 10%, variance of < 0.05, negative trend, cost ≤ (11-20) USD, side effects that do not involve major vital organs and narrow spectrum

Conclusions

We are concluded with significance that gentamicin, amoxicillin, cefoxitin and cefixime are the most effective antimicrobials to be considered in the future treatment protocols based on *E. coli* resistance profile. During the years 2016 to 2018, we found that the change in treatment protocols has led to significant reduction in the growing resistance of *E. coli* towards some broad-spectrum antibiotics. This was a major advancement in the project of finding out the ideal strategy in fighting antimicrobial resistance. Due to restrictions against improper prescriptions, misuse and overuse of antibiotics, a nota-

ble decline in antimicrobial resistance was achieved with a speed that sometimes exceeded the speed of acquiring this resistance. This study clearly implicates that *E. coli* can easily develop resistance in variable degrees among the same class of antibiotics necessitating protocols of prescribing antibiotics to be directed towards antibiotics individually.

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