Prevalence of Antimicrobial Resistance in Uropathogens among Patients Visiting Primary Health Centers: Implications for Empiric Therapy

Ebrahim Al Romaihi, MBBS, MRCP* Safaa Al Khawaja, MBBS, ABIM**
Nermin Saeed, MBChB, KSF, (D)ABMM*** Abdulrahman Mohamed Barakat, MBBCh****
Nashwa Fawzy Abd El Moez Azam***** Shereen Haji, MBBS, ABFP******

Background: Urinary tract infection (UTI) is one of the most frequent bacterial infections in the community; in the Kingdom of Bahrain, the currently recommended empirical antimicrobial regimen is based on international guidelines but not supported by local data.

Objective: To evaluate the local antibiotics profile of most common urinary pathogens among patients visiting primary health centers.

Design: A Retrospective Analytical Study.

Setting: Primary Health Center, Salmaniya Medical Complex.

Method: All outpatients seeking care in health centers for which the attending physician clinically suspected UTI and asked for the provision of urine culture from June 2016 to June 2017 were included. Mid-stream clean catch urine specimens were obtained from patients suspected clinically to be having UTI based on symptoms.

Mid-stream urine specimens were plated on Cystine-Lactose-Electrolyte-Deficient (CLED) agar plate using calibrated loops for the quantitative method to provide isolated colonies for identification and susceptibility testing.

Result: Total of 1,357 urine samples with significant bacterial growth were obtained; 1,230 (90.6%) were females and 943 (69.5%) were in the age group of 19-64 years. The four most common uropathogens that contributed to 90% of the cases were as follows: 829 (61.1%) Escherichia coli, 222 (16.4%) Klebsiella pneumonia, 123 (9.1%) Streptococcus agalactiae and 62 (4.6%) Enterococcus species.

Eight hundred twenty-nine (61.1%) specimens were E. coli; 731 (53.9%) demonstrated low sensitivity levels to cephalothin, and 777 (57.3%) to cotrimoxazole, 887 (65.38%) moderate sensitivity to amoxicillin-clavulanate, and 1,035 (76.3%) to norfloxacin, but 1,284 (94.6%) retained very high sensitivity to nitrofurantoin.

Conclusion: Based on this study, we recommend nitrofurantoin as the first choice of empiric antibiotics therapy for uncomplicated UTI in outpatient setting; despite the good sensitivity profile of fluoroquinolones, we recommend using it only as an alternative or second line. Other suggested therapy which might be proposed for use as possible alternative option is fosfomycin, but after confirming its local sensitivity profile.

Bahrain Med Bull 2018; 40(4): 207 - 211

* Consultant Internist
Head of General Medicine Unit
Department of Internal Medicine
Salmaniya Medical Center
Ministry of Health, Kingdom of Bahrain
** Infectious Diseases Consultant and Head of Infection Disease Unit
Salmaniya Medical Center
Chairperson of Infection Control
Ministry of Health, Kingdom of Bahrain
*** Consultant Microbiologist and Head
Microbiology Department
Salmaniya Medical Center
Ministry of Health, Bahrain
**** Senior Resident
Department of Internal Medicine
King Hamad University Hospital, Bahrain
***** Lecturer of Microbiology, High Institute of Public Health,
Alexandria University, Egypt
****** Consultant Family Physician
Ministry of Health, PO Box 12, Bahrain
E-mail: Eromaihi@health.gov.bh

Urinary tract infection (UTI) is one of the most frequent bacterial infections in the community; it has an estimated worldwide incidence rate of 17.5 per 1000 person[1]. It is the most common bacterial infection in women, and account for significant morbidity and associated health costs[2].

In Bahrain, according to health statistics, there is an average of 39,514 annual visits to health centers with a clinical diagnosis of UTI.

The antimicrobial resistance is growing alarmingly worldwide, in particular among gram-negative organisms such as E. coli and Klebsiella, which are considered as the most common uropathogens[3-5].

In many developing countries including the Middle East where unregulated dispensing of antibiotics is a common practice, the rate of resistance among uropathogens is frequently worrying. This emphasizes the value of formulating local antibiotic policy for each particular geographical area based on research data[6-10].

In the Ministry of Health, Kingdom of Bahrain, the current recommended empirical antimicrobial regimen for treating acute uncomplicated urinary tract infection is Cephalexin, Co-amoxiclavulenic, or Nitrofurantoin. Such initial empirical treatment was suggested based on international guidelines, but not supported by local epidemiological statistical research data due to lack of previous research data or published study of community-acquired UTI.

The aim of this study is to evaluate the antibiotics profile of the most common urinary pathogens among patients visiting primary health centers to validate the appropriate empirical antibiotics for uncomplicated community-acquired UTI based on local data.

METHOD

All outpatients seeking care in health centers for which the attending physician clinically suspected UTI and asked for the provision of urine culture from June 2016 to June 2017 were included.

Mid-stream clean catch urine specimens were obtained from patients suspected clinically to be having UTI based on symptoms, with requisition slip that includes the date of specimen collected, patient's ID number, age and sex.

Mid-stream urine specimens were plated on Cystine-Lactose-Electrolyte-Deficient (CLED) agar plate using calibrated loops for the quantitative method to provide isolated colonies for identification and susceptibility testing. Plates were incubated aerobically at 37°C for 24-48 hours. The used criterion for defining significant bacteriuria was the presence of $>10^5$ colony-forming unit (CFU) per milliliter of urine. In vitro activities of antimicrobials were determined by Kirby Bauer disc diffusion method; all interpretation of resistance and susceptibility were in reference to the standard guidelines published in Clinical Laboratory Standard Institute (CLSI)[11]. Antibiotics tested included the following: amoxicillin-clavulanate, cephalothin, cefuroxime, ciprofloxacin, ceftriaxone, cefepime, gentamicin, amikacin, nitrofurantoin, cotrimoxazole, imipenem, meropenem, penicillin G, ampicillin, ceftazidime, piperacillin/tazobactam, and vancomycin.

Screening for production of Extended-Spectrum β-lactamases (ESBLs) by isolates of E. coli, Klebsiella spp., and Proteus mirabilis was performed as recommended by CLSI[11].

Potential vancomycin resistance in Enterococcus faecium and Enterococcus faecalis (VRE) isolates was confirmed by automated Phoenix Identification System (BD Diagnostics, Oxford, United Kingdom), while the potential methicillin resistance in staphylococcal isolates was conducted by using the cefoxitin disk test described by the CLSI[11].

RESULT

A total of 1,357 urine samples with significant bacterial growth were obtained from outpatients attending primary health centers with a clinical diagnosis of UTI.

One thousand two hundred thirty (90.6%) were females and 943 (69.5%) were in the age group of 19-64 years old as shown in figure 1.

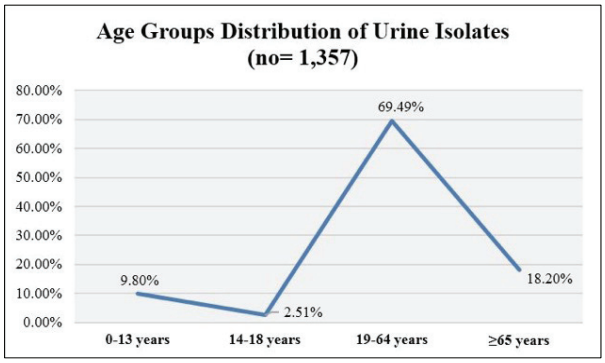

Figure 1: Age Distribution of UTI in Primary Health Centers (1,357)

One thousand one hundred twenty-nine (83.2%) isolates were Gram-negative, 228 (16.8%) were Gram-positive while 9 (0.66%) were identified as Candida species.

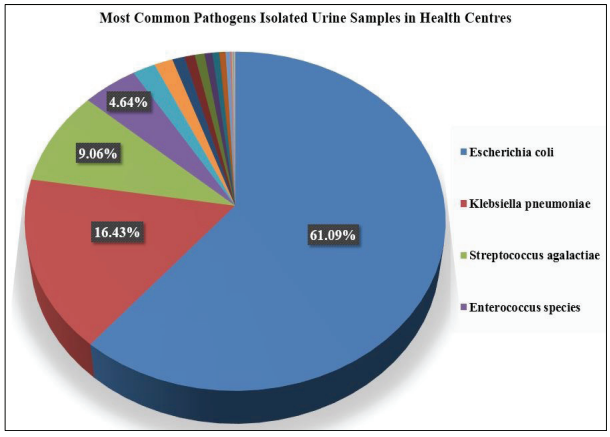

Figure 2: Most Common Uropathogens

The four most common uropathogens that contributed to 90% of the cases were as follows: 829 (61.1%) Escherichia coli, 222 (16.4%) Klebsiella pneumonia, 123 (9.1%) Streptococcus agalactiae and 62 (4.6%) Enterococcus species.

Table 1: Most Common Pathogens Isolated from Urine in the Health Centers

Organism	Number	Percentage
Escherichia coli	829	61.09%
Klebsiella pneumoniae	223	16.43%
Streptococcus agalactiae	123	9.06%
Enterococcus species	63	4.64%
Staphylococcus saprophyticus	26	1.92%
Citrobacter koseri	21	1.55%
Enterobacter species	14	1.03%
Pseudomonas aeruginosa	12	0.88%
Staph aureus	11	0.81%
Candida species	9	0.66%
Proteus mirabilis	8	0.59%
Acinetobacter baumannii	7	0.52%
Staph epi	5	0.37%
Proteus vulgaris	2	0.15%
Others	4	0.28%
Total	**1,357**	**100%**

Data were stratified further by sex and age group to define the 4 common uropathogens among each category.

In females, the most common isolated uropathogens were E. coli and Klebsiella in all age groups. Enterococcus spp. was the third most common isolate in the pediatric and geriatric age groups, while Streptococcus agalactiae was the third common uropathogens among 14-64 age group.

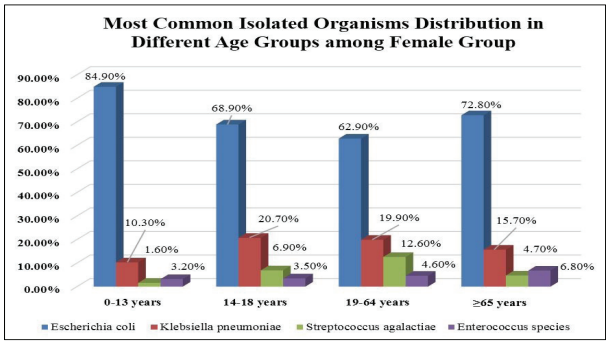

Figure 3: Most Common Uropathogens among Female Patients

Among males, 123 (9.06%) UTI cases were found. There were 4 pediatric cases (<14 years old); 3 (0.22%) of them were E.coli and the fourth was streptococcal agalctiae while among adolescent males (14-18 years) there were only 3 cases (1 E.coli, 1 Klebsiella and 1 Proteus Vulgaris). In the adult male group, the species distribution was similar to that in the adult female group with predominance of E.coli, followed by Klebsiella, S. agalactiae and Enterococcus, see figure 4.

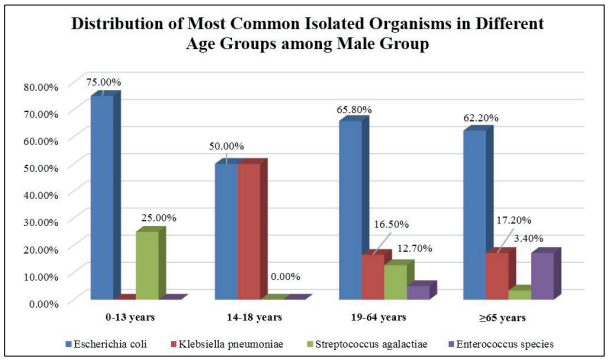

Figure 4: Most Common Uropathogens among Male Patients

Table 3: In vitro Activities of Oral Antimicrobial Agents against the Four Most Common Uropathogens Isolated from Outpatient Setting

Top 4 Uropathogen	Cephalothin Susceptibility Number (%)	Augmentin Susceptibility Number (%)	Cotrimoxazole Susceptibility Number (%)	Norfloxacin Susceptibility Number (%)	Nitrofurantoin Susceptibility Number (%)
Escherichia coli (no=829)	447 (53.92%)	542 (65.38%)	475 (57.30%)	633 (76.36%)	786 (94.81%)
Klebsiella pneumoniae (no=223)	153 (68.61%)	158 (70.85%)	146 (65.47%)	211 (94.62%)	65 (29.15%)
Streptococcus agalactiae (no=123)	123(100%)	123(100%)	123(100%)	123(100%)	123(100%)
Enterococcus species (no=63)	Not done	Ampicillin 62 (98.41%)	Not done	41 (65.08%)	61 (96.83%)

Among elderly male (> 64 years), E.coli, followed by Klebsiella were predominant, but again similar to elderly females; Enterococcus was the third common uropathogen.

E. coli demonstrated low sensitivity to Cephalothin (53.9%), and Cotrimoxazole (57.3%), with moderate sensitivity pattern to Amoxicillin-clavulanate (65.38%) and Norfloxacin (76.3%), but retained very high sensitivity to Nitrofurantoin (94.6%).

On the other hand, Klebsiella spp. showed very low sensitivity to Nitrofurantoin (29.15%) but retained very high sensitivity to Norfloxacin (94.8%).

Enterococcus and Streptococcus showed excellent in vitro sensitivity to Nitrofurantoin (96.3% and 100%, respectively).

ESBL rate was 27.39%, 16.59% and 12.50% among E.coli, Klebsiella and Proteus mirabilis, respectively. Three isolates were found to be Carbapenem-Resistant Enterobacteriaceae (CRE), 1 was E.coli (0.12% of total E.coli) and 2 were Klebsiella spp. (0.89% of total Klebsiella isolates). Multi-Drug Resistant (MDR) rate among Gram Negative Rods (GNR) was 12.5% among Acinetobacter spp. isolates and 25% among Pseudomonas aeruginosa isolates. The rate of methicillin resistance Staphylococcus aureus (MRSA) was 9.09%.

DISCUSSION

Uropathogens have different resistance patterns in different geographic locations in the world; accordingly, empiric therapy should be tailored in each part of the world based on their local research statistical data[12-15].

E. coli was the most common uropathogen (61.1%) isolated from the cultured urine samples; this is similar to the findings from many other studies in other neighboring Gulf countries, such as Kuwait, where E. coli was the predominant pathogen (54.9%), Oman (50%, 76%) and from other parts of the world, such as India (59%, 68%) and South Africa (75%)[16-21].

In our study, E. coli demonstrated low sensitivity to co-trimoxazole (57.3%), which makes this antibiotic not an appropriate option as first-line therapy for UTI in reference to Infectious Diseases Society of America (IDSA) guidelines where co-trimoxazole is not indicated as first-line if its resistance level exceeds 20% among E. coli[22].

E. coli isolates displayed low sensitivity to the first-generation cephalosporin represented by cephalothin (53.9%) with moderate sensitivity to amoxicillin-clavulanate (65.38%) and norfloxacin (76.3%), but retained high sensitivity to nitrofurantoin (94.8%), which makes nitrofurantoin as the first-line outpatient empiric therapy for uncomplicated UTI.

Other important uropathogens isolated from our study such as Enterococcus spp. and Streptococcus agalactiae showed in vitro high sensitivity to nitrofurantoin (96.3% and 100% respectively).

The only concern for nitrofurantoin sensitivity was Klebsiella spp. isolates, which was the second most common uropathogens isolated in our study (16.4% of UTI cases) as it did show very low sensitivity to nitrofurantoin (29.15%) which is much lower sensitivity rate in comparison to figures obtained from other countries which might warrant further research studies supported by molecular testing[23].

We recommend using fluoroquinolones only as an alternative or second line antimicrobials agent for acute uncomplicated UTI in individuals who have intolerance or contraindication to first-line therapy because of its collateral damage, cost consideration and it should be reserved for important uses[24-26].

According to our study, we recommend an appropriate empiric therapy for uncomplicated UTI based on our local data, the suggested first line therapy is nitrofurantoin considering its high sensitivity rate among uropathogens. Our recommendation is supported by the updated international guidelines that demonstrate the clinical efficacy of nitrofurantoin in addition to its reasonable cost and low propensity for collateral damage[22,27-29]. If nitrofurantoin is contraindicated (G6PD deficiency or severe renal impairment), amoxicillin-clavulanate or ciprofloxacin could be considered.

Fosfomycin could be considered as an alternative therapy considering its theoretical spectrum of activity and minimal propensity for side-effects; however, there is a need to have local microbiological data of its sensitivity pattern among the most common uropathogens isolated from our population.

The main limitations of this study are the absence of detailed clinical and outcome data; additionally, the presented data are only inclusive of patients attending governmental primary health centers which might not represent the whole Bahraini community.

CONCLUSION

The recommended empiric antimicrobial therapy for UTI in each geographical location should be tailored according to the updated local community resistance prevalence and to be individualized based on patient characteristics (comorbidity, risk and therapy failure, presence of drug allergy or other contraindication); in addition, to other important factors such as drug availability and cost.

Based on the presented data of uropathogens and its sensitivity pattern, we recommend nitrofurantoin 100 mg twice a day for 5-7 days as the first empiric antibiotics therapy for uncomplicated UTI in an outpatient setting, other alternative options would be amoxicillin-clavulanate or ciprofloxacin. Fosfomycin can be considered as an alternative therapy but we need to obtain its local susceptibility pattern among our population before considering it as an appropriate empiric therapy.

Author Contribution: All authors share equal effort contribution towards (1) substantial contributions to conception and design, acquisition, analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the manuscript version to be published. Yes.

Potential Conflicts of Interest: None.

Competing Interest: None.

Sponsorship: None.

Acceptance Date: 8 September 2018.

Ethical Approval: Approved by the Primary Health Center, Salmaniya Medical Complex, Bahrain.

REFERENCES

1. Laupland KB, Ross T, Pitout JD, et al. Community-Onset Urinary Tract Infections: A Population-Based Assessment. Infection 2007; 35(3):150-153.
2. Stamm WE, Norrby SR. Urinary Tract Infections: Disease Panorama and Challenges. J Infect Dis 2001; 183(Suppl. 1): S1–S4.
3. Pitout JD, Laupland KB. Extended-Spectrum Beta-Lactamase-Producing Enterobacteriaceae: An Emerging Public-Health Concern. Lancet Infect Dis 2008; 8: 159–166.
4. Ben-Ami R, Rodriguez-Bano J, Arslan H, et al. A Multinational Survey of Risk Factors for Infection with Extended-Spectrum Beta-Lactamase-Producing Enterobacteriaceae in Non-hospitalized Patients. Clin

Infect Dis 2009; 49: 682–690.
5. Tandogdu Z, FM Wagenlehner. Global Epidemiology of Urinary Tract Infections. Curr Opin Infect Dis 2016; 29(1):73-9.
6. Pourakbari B, Ferdosian F, Mahmoudi S, et al. Increase Resistant Rates and ESBL Production between E. coli Isolates causing Urinary Tract Infection in Young Patients from Iran. Braz J Microbiol 2012; 43:766–769.
7. Al-Assil B, Mahfoud M, Hamzeh AR. Resistance Trends and Risk Factors of Extended-Spectrum Beta-Lactamases in Escherichia Coli Infections in Aleppo, Syria. Am J Infect Control 2013; 41, 597–600.
8. Dayan N, Dabbah H, Weissman I, et al. Urinary Tract Infections Caused by Community-Acquired Extended-Spectrum Beta-Lactamase-Producing and Nonproducing Bacteria: A Comparative Study. J Pediatr 2013; 163:1417–1421.
9. Araj GF, Avedissian AZ, Ayyash NS, et al. A Reflection on Bacterial Resistance to Antimicrobial Agents at a Major Tertiary Care Center in Lebanon Over a Decade. J. Med. Liban 2012; 60:125–135.
10. Dotis J, Printza N, Marneri A, et al. Urinary Tract Infections Caused by Extended-Spectrum Beta-Lactamase-Producing Bacteria in Children: A Matched Case-Control Study. Turk J Pediatr 2013; 55: 571–574.
11. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing: 26th Informational Supplement M100-S26. Wayne, PA: CLSI; 2016.
12. Kahlmeter G. An International Survey of the Antimicrobial Susceptibility of Pathogens from Uncomplicated Urinary Tract Infections. J Antimicrob Chemother, 2003; 51: 69-76.
13. Kahlmeter G. Prevalence and Antimicrobial Susceptibility of Pathogens in Uncomplicated Cystitis in Europe. Int J Antimicrob Agents 2003; 22(2): 49-52.
14. Naber KG, Schito G, Botto H, et al. Surveillance Study in Europe and Brazil on Clinical Aspects and Antimicrobial Resistance Epidemiology in Females with Cystitis (ARESC): Implications for Empiric Therapy. Eur Urol 2008; 54:1164-75.
15. Zhanel GG, Hisanaga TL, Laing NM, et al. Antibiotic Resistance in Escherichia Coli Outpatient Urinary Isolates: Final Results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA). Int J Antimicrob Agents 2006; :468-75.
16. Al Benwan K, Al Sweih N, Vincent O, et al. Etiology and Antibiotic Susceptibility Patterns of Community- and Hospital-Acquired Urinary Tract Infections in a General Hospital in Kuwait. Med Princ Pract 2010; 19:440–446.
17. Khalid M, Al Naimi MK, Saleem HGM, et al. Antibiotics Resistance Profile of Uropathogens Isolated from Al Buraimi Hospital, Sultanate of Oman. Global Journal Of Health Science 2018; 10(1):98.
18. Hassali MA, Alrawhi Y, Nouri A. Antibiotic Sensitivity Pattern in Urinary Tract Infections at a Secondary Care Hospital in Oman. Acta Scientific Medical Sciences 2018; 2(1): 2-6.
19. Tambekar DH, Dhanorkar DV, Gulhane SR, et al. Antibacterial Susceptibility of Some Urinary Tract Pathogens to Commonly Used Antibiotics. Afr J Biotechnol 2006; 5(17):1562–1565.
20. Kothari A, Sagar V. Antibiotic Resistance in Pathogens Causing Community-Acquired Urinary Tract Infections in India: A Multicenter Study. J Infect Dev Ctries 2008; 2(5):354–358.
21. Bosch FJ, van Vuuren C, Joubert G. Antimicrobial Resistance Patterns in Outpatient Urinary Tract Infections − The Constant Need to Revise Prescribing Habits. S Afr Med J 2011; 101(5):328–331.
22. Gupta K, Hooton TM, Naber KG, et al. International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clinical Infectious Diseases 2011; 52(5): e103–e120.
23. Batool S, Shah AA. Prevalence of the Multi-Drug Resistant Gram-Negative Bacilli in Urinary Tract Infection (UTI). Imperial Journal of Interdisciplinary Research (IJIR) 2016; 2(12): 1826-1831.
24. Nicolle L, Anderson PA, Conly J, et al. Uncomplicated Urinary Tract Infection in Women. Current Practice and the Effect of Antibiotic Resistance on Empiric Treatment. Can Fam Physician 2006; 52:612–618.
25. Hooton TM, Besser R, Foxman B, et al. Acute Uncomplicated Cystitis in an Era of Increasing Antibiotics Resistance: A Proposed Approach to Empirical Therapy. Clin Infect Dis 2004; 39:75–80.
26. Mckinnell JA, Stollenwerk NS, Jung CW, et al. Nitrofurantoin Compares Favorably to Recommended Agents as an Empirical Treatment of Uncomplicated Urinary Tract Infections in a Decision and Cost Analysis. Mayo Clin Proc 2011;86(6):480–488.
27. Christiaens TC, de Meyere M, Verschraegen G, et al. Randomised Controlled Trial of Nitrofurantoin Versus Placebo in the Treatment of Uncomplicated Urinary Tract Infection in Adult Women. R J Gen Pract 2002; 52: 729-34.
28. Gupta K, Hooton TM, Roberts PL, et al. Short-Course Nitrofurantoin for the Treatment of Acute Uncomplicated Cystitis in Women. Arch Intern Med 2007; 167: 2207-12.
29. Stein GE. Comparison of Single-Dose Fosfomycin and a 7-Day Course of Nitrofurantoin in Female Patients with Uncomplicated Urinary Tract Infection. Clin Ther 1999; 21: 1864-72.