doi: 10.22100/ijhs.v4i2.631
Original Article

IJHS 2018;4(2):14-19
ijhs.shmu.ac.ir

IJHS
International Journal of Health Studies

Distribution and Antibiotic Resistance Pattern of Bacteria Isolated from the Patients with Community-Acquired Urinary Tract Infections in Iran: A Cross-Sectional Study

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Received: 10 July 2019
Accepted: 30 July 2019

Abstract

Background: *Urinary Tract Infections (UTIs) remain the common infections diagnosed in outpatients as well as hospitalized patients. Multi-Drug Resistance (MDR) and Extensively-Drug Resistance (XDR) in the bacteria is an alarming problem in the world. Thus, the present study was conducted to detect the etiologic agents associated with Community-Acquired Urinary Tract Infections (CA-UTIs) and investigate the antibiotic susceptibility patterns.*

Methods: *This study was conducted on the outpatients referred to Labbafinejad Hospital Clinic, Tehran, Iran from September 2014 to March 2015. The bacterial pathogenic diversity was identified by standard laboratory methods. The antimicrobial resistance rates were determined by Kirby-Bauer disc diffusion method.*

Results: *A total of 303 patients were enrolled in this study, among which 204 (67.3%) of them were female and 99 (32.5%) of them were male. Escherichia coli was the dominant species (69%), followed by Enterococcus faecalis (12.8%), and Klebsiella pneumoniae (4.6%). High resistance rate was observed to nalidixic acid (73.8%), trimethoprim/Sulfamethoxazole (54.3%), ciprofloxacin (54.3%) in E. coli, and tetracycline (89.7%) in E. faecalis strains as well as high susceptibility rate to meropenem (96.6%), imipenem (95.2%), amikacin (90.4%), cefoxtin (87.6%), and nitrofurantoin (82.8%) in E. coli, and nitrofurantoin (100%) in E. faecalis strains.In addition, 43.5% of the strains were found to be Multi-Drug-Resistant (MDR).*

Conclusions: *The results of this study showed that, E. coli was the predominant uropathogen of CA-UTIs in this geographical area. It was also found that, the empirical treatment of urinary tract infections may be difficult due to high resistance to commonly used antibiotics. Continuous monitoring of MDR organisms and drug resistance patterns is needed to prevent treatment failure and reduce selective pressure. These findings suggest the use of nitrofurantoin, cefoxitin, and amikacin in this area of the country.*

Keywords: Urinary tract infections, Bacteria, Antibiotic resistance.
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Please cite this paper as: Fallah F, Parhiz S, Azimi L, rashidan M. Distribution and antibiotic resistance pattern of bacteria isolated from the patients with community-acquired urinary tract infections in iran: a cross-sectional study. Int J Health Stud 2018;4(2):14-19.

Introduction

Urinary tract infections (UTIs) remain the common infections diagnosed in outpatients as well as hospitalized patients and the second most common cause of bacterial infection after respiratory tract in both settings. It is also estimated that, on a global scale, about 150 million people each year suffer from UTI and cost at least 6 billion dollars worldwide.[1,2] UTI is defined by the presence of 10^5CFU/mL uropathogenic bacteria in urine and reported in both sexes and in all age groups. The risk for UTIs in females is greater than males because of sexual activity, pregnancy and the short anatomy of the urethra.[3,4] In addition, long- term antibiotic use can also be increased the risk of UTIs. This could damage the periurethral flora and cause the establishment and infection of uropathogenic bacteria in the urinary tract.[5,6]

Most previously reported studies have shown that Escherichia coli is often a causative agent of UTI in both hospital and community-acquired infections. Additionally, Enterococci, Klebsiella pneumonia, Streptococcus agalactiae, Proteus mirabilis, Pseudomonas aeruginosa, Citrobacter freundii, Enterobacter cloacae and Acinetobacter spp. are known as causative agents of UTI.[7]

Given the rapid evolutionary adaptation strategies of bacteria, the antibiotic resistance patterns of the uropathogens in the recent years have also significantly changed, both in the community and hospital infections.[8,9]

On the other hand, treatment of UTI in the community is usually performed empirically before the result of the microbiological test; this can lead to the development of antibiotic resistance and treatment failure.[10] Furthermore, improper use of broad spectrum antimicrobial agents and poor infection control strategies, also contributes to increasing antibiotic resistance and the development of multi-drug resistant bacteria (MDR) in these patients, which has become a serious public health concern.[11,12] Recent studies have also shown an increase in antibiotic resistance in Iran, which there is no regular monitoring of the use of broad- spectrum antibiotics, so identification of local etiologic agents of UTIs and examination of antibiotic resistance patterns are essential to guide clinicians in empirical treatment in this geographical area. Therefore, the aim of this study was to detection of etiologic agents associated with community-acquired urinary tract infections (CA-UTIs) and investigation of antibiotic susceptibility patterns.

Materials and Methods

Isolate Collection and Identification

This cross-sectional descriptive study was conducted on the outpatients referred to Labbafinejad Hospital Clinic, Tehran, Iran from September 2014 to March 2015. Patients who treated with antibiotics or had a history of hospitalization were excluded from our study.

A midstream clean-catch urine specimen was collected from the outpatients and was inoculated on the Blood and

MacConkey (Merck, Germany) agar plates using calibrated loops. For colony count, the plates were incubated at 37oC for 24 hours. More than 105 colony -forming unit per milliliter was considered as bacteriuria. Then, the plates were transferred to the Pediatric Infections Research Center of Shahid Beheshti University of Medical Science at Mofid children's Hospital for further investigations. Identification of bacterial agents was done by conventional biochemical procedures in the patients.[13] All strains were stored at -70 oC in Trypticase Soy Broth (TSB) with 20% glycerol.

Antibiotic susceptibility of the studied strains was determined by the standard Kirby-Bauer disk diffusion method on Muller Hinton agar medium (MHA, Merck, Germany). The antibiotic discs of cefepime (CPM, 30µg), piperacillin (PRL, 100µg), ciprofloxacin (CIP, 5µg), amikacin (AK, 30µg), cefoxitin (FOX, 30µg), meropenem (MEM, 10µg), gentamicin (GEM, 10µg), ceftriaxone (CRO, 30µg), co-trimoxazole (SXT, 1.25/23.75µg), nitrofurantoin (NIT, 300µg), cefuroxime (CXM, 30µg), imipenem (IMI, 10µg), nalidixic acid (NA, 30µg), chloramphenicol (C, 30µg), ampicillin-sulbactam (SAM, 10µg), piperacillin-tazobactam (PTZ, 100µg), cefotaxime (CTX, 30µg), ceftazidime (CAZ, 30µg), ofloxacin (OFX, 5 µg), tigecycline (TGC, 15µg), ticarcillin (TIC, 75µg), aztreonam (ATM, 30µg), tobramycin (TOB, 10µg), clindamycin (CD, 2µg), erythromycin (ERY, 15µg), synercid (SYN, 15µg), linezolid (LZD, 30µg), ampicillin (AP, 10µg), tetracycline (TET, 30µg), minocycline (MN, 30µg), levofloxacin (LEV, 5µg), gatifloxacin (GAT, 5µg), vancomycine (VAN, 30µg), high-level gentamicin (GEM,120µg) and penicillin G (PEN, 10unit) were used (MAST group Ltd., United Kingdom) in this study. The results were interpreted according to the standard recommendation of the Clinical and Laboratory Standard Institute guidelines (CLSI 2014).[14] Control tests were conducted using reference strains of E. coli ATCC 25922, Staphylococcus aureus ATCC 25923, Streptococcus pneumonia ATCC 49619 and P. aeruginosa ATCC 27853.

Statistical Analysis

The data were analyzed using WHONET software 5.6 provided by the World Health Organization for antimicrobial resistance surveillance of uropathogenic bacteria.[15,16] Antibiotic resistance percentage and the rate of multi-drug resistance strains were also evaluated. According to the European Center for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC), multi-drug resistance strains are divided into MDR (Multiple Drug-Resistant), XDR (Extensively Drug-Resistant) and PDR (Pan Drug-Resistant).[17] MDR bacteria are defined as non-susceptibility to at least one agent in 3 or more antimicrobial categories, XDRbacteria are defined as non-susceptibility to at least 1 agent in all but 2 or fewer antimicrobial categories and the PDR bacteria are defined as non-susceptibility to all agents in all antimicrobial categories.

Results

A total of 303 patients were enrolled in this study, including 204 (67.3%) females and 99 (32.5%) males with an age range from 4 to 90 years old. Hence, with respect to gender, females had a higher prevalence of infection than males. The prevalence of UTI was significantly associated with the gender (P.V=0.0001).

Distribution of Uropathogenic Bacteria

9 different species of bacteria were isolated from the urine samples with significant bacterial growth. 82.1 % of the isolates had Gram-negative bacteria while, only 17.7% of them had Gram-positive bacteria (table 1). E. coli was the most common bacteria isolated (N=210, 69%), followed by Enterococcus faecalis (N=39, 12.8%), and Klebsiella pneumonia (N=14, 4.6%).

Table 1. Frequency of the isolated uropathogenic bacteria

Table 1. Frequency of uropathogenic bacteria isolated

Bacteria	Frequency (%)	Gram reaction (%)	Total
Escherichia coli	210 (69%)	Gram-negative N= 249 (82.1%)	303
Klebsiella pneumonia	14 (4.6%)		
Acinetobacter spp.	8 (2.6%)		
Pseudomonas aeruginosa	8 (2.6%)		
Citrobacter spp.	4 (1.3%)		
Proteus spp.	3 (0.9%)		
Enterobacter sp.	1 (0.3%)		
Edwardsiella sp.	1 (0.3%)		
Streptococcus agalactieae	11 (3.6%)	Gram-positive N= 54 (17.8%)	
Enterococcus spp.			
– E. faecalis	39 (12.8%)		
– E. faecium	4 (1.3%)		

Antibiotic Resistance of Uropathogenic Bacteria

Table 2 shows the prevalence of resistance among uropathogenic Gram-negative bacteria. E. coli showed the lowest resistance to meropenem (3.3%) and highest against nalidixic acid (73.8%). More than half of K. pneumonia were resistant to nitrofurantoin and piperacillin (57.1%) and 92.8% of them were sensitive to piperacillin/tazobactam. Proteus spp. was mostly resistant to trimethoprim/sulfamethoxazole, nitrofurantoin, nalidixic acid, and chloramphenicol (100%) and was also sensitive to piperacillin, amikacin, cefoxitin, meropenem, and cefuroxime (100%). Citrobacter spp. had 100% susceptibility to cefepime, amikacin, gentamicin, trimethoprim/sulfamethoxazole, imipenem, nalidixic acid and piperacillin/tazobactam. The least effective antibiotic in this isolate was nitrofurantoin. Enterobacter spp. was generally resistant to most of our tested antibiotics. This isolate did not show resistance to antibiotics such as amikacin, cefoxitin, meropenem, nitrofurantoin, imipenem, and chloramphenicol. Edwardsiella spp. was generally susceptible to our tested antibiotics. The least effective antibiotics in this isolate were piperacillin, gentamicin, trimethoprim/sulfamethoxazole, and ampicillin/sulbactam. Acinetobacter spp. showed the highest resistance to ceftriaxone and cefotaxime (87.5%) and lowest against meropenem and imipenem (37.5%). P. aeruginosa exhibited the highest resistance to gentamicin (75%) and lowest against piperacillin, ciprofloxacin, and imipenem (12.5%).

Table 2. Antibiotic resistance of uropathogenic Gram-negative bacteria against tested antibiotics

Table 2.Antibiotic resistance of uropathogenic Gram-negative bacteria against tested antibiotics

Antibiotic disks	Resistance rate, %							
	E.coli N=210	K. pneumonia N=14	Proteus spp N=3	Citrobacter spp N=4	Enterobacter spp N=1	Edwardsiella Spp N=1	Acinetobacter spp N=8	P. aeruginosa N=8
Piperacillin	147(70%)	8(57.1%)	0(0%)	2(50%)	1(100%)	1(100%)	5(62.5%)	1(12.5%)
Ciprofloxacin	114(54.3%)	4(28.5%)	1(33.3%)	1(25%)	1(100%)	0(0%)	6(75%)	1(12.5%)
Cefepime	50(23.8%)	3(21.4%)	1(33.3%)	0(0%)	1(100%)	0(0%)	8(100%)	3(37.5%)
Amikacin	20(9.5%)	2(14.3%)	0(0%)	0(0%)	0(0%)	0(0%)	6(75%)	4(50%)
Cefoxitin	26(12.4%)	3(21.4%)	0(0%)	1(25%)	0(0%)	0(0%)	-	-
Meropenem	7(3.3%)	1(7.1%)	0(0%)	1(25%)	0(0%)	0(0%)	3(37.5%)	0(0%)
Gentamicin	50(23.8%)	2(14.2%)	1(33.3%)	0(0%)	1(100%)	1(100%)	5(62.5%)	6(75%)
Ceftriaxone	95(45.2%)	5(35.7%)	1(33.3%)	1(25%)	1(100%)	0(0%)	7(87.5%)	
Trimethoprim/Sulfamethoxazole	114(54.3%)	6(42.8%)	3(100%)	0(0%)	1(100%)	1(100%)	5(62.5%)	-
Nitrofurantoin	36(17.1%)	8(57.1%)	3(100%)	4(100%)	0(0%)	0(0%)	6(75%)	-
Cefuroxime	101(48.1%)	5(35.7%)	0(0%)	1(25%)	1(100%)	0(0%)	6(75%)	-
Imipenem	10(4.8%)	3(21.4%)	1(33.3%)	0(0%)	0(0%)	0(0%)	3(37.5%)	1(12.5%)
Nalidixic Acid	155(73.8%)	5(35.7%)	3(100%)	0(0%)	1(100%)	0(0%)	-	-
Chloramphenicol	20(9.5%)	3(21.4%)	3(100%)	1(25%)	0(0%)	0(0%)	-	-
Ampicillin-sulbactam	90(42.9%)	5(35.7%)	2(66.7%)	1(25%)	1(100%)	1(100%)	5(62.5%)	-
Piperacillin/Tazobactam	16(7.6%)	1(7.1%)	1(33.3%)	0(0%)	1(100%)	0(0%)	0(0%)	0(0%)
Cefotaxime	-	-	-	-	-	-	7(87.5%)	5(62.5%)
Ofloxacin	-	-	-	-	-	-	-	2(25%)
Ceftazidim	-	-	-	-	-	-	5(62.5%)	5(62.5%)
Tetracycline	-	-	-	-	-	-	6(75%)	-
Tigecycline	-	-	-	-	-	-	6(75%)	-
Ticarcillin	-	-	-	-	-	-	-	3(37.5%)
Aztreonam	-	-	-	-	-	-	-	3(37.5%)
Tobramycin	-	-	-	-	-	-	-	5(62.5%)

Table 3 shows the prevalence of resistance among uropathogenic Gram-positive bacteria. High levels of tetracycline and minocycline resistance were observed in E. faecalis strains (89.7 and 87%). These strains did not show resistance to antibiotics such as vancomycin, nitrofurantoin, and linezolid. All 11 isolates of S. agalactiae were susceptible to erythromycin, ofloxacin, cefotaxime, ampicillin and linezolid and resistant to vancomycin.

Table 3. Antibiotic resistance of uropathogenic Gram-positive bacteria against tested antibiotics

Multi-Resistant Uropathogenic Bacteia

Table 3. Antibiotic resistance of uropathogenic Gram-positive bacteria against tested antibiotics

Antibiotic disks	Resistance rate, %		
	E. faecalis N=39	E. faecium N=4	S. agalactiae N=11
Penicillin G	3(7.6%)	2(50%)	-
Vancomycin	0(0%)	1(25%)	11(100%)
Tetracycline	35(89.7%)	2(50%)	-
Minocycline	34(87%)	2(50%)	-
Ciprofloxacin	10(25.6%)	2(50%)	-
Levofloxacin	9(23%)	2(50%)	0(0%)
Gatifloxacin	9(23%)	2(50%)	-
Nitrofurantoin	0(0%)	1(25%)	
Gentamicin (120 µg)	14(35.8%)	1(25%)	-
Erythromycin	-	-	0(0%)
Ofloxacin	-	-	0(0%)
Cefotaxime	-	-	0(0%)
Ampicillin	2 (5.1%)	2(50%)	0(0%)
Linezolid	0(0%)	1(25%)	0(0%)
Synercid	-	-	1(9.09%)
Clindamycin	-	-	0(0%)

Phenotypic detection of multi-resistant strains was carried out by WHONET software 5.6 as MDR, possible XDR or possible PDR (Figure 1). Among bacterial species presented, Acinetobacter spp. showed the highest percentage of MDR and XDR, 6(75%) and 5(62.5%) isolates, respectively. Among a total of 233 isolates of Enterobacteriaceae tested, 113 (48.4%) isolates were found to be MDR, 9 (3.8%) isolates were possible XDR and 1(0.4%) isolate was found to be PDR. In the Gram-positive bacteria, Enterococcus spp. showed 10(23.2%) isolates of MDR and 1 (2.3%) isolate of XDR.

MDR: Multi-Drug Resistant, Possible XDR; Extensively drug-resistant, Possible PDR; Pan drug-resistant

Discussion

Today, the increased antimicrobial resistance and the emergence of MDR bacteria causing CA-UTIs has become a serious public health concern resulting from the irrational and improper use of antimicrobials and the presence of antibiotics in the food chain.[18] Thus, an amendment to the current antimicrobial stewardship program is needed in this geographical area to improve the efficacy of CA-UTIs treatment.

In our study, the prevalence of UTI was significantly higher in females than males attributing to the physical and anatomical factors in females.[3,4] These findings were in accordance with the findings of similar studies in CA-UTIs.[19,20]

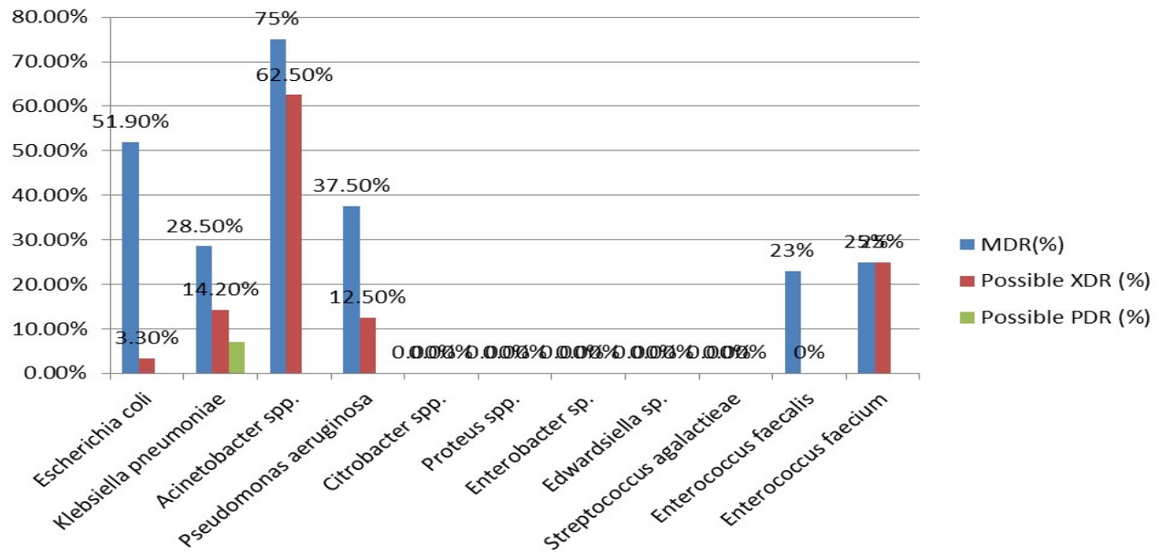

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Figure 1. Percentage of multi-drug resistance of uropathogenic bacteria. MDR; Multi-drug resistant, Possible XDR; Extensively drug-resistant, Possible PDR; Pan drug-resistant

Enterobacteriaceae are the most common cause of UTI in hospitals and the community, and are responsible for many current problems caused by transferable multi-antibiotic resistance.[21] Therefore, the ability to monitor the antimicrobial resistance trends in infections most commonly caused by these organisms, across all patient groups will provide valuable additional insight needed to inform public health action. In this study, the Gram-negative bacilli accounted for 84.43% of the total bacterial isolates, while Gram-positive cocci accounted for 15.57% of the total bacterial isolates. As expected, E. coli was the most prevalent uropathogen (69%) in CA-UTIs. This finding is in agreement with the previous studies conducted in Iran (51.5%),[22] as well as European studies (76%)[23] and studies carried out in Germany (74.5%)[24] and Denmark[25] but is higher than the reports from Ethiopia (39.4%)[26] and Nigeria (40.7%).[27] In this study, E. faecalis was the second predominate isolate accounting for 12.8% of the total bacterial isolates. This result was consistent with a similar study conducted in India[20] and Korea[28] and was contrary to other studies.[11,29,30] The similarities and differences in the type and distribution of uropathogens may be related to various environmental conditions and host factors and practices, such as health and educational programs and social and economic hygiene standards in each country.

Understanding the antibiotic resistance patterns in E. coli, as the most frequent uropathogen is important to choose an empirical antimicrobial therapy. As shown in table 2, E. coli showed high level of resistance to nalidixic acid (73.8%) and piperacillin (70%) followed by ciprofloxacin and trimethoprim/sulfamethoxazole (54.3%). The current results are similar to the previous studies conducted on CA-UTIs in Iran[31,32] and are less than that reported in other surveys performed in other parts of the world.[33-36]

On the other hand, ciprofloxacin and trimethoprim/sulfamethoxazole are used as a first -choice treatment for CA-UTIs in our region. The widespread use of these antimicrobials in the treatment of community-acquired infections may have contributed to the high levels of observed resistance. Therefore, these antibiotics should be carefully considered for empirical treatment. Maximum sensitivity was reported towards meropenem (96.6%), imipenem (95.2%), piperacillin/tazobactam (92.3%), chloramphenicol (90%) and amikacin (90.4%) followed by cefoxitin (87.6%), nitrofurantoin (82.8%), gentamicin and cefepime (76%). Similar results were reported in the studies conducted in other countries.[34,37,38] In another study, E. coli strains were highly resistant against cefepime (85%) and nitrofurantoin (80%) followed by cefoxitin (69%), gentamicin (64%) and amikacin (51%).[39] Therefore, our findings suggest that, nitrofurantoin is an appropriate empirical choice for treatment of CA-UTIs in this region. In this regards, different patterns of antimicrobial resistance in different regions may be due to the regional variation in antibiotic practice patterns.

In this study, the highest percentage of E. faecalis isolates was resistant to Tetracyclines (tetracycline, 89.7 and minocycline, 87%). This frequency was similar to the resistance rates reported in Taiwan (91.8%),[40] Iran (90.3%)[41] and Iraq (100%),[42] but higher than those reported in India (50%) and Brazil (59.2%).[40,43] The high-level resistance to Tetracyclines in these strains may be attributed to the overuse of antibiotics to treat human diseases and livestock in Iran.[44] Therefore, it is necessary to monitor the use of the antimicrobial in the community and to evaluate animal reservoirs of tetracycline-resistant E. faecalis strains. The most susceptibility was observed to vancomycin, nitrofurantoin, linezolid, ampicillin, and penicillin. The high susceptibility to these antibiotics, making them the first line of treatment for

CA-UTIs, as long as, the microbiological information is known.

Among 302 isolates, 43.5% of them were found to be multi-drug resistant. In this survey, a significant higher percentage of MDR and the possible XDR strains from CA-UTIs was observed. Among the tested uropathogens, Acinetobacter spp. exhibited the highest rates of MDR and the possible XDR followed by E. coli and P. aeruginosa. In our report, only K. pneumonia isolates were found to be the possible PDR phenotype. The contributing factors for the emergence of such a high bacterial antibiotic resistance in CA-UTIs may be the use of antibiotics in livestock, self-medication, excessive availability of antibiotics, dispensing them without proper prescriptions, non-compliance with an antibiotic regimen by patients, and indiscriminate use of antibiotics. The involvement of such drug-resistant bacteria in the development of community-acquired infections is a very serious concern in terms of public health. Therefore, some necessary steps should be taken immediately to control the situation.

The results of the current study showed an overview of the species diversity of the uropathogenic bacteria and antibiotic resistance patterns in Iran's community. A high prevalence of multi-drug resistance and the possible XDR strains were observed among uropathogenic bacteria. In particular, resistance to nalidixic acid, cotrimoxazole and ciprofloxacin was higher, thus the use of these drugs should be avoided for empirical UTI-based treatment. In such cases, empirical treatment with nitrofurantoin, cefoxitin and amikacin may provide better antibiotic coverage. These findings suggest the need for continuous antimicrobial surveillance of multi-drug resistance uropathogenic bacteria to fight the UTI caused by these bacterial pathogens.

Acknowledgement

The authors would like to thank the Pediatric Infectious Disease Research Center of Shahid Beheshti University of Medical Sciences for their support. The authors would also like to thank the members of the vice-chancellery in research affairs and those who assisted in the study.

Conflict of Interest

The authors declare that they have no conflict of interest.

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