Antimicrobial Susceptibilities of Urinary Extended-Spectrum β -lactamase *Escherichia coli* to Fosfomycin

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Abstract

Objectives: *Escherichia coli* (*E. coli*)-induced urinary tract infection (UTI) is very common infection associated with frequent use of antibiotics and increase in the global antibiotic resistances. We aimed to determine the susceptibility profile of Extended-Spectrum β -lactamase (ESBL) - producing *E. coli* isolated from the urinary samples to Fosfomycin and other antibiotics. **Methods**: The study retrospectively analyzed the clinical urine samples with ESBL-producing *E. coli* isolates; obtained from Jan 2018 to December 2019. We collected and analyzed all the data of the *E. coli* urinary isolates, and their antibiotic susceptibility pattern. **Results**: The study included 3044 *E. coli* isolates during the 2 years; 50.5% in 2018, and 49.5% in 2019; 38% (1161 isolates) were EBSL *E. coli,* and 0.7% (21 isolates) were Carbapenem-resistant Enterobacteriaceae (CRE). There were 1161 (38%) isolates with ESBL -producing *E.*

coli, 51% isolated in 2018, and 49% isolated in 2019. The antibiotic susceptibility of ESBL-producing *E. coli* during the study period showed susceptibility to Trimethoprim/sulfamethoxazole (TMP/SMX) in 46% of isolates (50% in 2018, dropped to 42% in 2019), to Ciprofloxacin in 49% of isolates (49.5% in 2018, dropped to 48% in 2019), to Nitrofurantoin in 94% of isolates (94 in 2018, dropped to 89% in 2019), and to Fosfomycin in 97.5% of isolates (99% in 2018 dropped to 96% in 2019). **Conclusions**: ESBL -producing *E. coli* is an important cause of UTI in Bahrain. Fosfomycin is a very effective oral antimicrobial that still retains high efficacy against ESBL -producing *E. coli*, which helps to decrease the need for parenteral therapy, and consequently hospitalization.

Key Words: Urinary tract infections; ESBL -producing *E. coli;* Fosfomycin, Bahrain.

Introduction

Urinary tract infection (UTI) is one of the most common health problems and the second most common clinical indication for empirical antibiotic treatment in primary and secondary health care settings which entails a high consumption of health system resources. It has a lifetime incidence of 50−60% in adult women with a significant personal, societal, and economic burden.[1,2] Due to the frequent use of antibiotics to treat UTI and the increase in global antibiotic resistances in recent years, it is common to find uropathogens with multiple resistance mechanisms. These uropathogens include quinolone-resistant bacteria, broad-spectrum β-lactamase producers, and Carbapenemase producers. The development of these resistances has limited the use of most of the available oral front-line antibiotics as empirical therapeutic options for uncomplicated UTI.[3]

Fosfomycin is an old broad-spectrum bactericidal antibiotic. Despite being used since 1969, it is recently included in the drug formulary of our hospital. It is an oral derivative of phosphonic acid able to inhibit the synthesis of the bacterial cell wall in both Gram-positive and Gram-

negative bacteria through inhibition of the initial step involving phosphoenolpyruvate synthetase with very low toxicity. Its pharmacokinetic profile encourages its use for UTIs. The mean peak urinary concentration of a single oral dose of 3 g Fosfomycin tromethamine occurs within 4 h. This concentration is sufficient to inhibit most of the urinary pathogens and is maintained for about 1 to 2 days.[4,5] It is effective against a wide range of resistant uropathogens, including MDR *Pseudomonas aeruginosa*, extended-spectrum β -lactamase (ESBL)-producing bacteria, carbapenem-resistant *Enterobacteriaceae* (CRE), and vancomycin-resistant *Enterococci* (VRE). It is usually given as a single dose for the treatment of cystitis.[6]

Fosfomycin trometamol, Nitrofurantoin, and Pivmecillinam are recommended as first choice antimicrobial therapy in acute uncomplicated cystitis in otherwise healthy women, according to the guidelines of the European Association of Urology, and the Infectious Diseases of America (IDSA).[7,8] Fosfomycin is a more convenient antibiotic due to the single-dose regimen, the in-vitro activity against the resistant organisms, and the minimal propensity for collateral damage. In contrast, Nitrofurantoin has an important limitation for use, especially in Bahrain, as it is contraindicated in patients with glucose-6 phosphate dehydrogenase deficiency, which is very common in Bahrain. Pivmecillinam is not available in Bahrain.

Cystitis is one of the most common encountered types of bacterial infections. Its antibiotic treatment is usually empirical and should be guided by the local resistance profile of the common uropathogens. In the current study, we aimed to determine the antimicrobial susceptibility profile of Extended-Spectrum β -lactamase (ESBL) - producing *E. coli* isolated from the urinary samples to Fosfomycin and other antibiotics, in patients attending Salmaniya Medical Complex, and to decrease the need to use intravenous therapy of UTI caused by ESBL-producing *E. coli*.

Methods

The study was a retrospective observational analysis of all ESBL-producing *E. coli* isolates from clinical urine samples obtained from Jan 2018 to December 2019 in the Microbiology Section, Pathology Department, Salmaniya Medical Complex, which is the main tertiary care hospital in the Kingdom of Bahrain. We retrospectively collected the data of all *E. coli* urinary isolates and their antibiotic susceptibility from the laboratory records and tabulated using the Microsoft Excel database. We analyzed the predominant *E. coli* isolates, including sensitive strain, ESBL -producing strains, and Carbapenem-resistant *E. coli* (*E. coli CRE*). We included all pure growth of *E. coli* with colony count $\geq 10^5$ CFU/mL. Duplicate samples and mixed infections were excluded.

All urine samples were inoculated into Cysteine Lactose Electrolyte Deficient medium (Oxoid, Basingstoke, Hampaire, UK) using a calibrated loop of 1 µl in safety cabinet. Inoculated plates were incubated at 37 °C for 18–24 h aerobically. Pure growth of bacteria with colony count of $\geq 10^5$ CFU/mL for midstream urine was considered significant and further identified using MALDI-TOF MS (Bruker Daltonics, Germany). Mixed infection was not encountered.

The antimicrobial susceptibility testing of all isolates was done by the standard Kirby-Bauer disk diffusion method using commercial disks (Oxoid) according to Clinical and Laboratory Standards Institute (CLSI) [9] to determine the bacterial susceptibility to Fosfomycin and other oral antibiotics, including Co-amoxiclav, Ciprofloxacin, Trimethoprim-sulfamethoxazole, and Nitrofurantoin. The turbidity of the suspension was adjusted to the density of a McFarland 0.5 (Mary-l'Etoil, France) to standardize the inoculum size. [9]

For the initial ESBL screening, the urine isolates with an inhibition zone size of ≤22 mm with Ceftriaxone (30 µg) were identified as potential ESBL producers. The conventional double-disc diffusion test with co-amoxiclav, ceftriaxone and ceftazidime were used to confirm the extended-spectrum β-lactamase (ESBL) production in Enterobacteriaceae strains. For the

quality control of susceptibility tests *Escherichia coli* ATCC 25922, *E. coli* ATCC 35218, strains were used.

We also documented the patients' age, gender, and nationality; and stratified the isolates according to the patients' age: less than 1 year, between 1-15 years, between 16-50 years, and those more than 50 years. The isolates were also classified according to their sensitivities into sensitive *E. coli* strains, ESBL -producing *E. coli* isolates, and *E. coli* CRE. Additionally, the isolates were classified into isolates from patients with the community or hospital-acquired infections. The trend of antibacterial sensitivity was followed to compare the isolates collected in 2019 to that collected in 2018.

We used TexaSoft, WINKS SDA Software 2011 (Sixth Edition, Cedar Hill, Texas, USA) to perform the statistical analysis. The percentages and frequencies were computed for different categorical variables, and a cross-tabulation was computed between every two categorical variables. Finally, the Chi-Squared test determined whether there were significant relationships between every two categorical variables (according to the years of isolates, the gender [male versus female], by age groups, whether community versus nosocomial infections). We considered a P-value of less than 0.05 as statistically significant. The study was approved by the Secondary Care Research Committee of Salmaniya Medical Complex, Ministry of Health, the Kingdom of Bahrain. The study had no ethical consideration as it was a retrospective study with no exposure to any patient data.

Results

The study included 3044 *E. coli* over the two years, 1539 (50.5%) in 2018 and 1505 (49.5%) in 2019, 38% (1161 isolates) were ESBL *E. coli* and 0.7% (21 isolates) were CRE. About 75% were observed from the females, with a male: female ratio of 1:3 [Figure 1]. According to the

age stratification, 8% of the isolates were observed in infants below the age of 1 year, 11.7% in patients between 1-15 years, 38.2% in patients between 16 -50 years, and 42% in patients older than 50 years. The antibiotic susceptibility showed that 49% of isolates were sensitive to Amoxycillin-Clavulanate (dropped from 55% in 2018 to 43% in 2019), 72% were sensitive to Ciprofloxacin (dropped from 74% in 2018 to 70% in 2019), 63% were sensitive to Trimethoprim-sulfamethoxazole (TMP/SMX) (dropped from 68% in 2018 to 57% in 2019), 94.6% were sensitive to Nitrofurantoin (dropped from 96.7% in 2018 to 92% in 2019), and 99% were sensitive to Fosfomycin (dropped from 99.5% in 2018 to 98.4% in 2019). [Figure 2]

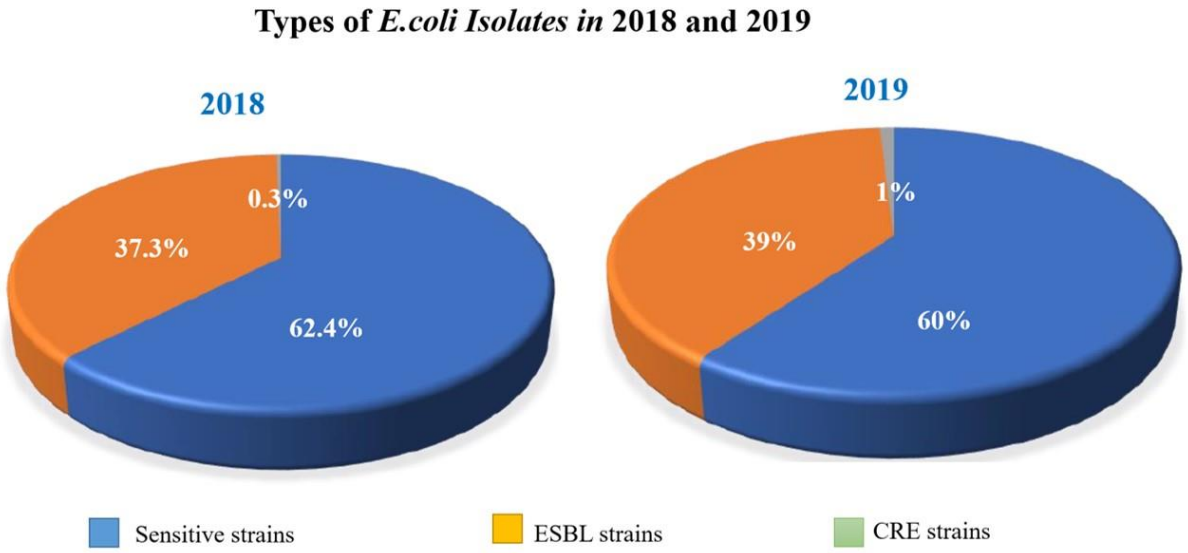

Figure 1: Types of *E. coli* Isolates in 2018 and 2019.

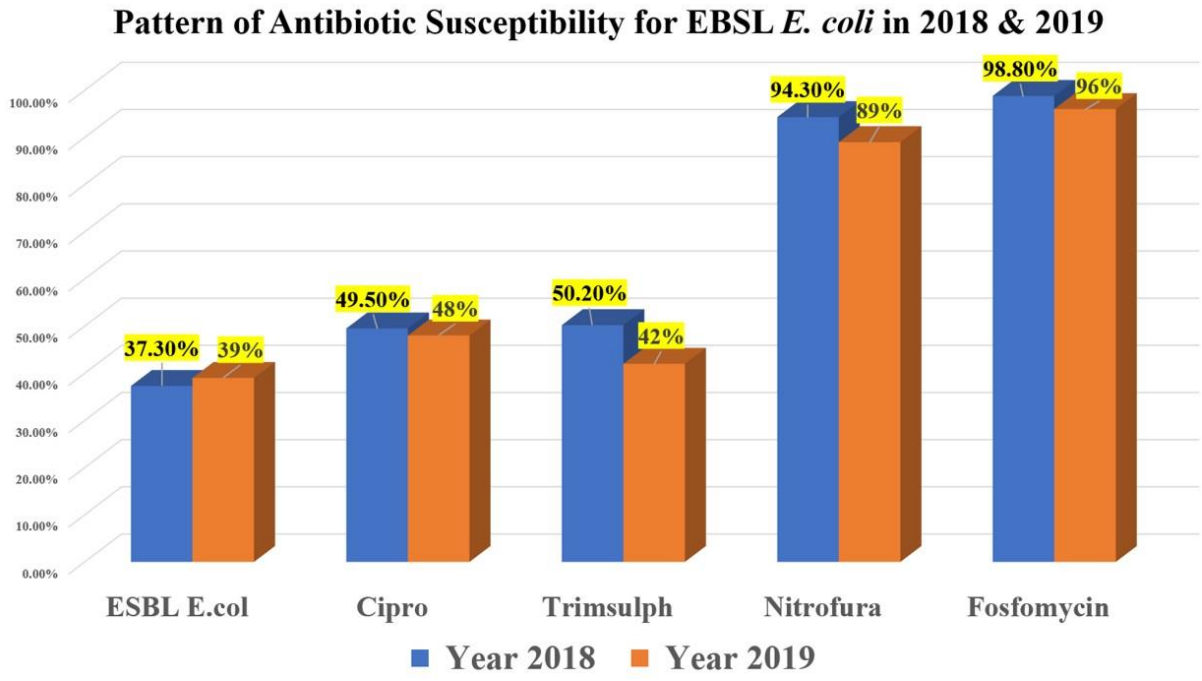

Figure 2: Pattern of Antibiotic Susceptibility for ESBL- Producing *E. coli* in 2018 and 2019.

Urinary Isolates with *E. coli* collected in 2018: a total of 1539

Table 1 showed the *E. coli* isolates collected in 2018 with a total of 1539 isolates. ESBL *E. coli* isolates formed 37.3% of the total isolates, and CRE *E. coli* formed 0.3%. Most of the isolates came from females (75%), with a male: female ratio of 1:3. However, this ratio increased to 1:2.3 in ESBL strains, and 1:1.5 in CRE strains. The age stratifications showed that most of the isolates were in the age group older than 50years (41%), followed by the age group between 16-50 years (39%). Table 1 also showed the percentage of the different strains and their antibiotic susceptibility. Fosfomycin sensitivity was observed in 99.5% of the total isolates and 98.8% of ESBL strains. Additionally, *E. coli* isolates showed also high susceptibility to Nitrofurantoin (96.7% in the total isolates and 94.3% in ESBL strains).

Table 1: The different strains of *E. coli* and its demographic data and antibiotic susceptibility for the case isolated in 2018 and 2019

		Total *E. coli*		*E. coli* CRE		*E. coli* Sensitive		*E. coli* ESBL	
		2018	**2019**	**2018**	**2019**	**2018**	**2019**	**2018**	**2019**
Total No of isolates		1539	1505 (100%)	5 (0.3%)	16 (1%)	960 (62.4%)	902 (60%)	574 (37.3%)	587 (39%)
Female		1151 (74.8%)	1133 (75.3%)	3 (60%)	6 (37.5%)	746 (77.7%)	733 (81.3%)	402	394 (67.1%)
Male		388 (25.2%)	372 (24.7%)	2 (40%)	10 (62.5%)	214 (22.3%)	169 (18.7%)	172	193 (32.9%)
M/F ratio		1:3	1:3	1:1.5	1.7:1	1:3.5	1:4.3	1:2.3	1:2
Age	**< 1 yr**	118 (7.8%)	118 (7.8%)	1 (6.26%)	1 (6.26%)	81 (8.4%)	59 (6.5%)	49 (8.5%)	58 (9.9%)
	1-15 yr	182 (12.1%)	182 (12.1%)	2 (12.5%))	2 (12.5%))	124 (13%)	124 (13.7%)	48 (8.4%)	61 (10.4%)
	16-50 yr	560 (37.2%)	560 (37.2%)	3 (18.75%)	3 (18.75%)	415 (43.2%)	379 (42%)	187 (32.6%)	164 (27.9%)
	> 50 yr	645 (42.9%)	645 (42.9%)	10 (62.5%)	10 (62.5%)	340 (35.4%)	340 (37.7%)	290 (50.5%)	304 (51.8%)
Oral Antibiotic Sensitivity %	**Amox-Clav**	841 (55%)	698 (43%)	0 (0%)	0%	847 (88%)	698 (77%)	0 (0%)	0%
	Ciprofloxacin	1135 (74%)	1060 (70%)	1 (20%)	0%	850 (88.5%)	855 (95%)	284 (49.5%)	284 (48%)
	TMP/SMX	1051 (68.3%)	864 (57%)	1 (20%)	2 (12.5%)	762 (79.4)	517 (57%)	288 (50.2%)	246 (42%)
	Nitrofurantoin	1488 (96.7%)	1392 (92%)	4 (80%)	13 (81%)	943 (98.2%)	767 (85%)	541 (94.3%)	524 (89%)
	Fosfomycin	1532 (99.5%)	1482 (98.4%)	5 (100%)	15 (94%)	100%	902 (100%)	567 (98.8%)	565 (96%)

CRE: Carbapenem-resistant Enterobacteriaceae, *E. coli*: Escherichia coli, ESBL: Extended-Spectrum β -lactamase, M: F: Male: Female TMP/SMX: Trimethoprim – Sulfamethoxazole

Urinary Isolates with *E. coli* collected in 2019:

Table 1 also showed the *E. coli* isolates collected in 2019 with a total of 1505 isolates. ESBL *E. coli* isolates formed 39% of the total isolates (higher than that observed in 2018), and CRE *E. coli* formed 1% (higher than that observed in 2018). Most of the isolates came from females (75%) with a male: female ratio of 1:3. However, this ratio increased to 1:2 in ESBL strains,

and to reach 1:1.5 in CRE strains. The age stratifications showed that most of the isolates were in the age group older than 50 years (43%), followed by the age group between 16-50 years (37%). Table 2 also showed the percentage of the different strains and their antibiotic susceptibility. Fosfomycin sensitivity was observed to be 98.4% of the total isolates and 96% of ESBL strains (slightly lower than observed in 2018). Additionally, *E. coli* isolates showed also high susceptibility to Nitrofurantoin (92% in the total isolates and 89.3% in ESBL strains; but significantly lower than observed in 2018). Table 2 showed the community and hospital-acquired UTI caused by *E. coli*. The hospital-acquired infection was observed in 10% of the total isolates. The percentages in males and the age group below 1 year were slightly higher in the hospital than in the community-acquired. The incidence of EBSL strain was much higher in hospital-acquired UTI to reach 51% compared to 37.6% in community-acquired. Table 2 also showed their antibiotic susceptibility.

Table 2: Comparison between Demographics, types of *E. coli* isolates and antibiotic susceptibility between community and hospital acquired UTI caused by *E. coli* in 2019

		Community Acquired	**Hospital Acquired**
No of isolates		1352 (90%)	153 (10%)
Female		1022 (75.6%)	111 (72.5%)
Male		330 (24.4%)	42 (27.5%)
M/F ratio		1:3	1:2.6
Age	**< 1 yr**	100 (7.4%)	18 (11.8%)
	1-15 yr	171 (12.6%)	11 (7.2%)

	16-50 yr	537 (39.7%)	49 (32%)
	> 50 yr	544 (40.3%)	75 (49%)
Nationality	**Bahraini**	1140 (84%)	123 (80%)
	Non-Bahraini	212 (16%)	30 (20%)
Sensitive *E. coli* strains		836 (62%)	66 (43%)
ESBL Producing strains		509 (37.6%)	78 (51%)
CRE *E. coli*		7 (0.5%)	9 (6%)
Oral Antibiotic Susceptibility %	**Amox-Clav**	651 (48%)	47 (31%)
	Ciprofloxacin	975 (72%)	86 (56%)
	TMP/SMX	792 (58,5%)	73 (47.7%)
	Nitrofurantoin	1261 (93.3%)	132 (86.2%)
	Fosfomycin	514 (out of 533) 96.4%	91 (out of 95) 96%

CRE: Carbapenem-resistant Enterobacteriaceae, *E. coli*: Escherichia coli, ESBL: Extended-Spectrum β -lactamase, M: F: Male: Female TMP/SMX: Trimethoprim – Sulfamethoxazole

ESBL-Producing *E. coli*

Out of 3044 isolates, ESBL *E. coli* formed 38% (1161 isolates); 51% isolated in 2018, and 49% isolated in 2019. Table 3 showed the characteristics of ESBL *E. coli* isolates according to the gender, and age groups during the study. Despite most of the isolates came from female patients (69%); the percentage of ESBL isolates from male patients (31.4%) was higher when compared to the percentage of males with sensitive *E. coli* strains (20.5%). This indicates that males are more liable to have ESBL *E. coli* strains than females. The age group older than 50 years had the highest incidence of ESBL *E. coli* isolates (52%), followed by the age group between 16-

60 years (33%). When we compare ESBL to the total number of the isolates in each group, the percentage of EBSL strains were 43% in the age group less than 1 year, 20% for the age group between 1-16 year of age, 33% for the age group between 16-50 years, and 47% for the age group older than 50 years.

Table 3: ESBL *E. coli* isolates antibiotic susceptibility according to the gender and the age group

	According to Gender		**According to Age**			
	Male	**Female**	**<1 yr**	**1-15 yr**	**16-50 yr**	**>50 yr**
Total No ESBL (1161)	365 (31%)	796 (69%)	107 (9%)	70 (6%)	383 (33%)	601 (52%)
ESBL in 2018	172 (47%)	427 (54%)	49 (46%)	48 (69%)	187 (49%)	290 (48%)
ESBL in 2019	193 (53%)	369 (46%)	58 (54%)	22 (31%)	196 (51%)	311 (52%)
Susceptibility to Ciprofloxacin %	184 (50%)	384 (48%)	67 (63%)	27 (39%)	165 (43%)	309 (51%)
Susceptibility to TMP/SMX %	175 (48%)	359 (41%)	50 (47%)	15 (21%)	162 (42%)	307 (51%)
Susceptibility to Nitrofurantoin %	325 (89%)	740 (93%)	76 (71%)	70(100%)	370(96.6%)	549 (91%)
Susceptibility to Fosfomycin %	354 (97%)	778 (98%)	84 (79%)	69 (99%)	382(99.7%)	597 (99%

ESBL: Extended-Spectrum β -lactamase, TMP/SMX: Trimethoprim – Sulfamethoxazole

The antibiotic susceptibility of ESBL *E. coli* during the study showed susceptibility to TMS in 46% of the isolates (50% in 2018 dropped to 42% in 2018), to Ciprofloxacin in 49% of isolates (49.5% in 2018 dropped to 48% in 2019), to Nitrofurantoin in 94% of isolates (94% in 2018 dropped to 89% in 2019), and to Fosfomycin in 97.5% of isolates (99% in 2018 dropped to 96% in 2019). ESBL *E. coli* isolates from the females showed a higher susceptibility to Nitrofurantoin (93%) and Fosfomycin (98%) compared to the isolates from the males which showed a susceptibility of 89% to Nitrofurantoin and 97% Fosfomycin. On the other hand, ESBL *E. coli* isolates from the males showed higher susceptibility to TSM (48%) and

Ciprofloxacin (50%) than observed in ESBL *E. coli* isolates from the females (41% to TSM, and 48% to Ciprofloxacin). According to the age groups, the ESBL isolates derived from infants > 1 year showed the least susceptibility to Fosfomycin (79%) while it keeps being high (around 99%) in the other age groups. The same also was observed for Nitrofurantoin, which had the lowest susceptibility in infants > 1 year (71%), while 90% of the ESBL isolates were susceptible to Nitrofurantoin in the other age groups. TMP/SMX had the lowest susceptibility among all the antibiotics, to be as low as 21% in the age group between 1-15 years. Ciprofloxacin showed moderate susceptibility, as observed in table 3.

Discussion

ESBL producing organisms are important causes of drug resistant UTI. ESBLs are enzymes capable of hydrolyzing penicillins, broad-spectrum cephalosporins, and monobactams.[10] An effective oral antibiotic against resistant strains of *E. coli* can reduce the need for parenteral antibiotics, and hence the need for hospitalization. In the current study, we observed the presence of high susceptibility of ESBL strains to Nitrofurantoin and Fosfomycin, and less extent to TMP/SMX and Ciprofloxacin. According to the newborn screening test, the rate of G6PD deficiency is very high in Bahrain [up to 18% in males, and 10% in females].[11] Many antibiotics; as Nitrofurantoin, TMP/SMX, and Ciprofloxacin are not safe for patients with G6PD deficiency; and better to be avoided, as they can trigger hemolytic crises in people with G6PD deficiency. For this reason, Fosfomycin is an ideal oral antibiotic and more suitable than the other 3 antibiotics included in our study. Fosfomycin is recently introduced into Bahrain drug formulary. The high susceptibility of *E. coli* to Fosfomycin observed in the current study is comparable to the work of Maraki et al from Greece, who observed that all *E. coli* isolates in their study were susceptible to Fosfomycin (100% susceptibility.[5] Similarly, Fajfr et al from

the Czech Republic, Ouzdi et al from Morocco, and Plate et al from Switzerland found high susceptibility of ESBL *E. coli* urinary isolates to Fosfomycin [95.8%, 96%, and 99.4% respectively].[12-14] This worldwide low rate of resistant of ESBL *E. coli* to Fosfomycin may be related to the type of the mechanism of development of resistance, which is due to chromosomal encoded and not plasmid dependent.[15]

However, the rate of susceptibility to Fosfomycin was relatively lowered in ESBL isolates from the Republic of Korea, and Israel [93.7%, and 69% respectively].[16,17]

In the current study, we found that the rates of ESBL *E. coli* are affected by the gender and the age of the patients. We observed an increase in the percentage of ESBL in the male gender (31.4% of total ESBL isolates compared to 20.5% from total E. coli isolates). At the same time, the rate of Fosfomycin susceptibility in ESBL *E. coli* isolates derived from females was relatively higher (98%) than those observed in isolates derived from males (97%). This also was observed in the study of Guneysel et al who observed that males are more liable to have more resistance to Fosfomycin than females, as UTI in males are usually complicated, with more chronicity and more frequent exposure to antibiotic therapies. However, their study was designed for uncomplicated UTI and had few numbers of isolates compared to our study.[18] Despite being more frequent in females than in males, UTIs in men are often complicated due to the higher chance of having malformation and renal involvement, and thus require more attention and meticulous investigations.[19] As the male gender is considered a risk factor for complicated UTIs, this may explain the relatively high ESBL rate in the male gender. In the current study, despite ESBL *E. coli* found in 9% of infants age 1 year or less, this age group had the lowest susceptibility rate to Fosfomycin among ESBL *E. coli* isolates compared to all the other age groups (79%). *E. coli* is one of the most common bacterial causes of early neonatal sepsis. Unfortunately, there are very little data on bacteremia caused by multidrug-resistant Gram-negative bacilli in the pediatric age. In a recent Italian study conducted as a part of the

Antibiotic Resistance and Prescribing in European Children (ARPEC) Project, and analyzed more than 1000 episodes of bacteremia, 26% of these episodes were caused by Gram-negative microorganisms, 39% of which were multidrug-resistant.[20] We do not have an explanation for the relative decrease in Fosfomycin susceptibility in ESBL *E. coli* in infants one year or less of age. A possible explanation is the transmission of these resistant strains from the mothers to their infants which needs to be proved in future research, as Fosfomycin is not used in our facility to treat young children due to lack of availability of liquid form.

At the same time, we observed a marked increase in ESBL and CRE *E. coli* isolates among hospital-acquired (51% and 6% respectively) compared to the community-acquired (37.6% and 0.5% respectively) UTIs observed in 2019. A similar finding from Kuwait was observed by Al Benwan et al who observed that EBSL was about 12% in community-acquired and 26% in hospital-acquired urinary tract infection.[21] Castillo-Tokumori et al. found that a history of previous hospitalization, surgery, and antibiotics are risk factors to have ESBL *E. coli* in community-acquired UTI and should be considered when treating this type of infection.[22] At the same time, Lee et al. found that a history of prior UTI within 1 year and underlying cerebrovascular disease are independent risk factors for the acquisition of ESBL-producing *E. coli*.[23] The percentage of EBSL *E. coli* increased from 37% in 2018 to 39% in 2019, and the susceptibility to Fosfomycin decreased from 99% in 2018 to 96% in 2019. This emphasizes the need to follow a strict antimicrobial stewardship guideline. Further studies are needed to evaluate the mechanism of resistance of *E. coli* as well as the other microorganisms to Fosfomycin.

The current study has some limitations. It was a retrospective study, and we did not do genetic testing for ESBL strain detected. We also did not correlate the clinical outcome with the laboratory resistance pattern.

Conclusion

ESBL *E. coli* is an important cause of UTI in Bahrain. Fosfomycin is a very effective oral antimicrobial. It still retains a high efficacy against ESBL *E. coli*, which helps to decrease the need for parenteral therapy, and consequently hospitalization. Judicious use of this promising antimicrobial is needed to avoid increasing the rate of microbial resistance to it.

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Statement of Ethics: The investigation was carried out in accordance with the latest version of the Declaration of Helsinki and was approved by the Research and Ethics Committee at the Ministry of Health, Kingdom of Bahrain. No consent was collected as the study is an observational one.

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Author Contributions: S.A., N S. and MA. designed the study. N.S. did the laboratory part of the study. S.A. collected the data. M.A. analyzed the data and wrote the manuscript. All 3 authors reviewed the manuscript and accepted the manuscript in its current status.

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