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ORIGINAL ARTICLE

Prevalence of Resistant Uropathogenic *Escherichia coli* in Bahrain: A Community Based Study

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Abstract

Background and objectives: Urinary tract infections (UTIs) are amongst the most common infections described in outpatients setting. This study was conducted to study the uropathogenic *Escherichia coli* isolated from patients with clinical diagnosis of community onset UTI. Such studies are crucial to assess the local antimicrobial resistance rates for the common uropathogens in our community and accordingly to suggest the best empirical therapy of UTI relying on the predictability of the agents causing UTI and knowledge of their antimicrobial susceptibility patterns.

Materials and Methods: Total of 829 consecutive non duplicate urine specimens with positive growth of significant *E.coli* collected from patients presenting to the primary health centers in the Kingdom of Bahrain with clinical suspicion of UTI during the year 2017 were included. Urine samples were processed in the Microbiology laboratory. Bacterial isolates were identified using standard conventional methods and antimicrobial susceptibility testing was performed using disk diffusion technique following Kirby-Bauer method.

Results: There was relatively high rate of resistance to commonly prescribed oral agents for UTI such as cotrimoxazole (42.7%), amoxicillin-clavulanic acid (34.6%), cefuroxime (32.21%), and norfloxacin (23.6%), which are the available first line options for treating UTI in primary health centers, but most isolates retains their susceptibility to nitrofurantoin (resistance of 5.19%). MDR phenotype (defined as exhibiting resistance to at least one agent in ≥3 antimicrobial classes) was observed among 34.8% of the isolates, ESBL production was confirmed among 27.39% of tested E. coli isolates.

Conclusion: Resistant strains of *E. coli* are prevalent in the community acquired UTI, nitrofurantoin is the only drug that showed an excellent sensitivity pattern and should be the preferred drug for empirical therapy of uncomplicated lower UTI as an outpatient.

Keywords: *Escherichia coli*, fever, outpatients, antimicrobial resistance, urinary tract infection.

Introduction

Urinary tract infections (UTIs) are among the most commonly encountered community acquired infections that mandate empirical antimicrobial therapy. This has contributed to the worldwide increase of antibacterial resistance within Enterobacteriaceae, specifically the main uropathogen *Escherichia coli*. Such spread of antibiotic resistant uropathogens have limited the use of most of the oral front-line antibiotics as empirical therapeutic options for community onset uncomplicated UTI.[1-3]

The rate of multidrug resistance among uropathogenic *E.coli* (UPEC) isolates shows wide variabilities across different geographic regions[4] and is of particular concern in developing countries where the capacity for regular resistance surveillance is limited and over-the-counter drug purchase (including antibiotics) is rampant in the community.[5-6] Extended-spectrum βeta-lactamases (ESBLs) are enzymes capable of hydrolyzing penicillins, broad-spectrum cephalosporins and monobactams, and are usually produced by Gram-negative bacteria, commonly uropathogenic Enterobacteriaceae such as *E. coli* and *Klebsiella*. It is more prevalent in the hospital setting, but nowadays a lot of community acquired cases are reported worldwide.[7] Its prevalence rates vary from country to country, with higher rates reported from Asia, Latin America, and the Middle East.[8]

E. coli is the main causative agent of UTIs, causing about 90% of community-acquired UTIs,[9-10] accordingly; defining its local community resistance prevalence is very important for consideration of the empiric antimicrobial therapy of acute uncomplicated UTI.

Infectious Diseases Society of America (IDSA)[11] has recommended that each country periodically determine its local resistance patterns among common uropathogens such as *E.coli*, and accordingly craft national antimicrobial regimens for empirical treatment of UTIs.

In the Kingdom of Bahrain, there were no previous studies illustrating the resistance profiles of UPEC in our community, while there have been many previous studies from neighboring countries such as Saudi Arabia illustrated the resistance profiles of UPEC,[12-13] an example is Al Kersh *et al*. who reported 77% of community onset UTI caused by UPEC with ESBL production rate of 44%.[14]

Such increased prevalence of resistant strains of UPEC worldwide including our region should guide us to define our local resistance pattern. This study aimed to identify the current local epidemiology of resistant UPEC with a special focus on ESBL positive strains, as well as new threats such as multi-drug-resistant (MDR) isolates causing community onset UTI in Bahrain and accordingly, to suggest the best oral empirical therapeutic option for community acquired uncomplicated UTI.

Materials and Methods

Ethical clearance was obtained from the Secondary Care Research committee of Salmaniya Medical Complex, Ministry of Health.

This was a retrospective observational study conducted on all clinical *E. coli* urine isolates in microbiology department in Salmaniya Medical Center in the Kingdom of Bahrain during the year 2017.

Non duplicate *E.coli* urine isolates were obtained by mid-stream clean catch urine specimens collected from patients attending governmental primary health center and suspected clinically to have UTI based on symptoms, with a requisition slip that included the date of specimen collected, patient's ID number, age and sex.

All urine specimens were plated on Cystine Lactose Electrolyte Deficient (CLED) agar using a calibrated loop for quantification. Isolated colonies were utilized for identification and susceptibility testing. The criterion used for defining significant bacteriuria was the presence of $>10^5$ colony forming units (CFU) per milliliter of urine.[15]

In vitro activity of antimicrobials was determined by Kirby Bauer disc diffusion method.[16] All interpretation of resistance and susceptibility were according to the standard guidelines published in Clinical Laboratory Standard Institute.[17] A panel of eight commercially available antibiotics was used; amoxicillin-clavulanate, cefuroxime, ceftriaxone, gentamicin, nitrofurantoin, trimethoprim-

sulfamethoxazole (cotrimoxazole), norfloxacin, and meropenem (Oxoid, Ltd.). For Carbapenem Resistant Enterobacteriasae (CRE) isolates; two additional antibiotics were tested: colistin and tigecycline. Information on these antibiotics and their concentrations are shown in Table 1.

MDR Phenotype

Percentage of clinical *E. coli* isolates exhibiting MDR phenotype was calculated, MDR is defined as exhibiting resistance to at least one agent in three or more antimicrobial class.[18]

Phenotypic Detection of ESBL Production

ESBL production was assessed using the CLSI recommendations for ESBL screening and phenotypic confirmation tests. For the initial ESBL screening, UPEC isolates showing an inhibition zone size of ≤22 mm with cefotriaxone (30 µg) were identified as potential ESBL producers. The double-disc synergy test (DDST) was carried out for the phenotypic confirmation of ESBL production. For this test, amoxicillin-clavulanic acid (20/10 mcg), ceftriaxone (30 mcg), ceftazidime (30 mcg) and cefotaxime (30 mcg) were used. The amoxicillin-clavulanic acid disc was placed in the center and the other discs were placed at 1.5 cm. Development of the zone of inhibition towards the clavulanate disc at 37°C after 24 hours incubation was indicative of a potential ESBL positive organism.

Results

Demographic Characteristics of Study Population

A total of 829 urine samples with growth of *E. coli* isolates was collected from outpatients attending primary health centers during this study period. Among these samples, 755 (91%) belonged to female patients while 74 (8.93 %) belonged to male patients. With regard to the patient age distribution, a total of 562 (67.79 %) samples were collected from adults aged 14-64 years, 157 (18.94%) samples belonged to elderly population >65 years, and 131 (15.78 %) were obtained from children less than 14 years old.

Antimicrobial Susceptibility Profiles and ESBL Prevalence

Antimicrobial susceptibility testing results are shown in Table 2.

Out of the 829 *E. coli* isolates; there was relatively high rate of resistance to commonly prescribed oral agents for UTI such as cotrimoxazole (42.7%), amoxicillin-clavulanate (34.6%), cefuroxime (46.08%) and norfloxacin (23.6%). Most isolates retains susceptibility to nitrofurantoin (resistance of 5.19%).

They also showed high rate of resistance to parenteral cephalosporin (27.9% resistance to ceftriaxone) but retained good susceptibility to other parenteral antibiotics such as gentamicin (10.13 % resistance) with excellent susceptibility to meropenem (0.1% resistance). Regarding ESBL production, 227 isolates (27.39%) of all *E. coli* isolates were confirmed to be ESBL producers, while 602 (72.61%) isolates were non-ESBL producers. The susceptibility profiles of ESBL-producing *E. coli* isolates revealed that all 227 isolates were also resistant to amoxicillin-clavulanic acid, 64.7% were resistant to trimethoprim-sulfamethoxazole,

Table 1: Details on antibiotics used in this study

Antibiotic class	Antibiotic name	Concentration (µg/disc)
β-lactam/β-lactamase inhibitors combination	Amoxicillin-clavulanate (AMC)	20/10 µg
Aminoglycosides	Gentamicin (GN)	10 µg
Second generation cephalosporins	Cefuroxime (CXM)	30 µg
Third generation cephalosporins	Ceftriaxone (CRO)	30 µg
Folate pathway inhibitors	Trimethoprim-sulfamethoxazole (SXT)	1.25/23.75 µg
Carbapenems	Meropenem (MEM)	10 µg
Fluoroquinolones	Norfloxacin (NOR)	10 µg
Nitrofurans	Nitrofurantoin (F)	300 µg

Table 2: Antibiotic resistance rates of *E. coli* isolates tested in this study

Antibiotics	Percentage of resistant isolates		
	ESBL producing Total =227 Number (%)	Non ESBL producing Total =602 Number (%)	All Isolates Total =829 Number(%)
Amoxicillin-clavulanate	227(100%)	60(9.97%)	287(34.62%)
Cefuroxime	227(100%)	155(25.75%)	382(46.08%)
Ceftriaxone	227(100%)	5(0.83%)	232(27.99%)
Gentamicin	57(25.11%)	27(4.49%)	84(10.13%)
Cotrimoxazole	147(64.76%)	207(34.39%)	354(42.70%)
Norfloxacin	116(51.10)	80(13.29%)	196(23.64%)
Nitrofurantoin	16(7.05%)	27(4.49%)	43(5.19%)
Meropenem	1(0.4 %)	0(0 %)	1 (0.1%)

ESBL prevalence among different sex & age groups

52.42% to norfloxacin and 25.55% to gentamicin. Most ESBL-producing *E. coli* retained sensitivity to nitrofurantoin (resistance of 7.05%) and all isolates except one remained sensitive to meropenem (single CRE isolate).

Among the non-ESBL-producing *E. coli* isolates, the antimicrobial resistance levels for all classes of antibiotics were lower than that of ESBL-producing isolates as shown in the Table 1.

Among different age groups, ESBL production of isolates was found to increase with the age of the patient, as shown in Figure 1.

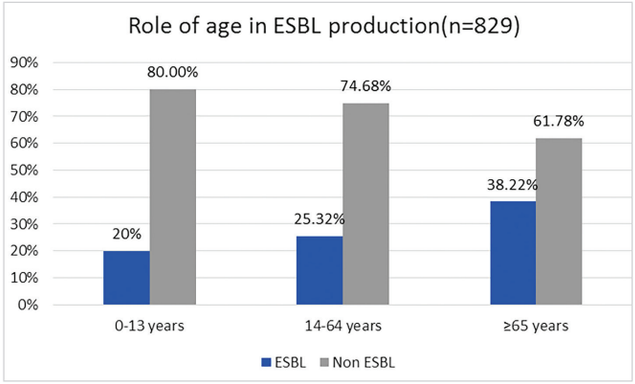
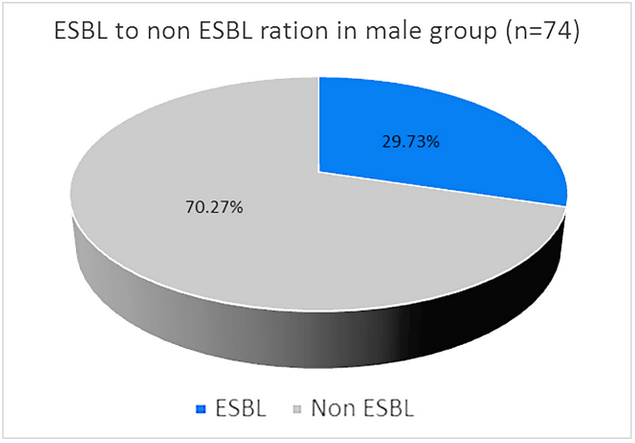


Figure 1: Production of ESBL in different age groups

There was no difference in the rate of ESBL production between either gender, as shown in **Figure** 2.



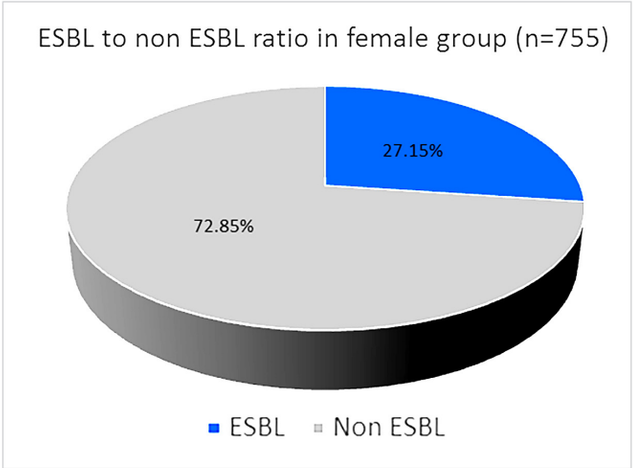


Figure 2: Production of ESBL among males & females

Multidrug Resistance (MDR) Phenotype of E. coli Isolates

Our results showed a high proportion of MDR phenotypes (defined as exhibiting resistance to at

least one agent of ≥3 antimicrobial classes) among the tested *E. coli* isolates (289/829, 34.8%).

Out of these 289 MDR isolates, 37 (12.8%) were resistant only to three out of eight antibiotic groups tested, 63 (21.79%) were extending their resistance to four antibiotic groups, and 73 (25.26%) were resistant to five antibiotic groups. The remaining results showed 78 (26.98%) and 37 (12.8%) illustrated resistance to six and seven antibiotic groups, respectively.

Single isolate (0.34%) showed resistance to all eight tested groups of antibiotics (CRE isolate), which was further tested for colistin and tigecycline which showed susceptibility to both (Figure 3).

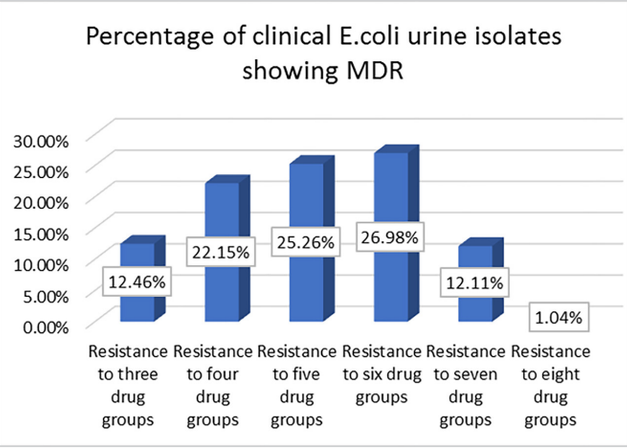


Figure 3: Percentage of clinical isolates with MDR

Discussion

Community onset UTI is one of the leading causes of morbidity among outpatients. Most infective organisms are primarily derived from the fecal flora, such as UPEC, which represent the primary pathogen in most cases of UTI. The emergence of drug-resistant *E. coli* is becoming a global concern, and infections caused by these organisms represent a major challenge to clinicians when treating community onset UTI.[19]

Among the 829 urine samples collected in this study, there was a high predominance of females (91%), consistent with several previous studies[20-21] that showed higher incidence of UTI among women, and which can be attributed to certain anatomical features such as a short urethra that allows easier access of bacteria from the perianal region.[22]

The rate of ESBL production among community acquired *E. coli* isolated in our study was 27.4%, like many other regional studies in the gulf countries. The Kingdom of Saudi Arabia reported a rate of 27% -33% of ESBL production among their community onset UPEC,[12-13] while in Qatar, Elshafie *et al*.[23] reported the occurrence of ESBL-resistant isolates among 34% of *E coli.*

European data have reported percentage of ESBL production that is almost comparable to that of our GCC rate, of 25-30%[24] on average, but with wide variability among different European countries, ranging from 3.3% (Iceland) to 40.4% (Bulgaria). Such variability of ESBL production rate among UPEC was mostly explained by difference in the practice of antimicrobial use among human as well as animal sectors.[25]

In agreement with other previously published studies, ESBL production was predominant among females and aged population,[25] and most ESBL isolates showed co-resistance to other tested antimicrobial agents such as aminoglycosides, amoxicillin-clavulanic acid, trimethoprim-sulphamethoxazole and fluoroquinolones.[26-27]

Our rate of MDR (defined as resistant to three or more classes of tested antibiotics) among isolated UPEC was 34.8%, comparable to other GCC countries[28-30] who have previously reported a similar range, but relatively high in comparison to developed countries such as USA (7%) and European countries (17%), yet much lower than the MDR rate of UPEC in many developing Asian countries such as India (90%), Pakistan (80%) and Iran (50%)[31] and African countries who have reported high prevalence of MDR-UPEC as well, such as Egypt, as in the study carried out by Salem et al. in 2010[32] who reported 87% MDR rate among UPEC. A high incidence of MDR *E. coli* was also observed in Sudan and Ethiopia with a prevalence rate of 92.2% and 74.6% respectively.[33-34] Such high trends of MDR among UPEC in developing countries is most likely related to the lack of policies for restricting and auditing antimicrobial prescriptions and the absence of guidelines for the use of antimicrobials in the animal industries as well.

High resistance pattern of our UPEC isolates to commonly available first line options for treating

UTI in primary health centers such as amoxicillin-clavulanate, cotrimoxazole, cefuroxime and fluoroquinolones is considered an important worrisome finding and should preclude the usage of cotrimoxazole as an empiric therapy for community onset UTI, given its high rate of resistance among our isolates (>20%) in reference to Infectious Diseases Society of America guidelines[11] which defined a threshold of 20% as the resistance prevalence at which cotrimoxazole is no longer recommended for empirical treatment of acute cystitis.

Though data are still insufficient to make a clear recommendation for other cystitis antimicrobials as to what resistance prevalence should be used to preclude their use for empirical treatment of acute cystitis[11]; we should be careful in prescribing other available oral antibiotics in health centers such as cefuroxime, amoxicillin-clavulanate and floroquinolones; given their high resistance levels (46.1%, 34.6% and 23.6% respectively).

Based on the results obtained from this study, the only two antibiotics that retain high level of sensitivity among our community onset UPEC are nitrofurantoin and meropenem. Meropenem cannot be recommended as first line agent for community acquired UTI among stable patients as it requires hospitalization for parenteral administration and its use demands extra caution considering the risk of spread of carbapenemases. Hence, use of carbapenems has to be restricted to complicated UTIs only.

Nitrofurantoin should be considered as the drug of choice to treat community acquired UTI among our population, given that most *E. coli* isolates (95%) tested in this study retained sensitivity to nitrofurantoin, in agreement with many international studies[35-36] with similar findings of low resistance rate of UPEC to nitrofurantoin, based on which updated international guidelines for treating UTI have repositioned nitrofurantoin as first-line therapy for community-acquired lower UTI.[12]

Another rational alternative is to go back to using older antibiotics, such as fosfomycin, that have been theoretically shown to retain excellent activity against ESBL-producing *E. coli*. However, studies to establish local antibiograms for fosfomycin would be required before recommending it as an empirical choice of treatment for community onset UTI in our community.

The main limitation in our study was that it was performed on urine samples collected from patients attending primary health centers only and it did not include patients attending private clinics or outpatient setting in other government hospitals. Therefore, the study may not necessarily reflect the antimicrobial resistance trends and epidemiological patterns of the whole Bahraini community. Another important limitation of our study was the lack of clinical characteristics of patients, such as the presence of comorbidities, history of prior attacks of UTI and previous usage of antibiotics, all of which definitely have an important impact on the risk of drug resistance among uropathogenic *E. coli*.

Future studies with more clinical details of patients including their risk factors of antimicrobial resistance would be of great value. Also illustrating the results of fosfomycin susceptibility as another potential treatment option for community acquired UTI will be helpful, specially now that it has been recently introduced in our antibiotics formulary and included in the antibiotics susceptibility testing as well. Of course, widening the study population to include other non-governmental sectors is crucial before developing a local national guideline for empirical treatment of UTI.

Conclusion

The increased prevalence of resistant strains of UPEC in our community should guide us to reevaluate our local guidelines in treating community onset UTI in outpatient settings such as health centers. The use of currently available options in the health centers such as cefuroxime, quinolones, cotrimoxazole and amoxycillin-clavulanate for treatment of UTI must be reconsidered due to reported high level of resistance (>20%). Nitrofurantoin should be repositioned as the preferred option for empirical therapy of uncomplicated community onset UTI in the outpatient setting, given its retained sensitivity among the UPEC isolates in our community and considering its low risk of collateral damage.

Conflict of Interest

The authors of this study have no conflict of interest to declare.

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