Original Article

ISSN 2465-8243(Print) / ISSN: 2465-8510(Online)
https://doi.org/10.14777/uti.2017.12.1.28
Urogenit Tract Infect 2017;12(1):28-34

Recent Antimicrobial Susceptibilities for Uropathogenic *Escherichia coli* in Patients with Community Acquired Urinary Tract Infections: A Multicenter Study

Woong Bin Kim, Kyu Hyoung Cho[1], Sang Wook Lee, Hee Jo Yang[2], Jong Hyun Yun[1], Kwang Woo Lee, Jun Mo Kim, Young Ho Kim, Youn Soo Jeon[2], Min Eui Kim

Department of Urology, Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine, Bucheon,
[1]Department of Urology, Soonchunhyang University Gumi Hospital, Soonchunhyang University College of Medicine, Gumi,
[2]Department of Urology, Soonchunhyang University Cheonan Hospital, Soonchunhyang University College of Medicine, Cheonan, Korea

Purpose: The aim of this study was to determine the prevalence and disease-specific antimicrobial susceptibility of *Escherichia coli* in urinary tract infections (UTIs).
Materials and Methods: A total of 862 patients older than 18 years of age, who were diagnosed with UTI between January 2013 and December 2015, were included. The results of urine culture, prevalence of extended-spectrum beta lactamase (ESBL)-producing *E. coli*, and antimicrobial susceptibility by disease were also examined.
Results: A total of 862 uropathogens were isolated. Among then, *E. coli* accounted for 756 (87.7%) isolates. The susceptibility rates of *E. coli* to the following antimicrobial agents were as follows: ampicillin 29.4%, cefazolin 70.5%, ceftazidime 75.1%, cefotaxime 75.0%, cefepime 76.2%, cefoxitin 88.8%, amoxicillin-clavulanic acid 63.6%, trimethoprim-sulfamethoxazole 60.6%, gentamicin 71.4%, ciprofloxacin 73.0%, piperacillin/tazobactam 93.9%, amikacin 99.2%, imipenem 99.1%, and ertapenem 99.3%. The frequency of ESBL-producing *E. coli* strains was 24.6%. The antimicrobial susceptibility of UTI varied by each disease, but without statistical significance.
Conclusions: It is necessary to regularly examine the disease-specific resistance rates to determine the appropriate empiric antibiotic treatment, and the national antibiotic usage policies must be reorganized according to the data obtained from these studies.

Keywords: *Escherichia coli*; Anti-bacterial agents; Susceptibility; Urinary tract infections

Received: 4 November, 2016
Revised: 9 December, 2016
Accepted: 25 December, 2016

Correspondence to: Young Ho Kim
http://orcid.org/0000-0003-3959-0928
Department of Urology, Soonchunhyang University Bucheon Hospital, 170 Jomaru-ro, Wonmi-gu, Bucheon 14584, Korea
Tel: +82-32-621-5463, Fax: +82-32-621-5018
E-mail: yhkuro@schmc.ac.kr

INTRODUCTION

Urinary tract infection (UTI) is one of the most common forms of bacterial infections, and it does not discriminate against age. Globally, about 250 million people are diagnosed with UTI each year, which is costly to not only patients, but also to healthcare-funding agencies [1]. Gram negative bacteria account for approximately 80-85% of UTIs, and the leading causative organism is *Escherichia coli*, which is followed by *Klebsiella* species [2]. Empirical treatment for UTI is often prescribed without a urine culture or prior to the availability of urine culture results. According to the treatment guidelines, empirical treatment choices should be based on local or regional susceptibility data [3,4].

Long-term exposure to antimicrobial agents directly increases the selection pressure for resistance [5]. Nowadays, in many countries, more than 20% of the responsible uropathogens are resistant to trimethoprim/sulfamethoxazole (TMP/SMX) and cephalosporins. This increasing resistance is also being observed for fluoroquinolones, with an increasing resistance rate of up to 10% [6,7]. Recently, extended-spectrum beta lactamase (ESBL)-producing organisms have been considered to be an important cause of nosocomial and community acquired infections [8]. It is important to analyze the bacteria for a specific disease and to understand the rate of antimicrobial resistance of such bacteria, as well as to be aware of the treatment of new resistant organisms. Hence, the purpose of this survey was to investigate the current situation of diseases-specific antimicrobial resistance trends in *E. coli* isolated from urine specimen of UTI patients between 2013 and 2015 and to assess the differences by disease types. Additionally, we investigated the current situation of the prevalence and regional differences of ESBL-producing *E. coli* in patients treated for UTI.

MATERIALS AND METHODS

This was a population-based, retrospective, observational study, conducted in three regions—Bucheon, Cheonan, and Gumi—in Korea. Three urological centers (tertiary care hospitals) participated in the study. The clinical characteristics of 862 patients, who were older than 18 years of age and diagnosed with UTI between January 2013 and December 2015, were assessed by examining the patients' medical records. All urine samples obtained in a community setting, which were positive for *E. coli* at $\geq 10^5$ colony forming unit (CFU)/ml, were included. Community acquisition was defined as samples taken from patients in emergency departments and in hospital outpatient clinics. Exclusion criteria were symptoms of or predisposing factors for complicated UTIs (pregnancy, known urological or nephrological problems, catheter indwelling, diabetes mellitus and other immunocompromising diseases). Based on medical records, those who have taken antibiotics within the last 2 weeks from other hospitals or clinics were also excluded. Although classified as complicated UTI, if male patients did not have the aforementioned factors of complicated UTI, they were enrolled in the study.

1. Collection of Urine Sample

Midstream urine specimens (collected in sterile plastic containers following the standard clean-catch midstream procedure) from suspected cases of UTI were processed for microbiological examination. Bacterial cultures were examined, and those containing bacterial growth of $\geq 10^5$ CFU/ml were considered to be significant culture results for bateriuria. Only one urine culture per patient was accepted in the study. Samples with more than two different species were considered contaminated and were excluded from the analysis.

2. Antimicrobial Susceptibility Testing

The antimicrobial agents tested were ampicillin, amoxicillin/clavulanic acid (AMX/CLA), amikacin, cefazolin, cefoxitin, cefepime, ceftazidime, cefotaxime, ciprofloxacin, ertapenem, gentamicin, imipenem, piperacillin/tazobactam (PIP/TAZ), and TMP/SMX. Test results were expressed as minimum inhibitory concentrations with an interpretation of the category of microbial susceptibility as susceptible, intermediate or resistant according to the breakpoints recommended by the National Committee for Clinical Standards (NCCLS). Gram-negative bacteria that met the NCCLS screening criteria for potential ESBL production were confirmed for ESBL production by Vitek® ESBL card (bioMerieux Inc., Hazelwood, MO, USA). UTI patients were classified as one of the following: Acute uncomplicated cystitis, acute pyelonephritis, acute bacterial prostatitis, and acute epididymitis, in accordance with the International Classification of Diseases (ICD)-9 criteria. The antimicrobial susceptibility for each disease was examined and compared.

3. Statistical Analysis

Data was compiled in excel spread sheet, and then exported to PASW Statistics ver. 18.0 (IBM Co., Armonk, NY, USA) for statistical analysis. Demographic characteristics were presented as the means±standard deviation for quantitative variables. Evaluations were carried out at 95% confidence level, and p-values of 0.05 were considered to be statistically significant.

RESULTS

1. Demographics

During the 36-month period, a total of 862 non-duplicate positive urinary cultures were collected. Of those, 756 (87.7%) samples were positive for the presence of *E. coli*. With respect to gender of patients with uropathogenic *E. coli*, 652 (86.2%, 52.6±21.7 years) were from females and 104 (13.8%, 52.2±24.2 years) were from males. The incidence of uropethogenic *E. coli* related UTIs was 334 (44.2%) in 40-64 years, followed by 224 (29.6%) in ≥65 years, and 198 (26.2%) in 18-39 years age group (Table 1).

2. Urine Culture and Uropathogens

Seven bacterial uropathogenic species were isolated and classified from 862 midstream urine samples. The causative uropathogens included *E. coli* (n=756, 87.7%), *Klebsiella* species (n=24, 2.8%), *Enterococcus* species (n=23, 2.7%), *Proteus* species (n=5, 0.6%), *Pseudomonas* species (n=3, 0.3%), Coagulase negative staphylococci (n=33, 3.8%), and group B *Streptococcus* (n=13, 1.5%). A total of 186 cases of ESBL producing *E. coli* (24.6%) were isolated from urine culture between 2013 and 2015, showing a gradual increase, but without significant difference (Table 2); 57 cases in 2013 (22.4%), 62 cases in 2014 (25.2%), and 67 cases in 2015 (26.2%).

3. Antimicrobial Susceptibility Testing

The susceptibility rates of *E. coli* to antimicrobial agents were demonstrated to be as follows: ampicillin 29.4%, amikacin 99.2%, AMX/CLA 63.6%, cefazolin 70.5%, cefoxitin 88.8%, cefepime 76.2%, ceftazidime 75.1%, cefotaxime 75.0%, ciprofloxacin 73.0%, ertapenem 99.3%, gentamicin 71.4%, imipenem 99.1%, PIP/TAZ 93.9%, and TMP/SMX 60.6%. Susceptibility of *E. coli* was highest against carbapenem (ertapenem, imipenem) and amikacin, with low resistance rates of 0.7%, 0.9%, and 0.8%, respectively. Twenty-seven percent of *E. coli* was resistant to ciprofloxacin and 39.4% to TMP/SMX. There were no statistical differences of any antimicrobial susceptibility among the three regions (Table 3). UTI was further classified into individual diseases and examined for their antimicrobial susceptibility. The susceptibility to ciprofloxacin was 73.6% in acute cystitis (295/401), 72.9% in acute pyelonephritis (183/251), 71.4% in acute bacterial prostatitis (40/56), and 72.4% in acute epididymitis (21/29), indicating that the

Table 1. Demographic and epidemiological characteristics of 756 patients with *Escherichia coli* positive urinary tract infection

Characteristic	No. of patients (mean±SD; age, y)	Percentage (%)
Examined patients	756 (53.2±17.9)	100
Gender		
Female	652 (52.6±21.7)	86.2
Male	104 (52.2±24.2)	13.8
Age group (y)		
18-39	198 (30.4±5.7)	26.2
40-64	334 (52.0±6.5)	44.2
≥65	224 (75.2±6.8)	29.6
Region		
Bucheon	274 (52.6±17.8)	36.2
Cheonan	289 (54.3±18.1)	38.2
Gumi	193 (52.4±17.8)	25.5
Year		
2013	254 (54.2±18.0)	33.6
2014	246 (51.3±17.6)	32.5
2015	256 (53.9±18.1)	33.9

SD: standard deviation.

Table 2. Microbial spectrum of patients with urinary tract infection

Isolated species	No. of isolates			Total (n=862)
	2013	2014	2015	
Escherichia coli	254	246	256	756 (87.7)
ESBL(+) *E. coli*	57	62	67	186/756 (24.6)
Klebsiella spp.	8	7	9	24 (2.8)
Enterococcus spp.	5	11	7	23 (2.7)
Proteus spp.	1	1	3	5 (0.6)
Pseudomonas spp.	0	2	1	3 (0.3)
Coagulase negative staphylococci	8	10	15	33 (3.8)
Group B *Streptococcus*	5	5	3	13 (1.5)
Others	2	1	1	4 (0.5)

Values are presented as number only or number (%).
ESBL: extended-spectrum beta lactamase, spp.: species.

Table 3. Regional antimicrobial susceptibility of *Escherichia coli* in urinary tract infection

Antimicrobials	Susceptibility of *E. coli*				
	Bucheon (n=274)	Cheonan (n=289)	Gumi (n=193)	p-value	Total (n=756)
Ertapenem	273 (99.6)	287 (99.3)	191 (99.0)	0.676	751 (99.3)
Amikacin	272 (99.3)	288 (99.7)	190 (98.4)	0.338	750 (99.2)
Imipenem	273 (99.6)	287 (99.3)	189 (97.9)	0.144	749 (99.1)
Piperacillin/tazobactam	260 (94.9)	268 (92.7)	182 (94.3)	0.545	710 (93.9)
Cefoxitin	244 (89.1)	259 (89.6)	168 (87.0)	0.669	671 (88.8)
Cefepime	210 (76.6)	218 (75.4)	148 (76.7)	0.929	576 (76.2)
Ceftazidime	207 (75.5)	215 (74.4)	146 (75.6)	0.934	568 (75.1)
Cefotaxime	206 (75.2)	213 (73.7)	148 (76.7)	0.757	567 (75.0)
Ciprofloxacin	199 (72.6)	215 (74.4)	138 (71.5)	0.769	552 (73.0)
Gentamicin	195 (71.2)	209 (72.3)	136 (70.5)	0.901	540 (71.4)
Cefazolin	194 (70.8)	201 (69.6)	138 (71.5)	0.891	533 (70.5)
Amoxicillin/clavulanic acid	180 (65.7)	190 (65.7)	111 (57.5)	0.124	481 (63.6)
Trimethoprim/sulfamethoxazole	168 (61.3)	173 (59.9)	117 (60.6)	0.940	458 (60.6)
Ampicillin	80 (29.2)	82 (28.4)	60 (31.1)	0.812	222 (29.4)

Values are presented as number (%).

Table 4. Disease-specific antimicrobial susceptibility of *Escherichia coli* in UTI

Antimicrobials	AC (n=401)	PN (n=251)	AP (n=56)	Epi (n=29)	Other UTI (n=19)	p-value	Total (n=756)
Ertapenem	400 (99.8)	250 (99.6)	55 (98.2)	28 (96.6)	18 (94.7)	0.118	751 (99.3)
Amikacin	399 (99.5)	248 (98.8)	56 (100)	29 (100)	18 (94.7)	0.727	750 (99.2)
Imipenem	399 (99.5)	248 (98.8)	55 (98.2)	29 (100)	18 (94.7)	0.028	749 (99.1)
PIP/TAZ	380 (94.8)	232 (92.4)	53 (94.6)	27 (93.1)	18 (94.7)	0.039	710 (93.9)
Cefoxitin	360 (89.8)	218 (86.9)	51 (91.1)	25 (86.2)	17 (89.5)	0.088	671 (88.8)
Cefepime	311 (77.6)	184 (73.3)	43 (76.8)	23 (79.3)	15 (78.9)	0.949	576 (76.2)
Ceftazidime	305 (76.1)	187 (74.5)	42 (75.0)	20 (69.0)	14 (73.7)	0.759	568 (75.1)
Cefotaxime	304 (75.8)	187 (74.5)	42 (75.0)	20 (69.0)	14 (73.7)	0.845	567 (75.0)
Ciprofloxacin	295 (73.6)	183 (72.9)	40 (71.4)	21 (72.4)	13 (68.4)	0.985	552 (73.0)
Gentamicin	290 (72.3)	179 (71.3)	38 (67.9)	21 (72.4)	12 (63.2)	0.780	540 (71.4)
Cefazolin	289 (72.1)	172 (68.5)	39 (69.6)	20 (69.0)	13 (68.4)	0.459	533 (70.5)
AMX/CLA	259 (64.6)	157 (62.5)	34 (60.7)	19 (65.5)	12 (63.2)	0.978	481 (63.6)
TMP/SMX	247 (61.6)	150 (59.8)	33 (58.9)	18 (62.1)	10 (52.6)	0.207	458 (60.6)
Ampicillin	122 (30.4)	68 (27.1)	16 (28.6)	10 (34.5)	6 (31.6)	0.988	222 (29.4)

Values are presented as number (%).
UTI: urinary tract infection, AC: acute cystitis, PN: acute pyelonephritis, AP: acute bacterial prostatitis, Epi: acute epididymitis, PIP/TAZ: piperacillin/tazobactam, AMX/CLA: amoxicillin/clavulanic acid, TMP/SMX: trimethoprim/sulfamethoxazole.

resistance rates against other UTI diseases were higher than that of acute cystitis, but without significant difference (p=0.985). The antimicrobial susceptibilities to TMP/SMX and cephalosporin were 61.6%/78.2% in acute cystitis, 59.8%/75.5% in acute pyelonephritis, 58.9%/77.5% in acute bacterial prostatitis, and 62.1%/74.5% in acute epididymitis, showing a slight difference between the diseases, but without significant difference. In all UTI diseases, there was a very low resistance to the carbapenem family and amikacin (Table 4).

DISCUSSION

The major causative organism of UTI was found to be Enterobacteriaceae, and in particular, *E. coli* has been shown to be the most common. A study on patients with uncomplicated UTI in the United States reported that *E. coli* accounts for 75-90% of all UTIs, *Staphylococcus* 5-15%, *Enterococcus* and other gram-negative bacteria 5-10% [2]. It was, however, found that the frequency of *E. coli* has decreased recently, and instead, the frequency of other gram-negative bacteria and gram-positive bacteria, such as *Pseudomonas*, *Proteus*, and *Klebsiella*, has been increasing [9]. Muratani and Matsumoto [10] reported that approximately 80% of

uncomplicated UTIs were caused by *E. coli*, while complicated UTIs were caused largely by *Enterococcus*, followed by *E. coli*, and *Pseudomonas*. In Korea, Ko et al. [11]. found that gram-negative bacteria increased from 75.5% in 1994 to 83.3% in 1998. Among this, while infection by *E. coli* decreased from 50.8% in 1994 to 41.3% in 1998, infection by other gram-negative bacteria, including *Pseudomonas*, *Klebsiella*, *Enterobacter*, *Proteus*, and *Acinetobacter*, increased from 24.8% in 1994 to 42.6% in 1998. However, gram-positive bacteria decreased from 24.4% in 1994 to 16.2% in 1998. In 2006, a multicenter study on patients with acute uncomplicated cystitis revealed that the most common causative organism was *E. coli*, accounting for 71.1% [12]. In this study, *E. coli* was found to be the main uropathogen, accounting for 756 cases (87.7%) out of 862 cases, which is similar with the result from a previous multicenter study in Korea [12]. Higher frequency seems to be due to the fact that previous multicenter studies limited the subject group to those between the age of 18 and 65, and included outpatients with acute uncomplicated cystitis, excluding hospitalized patients, while the present study included patients with various UTI conditions commonly seen in the department of urology, as well as those who were older than the specified age group above.

Since antimicrobial susceptibility varies depending on the region, it is important to check the regional susceptibility when selecting empirical antibiotics for UTI. The Infectious Diseases Society of America (IDSA) suggests that physicians should know and continue to monitoring of changes on the information regarding antimicrobial susceptibility of uropathogens in their regions [13]. Although the three participating hospitals of this study are all located in urban regions, the study assumed that they might show a difference in their antimicrobial susceptibility due to the differences in size, population, characteristics, and cultures of each city. However, the findings showed that there was no significant difference in antimicrobial susceptibility, and their resistances were actually similar. This seems to be attributable to the fact that similar groups of patients participated in the study because all the participating hospitals were tertiary hospitals representing their respective regions. It can also be due to unique characteristics pertaining to Korea, which is relatively small land mass, close proximity between the regions, and relative ease of movement due to the recent developments of transportation.

Due to the increased resistant strains against antibiotics in UTIs, the IDSA suggests that fluoroquinolone, nitrofurantoin, or fosfomycin should be used, instead of TMP/SMX, as the primary empirical antibiotic for uncomplicated UTI in female patients who live in a region with more than 20% of resistance rate to TMP/SMX and have a history of recent hospitalization, repeated UTI or using TMP/SMX or other antimicrobial agents [13]. In this study, the resistance rate of TMP/SMX, reached 40%, which was higher than 29.4% from a previous multicenter study in 2006, indicating that it has almost no value as a drug for an empirical therapy of UTI patients.

Recently, the percentage of prescribing fluoroquinolone for UTI is very high in Korea. It is, however, known that the effectiveness of fluoroquinolone is not that high compared with other less expensive drugs, especially considering that it can only be used in a limited manner for gram-positive bacteria, although it works well for gram-negative bacteria, and that in particular, it is less effective for Enterococcus. Goettsch et al. [14] investigated the susceptibility to fluoroquinolone in 91,669 *E. coli* strains obtained from causative organisms found in UTI patients between 1989 and 1998, and reported that the resistance rate was increasing year by year, which was associated with an increased prescription of fluoroquinolone. Ko et al. [11] reported that the susceptibility rate of *E. coli* to ciprofloxacin was 74.7% and that of *Enterococcus* was 52.5%, while a previous multicenter study in Korea in 2006 found the susceptibility rate to be 76.6% [12]. We found the susceptibility of *E. coli* to ciprofloxacin to be 73.0%, which was lower than the two aforementioned studies. This indicates that the use of fluoroquinolone will continue to increase because the frequency of using fluoroquinolone as empirical antibiotics is very high, and the drug should be fully considered when selecting antibiotics.

The findings of this study showed that cephalosporin generally had a higher susceptibility than fluoroquinolone, although this varied by generation. In practice, the third-generation cephalosporin with a relatively low resistance rate is used for empirical therapy. However, it has the following drawbacks. First, the third-generation cephalosporin is less effective than fluoroquinolone, nitrofurantoin, fosfomycin, and pivmecillinam, which were

suggested by the IDSA guidelines in 2010 as the primary drugs for acute uncomplicated cystitis [13]. Second, if cephalosporin is widely used for empirical therapy, there is a risk of increasing the population of carbapenem resistant bacteria, including community-acquired ESBL positive strain and New Delhi Metallo-beta-lactamase-1 (NDM-1) strain; this is currently a worldwide problem [15]. Therefore, cephalosporin should not be excessively used in uncomplicated UTIs with minor symptoms. As an alternative, a specific consideration needs to be made in Korea: whether to concurrently use fluoroquinolone, nitrofurantoin, fosfomycin, and pivmecillinam, as suggested by the IDSA guidelines and commonly used in North America.

Previous studies found that *E. coli* causing acute pyelonephritis shows a higher prevalence of phylogenetic group B2, O antigen, and virulence factors (*pap*A/C/EF/G, iha, *fyu*A, *iut*A, etc.) than *E. coli* causing acute cystitis, but has a relatively low bacteria colony in the bladder [16-18]. In theory, since most of the acute pyelonephritis starts from the bladder, antimicrobial susceptibility of causative organisms of acute cystitis and acute pyelonephritis are expected to be the same. However, there is a possibility that the results of antimicrobial susceptibility of these two diseases are not the same because there is a bacteriological difference between the causative organisms of the two diseases. In this present study, the antimicrobial susceptibility of the causative organisms of these two diseases was found to be similar with that of major antibiotics. However, antibiotics need to be selected by considering the possible bias in this study, which was the exclusion of patients with acute cystitis without urine culture.

The limitations of this study are as follows. First, there were no consistent criteria for diagnosing patients with individual diseases of UTI. Since this study was a multicenter, retrospective study based on medical records, it is highly likely that subjective opinion of clinicians of each hospital was involved during the diagnosis. Second, the participating hospitals were large-scale hospitals. In general, a large portion of patients visiting the these hospitals were those who had severe conditions with underlying diseases, compared with those visiting primary hospitals. It is also possible that patients who sought re-treatment due to repeated infection or those who were already diagnosed with UTI from other hospitals were included in the study. Therefore, there is a possibility of selection bias, despite the careful selection of participants based on the restriction criteria of the author. Third, the study was a retrospective study, which recruited patients based on the ICD code diagnosis from medical records. The fact that the performance rate of urine culture over 80% in acute cystitis seems to be a bias that inevitably occurs in a retrospective study, as acute cystitis is a disease in which culture is generally not performed and insurance benefit is not available during the time of performing the culture. In addition, because investigation was made based on medical records, there is a possibility that past history of patients may not be accurate. In particular, the possibility of error or absence of information on UTI history or antimicrobial use, which are factors that can significantly affect the result of antimicrobial susceptibility, is considered to be a limitation of this study.

CONCLUSIONS

When selecting empirical therapy for UTI patients, in vitro susceptibility patterns of common uropathogens, such as those reported here, must be considered along with other factors, such as expected efficacy, adverse effect, cost, cost-effectiveness, and selection of resistant strains. Continued evolution of antimicrobial resistance among community-acquired isolates is worrisome, and it mandates both further surveillance and new approaches to slow the emergence of resistance.

In addition, antimicrobial resistance of causative organisms of UTI in Korea is relatively higher than that in North America or in Europe and is on the rise. Therefore, when there is a suspicion of community-acquired UTI, the selection of antibiotics should be allowed in accordance with the results of antimicrobial susceptibility by performing urine culture. Further, research and clinical study on the susceptibility of fosfomycin, nitrofurantoin, and pivmecillinam, which are suggested by the IDSA guidelines, need to be conducted.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

This study was supported by the Soonchunhyang University Research fund.

REFERENCES

1. Ronald AR, Nicolle LE, Stamm E, Krieger J, Warren J, Schaeffer A, et al. Urinary tract infection in adults: research priorities and strategies. Int J Antimicrob Agents 2001;17:343-8.
2. Hooton TM, Stamm WE. Diagnosis and treatment of uncomplicated urinary tract infection. Infect Dis Clin North Am 1997;11:551-81.
3. Dielubanza EJ, Schaeffer AJ. Urinary tract infections in women. Med Clin North Am 2011;95:27-41.
4. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol 2015;13:269-84.
5. Shah AA, Hasan F, Ahmed S, Hameed A. Characteristics, epidemiology and clinical importance of emerging strains of Gram-negative bacilli producing extended-spectrum beta-lactamases. Res Microbiol 2004;155:409-21.
6. De Backer D, Christiaens T, Heytens S, De Sutter A, Stobberingh EE, Verschraegen G. Evolution of bacterial susceptibility pattern of Escherichia coli in uncomplicated urinary tract infections in a country with high antibiotic consumption: a comparison of two surveys with a 10 year interval. J Antimicrob Chemother 2008;62:364-8.
7. Schito GC, Naber KG, Botto H, Palou J, Mazzei T, Gualco L, et al. The ARESC study: an international survey on the antimicrobial resistance of pathogens involved in uncomplicated urinary tract infections. Int J Antimicrob Agents 2009;34:407-13.
8. Pitout JD. Extraintestinal pathogenic Escherichia coli: an update on antimicrobial resistance, laboratory diagnosis and treatment. Expert Rev Anti Infect Ther 2012;10:1165-76.
9. Stamm WE, Norrby SR. Urinary tract infections: disease panorama and challenges. J Infect Dis 2001;183 Suppl 1:S1-4.
10. Muratani T, Matsumoto T. Bacterial resistance to antimicrobials in urinary isolates. Int J Antimicrob Agents 2004;24 Suppl 1:S28-31.
11. Ko YH, Oh JS, Cho DY, Bea JH, Koh SK. Changes of causative organisms and antimicrobial sensitivity of urinary tract infection between 1979 and 2001. Korean J Urol 2003;44:342-50.
12. Kim ME, Ha US, Cho YH. Prevalence of antimicrobial resistance among uropathogens causing acute uncomplicated cystitis in female outpatients in South Korea: a multicentre study in 2006. Int J Antimicrob Agents 2008;31 Suppl 1:S15-8.
13. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52:e103-20.
14. Goettsch W, van Pelt W, Nagelkerke N, Hendrix MG, Buiting AG, Petit PL, et al. Increasing resistance to fluoroquinolones in escherichia coli from urinary tract infections in the Netherlands. J Antimicrob Chemother 2000;46:223-8.
15. Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: a clinical update. Clin Microbiol Rev 2005;18:657-86.
16. Johnson DE, Lockatell CV, Russell RG, Hebel JR, Island MD, Stapleton A, et al. Comparison of Escherichia coli strains recovered from human cystitis and pyelonephritis infections in transurethrally challenged mice. Infect Immun 1998;66:3059-65.
17. Johnson JR, Kuskowski MA, Gajewski A, Soto S, Horcajada JP, Jimenez de Anta MT, et al. Extended virulence genotypes and phylogenetic background of Escherichia coli isolates from patients with cystitis, pyelonephritis, or prostatitis. J Infect Dis 2005;191:46-50.
18. Johnson JR, Owens K, Gajewski A, Kuskowski MA. Bacterial characteristics in relation to clinical source of Escherichia coli isolates from women with acute cystitis or pyelonephritis and uninfected women. J Clin Microbiol 2005;43:6064-72.