Original Article

What Left for Us for Urinary Tract Infection Treatment? An Experience from the South of Iran

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Abstract

Background: The aim of the study is to define the prevalence and antimicrobial susceptibility pattern of bacteria from cases of urinary tract infections (UTIs). **Materials and Methods:** A retrospective analysis of urinary pathogens and their antimicrobial susceptibility was done on urine cultures at Shiraz University Laboratory from 2015 to 2017. Antimicrobial susceptibility tests have done using the disk-diffusion technique as per the standard of CSLI. **Results:** During 2 years of study, 3489 samples were culture positive. *Escherichia coli* was the dominant isolate (84%), followed by *Klebsiella* spp. (10.7%) and *Enterococci* spp. (2,2%). The overall resistance rates to trimethoprim-sulfamethoxazole, ceftriaxone, and ciprofloxacin were 56.1%, 47.2%, and 37%, respectively. The most frequently isolated bacteria were *E. coli*, which had resistance rates of 58.6%, 49.1% to TMP-STX, and cefixime, also sensitivity rates of 95.1% to nitrofurantoin (FM). **Conclusions:** In the study area, resistance rates to fluoroquinolones and cephalosporins were high. Because most isolates were sensitive to FM and aminoglycoside, they are suggested as appropriate antimicrobials for empirical treatment of UTIs before available urine culture results.

Keywords: *Antibiotic resistance, antibiotic therapy, urinary tract infection*

Introduction

Urinary tract infections (UTIs) are among the most important human bacterial infections that cause a high burden to the health-care system (approximately 1.6 billion dollars per year in the United States of America).[1]

When antibiotics use excessively, unsuitable emergency resistance pathogens are associated with them.[2]

It has been categorized in different methods; one is community-acquired and hospital-acquired and another is iatrogenic. Other categorizations are complicated and uncomplicated, upper UTIs (kidneys and ureters), and lower UTIs (bladder and urethra).[3]

Isberg *et al*. showed no difference existed in dues incidence within 30 days between men treated with narrow- or broad-spectrum antibiotics.[4]

For proper antibiotic therapy, there are important factors which we should consider as follows: patient acceptance, cost, and insurance supports; duration of treatment; drug side effects; and microorganisms cause infection and their antibiotic resistance.[3,5] Globally, many studies conducted to evaluate the pathogens cause UTI and antibiotic resistance among them because it leads us to empirical proper therapy as it minimizes complications and patient morbidity.[6-10]

Escherichia coli (75%–95% in different societies) and other *Enterobacteriaceae* such as *Klebsiella pneumonia* and *Proteus mirabilis* and some pathogens such as *Staphylococcus saprophyticus* are the most typical pathogens which cause UTIs in most studies.[7,11-13]

For empirical therapy, according to the latest Infectious Diseases Society of America (IDSA) guideline, the first-line treatment of cystitis is trimethoprim/sulfamethoxazole (STX), nitrofurantoin (FM), and fosfomycin. The second line of antibiotic therapy is considered quinolones such as ciprofloxacin, levofloxacin, and ofloxacin. Other alternative treatments are amoxicillin-clavulanate, cefdinir, cefaclor, cefpodoxime, and cefuroxime. Pyelonephritis ambulatory treatments

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are considered as fluoroquinolones, trimethoprim-STX, aminoglycoside, ceftriaxone, and aztreonam oral beta-lactam (with less efficacy).[11]

Till this time, studies revealed increasing resistance among antibiotics such as STX-trimethoprim that previously, in guidelines suggested as the first line of empirical therapy for both cystitis and pyelonephritis in outpatient settings, so only in community with a low level of resistance can be used as empirical therapy.[11,14] For example, in the study conducted in Spain and published in 2017, STX-trimethoprim has come to the second line of empirical therapy of cystitis.[14]

These findings emerge us to restudy UTI bacterial patterns and their resistance patterns in different countries and communities. Among these studies, some of them focused on community-acquired UTIs that are most UTIs to suggest proper empirical therapy and reveal the bacterial and resistance patterns in community-acquired UTI.

In Iran, many studies are performed but have not focused on the community-acquired ones alone. In Shiraz and Fars province, no study has been conducted to evaluate bacterial patterns and antibiotic resistance patterns of community-acquired UTI alone. The only research was about seasonal patterns and bacterial resistance of *E. coli* in three neighbor city Shiraz, Marvdasht and Saadat Shahr with about 300 samples.[15-22]

Hence, in this study, we have tried to find bacterial and antibiotic resistance patterns among community-acquired UTI of ambulatory patients referred to OPD diagnostic center with high referral population from southern Iran, Shahid Motahari Diagnostic Center in Shiraz, Fars, which means community-acquired UTI that includes upper UTIs (pyelonephritis) and lower UTIs (cystitis).

Materials and Methods

Study design

A retrospective analysis of urine culture results was performed at the primary Shiraz University of Medical sciences affiliated clinic (Motahari) during the 2 years, from March 2015 to March 2017. The age and sex of patients, the microorganism isolated, and the antimicrobial susceptibility profiles were collected from the records using a standard data collection form.

Culture and identification

A midstream urine sample had taken from all referral patients who suspicious of UTI. Samples were cultured before 2 h after obtaining, at 36°C for 18–24 h on MacConkey and Blood agars. When bacterial growth of a uropathogen happened, disk-diffusion tests were performed using the Kirby–Bauer method and the Clinical and Laboratory Standards Institute (CLSI) criteria.[23,24] A significant bacterial infection had defined as the growth of more than 10^5 colony-forming units/ml of a single species cultured from urine.[23] Samples with mixed results were excluded from the study.

Antimicrobial susceptibility tests

According to the standard operational procedures, antimicrobial susceptibility tests were performed with the disk-diffusion method, taken out from standard CLSI method, for checking the resistance pattern of uropathogen.[24]

Resistance rates to the following antibiotics were examined as follows: nalidixic acid (NA)(30 micg), trimethoprim/STX (25 micg), cephalexin (30 micg), cefixime (CFM) (5 micg), norfloxacin (NOR) (10 micg), ceftriaxone (CRO) (30 micg), cefotaxime (CTX) (30 micg), ciprofloxacin (CP) (5 micg), ceftizoxime (CT) (30 micg), gentamycin (GEN) (10 mg), imipenem (IMP) (10 micg), amikacin (AN) (30 micg), and FM (30 micg).

Nonsusceptibility to the third-generation cephalosporin, ceftriaxone, was considered an indicator of extended-spectrum beta-lactamase (ESBL) production.[24]

Statistical analysis

In this study, analysis of data was performed by IBM SPSS Statistics Version 22.0 (IBM Corp., Armonk, NY, USA) 21. A descriptive study of data such as bacterial patterns, bacterial resistance patterns, sex and age of patients, frequencies, and its percentage, age of patients performed by mean ± standard deviation (SD).

Pearson's Chi-squared test is used for comparing qualitative variables and analysis of variance test is used for average age expression in bacterial pattern and antibiotically resistance pattern. In all tests, the percentage error of 5% has considered.

Results

In total, we captured valid urine culture results for 3489 patients during 2 years of the study. The majority of the positive samples (89.3%) had collected from female patients. The age of the patients ranged from 1 year to 93 years, with a mean age of 39.17 (SD = 20.45) years [Table 1].

The most common pathogen was *E. coli* that responsible for about 2932 (84%) of all positive samples, and other pathogens were grown in about 10.3% of samples with the least role for *Citrobacter* by 0.1 positive rates [Table 2]. Gram-negative and Gram-positive bacteria were responsible for 97.8% and 2.2% of the isolates, respectively [Table 2]. The distribution of uropathogen among the sexes, on the other hand, was mainly the same. *E. coli* and *Klebsiella* were the most responsible bacteria in both sexes [Table 3].

The specific susceptibility profiles of each bacterial isolate are shown in Table 4. *E. coli* (n = 2932)

showed high resistance rates against NA (59.8%), trimethoprim-STX (58.6%), cephalexin (49.1%), cefixime (43.4%), ceftriaxone (39%), ciprofloxacin (35.9%), ceftizoxime (27.7%), and imipenem (20.3%). The only drugs against *E. coli* to which the resistance rate was detected under 20% were gentamicin (17.8%), amikacin (5.3%), and FM (4.9%). For other bacteria that were responsible for UTI in ambulatory patients, some similar resistance patterns can be found.

The overall susceptibility profiles of bacterial isolates are shown in Table 5. trimethoprim/STX had the highest total resistance of 56.1%, followed by cephalexin (47.2%) and cefepime (42.8%). FM and amikacin had overall resistance rates of 8.3% and 10.3%, respectively.

In terms of ESBL production, 1,146 (39%) strains of *E. coli* have been suspected of ESBL production. Furthermore, results show ESBL suspiciousness among 22.5% of *Klebsiella* and 40% of *Citrobacter* growths.

In this study, we found no meaningful statistical relation between age and bacterial pattern ($P = 0.1$).

Discussion

UTI is one of the most common infectious diseases diagnosed worldwide. New antimicrobials have improved the management of this infection among patients in hospital or ambulatory settings. However, these days, the management of UTI infections has been complicated by increasing the emergence of antimicrobial drug resistance.

For many years ago, multidrug persistence has appeared threat due to misuse of antibiotics. Therefore, it is necessary that we know about the changing in the spectrum of drug resistance to decrease the threats to the failure of treatment or the complexities associated with chronic infection.[25]

Plate *et al*. showed that two-thirds of women who would not care for an UTI episode are willing to postpone their antibiotics.[2]

Although the prevalence of etiologic microorganism in different parts of the world is slightly similar, antimicrobial resistance patterns described from other regions are notably different, and antimicrobial resistance increases. In our study, *E. coli* was the most predominant bacterium isolated from urine, followed by *Klebsiella* spp., *Enterobacter* spp., *Acinetobacter* spp., *Pseudomonas* spp., *Proteus spp*., and *Citrobacter* spp. The isolation rates of *E. coli* and other pathogens in this study were comparable to the rates documented previously in our region and worldwide but a lower role for *Citrobacter* and *Proteus* spp.[5-7] In our study, the age and sex distribution of UTI matched with that found in other studies.[26,27]

Statistically, a significant difference was observed between genders as some of the pathogens were isolated, such as *Streptococcus faecalis*, *Citrobacter*, and *Acinetobacter*

Table 1: The frequency distribution of patients in different age group

Age group (years)	Male, *n* (%)	Female, *n* (%)
1-5	17 (4.5)	204 (6.4)
5-18	30 (7.8)	304 (9.5)
18-65	245 (64.5)	2417 (75.5)
65	88 (23.2)	274 (8.6)

Table 2: The bacterial patterns of positive culture urinary tract infection during the year 2015-2017

Isolated bacteria	*n* (%)
Escherichia coli	2932 (84)
Klebsiella pneumoniae	375 (10.7)
Streptococcus faecalis	77 (2.2)
Enterobacter	55 (1.5)
Acinetobacter	17 (0.48)
Pseudomonas	16 (0.45)
Proteus	12 (0.34)
Citrobacter	5 (0.14)
Total	3489 (100)

Table 3: The bacterial patterns of ambulatory patients with positive urine culture in different patients' sex

Microorganism	Sex	
	Female, *n* (%)	Male, *n* (%)
Escherichia coli	2626 (81.2)	306 (81.1)
Klebsiella pneumoniae	337 (10.4)	36 (9.3)
Enterobacter	47 (1.5)	8 (2.1)
Proteus	11 (0.3)	1 (0.3)
Pseudomonas	13 (0.4)	3 (0.8)
Citrobacter	5 (0.2)	0
Streptococcus faecalis	65 (2)	12 (3.2)
Acinetobacter	11 (0.3)	6 (1.6)

Table 4: Antibiotic resistance pattern in Gram-positive and negative bacteria in positive cultured urine sample

Antibiotic resistance pattern	Resistant	Intermediate	Sensitive
STX	2030 (56.1)	101 (2.8)	1489 (41.1)
GM	756 (20.9)	172 (4.8)	2691 (74.4)
AN	370 (10.3)	280 (7.7)	2970 (82)
IMP	742 (20.5)	148 (4.1)	2730 (75.4)
CP	1205 (33.3)	131 (3.6)	2284 (63.1)
CRO	1340 (37)	71 (2)	2210 (61)
FM	300 (8.3)	155 (4.3)	3166 (87.4)
NOR	1452 (40.1)	77 (2.1)	2092 (57.8)
CN	1708 (47.2)	229 (6.3)	1683 (46.5)
CFM	1550 (42.8)	330 (9.1)	1741 (48.1)
CT	993 (27.4)	103 (2.8)	2524 (69.7)
CTX	1313 (36.3)	68 (1.8)	2239 (61.9)
NA	2088 (57.7)	80 (2.2)	1452 (40.1)

IMP: Imipenem, CP: Ciprofloxacin, CRO: Ceftriaxone, FM: Nitrofurantoin, NOR: Norfloxacin, CN: Cephalexin, CFM: Cefixime, CT: Ceftizoxime, CTX: Cefotaxime, NA: Nalidixic acid, AN: Amikacin, GM: Gentamycin, STX: Sulfamethoxazole

Table 5: Antibiotic resistance pattern in both Gram-negative and positive bacteria in Shahid Motahari diagnostic center

Antibiotic	Resistance ratio						
	Escherichia coli (%)	*Klebsiella pneumoniae* (%)	*Enterobacter* (%)	Proteus (%)	*Pseudomonas aeruginosa* (%)	*Citrobacter* (%)	Acetobacter (%)
TMP-STX	58.6	33.8	25.5	50	100	20	47.1
Gentamicin	17.8	11.5	10.9	16.7	25	0	17.6
AN	5.3	5.9	9.1	8.3	18.8	0	5.9
IMP	20.3	14.7	11.1	0	18.8	20	35.3
CP	35.9	14.2	12.7	0	31.3	20	23.5
NOR	40.4	18.8	14.5	8.3	37.5	20	58.8
CN	49.1	36.7	61.8	16.7	93.8	60	76.5
CFM	43.4	29.8	36.4	33.3	87.5	40	64.7
CRO	39	22.5	23.6	8.3	62.5	40	52.9
CT	27.7	19.3	18.2	8.3	81.3	20	41.2
CTX	38.4	21.2	21.8	16.7	68.8	40	52.9
FM	4.9	29.5	30.9	58.3	81.3	20	29.4
NA	59.8	23.6	30.9	25	100	20	64.7

TMP-STX: Trimethoprim-sulfamethoxazole, AN: Amikacin, IMP: Imipenem, CP: Ciprofloxacin, NOR: Norfloxacin, CN: Cephalexin, CFM: Cefixime, CRO: Ceftriaxone, CT: Ceftizoxime, CTX: Cefotaxime, FM: Nitrofurantoin, NA: Nalidixic acid

rates ($P < 0.001$) in our study. Studies conducted worldwide have shown the differences in the prevalence rates between males and females.[28,29] Anatomical and physiological differences are responsible for the differences in males' and females' UTI rates and etiologic microorganisms. The short anatomical distance of the female's urethra and vagina makes it predisposed to trauma during sexual intercourse and urethral colonization by normal GI tract flora and heading up from the urethra into the bladder.[30]

E. coli and *Klebsiella* spp. were responsible for more than 90% of bacterial isolates from ambulatory UTI cases in our study. These microorganisms were found to be highly resistant to trimethoprim-STX, fluoroquinolones, and all generations of cephalosporins but sensitive to FM and amikacin. These findings are similar to some other reports in Iran.[15,31] However, a very high rate of resistance can be found in comparison to reports from other countries.[32,33] We observed the growth of *Pseudomonas* spp and 16 cases (0.4%) had resistance profile majority of antibiotics and 18.8% sensitivity to only carbapenems and amikacin. These rates are higher than those reported from our country in other studies about outpatient UTI settings during previous years[15,34] and other countries.[30,32,33]

Worldwide and especially in our region, the emerging problem of ESBL-producing pathogens is a nightmare. Various researchers have shown a high prevalence of ESBL pathogens in Iran in recent years, varying from 26.6% to 51.9% in *E. coli*.[35-37] Our study supports the previously described high prevalence of ESBL-producing Gram negatives by reporting 49.1% of the *E. coli* strains as suspected for ESBL. However, the prevalence of ESBL-producing pathogens in community-acquired UTIs is high in our study compared to other investigations in western countries.[38-40] In our research, more than 85% of the ESBL-producing organisms were resistant to quinolone and trimethoprim-STX. The most effective antibiotic was FM, with 95%, followed by amikacin with an 83% efficacy rate.

In a previous study conducted that the prevalence of *E. coli* was higher in females than males, 11.5% and 8.3%, respectively,[41] while in our study, this prevalence was approximately equal in both sex (81.1%).

Resistance against FM, the first-choice antibiotic in uncomplicated lower UTIs in Iran, seems to be significant in various studies.[18,42,43] We also found the same pattern with 8.3% overall to FM. This increase demonstrates that frequent use of the antibiotic for an extended period will elevate the resistance.

Chardavoyne *et al*. survey the usage of suitable different types of antibiotics besides on guideline. They conclude that subordination to the IDSA opinions and narrow-spectrum antibiotics can be effective and lead to decreasing unnecessary antibiotic days.[44]

This retrospective study is based on the results of routine microbiological tests which were done between 2015 and 2017. Due to the nature of the retrospective analysis, we could not follow patients' clinical settings. Thus, the study did not support clinical data such as underlying disease or specific symptoms of patients.

Conclusion

The situation, we face in Iran, is challenging because of the increasing resistance of bacteria to available antibacterial, resulting in a growing lack of acceptable therapeutic options for UTIs. The ever increasing use of third-generation cephalosporin for any probable infectious disease has led to an increasing rate of ESBL among Gram-negatives. The

emergence of ESBL-producing *E. coli* is so alarming and the appearance of resistant *Klebsiella* spp. in the population.

The optimal drug for the therapy of a patient with UTIs depends on many factors. Each agent has pros and cons related to its use or misuse, and the choice of therapy is made on an individual basis. One of the most crucial factors for choosing the first-line agent depends on the local pattern of resistance.

In respect to our finding, in cases of uncomplicated lower UTIs, we suggest a 5–7-day course of FM as the first-choice empirical treatment. Particular attention should be given to patients who have tissue involvement symptoms and developing signs of an upper UTI. For this group, FM should not be a therapeutic consideration because of the reduced tissue penetration of this medicine.

The catastrophe is empirical therapy for outpatient management of upper UTIs. We do not have any oral medication with an acceptable sensitivity profile. Our therapeutic options are running out. Regarding resistance rates, parenteral use of aminoglycoside should be considered as first-choice empirical therapy in all cases of upper UTI and changing based on individual urine culture result and pattern of antibiotic susceptibility.

Limitation of the study

Such all retrospective studies, we had limitation in gathering more specific detail of demographic and clinical manifestation data. Furthermore, we had no data about MIC of antibiotics for etiologic agents.

MeSH terms: urinary tract infection; urinary anti-infective agents; antibiotic resistance, bacterial.

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Conflicts of interest

There are no conflicts of interest.

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