

## Original Article



# Antimicrobial Resistance in Hospitalized Patients with Community Acquired Urinary Tract Infection in Isfahan, Iran

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## Abstract

**Background:** Antibiotic resistance against uro-pathogens is a worldwide health concern. The aim of this study was to determine the causative bacteria and antibiotic susceptibility patterns among hospitalized patients with community acquired urinary tract infection (UTI).

**Methods:** This cross-sectional study was performed in 2016-2018 in Isfahan, Iran. Urine samples were examined for strain identification and antimicrobial resistance pattern using standard tests. Stratification was done based on gender and age (<20 and >20 years) groups. Chi-square and Fisher exact tests were applied to assess differences in etiology and susceptibility rates between groups.

**Results:** Among 1180 patients, *Escherichia coli* was the commonest pathogen (68.1%) followed by *Enterococcus* spp. (8.8%) and *Klebsiella pneumonia* (8.0 %). Non-*E. coli* pathogens were more frequent among males (41.8% versus 24.8% in females,  $P<0.01$ ) and in those aged under 20 years (61.0% versus 22.2% in older than 20 years,  $P<0.01$ ). Isolated bacteria revealed high susceptibility to imipenem (94.9%), meropenem (92.2%), and amikacin (91.9%); moderate sensitivity to gentamicin (64.4%), cefepime (52.6%) and ceftazidime (47.2%); and low susceptibility to ceftriaxone (41.8%), cefotaxime (40.0%), ciprofloxacin (38.6%) and trimethoprim-sulfamethoxazol (31.3%). The sensitivity of isolates to ceftriaxone, ceftazidime, cefepime, imipenem, meropenem, amikacin and ciprofloxacin was significantly higher in females. Compared to the older age group, uro-pathogens were more susceptible to ciprofloxacin, ceftazidime and gentamicin in patients aged under 20 years.

**Conclusion:** We found that imipenem, meropenem and amikacin were good choices for empiric therapy of complicated or severe hospitalized patients with community acquired UTI; and gentamicin, cefepime and ceftazidime were acceptable as initial choices in non-severe infections in the area.

**Keywords:** Antimicrobial susceptibility, Community acquired, Hospitalized, Infection, Iran, Urinary tract

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## Introduction

Urinary tract infection (UTI) is a worldwide bacterial infection with significant mortality, morbidity, and health expenses in all ages.<sup>1</sup> The main bacterial etiology of the infection includes *Escherichia coli*, *Proteus* sp., *Pseudomonas*

*aeruginosa*, *Acinetobacter* spp., *Klebsiella* spp., *Enterobacter* sp., *Citrobacter* sp., *Staphylococcus saprophyticus*, *Enterococcus* sp., and *Staphylococcus epidermidis*.<sup>2</sup>

Clinical manifestations vary largely from asymptomatic or mild dysuria to high fever, vomiting, back pain, and

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even bacteremia, sepsis or death.<sup>3</sup> Treatment of patients with severe or complicated disease requires hospital admission and prompt intravenous antibiotic therapy before obtaining the results of urinary culture.<sup>4,5</sup>

Unfortunately, during recent years, the increasing resistance of microorganisms to antibiotics has become a global concern; urinary pathogens are not an exception.<sup>6,7</sup> In addition, the susceptibility pattern of uro-pathogens differs in various geographic locations and different settings, i.e. outpatient versus hospitalized, community acquired hospitalized patients versus hospital-acquired hospitalized patients.<sup>6-8</sup> Therefore, periodic evaluation of susceptibility pattern of uro-pathogens in each area and in different settings is necessary to select the best antibiotics for empiric treatment of UTIs.<sup>6-9</sup> According to our literature review, few studies have been performed on antibiotic susceptibility of microorganisms causing UTI in hospitalized patients all around the world, and none of them have specifically studied the community-acquired cases.<sup>9-13</sup>

The aim of this study is to determine the etiology and total antibiotic susceptibility of community-acquired uro-pathogens in patients who were admitted to three large hospitals which participate in the Isfahan Antimicrobial resistance Surveillance-1 (IAS-1) study.

## Materials and Methods

### Study Design

The study was designed to report the results of antibiotic susceptibility patterns of pathogens in patients who were admitted to hospitals because of community-acquired UTI. They were recruited during the time period of March 2016 to March 2018 and participated in the IAS-1 project which is a cross-sectional study planned to investigate the antimicrobial susceptibility profile of clinically important microorganisms, conducted in Isfahan, Iran.<sup>14</sup>

Indications for admission of the patients include hemodynamic instability, complicating factors (such as urinary stones), severe symptoms, intolerance of oral antibiotics, and poor adherence to medications. The IAS-1 study was planned to investigate the main microorganisms and antibiotic susceptibility profile of infections in cases who were admitted to three large medical centers in Isfahan city, Iran (Project No: 194042). In addition to recording antibacterial resistance of clinical isolates, it aimed to eliminate contaminant isolates, and determine healthcare/community source of the infection by cooperation of skilled infectious control nurses and physicians in the enrolled hospitals. The study aimed to help the clinicians in selecting the most appropriate antibiotic for treatment of infections in the area. The medical centers that participate in the research were the main large hospitals of Isfahan city, i.e. Al-Zahra, Dr. Shariati and Dr. Gharazi hospitals. The laboratories of these medical centers attained Quality Credit for microbiological report from the Iranian Ministry

of Health and collaborated in the Global Antimicrobial Resistance Surveillance System (GLASS) program of the World Health Organization (WHO).<sup>15</sup>

### Organism Identification and Antibiotic Susceptibility Testing

Urine samples were obtained from patients with suspected UTI. UTI was defined as presence of pyuria in urine analysis ( $\geq 10$  WBC/mL of urine) in addition to growth of  $\geq 10^5$  colony count of a single urinary pathogen in one urine sample or single non-urinary pathogens in 2 urine specimen with the same resistance profile. Patients with healthcare-associated UTI were excluded from the study. Data on age, sex, nosocomial or community acquisition of the infection as well as the etiological agent and susceptibility profile of the isolated bacteria were prepared using the WHONET software.

For detection of uro-pathogens, urine samples were collected according to local hospital guidelines and were inoculated with a standard wire loop onto sheep blood agar and MacConkey agar or eosin–methylene blue agar and were incubated overnight at 37°C. Isolation of uro-pathogens (*E. coli*, *Proteus* spp., *Klebsiella* spp., *Enterobacter* spp., *Citrobacter* spp., *P. aeruginosa*, *Acinetobacter* spp., *Enterococcus* spp., *S. saprophyticus* and *S. epidermidis*) was done by routine conventional methods such as catalase and oxidase test, sugar fermentation, growth on selective media, susceptibility or resistance to specific agents and other standard microbiology tests.

Antimicrobial susceptibility testing was performed using the Kirby-Bauer method, as recommended by the Clinical Laboratory Standard Institute.<sup>15</sup> The following antibiotics were tested: cefotaxime (30 µg), ceftriaxone (30 µg), ceftazidime (30 µg), cefepime (30 µg), imipenem (10 µg), meropenem (10 µg), gentamicin (10 µg), amikacin (30 µg), ciprofloxacin (5 µg), trimethoprim-sulfamethoxazol (1.25–23.75 µg), ceftazidime (30 µg), penicillin (10 units), ampicillin (10 µg) and vancomycin (30 µg) (Mast Group Ltd, UK). The minimum inhibitory concentrations (MICs) of vancomycin for *Staphylococcus* spp. were obtained by an E-test (Liofilchem, Italy), as described in the manufacturer's instructions.

### Statistical Analysis

Data on age group ( $\leq 20$  years,  $> 20$  years), sex, etiology and antibiotic susceptibility were extracted from the WHONET version 5.6 software in each laboratory and analyzed with SPSS version 18.0. Chi-square and Fisher exact tests were applied for analysis of the study variables. *P* value of  $< 0.05$  was considered as significant.

## Results

A total number of 5844 urine specimens were received for culture from March 21, 2016 to March 20, 2018, of which 3586 (61.4%) samples showed no growth, 284

(4.9%) samples were positive for fungus and yeast, 511 (8.7%) samples were considered as contamination, and 283 (4.8%) cases were nosocomial acquired. Of 1180 isolates from patients with confirmed CAI-UTI, 488 (41.4%) belonged to males and 295 (25.0%) were less than 20 years old.

Gram-negative bacteria represented 84.0% (991) of the isolates and *E. coli* was the leading pathogen (68.1%) followed by *K. pneumonia* (8.0%), *P. aeruginosa* (7.4%) and other gram-negative rods (*Acinetobacter* spp., *Citrobacter* spp., *Klebsiella* spp., *Enterobacter* spp., *Proteus* sp., *Stenotrophomonas maltophilia*) (5.5%) (Table 1).

*Enterococcus* spp. was the most frequent gram-positive pathogen (104, 8.8%). Other gram-positives isolates included: *Staphylococcus* spp. (5%), and *Streptococcus* spp. (2.2%) (Table 1).

The isolated bacteria showed high susceptibility to imipenem (94.9%), meropenem (92.2%) and amikacin (91.9%); moderate sensitivity to gentamicin (64.4%), cefepime (52.6%) and ceftazidime (47.2%); and low sensitivity to ceftriaxone (41.8%), cefotaxime (40.0%), ciprofloxacin (38.6%) and trimethoprim-sulfamethoxazol (31.3%). Uro-pathogens in female patients had more susceptibility to imipenem, meropenem, amikacin, cefepime, ceftazidime, ceftriaxone and ciprofloxacin. In addition, in the younger age group (<20 years), the isolated organisms has significantly higher susceptibility to gentamicin, ceftazidime, cefepime and ciprofloxacin

(Table 2). The antibiotic susceptibility of the common isolated bacteria is presented in Table 3.

## Discussion

Our study reveals that *E. coli* is the most common cause of community-acquired UTI in patients who need hospitalization. Furthermore, it shows a high bacterial resistance rate to several antibiotics including cefotaxime, ceftriaxone, ceftazidime, cefepime, trimethoprim-sulfamethoxazole, and ciprofloxacin. In addition, it demonstrates a high susceptibility rate of causative agents to imipenem, meropenem and amikacin.

To the best of our knowledge, no earlier investigation has reported common pathogens and their sensitivity profile in hospitalized patients with community-acquired UTI. Recognition of the antibacterial susceptibility patterns of uropathogens in these patients is an essential factor for selecting a proper empirical antimicrobial treatment in each area.<sup>6,7</sup> Previous studies on the resistance pattern of uropathogens all around the world usually did not exclude the cases of contamination<sup>8,10</sup> or outpatient isolates from the analysis.<sup>10,12</sup> A few investigations which were performed in hospitalized patients did not exclude the cases of healthcare-associated UTIs from their studies.<sup>8-13</sup> To decrease the rate of contamination in final analysis, we excluded the urinary isolates with no concomitant pyuria in urinalysis. Moreover, we recognized community source of the isolates with help from experienced infectious

**Table 1.** Frequency of Microorganisms Causing Community-Acquired Urinary Tract Infection in Patients Hospitalized in Three Hospitals in Isfahan, Iran During 2016-2018 According to Sex and Age Groups: Results of the IAS-1 Project

Organisms	Sex			Age Group (y)			Total
	Male No. (%)	Female No. (%)	OR (95% CI) P Value <sup>a</sup>	< 20 No. (%)	>20 No. (%)	OR (95% CI) P Value	
<i>E. coli</i>	284 (58.19)	520 (75.14)	0.342 (0.267–0.438) <0.001	115 (38.98)	689 (77.85)	0.182 (0.137–0.241) <0.001	804 (68.13)
<i>K. pneumonia</i>	46 (9.42)	48 (6.93)	1.396 (0.915–2.130) 0.120	87 (29.49)	7 (0.79)	52.463 (23.93–114.987) <0.001	94 (7.96)
<i>P. aeruginosa</i>	19 (3.89)	9 (1.30)	3.074 (1.379–6.854) 0.004	23 (7.79)	5 (0.56)	14.882 (5.604–39.520) <0.001	28 (2.37)
Other gram-negative organisms <sup>b</sup>	42 (8.60)	23 (3.32)	2.739 (1.625–4.618) <0.001	61 (20.67)	4 (0.45)	56.451 (20.322–156.813) <0.001	65 (5.50)
Total gram-negative organisms	391 (80.12)	600 (86.70)	0.618 (0.452–0.845) 0.002	286 (96.94)	705 (79.66)	8.113 (4.096–16.070) <0.001	991 (83.98)
<i>Enterococcus</i> spp.	56 (11.47)	48 (6.93)	1.739 (1.161–2.606) 0.007	4 (1.35)	100 (11.29)	0.108 (0.39–0.296) <0.001	104 (8.81)
<i>Staphylococcus</i> spp.	30 (6.14)	29 (4.19)	1.498 (0.887–2.529) 0.129	4 (1.35)	55 (6.21)	0.207 (0.75–0.577) 0.001	59 (5)
<i>Streptococcus</i> spp.	11 (2.25)	15 (2.16)	1.041 (0.474–2.286) 0.921	1 (0.33)	25 (2.82)	0.117 (0.16–0.867) 0.010	26 (2.20)
Total gram-positive organisms <sup>c</sup>	97 (19.86)	92 (13.29)	1.618 (1.184–2.211) 0.002	9 (3.05)	180 (20.33)	0.123 (0.062–0.244) <0.001	189 (16.01)
Total organisms	488 (100)	692 (100)	—	295 (100)	885 (100)	—	1180 (100)

<sup>a</sup> P value obtained from chi-square test if expected cell count was greater than 5 and Fisher exact test if expected cell count was less than 5.

<sup>b</sup> Including *Acinetobacter* spp., *Citrobacter* spp., *Klebsiella* spp., *Enterobacter* spp., *Proteus* sp., and *Stenotrophomonas maltophilia*

<sup>c</sup> Including *Staphylococcus* spp., and *Streptococcus* spp.

**Table 2.** Antimicrobial Sensitivity of Microorganisms Causing Community-Acquired Urinary Tract Infection in Patients Hospitalized in Three Hospitals in Isfahan, Iran During 2016-2018 According to Sex and Age Groups: Results of the IAS-1 Project

Antibiotic	Sex		OR (95% CI) P Value	Age Group		OR (95% CI) P Value	Total
	Male No. (%)	Female		<20	>20		
Cefazolin	47/167 (28.1)	123/303 (40.6)	0.965 (0.649–1.435) 0.860	31/83 (37.3)	139/387 (35.9)	0.892 (0.553–1.440) 0.640	170/470 (36.1)
Cefotaxime	71/177 (40.1)	125/313 (39.9)	1.007 (0.692–1.467) 0.969	33/82 (40.2)	164/408 (40)	1.002 (0.618–1.625) 0.994	196/490 (40)
Ceftriaxone	74/187 (39.6)	130/300 (43.3)	0.517 (0.364–0.737) <0.001	37/83 (44.6)	167/404 (41.3)	1.141(0.709–1.837) 0.586	204/487 (41.8)
Ceftazidime	144/356 (40.4)	274/528 (51.9)	0.630 (0.480–0.826) <0.001	60/113 (53.1)	358/771 (46.4)	2.438 (1.650–3.602) <0.001	418/884 (47.2)
Cefepime	154/341 (45.2)	289/501 (57.7)	0.604 (0.458–0.797) <0.001	63/105 (60)	381/737 (51.6)	1.402 (0.924–2.125) 0.111	443/842 (52.6)
Imipenem	264/287 (92)	430/444 (96.8)	0.374 (0.189–0.739) 0.003	90/94 (95.7)	604/637 (94.8)	1.229 (0.425–3.552) 0.702	694/731 (94.9)
Meropenem	220/253 (87)	360/376 (95.7)	5.852 (3.939–8.694) <0.001	91/95 (95.8)	489/637 (94.8)	6.885 (2.488–19.057) <0.001	580/629 (92.2)
Amikacin	307/348 (88.2)	478/506 (94.5)	0.439 (0.266–0.724) 0.001	102/110 (92.7)	683/744 (91.8)	1.139 (0.529–2.449) 0.739	785/854 (91.9)
Gentamicin	155/253 (61.3)	270/406 (66.5)	0.797 (0.575–1.104) 0.172	74/100 (74.0)	351/559 (62.8)	1.687 (1.045–2.722) 0.031	425/659 (64.4)
Ciprofloxacin	132/450 (29.3)	283/623 (45.4)	0.499 (0.386–0.645) 0.000	72/104 (69.2)	343/969 (35.4)	4.106 (2.653–6.355) <0.001	415/1073 (38.6)
Trimethoprim sulfamethoxazol	85/296 (28.7)	158/478 (33.1)	0.816 (0.595–1.119) 0.206	35/113 (31)	208/661 (31.5)	0.816 (0.595–1.119) 0.917	243/774 (31.3)
Nitrofurantoin	231/285 (81.1)	385/447 (86.1)	0.689 (0.462–1.027) 0.067	100/106 (94.3)	516/626 (82.4)	3.553 (1.520–8.305) 0.002	616/732 (84.1)

\*P value obtained from chi-square test if expected cell count was greater than 5 and Fisher exact test if expected cell count was less than 5.

**Table 3.** Antimicrobial Sensitivity of Major Microorganisms Causing Community-Acquired Urinary Tract Infection in Patients Hospitalized in Three Hospitals in Isfahan, Iran During 2016–2018 According to Etiology of the Infections: Results of the IAS-1 project

Antibiotic [Number of Sensitive/Total Examined Isolates (%)]	Etiology (Total Isolates)			
	<i>E. coli</i> (804)	<i>K. pneumonia</i> (94)	<i>Enterococcus</i> spp. (104)	<i>Staphylococcus</i> spp. (59)
Cefotaxime	167/418 (40)	15/42 (35.7)	—	—
Ceftriaxone	134/337 (39.8)	14/37 (37.8)	—	—
Ceftazidim	348/718 (48.5)	31/85 (36.5)	—	—
Cefepime	320/604 (53)	32/79 (40.5)	—	—
Imipenem	598/611 (97.9)	46/56 (82.1)	—	—
Meropenem	411/419 (98.1)	45/61 (73.8)	—	—
Amikacin	593/618 (96)	72/88 (81.8)	—	—
Gentamicin	314/478 (65.7)	24/39 (61.5)	25/41 (61.0)	34/50 (68.0)
Ciprofloxacin	286/732 (39.1)	32/88 (36.4)	26/96 (27.1)	31/55 (56.4)
Trimethoprim- sulfamethoxazol	183/597 (30.7)	23/68 (33.8)	0/3 (0.0)	26/54 (48.1)
Vancomycin	—	—	62/86 (72.1)	45/45 (100)
Ampicillin	55/681 (8.1)	1/34 (2.9)	58/96 (60.4)	—
Penicillin G	—	—	16/34 (47.1)	—
Cefoxitin	—	—	—	24/46 (52.2)

control nurses at the bed of patients in enrolled hospitals.<sup>14</sup>

The sex pattern of patients in our study reveals relatively equal distribution in both sexes. Approximately 41% of admitted patients in our study were males. This finding is in accordance with findings of previous researches in hospitalized patients with UTI.<sup>8,9</sup>

In our study, consistent with some other investigations,

the most frequent bacterium in the UTI cases was *E. coli*, accounting for 68.1% of the isolates. The percentage of the isolate is comparable to those reported in several former investigations.<sup>10</sup> *Enterococcus* spp. was the second most common organism followed by *Klebsiella* spp. and *Staphylococcus* spp. Our study is different from some researches that reported *Klebsiella* spp. or other Gram-

negative rods as the second most prevalent urinary pathogen. As we included only hospitalized patients with community-acquired UTI in the analysis, the finding could be different from other investigations that had included outpatient cases<sup>12,13</sup> or nosocomial hospitalized individuals.<sup>10,11,12,16</sup>

Our study, in accordance with findings of some previous investigations, shows that non-*E. coli* uro-pathogens were significantly more common in male<sup>8,9,10</sup> and younger (<20 years) UTI cases.<sup>8</sup>

The most effective antibiotics in our study were carbapenems (imipenem, meropenem) and amikacin. This finding can suggest them as the first line for empiric treatment of hospitalized UTI patients with severe symptoms in the area.

Carbapenems are effective drugs for multidrug resistant (MDR) *Enterobacteriaceae*, and our results are in agreement with the frequency of resistance to these antibiotics from earlier studies in Canada, Greece, and India (less than 10%).<sup>10-12</sup> However, due to the frequent administration of the drugs in recent years, resistance to this class of antibacterial medications is growing.<sup>17</sup> Therefore, carbapenems should be kept for empiric therapy of severely ill patients with UTI. However, after obtaining the culture results, another appropriate antibiotic might be started.

Amongst aminoglycosides, we found that amikacin had high activity against urinary pathogens, as described in previous studies.<sup>9,11,12</sup> More than 90% of the isolates showed susceptibility to this medication in disk diffusion test. Amikacin has a dose-dependent bactericidal activity, achieves enough concentrations in renal parenchyma and can be administered via the intramuscular route; thus, it could be a good suggestion for treatment of patients who cannot tolerate oral medications and are planned to be treated in an outpatient setting.<sup>18,19</sup> However, because of the nephrotoxicity of this medication, administration of amikacin for treatment of renal infections has decreased in recent years.<sup>18,19</sup>

In our study, the sensitivity of isolates to gentamicin was about 64%. This finding is in concordance with the study in Bosnia<sup>13</sup> and in contrast to previous studies in Iran and Canada that reported more than 90% susceptibility of urine pathogens to this antibiotic.<sup>9,10</sup> These differences are probably due to difference in year of the research or difference in antibiotic prescription in different societies.<sup>20</sup>

Our analysis revealed that urinary isolates were highly resistant to cefotaxime (60.0%), ceftriaxone (58.2%), ceftazidime (52.8%), and cefepime (47.3%), therefore making these antibiotics unsuitable for empiric treatment of UTI in severely ill inpatient cases. These findings should be considered in spite of the fact that cephalosporins are amongst the most commonly prescribed medications for treatment of UTI all around the world. This high resistance rate to cephalosporins was also reported in

previous studies conducted in Iran.<sup>9</sup> However, reports from the USA, Canada, and Greece have shown susceptibility rates of greater than 90% in urinary isolates; this might be because of the difference in the study time or geographical settings.<sup>8,10,11</sup>

Ciprofloxacin and other fluoroquinolones are broadly prescribed for treatment of upper and lower UTIs in recent years.<sup>21</sup> We found a low susceptibility rate of uropathogens to ciprofloxacin (38.6%). Therefore, this agent is not appropriate for empirical treatment of inpatient UTI cases and should be reserved for de-escalation therapy, after confirmation of sensitivity of uropathogen to it, based on the opportunity of its oral usage.<sup>21</sup> This finding is consistent with previous researches performed in Iran and Bosnia,<sup>9,13</sup> and in contrast to reports from the USA and Canada.<sup>8,10</sup>

In our study, most of the isolates (68.7%) showed resistance to trimethoprim-sulfamethoxazole, as reported in previous investigations in Iran, India, and Bosnia.<sup>9,12,13</sup> Extensive use of this antibiotic in outpatients with urinary or respiratory tract infections could explain this high level of resistance in different communities.<sup>20,21</sup> However, as this medication has an oral formulation, it would be a good choice for de-escalation therapy and for completion of the duration of therapy. This high level of resistance to trimethoprim-sulfamethoxazole was previously reported from a study in Bosnia.<sup>13</sup> In some earlier studies, urinary isolates had better susceptibility to this agent, probably due to the time and location of the research<sup>8,10,11</sup> or inclusion of outpatient cases in the final analysis.<sup>10</sup>

Our study had some limitations. First, our investigation was performed in three referral and large hospitals; thus, generalization of the results to all hospitalized patients with UTI should be done with caution. The second limitation is that the study was laboratory-based and information on previous antibiotic administration or anatomical abnormalities of the patients is lacking. Such data could provide meaningful clues to allow a better understanding of the sensitivity pattern of causative bacteria in clinical settings. The third is that our data were extracted from the routine work of the clinical laboratories and all antibiotic disks and strips were not available at the time of isolation of the bacteria. So, all microorganisms were not tested by all antibiotic disks and strips.

## Conclusion

Our data revealed that *E. coli*, *Enterococcus* spp. and *K. pneumonia* were the predominant isolates among hospitalized patients with community-acquired UTI. In addition, we found a high susceptibility rate of uropathogens to imipenem, meropenem, and amikacin, suggesting them as good choices for empiric therapy of complicated or severe infections. Moderate sensitivity to gentamicin, cefepime, and ceftazidime suggests them as

acceptable initial therapy in non-severe cases; while low susceptibility to cefotaxime, ceftriaxone, ciprofloxacin, and trimethoprim- sulfamethoxazole makes them unsuitable for empiric therapy of inpatients with community-acquired UTI in the area.

#### Authors' Contribution

SNM was the main investigator and proposed the main idea, designed the study, wrote the protocols and guidelines and revised the manuscript. SR was project manager and collected the data. YR analyzed the data and wrote the first draft of the manuscript. BA, SM, ACh, SH, MH, RE, NA, SM, MM and RK were members of the Scientific committee. SN, AP, PA, NA, LH, KN, SK, ShN, LM, ZN, MB, DSH, and MR were members of the executive committee.

#### Conflict of Interest Disclosures

None declared.

#### Ethical Statement

The research protocols were reviewed and approved by the Institutional Review Board of Isfahan University of Medical Sciences (Approval number: IR.MUI.MED.REC.1398.232).

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