

## Pattern of Antibacterial Resistance in Urinary Tract Infections: A Systematic Review and Meta-analysis

### Abstract

**Background:** Urinary tract infection (UTI) is one of the most common infectious diseases ranking next to upper respiratory tract infections. UTIs are often significantly associated with morbidity and mortality. The inappropriate administration of antibiotics to treat these infections increased infection resistance to antibiotics. The aim of this study is to determine the frequency of antibiotic resistance pattern in UTIs. **Methods:** We searched several databases including PubMed, Web of Science, Scopus, Google Scholar, Iran Medex, Magiran, IranDoc, MedLib, and Scientific Information Database to identify the studies addressing antibacterial resistance patterns of the most common uropathogenic bacteria in UTIs in Iran. A total of 90 reports published from different regions of Iran from 1992 to May 2015 were involved in this study. **Results:** It is shown that the most common pathogen causing UTIs is *Escherichia coli* with 62%. The resistance among the isolates of *E. coli* was as follows: ampicillin (86%), amoxicillin (76%), tetracycline (71%), trimethoprim-sulfamethoxazole (64%), cephalexin (61%), and cefalothin (60%). The highest sensitivity among isolates of *E. coli* was as follows: imipenem (86%), nitrofurantoin (82%), amikacin (79%), chloramphenicol (72%), and ciprofloxacin (72%). **Conclusions:** The results of this study showed that the most common resistance are antibiotics that are commonly used. The most effective antibiotics for *E. coli* were imipenem, nitrofurantoin, amikacin, chloramphenicol, and ciprofloxacin. Considering this study, it had better, use less gentamicin, second-generation cephalosporins, and nalidixic acid in the initial treatment of infections caused by *E. coli*, and no use penicillins, tetracyclines, cotrimoxazole, and first-generation cephalosporins.

**Keywords:** Antibiotics, antimicrobial resistance, Gram-negative bacteria, Gram-positive bacteria, urinary tract infections

### Introduction

After respiratory infections, urinary tract infections (UTIs) as one of the most common bacterial infections are considered human. Several studies suggest that Gram-negative bacilli, including *Enterobacteriaceae* bacteria family, are the most common microorganisms in the appearance of UTIs. In the meantime, *E. coli* is causing more than 81% of cases of UTIs;<sup>[1,2]</sup> afterward, *Staphylococcus saprophyticus*, *Klebsiella*, *Enterobacter*, *Proteus*, and *Enterococci* have identified as the causes of UTIs.<sup>[3]</sup> Quick and accurate diagnosis of UTI is very important to shorten the course of illness, as well as to prevent disease progression toward upper UTIs and renal impairment.<sup>[4]</sup> Resistances to antibiotics in different parts of the world due to genetic changes in strains, diversity in the use of antibiotics, and division in the availability to broad-spectrum of

new antibiotics are different.<sup>[5]</sup> In many infectious diseases including UTIs, a physician needs to start the treatment before a definitive diagnosis of infection cause and antibiogram; therefore, to administer the appropriate antibiotic, the physician must have sufficient information about the probable cause of infection and antibiotic susceptibility;<sup>[6]</sup> hence, UTI agents and their antibiotic resistance are identified in each region to start treatment before culture and antibiotic sensitivity test results.<sup>[5,7]</sup> Studies to identify the pathogens responsible for UTIs and antibiotic resistance are significant to their specific therapy to eradicate the infectious agent.<sup>[8,9]</sup> According to the numerous studies in the field of bacterial drug resistance patterns of UTIs, for validating the results of this study to give more precise and valid results, the current study is carried out through systematic review and meta-analysis.

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## Methods

A database was built for the most common resistance pattern of bacteria that causes UTIs in Iran from 1991 to 2015 using internal and external databases, including Scientific Information Database, Magiran, IranDoc, IranMedex, MedLib, PubMed, Web of Science, Scopus, and Google Scholar. Search was limited to research papers about the most common bacterial causing UTIs and their antibiotic resistance patterns that have published in Persian and English magazines. The keywords, titles, and abstracts were used by Boolean operator assistance. Keywords involved are UTIs, Gram-negative bacteria, Gram-positive bacteria, antibiotics, and antibiotic resistance. Likewise, titles and search results were evaluated and their suitability was determined for potential inclusion in the study. Furthermore, the references of selected articles were examined. Related studies in the list of references for inclusion in the study were selected.

### Inclusion and exclusion criteria

All cross-sectional or group studies were considered in relation to antibiotic resistance patterns of bacteria that cause UTIs. Study selection for inclusion in the assessment was done in three stages based on papers review: title, abstract, and full text. In some cases, due to ambiguity in the results of a study, the author should be contacted by for more information. Related studies involved the prevalence of bacteria causing UTIs and antibiotic resistance pattern. Studies excluded from the analysis in each of the following reasons: studies that had insufficient information, studies not included in epidemiological studies, studies not included in cross-sectional studies, and studies that have relation with other infections than UTIs. Furthermore, overview studies, summary of congresses, studies published in other languages except for Persian and Latin, systematic studies and meta-analyses, and repetitive publications were excluded from the analysis.

### Data extraction

The data extracted from all studies were first author, publication year, study year, study location, sample size, average and age group, gender, type of insulation, urinary pathogen prevalence, bacterial factors, resistance to different antibiotics, antibiotic susceptibility test methods, and antibiotics susceptibility report criteria [Table 1]. Abstract and full-text search and examination were performed independently by two people, and if the results did not have any corresponding together, studies coexamined jointly to resolve the dispute.

### Statistical analysis

With regard to the prevalence of antibiotic resistances and sample numbers that were obtained in each article, for

calculating the variance of each study and combined with the amounts of various studies, the prevalence of binomial distribution and weighted average were used, respectively. However, weight was given to each study proportional to its variance inverse. Due to the large difference in prevalence in different studies (heterogeneity in studies) and know the significance of the homogeneity index ( $I^2$ ), the random-effects model was used in the meta-analysis.

## Results

As a result of the initial search, 184 articles were obtained. In the next stage, 34 articles were rejected based on titles and abstracts assessment and the full-text 150 articles remained were studied. After this, 137 papers were selected to be involved the next stage. Then, 47 articles were eliminated (8 reviews, 19 duplicates, 7 low-quality articles, and 13 articles due to insufficient information). Finally, after a precise review of selected articles, 90 studies conducted in 1991–2015 have been entered in the meta-analysis [Figure 1]. General specifications and data sheet are depicted in Table 1.

In reviewing studies in this meta-analysis, by a total number of urine samples collected in national and private laboratories, based on standard methods, 35,118 people with UTI (65.37% female and 34.63% male), also 78.40% of urinary infections were common outpatient and hospitalized patients were 21.60%.

Among the most common pathogens causing UTIs were *E. coli*, *Klebsiella*, *Staphylococcus*, and *Streptococcus* with a frequency of 62%, 13%, 12%, and 11% took place the next ranks, respectively [Figure 2]. Other bacteria *Enterococcus*, *Citrobacter*, *Acinetobacter*, *Pseudomonas*, *Proteus*, and *Enterobacter* had a marginal role in UTI with the frequency of 2% [Table 2].

Resistance of *E. coli* to different antibiotics in the included studies at meta-analysis is summarized in Table 3. The analysis results of the most common resistance isolates

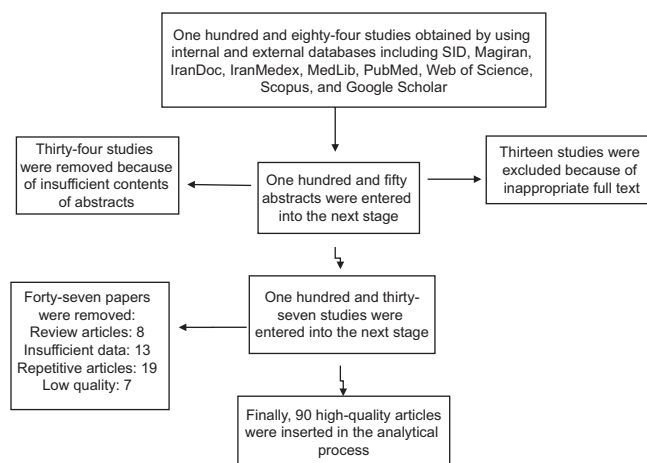


Figure 1: Studies entry to systematic review and meta-analysis

Table 1: General data and specifications reviewed articles in the meta-analysis

First author	Publishing year	Study year	Location of study	Number of samples	The Prevalence of Pathogens (percent)										
					<i>Streptococcus</i>	<i>Enterobacter</i>	<i>Proteus</i>	<i>Pseudomonas</i>	<i>Citrobacter</i>	<i>Enterococci</i>	<i>Staphylococcus</i>	<i>Klebsiella</i>	<i>E. coli</i>		
Molazadeh <sup>[74]</sup>	1391	1383	Western Azerbaijan	1900	-	-	-	-	-	-	-	-	-	-	39.3
Mohajeri <sup>[75]</sup>	1390	1387	Kermanshah	1114	-	-	-	-	-	-	-	-	-	-	75
Molazadeh <sup>[7]</sup>	1393	91-92	Fasa	2484	-	5.4	-	-	-	-	-	-	-	-	16.6
Mosavian <sup>[76]</sup>	1383	1382	Ahvaz	38	-	18	-	6	-	-	-	14	-	-	34
Madani <sup>[77]</sup>	1387	1358	Kermanshah	1815	-	-	-	-	-	-	-	-	-	-	45.4
Sorkhi <sup>[78]</sup>	1384	1381	Babol	188	-	-	-	-	-	-	-	-	-	-	59.5
Ghoutsalou <sup>[79]</sup>	1384	91-92	Tabriz	213	-	5.2	-	4.2	-	-	-	-	-	-	79
Norouzi <sup>[80]</sup>	1379	1377	Tehran	313	-	1.6	-	5.9	-	-	-	-	-	-	53.5
Alaie <sup>[81]</sup>	1387	84-83	Tehran	510	-	2.4	-	7.6	-	-	-	-	-	-	72
Torabi <sup>[82]</sup>	1368	1385	Zanjan	118	-	3.9	-	-	-	-	-	-	-	-	48.4
Hajizade <sup>[83]</sup>	1382	1381	Tehran	150	-	-	-	5	-	-	-	-	-	-	50
Eghbalian <sup>[84]</sup>	1384	83-84	Hamedan	156	-	6.4	-	2.6	-	-	-	-	-	-	82
Jarsiah <sup>[72]</sup>	1393	90-91	Tehran	208	-	-	-	3.4	-	-	-	-	-	-	73.1
Mirmostafa <sup>[85]</sup>	1392	1379	Karaj	100	-	-	-	-	-	-	-	-	-	-	83
Mobasher <sup>[86]</sup>	1381	139	Gorgan	33	-	-	-	3	-	-	-	-	-	-	33.3
Asgharian <sup>[87]</sup>	1391	89-90	Tenekanon	307	-	-	-	-	-	-	-	-	-	-	84.6
Sharifi <sup>[88]</sup>	1378	74-76	Kashan	152	-	0.8	-	-	-	-	-	-	-	-	52
Rahimi <sup>[89]</sup>	1393	90-91	Esfahan	301	-	-	-	2	-	-	-	-	-	-	65.5
Mokhtarian <sup>[90]</sup>	1385	80-84	GONABAD	353	-	-	-	2.3	-	-	-	0.65	-	-	66
Assefzadeh <sup>[91]</sup>	1383	1386	Ghazvin	224	-	3.1	-	2.7	-	-	-	3.1	-	-	61.2
Tarhani <sup>[64]</sup>	1382	80-81	Khoram abad	127	-	3.1	-	12.6	-	-	-	0.8	-	-	23.2
Hamid-Farahani <sup>[92]</sup>	1391	87-88	Tehran	456	-	8.6	-	-	-	-	-	2	-	-	60.3
Mohammadi <sup>[93]</sup>	1385	1380	Falavarjan	209	-	6.2	-	2.4	-	-	-	3.3	-	-	54.1
Fahimi <sup>[94]</sup>	1382	75-82	Tehran	120	-	-	-	0.5	-	-	-	1.4	-	-	54.1
Saeedi <sup>[95]</sup>	1392	89-91	Mashhad	102	-	-	-	14.5	-	-	-	14.5	-	-	61.1
Yazdi <sup>[96]</sup>	1389	88-89	Tehran	444	-	-	-	-	-	-	-	-	-	-	16.3
Yadollahi <sup>[97]</sup>	1381	71-76	Chaharmahal va Bakhtiari	202	-	6.5	-	2.5	-	-	-	-	-	-	55.4
Soleimani <sup>[98]</sup>	1392	91-92	Semnan	100	-	-	-	-	-	-	-	-	-	-	80
Moulana	1392	87-88	Babol	770	-	12.1	-	-	-	-	-	5.9	-	-	70
Heidari-soreshjani <sup>[100]</sup>	1392	90-91	Chaharmahal va Bakhtiari	74	4.5	-	-	-	-	-	-	-	-	-	48.6
Soltan Dallal <sup>[101]</sup>	1390	88-89	Tabriz	400	-	-	-	-	-	-	-	-	-	-	70.3
Yazdi <sup>[102]</sup>	1392	-	Tehran	300	22.3	-	-	-	-	-	-	22.3	-	-	47
Fesharaki <sup>[103]</sup>	1391	88-89	Birjand	100	-	-	-	11	-	-	-	-	-	-	77.7
Jalalpour <sup>[104]</sup>	1388	1387	Esfahan	91	-	-	-	-	-	-	-	-	-	-	75
Mohammadimehr <sup>[105]</sup>	1390	86-87	Tehran	77	-	6.5	-	9.1	-	-	-	-	-	-	84.6
Sahebnaigh <sup>[106]</sup>	1393	1392	Tehran	1123	-	-	-	-	-	-	-	-	-	-	45.4
Safkhami <sup>[107]</sup>	1393	1392	Tehran	136	-	-	-	4.4	-	-	-	1.5	-	-	50
															11.8
															13.2
															8.8
															4.4
															13.2
															11.8
															51.5

Contd...

Table 1: Contd...

First author	Publishing year	Study year	Location of study	Number of samples	The Prevalence of Pathogens (percent)											
					<i>Streptococcus</i>	<i>Enterobacter</i>	<i>Proteus</i>	<i>Pseudomonas</i>	<i>Acinetobacter</i>	<i>Citrobacter</i>	<i>Enterococci</i>	<i>Staphylococcus</i>	<i>Klebsiella</i>	<i>E. coli</i>		
Soltan Dallal <sup>[100]</sup>	1393	91-92	Tehran	400	-	-	-	-	-	-	-	-	-	24	-	
Asghari	1393	89-90	Tehran	116	-	-	-	10.3	-	-	-	-	-	-	-	-
Moghadam <sup>[108]</sup>																
Mortazavi <sup>[109]</sup>	1393	1391	Yasouj	200	-	-	-	-	-	-	-	-	-	-	61.5	-
Asadi Manesh <sup>[5]</sup>	1393	1391	Yasouj	145	-	3.5	6.2	2.8	-	-	-	-	3.4	10.3	72.4	-
Dehbashi <sup>[100]</sup>	1393	92-93	Tehran	522	10.3	-	-	-	-	-	-	-	-	-	-	-
Savadkoochi <sup>[111]</sup>	1392	89-90	Babol	128	-	-	-	4.1	-	-	-	-	-	-	3.1	8.9
Sharif <sup>[112]</sup>	1393	91-92	Kashan	180	-	-	1.7	1.1	2.8	1.2	5.6	4.4	4.4	19.4	64.3	-
Isvand <sup>[3]</sup>	1393	1391	Dezfool	160	3.1	1.9	-	1.3	-	2.5	-	4.4	4.4	20.1	63.3	-
Esmaili <sup>[113]</sup>	1392	90-91	Hamedan	141	-	10.7	7.1	7.9	-	-	-	8.5	-	61	61	-
Hosseini <sup>[114]</sup>	1393	91-92	Ghazvin	12.4	-	-	-	-	-	-	-	-	-	10.6	61.1	-
Shahraki <sup>[115]</sup>	1393	1391	Zahedan	122	-	-	-	-	-	-	-	-	-	8.2	-	-
Bagheri <sup>[116]</sup>	1393	90-91	Gorgan	111	-	26.1	6.3	13.5	1.8	-	-	-	-	40.5	-	-
Molazade <sup>[117]</sup>	1393	91-93	Fasa	283	-	5.7	5.7	-	-	-	-	6.4	-	14.5	64.3	-
Molazade <sup>[118]</sup>	1393	91-92	Fasa	24-84	-	5.8	3.5	1.7	-	-	-	-	-	23.9	64.7	-
Molaabaszadeh <sup>[119]</sup>	1392	1390	Tabriz Fasa	5701	-	-	-	-	-	-	-	-	-	58.4	58.4	-
Farajnia <sup>[20]</sup>	1388	86	Tabriz	676	-	1.2	1.2	2.7	-	-	1.2	8	-	11.7	74.6	-
Ahangarkani <sup>[121]</sup>	1393	92-93	Babol	128	-	-	-	-	-	-	-	-	-	-	78	-
Nasiri <sup>[122]</sup>	1379	78-79	Birjand	111	-	-	-	-	-	-	-	-	-	-	65	-
Savadkoochi <sup>[111]</sup>	1386	82-83	Babol	160	-	11.9	3.1	6.3	-	-	-	6.5	-	-	70	-
Panahi <sup>[123]</sup>	1387	80-84	Tehran	28	-	-	-	17.9	-	-	-	17.9	43	21.4	21.4	-
Esmaili <sup>[124]</sup>	1384	80-81	Mashhad	166	-	1.8	6	0.6	-	2.4	3.6	4.3	7.2	74.1	74.1	-
Jalalpoor <sup>[125]</sup>	1390	88-89	Esfahan	211	-	-	-	-	-	-	-	-	-	14	64	-
Jalalpoor <sup>[125]</sup>	1390	88-89	Esfahan	167	-	-	-	-	-	-	-	-	-	15	52	-
Zamanzad <sup>[126]</sup>	1384	1383	Shahre Kord	100	-	2	-	6	-	-	-	12	38	42	42	-
Zamanzad <sup>[126]</sup>	1384	1383	Shahre Kord	100	-	6	4	2	-	1	-	7	16	58	58	-
Norouzi <sup>[127]</sup>	1385	1	Jahrom	351	-	3.7	56	1.4	-	1.2	-	0.84	10.7	80.3	80.3	-
Abdollahi <sup>[128]</sup>	1383	86-87	Tehran	5400	15.7	1.3	2.3	-	-	0.8	2	14.1	8.8	44.5	44.5	-

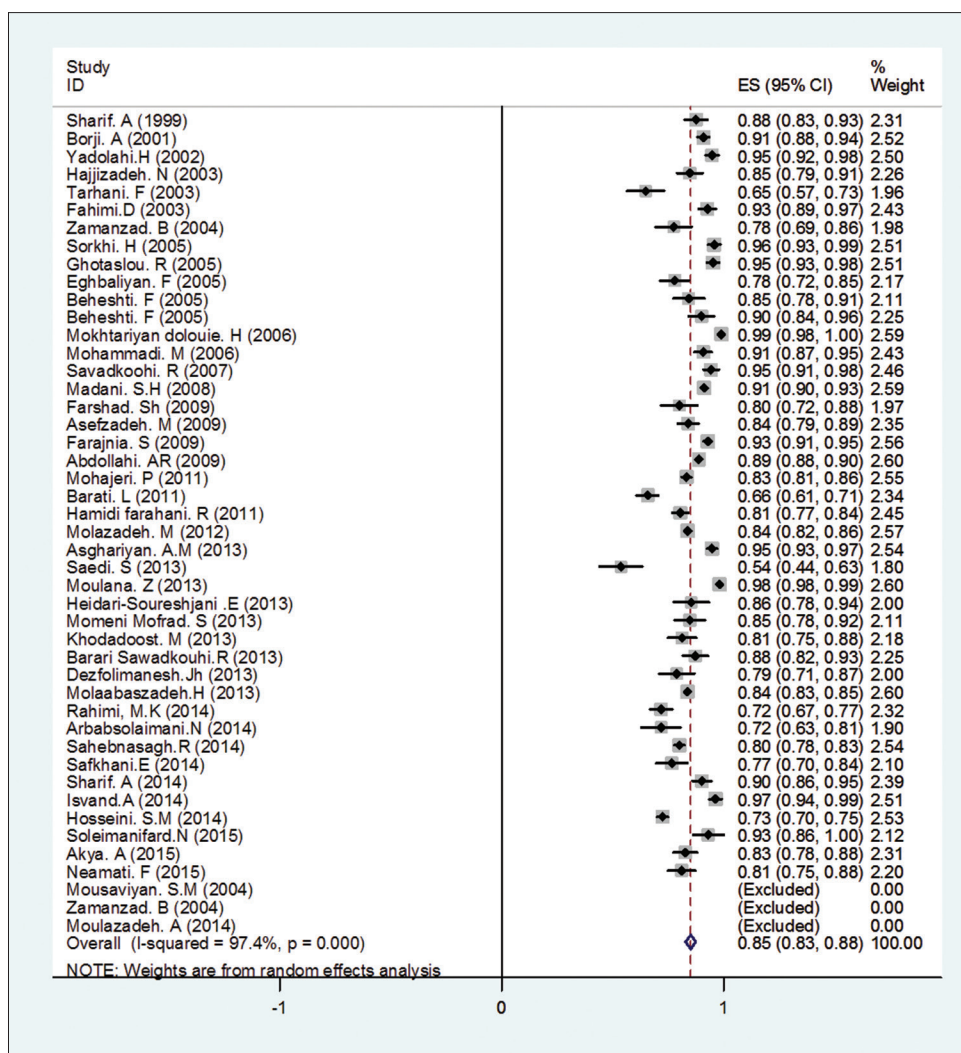


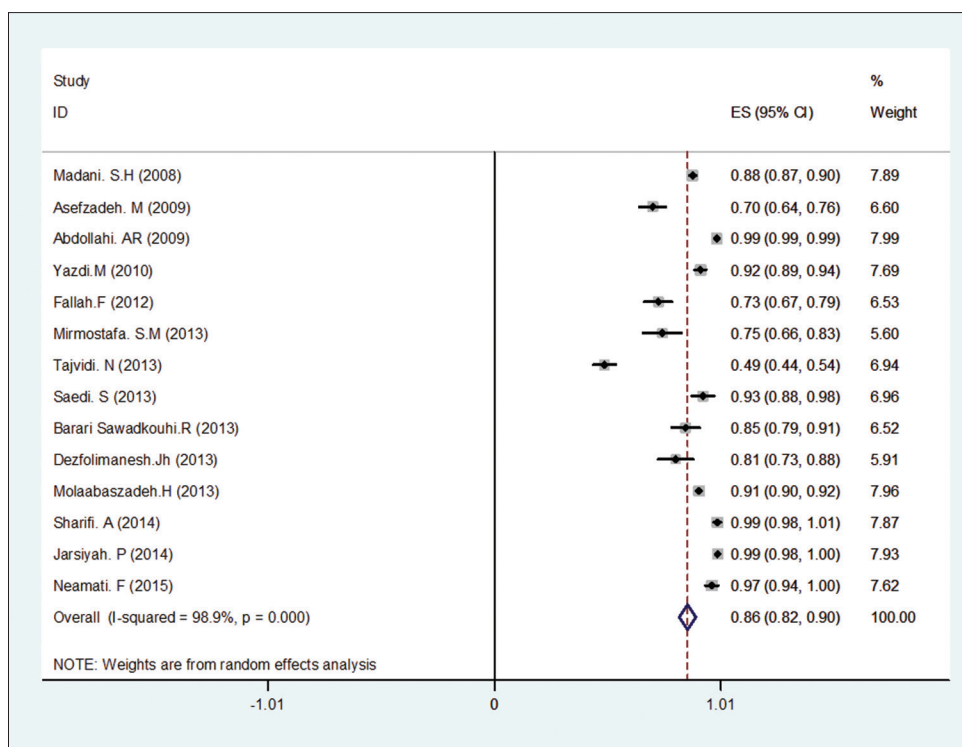
Figure 2: Resistances rate of Escobar isolates to Ampicillin based on a random-effects model. The midpoint of each piece represents an estimate of the prevalence, each piece represents a confidence interval of 15% in each study and diamond mark is indicative of all the studies in the whole country

Table 2: Frequency distribution of bacteria causing UTIs examined in the meta-analysis

P	Heterogeneity index $I^2$ (%)	Confidence interval (CI%95)	Prevalence	The number of studies	Bacteria type
<.001	97.9	58-65	62%	58	<i>E. coli</i>
<.001	95.6	11-15	13%	44	<i>Klebsiella</i>
<.001	98	0.09-15	12%	32	<i>Staphylococcus</i>
<.001	96	0.06-16	11%	6	<i>Streptococcus</i>
<.001	91.5	0.04-0.07	05%	12	<i>Enterococcus</i>
<.001	26.4	0.01-0.02	01%	14	<i>Citrobacter</i>
<.001	79.6	0.03-10	06%	5	<i>Acinetobacter</i>
<.001	72.8	0.02-0.04	03%	28	<i>Pseudomonas</i>
<.001	82.6	0.03-0.04	04%	28	<i>Proteus</i>
<.001	93	0.04-0.07	05%	28	<i>Enterobacter</i>
<.001	91.6	1.2-2.4	1.76	15	Other Species

causing UTIs to antibiotics are given in Table 4. As it can be seen, there is most resistance among *E. coli* isolates to ampicillin (86%) [Figure 2], amoxicillin (76%), tetracycline (71%), trimethoprim-sulfamethoxazole (64%), cephalexin (61%), and cefalothin (60%) antibiotics.

Likewise, the lowest rate of resistance had been observed in imipenem (14%) [Figure 3], nitrofurantoin (18%), amikacin (21%), chloramphenicol (28%), and ciprofloxacin (28%) antibiotics, and the resistance of *E. coli* isolates as compared to other used antibiotics



**Figure 3:** Resistances rate of *E.coli* isolates to Imipenem based on a random-effects model. The midpoint of each piece represents an estimate of the prevalence, each piece represents a confidence interval of 15% in each study and diamond mark is indicative of all the studies in the whole country

was as follows: gentamicin (32%), ceftriaxone (35%), cefazolin (48%), cefixime (45%), nalidixic acid (43%), cefotaxime (42%), and ceftazidime (40%).

In examining *Klebsiella* isolates, the lowest level of resistance to imipenem (13%), ciprofloxacin (19%), and amikacin (27%) were found. The resistance rate of *Klebsiella* isolates to other antibiotics was as follows: cefalothin (55%), trimethoprim-sulfamethoxazole (54%), tetracycline (53%), cefixime (53%), chloramphenicol (47%), nitrofurantoin (42%), ceftazidime (40%), ceftriaxone (40%), gentamicin (38%), cefotaxime (38%), and nalidixic acid (33%). In *Staphylococcus* isolates, the highest rate of resistance to ampicillin (87%), cephalixin (72%), and ceftriaxone (66%) antibiotics and the lowest rate of resistance to ciprofloxacin (20%) antibiotic was observed; furthermore, a resistance rate had also been seen in antibiotics of sulfamethoxazole (58%), nalidixic acid (51%), gentamicin (49%), cephalothin (43%), nitrofurantoin (42%), and amikacin (41%).

## Discussion and Conclusions

In the current study, the prevalence rate of UTI in women was several times more than men (women, 65.37% and men, 34.63%). In studies conducted in other parts of the world such as New York,<sup>[10]</sup> America,<sup>[11,12]</sup> Washington,<sup>[13]</sup> Portugal,<sup>[14]</sup> Mexico,<sup>[15]</sup> Nigeria,<sup>[16,17]</sup> Taiwan,<sup>[18]</sup> India,<sup>[19]</sup> and Pakistan,<sup>[20]</sup> the incidence of UTIs in women also was higher. The results of these studies are consistent with the results of our study, due to anatomical differences between

men and women, including a short urethra and its external opening adjacent to the vagina and anus in women.<sup>[21,22]</sup>

The current study showed that *Enterobacteriaceae* family bacteria are the most common causes of UTIs; due to the presence of these bacteria in the digestive tract, a possible UTI may occur.<sup>[9]</sup> In the present study, *E. coli* was the most common pathogen that causes UTI; this result has to correspond to more studies in other parts of the world. *E. coli* prevalence reported 50%–80% in Asia (58% in Saudi Arabia,<sup>[23]</sup> 70% in India,<sup>[19]</sup> 75.3% in Turkey,<sup>[24]</sup> 65.9% in South Korea,<sup>[25]</sup> 74.8% in Bangladesh,<sup>[26]</sup> 60.29% in Africa<sup>[27]</sup>, 90%–60% in Europe (64.5% in Portugal<sup>[14]</sup> and 85.9% in Russia<sup>[28]</sup>) 90%–75% in the USA,<sup>[29]</sup> and 76.6% in Brazil.<sup>[30]</sup> *E. coli* in the current and mentioned studies is the most common pathogen causing UTIs.

In other articles, other pathogens that cause UTIs more than *E. coli* have also been mentioned. In our study, *Klebsiella* was the second most common cause of UTIs; this result is consistent with the studies conducted in Australia,<sup>[31]</sup> South Africa,<sup>[32]</sup> Taiwan,<sup>[18]</sup> Bangladesh,<sup>[26]</sup> Pakistan,<sup>[20]</sup> and India.<sup>[33]</sup> However, in the studies conducted in South Korea and Europe, this had been reported that *Enterobacter* is the second UTI factor after *E. coli*.<sup>[25,34]</sup> In a study in Portugal on *Enterobacter* and *Klebsiella* bacteria, it has found that both bacteria have the same effect on UTIs after *E. coli*.<sup>[14]</sup> In regard to carried study in France, in urinary infections after *E. coli*, Gram-positive cocci were the most common cause of infection.<sup>[35]</sup> According to the current study

and noted articles in this context, it is reported that the bacteria causing UTIs are approximately the same in the world. In general, *E. coli* are the most common bacteria. Then, *Klebsiella*, *Staphylococcus*, *Enterobacter*, and other species with slight differences in different geographical locations in the next category are placed. The resistance rate of *E. coli* and *Staphylococcus* ampicillin was 86% and 87%, respectively. In a study in South Korea, the resistance rates of *E. coli* and *Klebsiella* isolates to ampicillin were 6.63% and 99%, respectively.<sup>[25]</sup> In the same study in Taiwan, the rates of resistance in *E. coli* and *Klebsiella* were 100% and 70%, respectively.<sup>[18]</sup> *E. coli* resistance to ampicillin in studies conducted in Bangladesh was 80%,<sup>[36]</sup> Ethiopia 80%,<sup>[27]</sup> Mexico 79%,<sup>[37]</sup> UAE 72%,<sup>[38]</sup> Brazil 55%,<sup>[39]</sup> Turkey, 74%,<sup>[40]</sup> Greece 50%,<sup>[41]</sup> and America 48%.<sup>[42]</sup> Studies in North America, Canada, and Lebanon have reported similar results.<sup>[43-45]</sup> In the present and cited studies, the abundance of resistance to ampicillin was higher than other antibiotics. However, in the cited cases, as it can be seen, countries such as America, Brazil, and Greece had a lower rate of resistance than this study. The results of these studies suggest that antibiotics such as ampicillin are practically useless and even recommended not to be used for antibiogram.

In this study, the resistance rate of *E. coli* after ampicillin compared with amoxicillin (76%) and tetracycline (71%) higher. In a study in Ethiopia, the sensitivity of *E. coli* to amoxicillin was 15.4%, tetracycline was 17.8%, and ampicillin was 20%; for *Klebsiella*, it has been reported 30% to amoxicillin, 34.6% to tetracycline, and 8.1% to ampicillin.<sup>[26]</sup> In the same study as the current one, almost total resistance to amoxicillin, ampicillin, and tetracycline in the aforementioned isolates exists. The resistance to amoxicillin in urinary tract pathogens is similar to other studies that have conducted in other parts of the world, for example, the *E. coli* resistance to these antibiotics has been reported to be 85% in Ethiopia,<sup>[26]</sup> 67.5% in Senegal,<sup>[46]</sup> and 72% in India.<sup>[47]</sup> In Turkey, the rate of this resistance in separate studies had increased from 32.7% to 50% in 2009 and 2013.<sup>[24,48]</sup> In a Spanish study, *E. coli* antibiotic resistance at 2005, 2009, and 2011 was examined; the results showed that resistance to amoxicillin had increased from 4.5% in 2005 to 55.6% in 2011.<sup>[49]</sup> In a study in European countries, the resistance rate to amoxicillin was reported to be 48% in Poland and 60% in Belgium.<sup>[50]</sup> In all of these studies, the higher resistance to amoxicillin had reported, although the results of the current study similar to developing countries. Resistance to tetracycline in *E. coli* and *Klebsiella* isolates in Ethiopian<sup>[27]</sup> and Senegal<sup>[46]</sup> studies was similar to the present study. In this study, amoxicillin and tetracycline were taking place in another group of ineffective drugs. The reason for such resistance may be the somewhat irregular use of medication among patients, whether by prescription or willfulness, so they are not recommended as a treatment for UTI.

Cotrimoxazole is another antibiotic that is prescribed for UTI treatment. According to the results, all of the studied bacteria were resistant to the cotrimoxazole. *E. coli* resistance to cotrimoxazole in most developing countries illustrates similar results. For example, the rate of this resistance was 68.1% in Senegal,<sup>[46]</sup> 58% in Turkey,<sup>[24]</sup> and 53% in Lebanon.<sup>[45]</sup> Unlike the results of this study, some studies, especially that conducted on isolates of *E. coli* in developed countries, have reported low resistance to cotrimoxazole. For example, the rate of resistance in the studies conducted in Italy,<sup>[51]</sup> Canada,<sup>[44]</sup> Croatia,<sup>[52]</sup> America,<sup>[43]</sup> and Australia<sup>[31]</sup> was reported to be 27.1%, 22%, 20.59%, 21.3%, and 14.5%, respectively.

In the current study, based on resistance rate to antibiotics tetracycline and cotrimoxazole in uropathogenic *E. coli* (UPEC), it can be said that the antibiotic resistance rate of in Iran is higher than some developed countries. This difference may be due to the strains of microorganisms, self-medication by patients, incomplete treatment course, prescribe inappropriate antibiotics by physicians, the dosage of medication, manufacturer-based drug quality, relying on empirical treatment regardless of culture and antibiotic susceptibility test results. Therefore, strict measures of clinical practitioners should be put at the head of affairs, for infection control and prevention from resistance spread.

Furthermore, in the present study, quinolone family antibiotics such as nalidixic acid (first generation) and ciprofloxacin (second generation) were studied. In this study, resistance rates to nalidixic acid in *E. coli*, *Klebsiella*, and *Staphylococcus* were reported as 43%, 33%, and 51%, respectively, which shows the relatively high resistance. Regarding the past nalidixic acid in the first step used in treating UTIs, therefore, higher resistance is expected to these antibiotics than the other quinolone family antibiotics<sup>[51]</sup> that correspond with the findings of our study in this case. In Ethiopia, *E. coli* sensitivity rate to nalidixic acid, 86% reported<sup>[27]</sup> that toward the present study is higher but in Bangladesh has the lowest sensitivity (27%);<sup>[36]</sup> likewise, in Pakistan, resistance to nalidixic acid in urinary isolates of *E. coli*, 84.16% reported.<sup>[53]</sup> The results of these two studies are very different from the current study results that may be produced by overuse of cited drugs in developing countries without exact surveillance.

The high sensitivity to ciprofloxacin in all isolates (*E. coli* 72%, *Klebsiella* 81%, and *Staphylococcus* 80%) had been found. *E. coli* resistance to ciprofloxacin in the most done studies by other researchers reported, for example, resistance rates in Nigeria, Ethiopia, Senegal, India, South Korea, Turkey, Mexico, America, North America, Canada, Italy, and Germany about 5.5%–31.9%.<sup>[24,25,27,43,44,46,51,54-58]</sup> The resistance rate in urinary isolates of *E. coli* to ciprofloxacin in studies done in Pakistan and Bangladesh<sup>[36,53]</sup> was medium while in Lebanon with a frequency of 54% was too high. In this study, like







**Table 4: Sensitivity and resistance rate to different antibiotics in selected studies to the meta-analysis**

Antibiotic	<i>Staphylococcus</i>		<i>Klebsiella</i>		<i>E. coli</i>	
	Resistance	Sensitivity	Resistance	Sensitivity	Resistance	Sensitivity
Cotrimoxazole	58	42	54	46	64	36
Ampicillin	87	13	80	20	85	15
Amoxicillin	-	-	76	24	76	24
Tetracycline	-	-	53	47	71	29
Gentamicin	49	51	38	62	32	68
Amikacin	41	59	27	73	21	79
Ciprofloxacin	20	80	19	81	28	72
Nalidixic acid	51	49	33	67	43	57
Ceftazidime	-	-	40	60	40	60
Ceftriaxone	66	34	40	60	35	65
Cefotaxime	-	-	38	62	42	58
Cefixime	-	-	53	47	45	55
Cephalexin	72	28	67	33	61	39
Cefalotin	43	57	55	45	60	40
Imipenem	-	-	13	87	14	86
Nitrofurantoin	42	58	42	58	18	82
Chloramphenicol	-	-	47	53	28	72

many other studies, it has been determined that urinary tract pathogens have high sensitivity to quinolones and particularly ciprofloxacin that can be used as the first drug in the treatment of patients with UTI.<sup>[59]</sup> In Talon *et al.*'s study, fluoroquinolones had been recommended for the uncomplicated UTI treatment, especially when resistance to cotrimoxazole in a society does not exceed from 20% to 10%.<sup>[60]</sup> In general, this study illustrates that ciprofloxacin still can be used as the first-line therapy of UTIs in Iran.

Aminoglycosides are another group of antibiotics that are used in UTIs. In this study also, isolates resistant to amikacin and gentamicin were evaluated in this category. Resistance to amikacin in *E. coli* 21%, *Klebsiella* 27% and *Staphylococcus* 41% reported. Resistance to gentamicin in *E. coli*, *Klebsiella*, and *Staphylococcus* was reported to be 32%, 38%, and 49%, respectively. In most studies similar to our study, high sensitivity to amikacin was reported in UPEC. For example, *E. coli* sensitivity to amikacin in India was found to be 90.6%,<sup>[61]</sup> Saudi 93.7%,<sup>[61]</sup> South Korea 99.4%,<sup>[25]</sup> and Taiwan 100%.<sup>[18]</sup> Similarly, *E. coli* resistance to amikacin in Brazil was found to be 2%,<sup>[39]</sup> America 0%,<sup>[42]</sup> and China 11.7%.<sup>[62]</sup> In a study conducted in North America and Europe, *E. coli* sensitivity to amikacin was found to be about 98.5%–97.8%.<sup>[63]</sup> *Klebsiella* sensitivity to amikacin in South Korea was reported to be 95%<sup>[25]</sup> and Taiwan 100%,<sup>[18]</sup> which is consistent with our results.

In this study, founded relatively high sensitivity to gentamicin in *E. coli*, but sensitivity to gentamicin in *Staphylococcus* and *Klebsiella* obtained the average. *E. coli* sensitivity to gentamicin in South Korea was reported as 74.2%,<sup>[25]</sup> Taiwan 77%,<sup>[18]</sup> and Ethiopia 66%.<sup>[27]</sup> Likewise, in the study conducted in Europe, the resistance of *E. coli* to aminoglycosides was reported

to be about 4.21%–5.2%.<sup>[64]</sup> These results are consistent with the results of our study. *Klebsiella* sensitivity to gentamicin in both South Korea<sup>[25]</sup> and Taiwan 95%<sup>[18]</sup> that toward to our study was higher, but in Ethiopia, 57.1% was reported,<sup>[27]</sup> which corresponds to the results of this study. In a study in China, most *E. coli* isolates resistance to gentamicin (95.1%) was also reported.<sup>[62]</sup> The reasons for the difference in the frequency of resistance to aminoglycosides in above studies than ours can be the various distributions of resistance genes in different geographical areas, consumption of antibiotics, and prescribing pattern. Gentamicin is one of the drugs that can be used as initial treatment of UTIs until the culture results prepared. One of the interesting features about old antibiotics such as gentamicin and amikacin is good penetration into the bacteria cell.<sup>[65]</sup> however, due to the increased use and availability of gentamicin, its resistance is greater than other aminoglycosides in many regions, and on the other hand, less resistance to amikacin, the frequency of resistance to these effective and inexpensive drugs varies from region to region. For these reasons, antimicrobial susceptibility testing required before treatment. The results of this study showed that amikacin could be used as the first-line therapy for the treatment of UTIs in Iran. However, in the case of gentamicin, since the resistance rate of these organisms to gentamicin in the present study obtained as 32%–49%, it is a kind of alarm for the spread of organisms resistant to these antibiotics and is recommended to be taken with caution.

In the present study, cephalexin and cefalotin (the first generation of cephalosporins) investigated. All isolates causing UTI were resistant to cephalexin. *E. coli* also had a high resistance to cefalotin, but *Klebsiella* and *Staphylococcus* had an intermediate resistant to

these antibiotics. Furthermore, ceftazidime, ceftriaxone, cefotaxime, and cefixime (third-generation cephalosporins) investigated. The resistance rate of studied isolates to these group antibiotics was 65%–55%. Ethiopian,<sup>[27]</sup> Senegal,<sup>[46]</sup> and Lebanon<sup>[45]</sup> studies were consistent with the current study in this case. In these studies, intermediate resistance has reported in isolates of *Escherichia* to cephalosporins, but in the study of Taiwan, high sensitivity was observed in *E. coli* (cefazolin 81%, ceftriaxone 74%, and ceftazidime 89%) and also in isolates of *Klebsiella* (cefazolin 80%, ceftriaxone 85%, and ceftazidime 83%),<sup>[18]</sup> in South Korea, high sensitivity to cephalosporins was observed in *E. coli* (cefotaxime 89.4%, ceftazidime 89.2% and cephalotin 58.4%) and in *Klebsiella* (cefotaxime 78.8%, ceftazidime 77.8%, and cephalotin 70.5%)<sup>[25]</sup> has reported. A conducted study in Europe suggested *E. coli* resistance to the third generation of cephalosporins was around 19.2%–1.8%<sup>[64]</sup> and also low resistance has reported to these antibiotics in America.<sup>[57]</sup> In more advanced countries that have better performance in health and planning level, resistance to these antibiotics is less than Iran. Furthermore, in Greece, resistance to cefotaxime and ceftazidime 3.7% and 4% has been reported, respectively.<sup>[66]</sup> The different results of these studies than current study could be more accurate monitoring programs in that country and the unavailability of these drugs. This pharmaceutical group is the most common drugs in the treatment of infections, due to the high function and a wide range effect, but the results of this study and other studies indicative increasing resistance to these drugs in our country. In many countries such as Iran, this family of antibiotics is suitable as antimicrobial agents used in the treatment of UTIs, and this could be one of the main reasons for resistance to these antibiotics. Therefore, to avoid increasing resistance to this antibiotic group being used with caution and intransitive proceedings should be done.

In the present study, isolates were most sensitive to imipenem (86% in *E. coli* and 87% in *Klebsiella*). *E. coli* sensitivity to imipenem in Taiwan was 100%,<sup>[18]</sup> South Korea 100%,<sup>[25]</sup> India 98.89%,<sup>[55]</sup> Saudi Arabia 91.71%,<sup>[61]</sup> Turkey 93%,<sup>[24]</sup> and Europe and North America 99.7% and 99.8%,<sup>[63]</sup> respectively. Likewise, *Klebsiella* sensitivity to imipenem in Taiwan<sup>[18]</sup> and South Korea both was 100%<sup>[25]</sup> that these results were consistent with the results of this study. As mentioned above, the most effective antimicrobial agent was imipenem in this study that was consistent with the results of previous studies. This resistance reduction could be due to the limitation of drug usage in nosocomial infections, lack of necessary conditions (intravenous injection) in UTIs treatment in outpatients, lack of access to this drug, as well as being more expensive in compared with other drugs.<sup>[67]</sup>

In *E. coli*, highest sensitivity obtained to nitrofurantoin 82% after imipenem, but moderate sensitivity to these antibiotics was observed in *Staphylococcus* and *Klebsiella*

isolates (58% each). In the United Kingdom<sup>[68]</sup> and extensive studies conducted in both America and Canada, very low resistance prevalence has been reported in urinary isolates of *E. coli* to nitrofurantoin (1.1% and 4%).<sup>[43,44]</sup> In studies conducted in China and Saudi Arabia, *E. coli* resistance rate to nitrofurantoin was 8% and 6.5%–2.4% reported, respectively.<sup>[69,70]</sup> The sensitivity of *E. coli* to nitrofurantoin in Ethiopia was 89.6%<sup>[27]</sup> and India 77.4% reported.<sup>[19]</sup> These studies are consistent with the present study. In this study, *E. coli* has a high sensitivity to chloramphenicol (72%), which is consistent with other studies.<sup>[19,24,27]</sup> According to the results of this study, the use of imipenem and nitrofurantoin antibiotics suggests because of their positive role has been evaluated by various articles. The UTIs are the most common infections seen in all parts of the world. However, the infection is not threatening, but if specific therapy is done, its side effects can be very severe.<sup>[21,71,72]</sup> The initial treatment of the infection is often experimental, and antibiotics selection depends on various factors such as intensity of symptoms, drug toxicity, and the effectiveness of treatment; however, the common types of urinary pathogens in the community and their susceptibility antimicrobial patterns are effective in antibiotic selection.<sup>[73]</sup> It is noteworthy that this antibiotic resistance of these bacterial agents is different in diverse parts of the world. Hence, in the treatment of urinary infections, antibiotic selection should be based on knowledge of the region, and international reports are not an appropriate choice for antimicrobial drug selection.<sup>[68,74]</sup> Due to the additive prevalence of resistance to antibiotics, early and timely diagnosis of the resistant bacterial isolates is considered necessary, to select appropriate treatment options and prevent the proliferation of resistance.

### Limitations

The limitations of this study were the lack of resistance rate estimation in urinary uropathogenic for all antibiotics used in Iran, due to the lack of information in this field of compiled researches. Nonentity of calculation for antibiotic resistance rate in isolates that cause UTIs in males and females separately is one of the limitations of this study because only a limited number of resistance studies were calculated separately for these genders. In most studies, age category is one of the affecting factors on mentioned resistance rate; however, due to nonentity in mentioning of the age group in a large number of studies and also due to the lack of entity similar age groups in the number of other studies, we could not calculate the resistance rate in terms of age; another limitation of this study was the lack of determined resistance rate by type of patient admission because such information did not exist in large number of compiled studies.

### Conclusions

According to the present study, *E. coli* was the most common cause of UTI, and after that, *Klebsiella*,

*Staphylococcus aureus*, and *Enterobacter* rank the next category. The results of this study showed that resistance is likely to be against the most common used antibiotics. The most effective antibiotics for *E. coli* are imipenem, nitrofurantoin, amikacin, chloramphenicol, and ciprofloxacin. By considering the results of this study, less use of gentamicin, the second generation of cephalosporins and nalidixic acid recommended, on the other hand, consuming of the penicillin, tetracycline, trimethoprim-sulfamethoxazole and the first generation of cephalosporins prescribed in the initial treatment of infections caused by *E. coli*. For *Klebsiella* isolates that separate from urine samples, effective antibiotics are imipenem, ciprofloxacin, amikacin, and nalidixic acid. Similarly, the use of ampicillin and cephalexin is not recommended in this case. In the treatment of UTIs that caused by *Staphylococcus*, ciprofloxacin is prescribed and consumed. It is obvious that due to the more use of antibiotics, uncontrolled use, and antibiotics misuse, antibiotic resistance emerging control is essential and this is one of the most important factors affecting these phenomena and attempts should be made for proper use of antibiotics.

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