Original Article

The Significance of Age and Causative Bacterial Morphology in the Choice of an Antimicrobial Agent to Treat Acute Uncomplicated Cystitis

Shinya Uehara[a,b]*, Kei Fujio[a], Tomoya Yamasaki[a], and Hideo Otsuki[a]

[a]*Department of Urology, Abiko Toho Hospital, Chiba 270-1166, Japan,*
[b]*Department of Urology, Kawasaki Medical School General Medical Center, Okayama 700-8505, Japan*

Differentiating patients by age and causative bacterial morphology might aid in making the appropriate choice of antimicrobial agent when treating acute uncomplicated cystitis. In this retrospective analysis, the non-susceptibility rates of the causative bacteria to cefcapene-pivoxil (CFPN-PI) and levofloxacin (LVFX) were determined after dividing patients with acute uncomplicated cystitis by age group (15-54 and 55-74 years old) and by bacterial morphology: gram-positive cocci (GPC) or gram-negative rod (GNR). The overall non-susceptibility rates for CFPN-PI and LVFX were 19.4% and 15.3%, respectively. When the subjects were divided by age, only the non-susceptibility rate for LVFX in the younger group significantly decreased (to 8.7%). When the groups were divided by both age and bacterial morphology, the younger GNR group had non-susceptibility rates of 6.9% to CFPN-PI and 7.8% to LVFX, whereas the younger GPC group showed 10.2% non-susceptibility to LVFX. The older GNR group showed 9.8% non-susceptibility to CFPN-PI, while the older GPC group showed 7.2% non-susceptibility to LVFX. All the non-susceptibility rates were lower than 10.2% in the sub-divided groups. Differentiating patients by age and the morphology of causative bacteria can aid in making the appropriate choice of antimicrobial agent and may improve treatment outcomes in patients with acute uncomplicated cystitis.

Key words: acute uncomplicated cystitis, oral antimicrobial agents, antimicrobial susceptibility, menopause, Gram stain

A bout half of all women experience a urinary tract infection (UTI) sometime in their lives, and a quarter of women contract a UTI multiple times [1]. Most UTIs in young women are acute uncomplicated cystitis [2]. The issue of acute uncomplicated cystitis being resistant to antibiotics has been widely raised recently [3], with resistance to quinolone antibiotics being especially noticeable [4-6]. There is also a rise in extended-spectrum beta-lactamase (ESBL)-producing bacteria. These trends mean that appropriate drug choice is more vital now than ever.

The causative bacteria in acute uncomplicated cysti-tis have been shown to differ between pre- and post-menopausal females. Specifically, the ratio of Gram-positive cocci (GPC) to Gram-negative rod (GNR) bacteria declines in postmenopausal cases, and the percentages of quinolone-resistant bacteria and ESBL-producing bacteria tend to increase. Therefore, the drug susceptibility of pre- and postmenopausal patients is considered to be different [3]. Another tendency is that antibacterial agents are less effective for short-term treatment in postmenopausal women than in premeno-pausal women [7]. In addition, it is reasonable to diag-nose acute uncomplicated cystitis in patients younger than 40 years of age based on the results of a urine test,

a urine culture and symptoms. However, for patients over 40, the underlying conditions of the UTI need to be differentiated when making a diagnosis [8,9].

According to the Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy (JAID/JSC) Guidelines for Clinical Management of Infectious Diseases 2015 (2015 Guidelines) [10], the first-line agent for treating acute uncomplicated cystitis in pre-menopausal patients is quinolone antibiotics, whereas the first choice for postmenopausal patients is either cephem antibiotics or penicillin combined with a beta-lactamase inhibitor. The 2015 Guidelines marked a change from previous editions, which always recommended quinolone antibiotics as the first choice, with no consideration of menopausal status. The 2015 Guidelines do, however, state that the causative bacterial morphology should be classified as GNR or GPC before the administration of any antimicrobial agent, and they stress the importance of choosing the most appropriate antimicrobial agent [10].

This study divided patients by age and bacterial morphology in order to examine their susceptibility to various antimicrobial agents with the aim of obtaining useful data to guide the choice of antimicrobial agent when treating acute uncomplicated cystitis.

Research Material and Methods

Subjects. The subjects for this retrospective study were 935 women clinically diagnosed with acute uncomplicated cystitis at the Department of Urology in Abiko Toho Hospital between January 1st, 2012 and December 31st, 2018. Acute cystitis was diagnosed in cases with clinical symptoms, pyuria and bacteriuria. Pyuria was defined as the presence of a urine sediment specimen with at least 5 white blood cells (WBCs) per high-power field. Bacteriuria was defined as a viable bacterial count equivalent to or greater than 10^4 CFU/ml in the midstream urine. An ultrasound test was done to exclude complicated UTI. Patients younger than 15 and older than 75 years of age were excluded due to the possibility of having potential underlying conditions in the urinary tract.

Methods. Urine samples were incubated at 37°C for 24 h, and the bacterial counts and strains were identified. Drug susceptibility testing was performed using a broth microdilution method, and the drug susceptibility was categorized as "susceptible" (S), "inter-

mediate" (I) or "resistant" (R), with I and R considered to be non-susceptible to the tested drug according to the breakpoints recommended by the Clinical and Laboratory Standards Institute in document M100-S17 [11]. If the minimum concentration of ceftazidime needed to inhibit Enterobacteriaceae was more than 2 µg/ml, the presence of ESBL-producing bacteria was suspected, and a double-disk synergy test was added to confirm the presence of ESBL.

The susceptibility of bacteria to the oral cephem agent cefcapene-pivoxil (CFPN-Pl) and the quinolone agent levofloxacin (LVFX) was examined. Amoxicillin (AMPC), minocycline (MINO), cefotiam (CTM), ceftriaxone (CTRX), tazobactam/piperacillin (TAZ/PIPC), and meropenem (MEPM) were also tested.

The patients were divided by age into 10-year groups from 15 to 74. Next, to determine an approximate cut-off for dividing the cases into pre- and postmenopausal groups, the GNR/GPC ratio, the percentage of ESBL-producing bacteria and the non-susceptibility to LVFX were determined for each age group. Using that data, the patients were divided into just 2 age groups, 15-54 and 55-74 years old. For both age groups, the following data were gathered: the non-susceptibility rate for each drug for each age and GNR/GCP status group, and the percentage of ESBL-producing bacteria.

Statistical analysis. The median value (interquartile range) of the results of each test was used as a continuous variable, and n (%) was used as a categorical variable. A chi-squared test was used to compare the categorical variables, with significance at $p < 0.05$. EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) statistical software was used to conduct the analysis.

Ethical considerations. This study was examined and approved by the Ethics Committee at Abiko Toho Hospital (approval number: 201918).

Results

The final number of subjects was 935. Their median age was 58 years old (interquartile range: 43-67 years old). The distribution of the causative bacteria is shown in Fig. 1; 82.1% of the isolates were GNR bacteria and 17.9% were GPC bacteria. Bacterial classification found 67.0% *Escherichia coli* (*E.coli*), followed by 11.4% *Enterococcus*, 5.7% *Klebsiella pneumonia*, and 3.7% *Streptococcus*. Table 1 shows the non-susceptibility rates
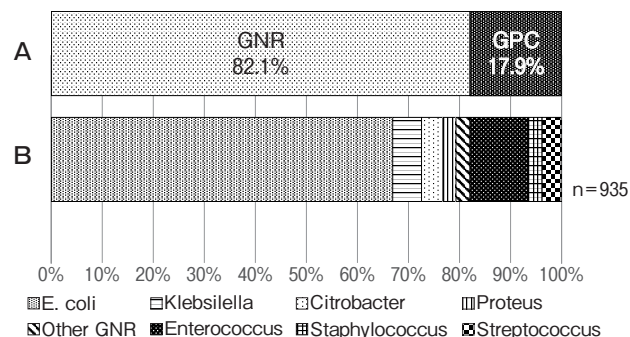
Fig. 1 Isolates of acute uncomplicated cystitis. **A**, Classification by gram staining; **B**, Classification of isolated bacteria

Table 1 Antibiotic non-susceptibility rate

antimicrobials	Overall (%) (n = 935)	E. coli (%) (n = 626)
oral		
AMPC	37.4	33.9
CFDN-PI	19.4	8.8
LVFX	15.3	20.1
MINO	17.2	6.9
intravenous		
CTM	20.0	6.1
CTRX	16.1	5.3
TAZ/PIPC	1.7	0.6
MEPM	2.2	0.0

Table 2 GNR/GPC distribution by age group

	GNR	GPC
15−54 (y.o.)	76.6	23.4
55−74 (y.o.)	86.6	13.4(%)

Table 3 Non-susceptibility rates by age group

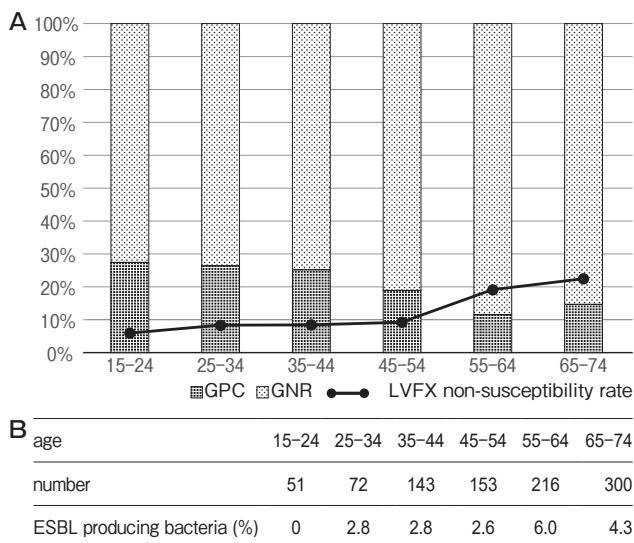|	15−54 (y.o.)	55−74 (y.o)
AMPC	32.2	41.7
CFPN-PI	20.0	18.2
LVFX	8.4	20.9(%)

Fig. 2 GNR/GPC distribution, LVFX non-susceptibility and ESBL-producing bacteria by age group. **A**, GNR/GPC distribution and the rate of non-susceptibility to LVFX by age group; **B**, Percentage of ESBL-producing bacteria by age

of all of the bacteria collectively and that of *E. coli* specifically, since it accounted for over two-thirds of the cases. Overall, the non-susceptibility rates were 19.4% for CFPN-PI and 15.3% for LVFX, showing little difference between the 2 agents. The injectable cephem antibiotics CTM, CTRX, TAZ/PIPC and MEPM had non-susceptibility rates of 20.0%, 16.1%, 1.7% and 2.2%, respectively. The non-susceptibility rates of CFPN-PI and LVFX in just the *E. coli* portion of the cases were 8.8% and 20.1%, respectively, indicating that quinolone antibiotics had a higher non-susceptibility rate than cephem antibiotics. The non-susceptibility rates of injectable CTM, CTRX, TAZ/PIPC or MEPM

in just the *E. coli* portion of cases were 6.1%, 5.3%, 0.6% and 0%, respectively.

The patients were divided by age into 10-year groups from 15 to 74, and the following data were compiled: the ratio of GPC to GNR cases, the rates of non-susceptibility to LVFX, and the percentage of cases with ESBL-producing bacteria (Fig. 2). The ratio of GPC occurrence tended to decrease with age, while non-susceptibility to LVFX and the percentage of cases with ESBL-producing bacteria rose in patients over 55 years old. Based on these findings, the patients were subsequently divided into two age groups of 15-54 and 55-74 years old.

The relationship between age and GPC/GNR classification was examined (Table 2). The younger, 15-54 year-old group had 76.6% GNR and 23.4% GPC bacteria. The older, 55-74 year-old group had 86.6% GNR and 13.4% GPC bacteria. The older group had a significantly higher GNR isolation rate ($p < 0.001$).

Next, the relationship between age and oral antibiotic resistance was examined (Table 3). The rates of

non-susceptibility to AMPC, CFPN-PI and LVFX in the younger group were 32.2%, 20.0% and 8.4%, respectively, with the older group showing 41.7%, 18.2% and 20.9% rates of non-susceptibility, respectively. The non-susceptibility rate of LVFX in the younger group was significantly lower than that in the overall group ($p < 0.001$), while the rates for AMPC and CFPN-PI were not improved in the younger group compared to the overall group. In the older group, the non-susceptibility rates to AMPC, LVFX, and CFPN-PI did not decrease in comparison to the overall group.

The percentage of cases with ESBL-producing bacteria was also examined by age group. Overall, 2.4% of the younger group and 5.0% of the older group had ESBL-producing bacteria. When only *E. coli* cases were examined, 3.4% of the younger group and 7.2% of the older group had ESBL-producing bacteria. The older group had a higher percentage of ESBL-producing bacteria, but the difference was not statistically significant (overall: $p = 0.054$; *E.coli*: $p = 0.052$).

The patients were divided into 4 groups by age group and GNR/GPC status to examine the drug non-susceptibility rates (Table 4). The younger GNR group had a non-susceptibility rate of 6.9% to CFPN-PI and 7.8% to LVFX, whereas in the younger GPC group the non-susceptibility rate to LVFX was 10.2%. The older GNR group had a non-susceptibility rate of 9.8% to CFPN-PI, and in the older GPC group the rates were 1.4% to AMPC and 7.2% to LVFX. By dividing the subjects into sub-groups and choosing the appropriate antibiotic for each group, the non-susceptibility rates declined to 10.2% or lower.

Table 4 clearly shows that, in younger patients, either cephem or quinolone antibiotics should be chosen to treat GNR bacteria, and only quinolone antibiotics should be chosen to treat GPC bacteria. In older patients, cephem antibiotics should be used to treat GNR bacteria and penicillin or quinolone antibiotics should be used to treat GPC bacteria.

Table 4 Non-susceptibility rates by age group and GNR/GPC status

	15–54 (y.o.)		55–74 (y.o.)	
	GNR	GPC	GNR	GPC
AMPC	38.0	13.3	47.9	1.4
CFPN-PI	6.9	63.3	9.8	76.8
LVFX	7.8	10.2	23.0	7.2 (%)

Discussion

When determining which antimicrobial agent to use to treat acute uncomplicated cystitis, the JAID/JSC 2015 Guidelines state that for premenopausal patients, quinolone antibiotics are the first-line agent and are also recommended for premenopausal patients with GPC bacteria. For postmenopausal patients, the first choice is either cephem antibiotics or penicillin with a beta-lactamase inhibitor, and quinolone antibiotics are a second choice, but should be chosen when the patient has GPC bacteria [10]. The Guidelines emphasize that quinolone antibiotics should not be chosen unconditionally, and that the bacteria should be classified by Gram staining before any antibiotic is chosen.

This retrospective study reviewed a large number of cases from general clinical practices and examined how classifying patients by age and bacterial morphology might help with selecting the appropriate antimicrobial agent. When the patients were divided into two age groups (15-54 and 55-74 years-old), only the non-susceptibility to quinolone antibiotics in the younger group improved significantly compared to overall non-susceptibility. The older group showed no significant difference in susceptibility compared to the overall rates. However, when the subjects were divided more precisely by age, GPC/GNR morphology and drug, the non-susceptibility rates fell to 10.2% or lower for LVFX when treating GPC bacteria in the younger group, for both LVFX and CFPN-PI in the younger GNR group, for AMPC and LVFX in the older GPC group, and for CFPN-PI in the older GNR group. Dividing patients not only by age but also by Gram-staining to determine the bacterial morphology in detail can determine the appropriate choice of antimicrobial agent. This detailed division of cases shows the potential of directed therapy to improve treatment decisions and also reinforces the validity of the 2015 Guidelines.

The overall distribution of bacteria was 82.1% GNR and 17.9% GPC, with 67.0% of the overall bacteria identified as *E. coli*. This distribution closely matched the distribution results previously reported in Japan [3,12,13], so this study's cohort can be considered to be a similarly representative sample. The overall non-susceptibility rates were 20% to oral cephem antibiotics and 15% to quinolone antibiotics, which were equivalent to the findings of previous reports [7,13]. Taking these findings together, the efficacy of oral

cephem antibiotics can theoretically be considered to be 80% and that of quinolone antibiotics to be 85%. *E. coli* showed non-susceptibility rates in this study of roughly 9% to oral cephem agents and about 20% to quinolone agents, results that were equivalent to those in another published report [3]. Matsumoto *et al.* [14] reported on drug susceptibility in the treatment of acute uncomplicated cystitis. Their patients were divided into pre- and postmenopausal groups, with postmenopausal patients having about a 5% higher non-susceptibility rate to both cephem and quinolone antibiotics. Koguchi *et al.* [13] conducted a similar examination in which the cohort was divided at the age of 50, and although the results were not significant, the rate of non-susceptibility to quinolone antibiotics was 5% lower among patients under 50 years old.

The 2015 Guidelines state that antimicrobial agents should be chosen based on menopause status, but there are no detailed guidelines regarding age. To determine the specific age groups used in this study, the patients were first divided by age into 10-year groups from 15 to 74. Then, the distribution of the causative bacteria, the rate of non-susceptibility to LVFX and the percentage of cases with ESBL-producing bacteria were established. From the age of 55, there was a decrease in the ratio of GPC cases, as well as increases in LVFX non-susceptibility and the percentage of ESBL-producing bacteria. Studies on age at menopause in Japan indicated that 50% of women aged 50.54 years old were in menopause and 90% of women aged 56.34 years old were in menopause [15,16]. Thus, it is reasonable to define postmenopausal as 55 years old and older. Accordingly, in this study we divided the cases into two age groups, 15-54 and 55-74 years old.

The younger group was ≈ 20% non-susceptible to oral cephem antibiotics and ≈ 9% non-susceptible to quinolone antibiotics. The older group was ≈ 18% non-susceptible to oral cephem antibiotics and ≈ 21% non-susceptible to quinolone antibiotics. The younger group had a lower non-susceptibility to quinolone antibiotics than the overall cohort. However, dividing the subjects by age did not show any improvement in non-susceptibility to cephem antibiotics in the younger group, nor to either antibiotic category in the older group. These tendencies were similarly reported by Koguchi *et al.* [13], whose study divided the patients at age 50. The fact that the younger group had a higher ratio of GPC cases is considered to be related to the improvement of

the rate of non-susceptibility to quinolone antibiotics in that group as well as the non-improvement of the rate of non-susceptibility to cephem antibiotics. Because the ratio of GNR bacteria in the older group was higher, the rate of non-susceptibility to cephem antibiotics was expected to go down, but no trend of improvement was seen, possibly due to the higher prevalence of ESBL-producing bacteria in the older group.

The percentage of ESBL-producing bacteria increased to 5.0% in the older group, indicating that the presence of ESBL-producing bacteria greatly affects the rate of non-susceptibility to cephem antibiotics in GNR bacteria. Heytens *et al.* [17] found that ESBL-producing bacteria accounted for 2.5% of all *E. coli*, and that ESBL-producing bacteria were present in 1.7% of patients 18-55 years old and 5.8% of those ≥ 56 years old. Our study detected ESBL-producing bacteria in 7.2% of the older group, and this is considered to have affected the decrease in drug susceptibility.

When we divided subjects by both age and GNR/GPC status, the younger GNR group was ≈ 7-8% non-susceptible to both cephem and quinolone antibiotics, and the younger GPC group was ≈ 10% non-susceptible to quinolone antibiotics. The older GNR group had a non-susceptibility rate of ≈ 10% to cephem antibiotics, and the older GPC group was ≈ 7% non-susceptible to quinolone antibiotics and ≈ 2% to penicillin. Thus, the non-susceptibilities had improved to ≈ 10% or lower. Therefore, for younger premenopausal patients with GNR bacteria, either cephem or quinolone antibiotics can be chosen, and when premenopausal patients have GPC bacteria, quinolone antibiotics should be chosen. For postmenopausal patients, cephem antibiotics should be chosen to treat GNR bacteria, and quinolone or penicillin antibiotics should be chosen when GPC bacteria are present. Choosing the appropriate antibiotic can improve the treatment efficacy to over 90% in some instances. The importance of differentiating patients by both age and bacterial morphology, especially for older postmenopausal patients, has been clearly shown.

This study did not examine penicillin with a beta-lactamase inhibitor, did not evaluate clinical outcomes, and did not evaluate how ESBL-producing bacteria were treated. Although there are some issues to be resolved, differentiating patients by age and causative bacteria morphology can help determine the treatment choice for acute uncomplicated cystitis.

Considering the collateral damage caused by quinolone-resistant GNR bacteria, always choosing quinolone antibiotics as the first-line treatment should be avoided [10]. If antimicrobial agents are chosen in the way indicated in this study, and cephem antibiotics and even penicillin with a beta-lactamase inhibitor are appropriately used, overall drug effectiveness can be improved while simultaneously decreasing the amount of quinolone agents used.

References

1. Mehnert-Kay SA: Diagnosis and management of uncomplicated urinary tract infections. Am Fam Physician (2005) 72: 451–456.
2. Hooton TM, Scholes D, Hughes JP, Winter C, Roberts PL, Stapleton AE, Stergachis A and Stamm WE: A prospective study of risk factors for symptomatic urinary tract infection in young women. N Engl J Med (1996) 335: 468–474.
3. Hayami H, Takahashi S, Ishikawa K, Yasuda M, Yamamoto S, Wada K, Kobayashi K, Hamasuna R, Minamitani S, Matsumoto T, Kiyota H, Tateda K, Sato J, Hanaki H, Masumori N, Nishiyama H, Miyazaki J, Fujimoto K, Tanaka K, Uehara S, Matsubara A, Ito K, Hayashi K, Kurimura Y, Ito S, Takeuchi T, Narita H, Izumitani M, Nishimura H, Kawahara M, Hara M, Hosobe T, Takashima K, Chokyu H, Matsumura M, Ihara H, Uno S, Monden K, Sumii T, Kawai S, Kariya S, Sato T, Yoshioka M, Kaneda H, Matsushita S, Nishi S, Hosokawa Y, Shirane T, Yoh M, Watanabe S, makinose S, Uemura T and Goto H: Second nationwide surveillance of bacterial pathogens in patients with acute uncomplicated cystitis conducted by Japanese Surveillance Committee from 2015 to 2016: antimicrobial susceptibility of Escherichia coli, Klebsiella pneumonia, and Staphylococcus saprophyticus. J Infect Chemother (2019) 25: 413–422.
4. Kahlmeter G and Pousen HO: Antimicrobial susceptibility of Escherichia coli from community-acquired urinary tract infection in Europe: the ECO・SENS sutudy revised. Int J Antimicrobial Agents (2012) 39: 45–51.
5. Kahlmeter G, Ahman J and Matuschek E: Antimicrobial resistance of Escherichia coli causing uncomplicated urinary tract infections: a european update for 2014 and comparison with 2000 and 2008. Infect Dis Ther (2015) 4: 417–427.
6. Shigemura K, Tanaka K, Adachi M, Yamashita M, Arakawa S and Fujisawa M: Chronological change of antibiotic use and antibiotic resistance in Escherichia coli causing urinary tract infections. J Infect Chemother (2011) 17: 646–651.
7. Nicolle LE, Madsen KS, Debeeck GO, Blochlinger E, Borrild N, Bru JP, Mckinnon C, O'Doherty B, Spiegel W, Van Balen FAM and Menday P: Three days pivmecillinam or norfloxacin for treatment of acute uncomplicated urinary infection inwomen. Scand Infect Dis (2002) 34: 487–492.
8. Stamm WE and Hooton TM: Management of urinary tract infections in adults. N Engl Med (1993) 329: 1328–1334.
9. Haarst EP, Andel G, Heldeweg EA, Schlatmann TJ and Horst HJ: Evaluation of the diagnostic workup in young women referred for recurrent lower urinary tract infections. Urology (2001) 57: 1068–1072.
10. The Japanese Association for Infections Disease/Japanese Society of Chemotherapy, The JAID/JSC Guide/Guidelines to Clinical Management of Infections Disease Preparing Committee, Urinary tract infection/male genital infection working group, Yamamoto S, Ishikawa K, Hayami H, Nakamura T, Miyairi I, Hoshino T, Hasui M, Tanaka Kazushi, Kiyota H and Arakawa S: JAID/JSC Guidelines for Clinical management of Infections Disease 2015- Urinary tract infection/male genital infection. J Infect Chemother (2017) 23: 733–751.
11. Clinical and Laboratory Standards Institute: Performance standards for antimicrobial susceptibility testing; twenty-sixth informational supplement. Document M100-S17. Wayne, PA: CLSI; 2007.
12. Etani T, Naiki T, Yamaguchi S, Mori S, Nagai T, Iida K, Ando R, Kawai N, Tozawa K, Morigami T and Yasui T: Antimicrobial susceptibility of patients in acute umcomplicated cystitis cases in the urology department of a community hospital in Japan: Comparison with treatment outcome and hospital-wide antibiogram: J Infect Chemother (2017) 23: 693–697.
13. Koguchi D, Murakami Y, Ikeda M, Dobashi M and Ishii J: Cefaclor as a first-line treatment for acute uncomplicated cystitis: a retrospective single-center study. BMC Urol (2020) 20: 38.
14. Matsumoto T, Hamasuna R, Ishikawa K, Takahashi S, Yasuda M, Hayami H, Tanaka K, Muratani T, Monden K, Arakawa S and Yamamoto S: Sensitivities of major causative organism isolated from patients with acute uncomplicated cystitis against various antimicrobial agents: results of subanalysis based on the presence of menopause. J Infect Chemother (2012) 18: 597–607.
15. Tamada T and Iwasaki H: Age at Natural Menopause in Japanese Women. Nihon Sanka Fujinka Gakkai Zasshi (1995) 47: 947–952 (in Japanese).
16. Kono S, Sunagawa Y, Higa H and Sunagawa H: Age of menopause in Japanese women: Trends and recent changes. Maturitas (1990) 12: 43–49.
17. Heytens S, Boelens J, Claeys G, DeSutter and Christiaens T: Uropathogen distribution and antimicrobial susceptibility in uncomplicated cystitis in Belgium, a high antibiotics prescribing country: 20-year surveillance. Eur J CIin MIcrobiol Infect Dis (2017) 36: 105–113.